Iron- and Ruthenium-Catalyzed Site-Selective C–C Forming Direct C–H Functionalizations

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Erklärung

Ich versichere, dass ich die vorliegende Dissertation in der Zeit von

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auf Anregung und unter Anleitung von

Herrn Prof. Dr. Lutz Ackermann

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Contents

Abbreviations

Ac	acetyl
acac	acetylacetone
Ad	adamantyl
Alk	alkyl
AMLA	ambiphilic metal-ligand activation
PMP	*p*-methoxyphenyl
APT	attached proton test
aq.	aqueous
Ar	aryl
atm	atmosphere
ATR	attenuated total reflectance
BDMAE	bis(2-dimethylaminoethyl)ether
bpy	2,2'-bipyridine
Bn	benzyl
Bu	butyl
$ß_n$	bite angle
cat.	catalytic
CMD	concerted metalation-deprotonation
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
Cy	cyclohexyl
DavePhos	2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl
dbm	dibutoxymethane
DCE	1,2-dichloroethane
DCIB	1,2-dichloro-2-methylpropane
DDQ	2,3-dichlor-5,6-dicyano-1,4-benzochinon
DG	directing group
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinon
DMSO	dimethylsulfoxide
D*o*M	directed *ortho*-metalation
DPEN	1,2-diphenyl-1,2-diaminoethane
dppbz	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppen	1,2-bis(diphenylphosphino)ethylene
dppf	1,3-bis(diphenylphosphino)ferrocene
dppp	1,1'-bis(diphenylphosphino)propane
dtbpy	4,4'-di-*tert*-butyl bipyridine

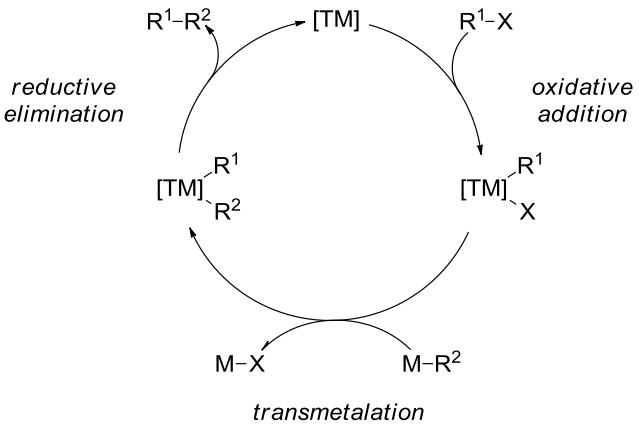
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
et. al.	et alia
FTICR	Fourier transform ion cyclotron resonance
FG	functional group
GC-MS	gas chromatography-mass spectrometry
HASPO	heteroatom-substituted secondary phosphine oxide
Hex	hexyl
HiPrCl	1,3-bis-(2,6-di-*iso*-propylphenyl)imidazolium chloride
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half maximal inhibitory concentration
IES	internal electrophilic substitution
IPr	1,3-bis(2,4,6-isopropylphenyl)-imidazolium
i-Pr	*iso*-propyl
i. e.	*id est*
IR	infrared
JohnPhos	2-(di-*tert*-butylphosphino)biphenyl
KIE	kinetic isotopic effect
L	ligand
LA	Lewis acid
LDA	lithium di-*iso*-propylamide
Mes	2,4,6-trimethylphenyl
Me	methyl
m-	*meta*
MMO	methane monooxygenase
mol.	molecular
M. p.	melting point
Mt/a	million tonnes per year
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement and exchange spectroscopy
o-	*ortho*
p-cymene	4-*iso*-propyltoluene
PEG	polyethylene glycol
Pent	pentyl
phen	phenanthroline

Ph	phenyl
Pin	2,4,4,5,5-pentamethyl-1,3,2-dioxaborolan-2-yl
Piv	2,2-dimethylpropanoyl
PMP	*para*-methoxyphenyl
ppm	parts per million
p-	*para*
Q	quinolin-8-amine
R	rest
S_EAr	electrophilic aromatic substitution
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
SIPr	1,3-bis-(2,6-diisopropylphenyl)imidazolidinium
SPO	secondary phosphine oxide
T	temperature
t-Am	2-methylbut-2-yl
TAM	triazolyldimethylmethyl
TEA	triethylamine
TDS	turnover-determining step
Tf	trifluoromethanesulfonyl
THF	tetrahydrofurane
TLC	thin layer chromatography
TM	transition metal
TMEDA	tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	tolyl
TON	turn over number
TS	transition state
Ts	tosyl
UV	utraviolet
X	halide
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

1. Introduction

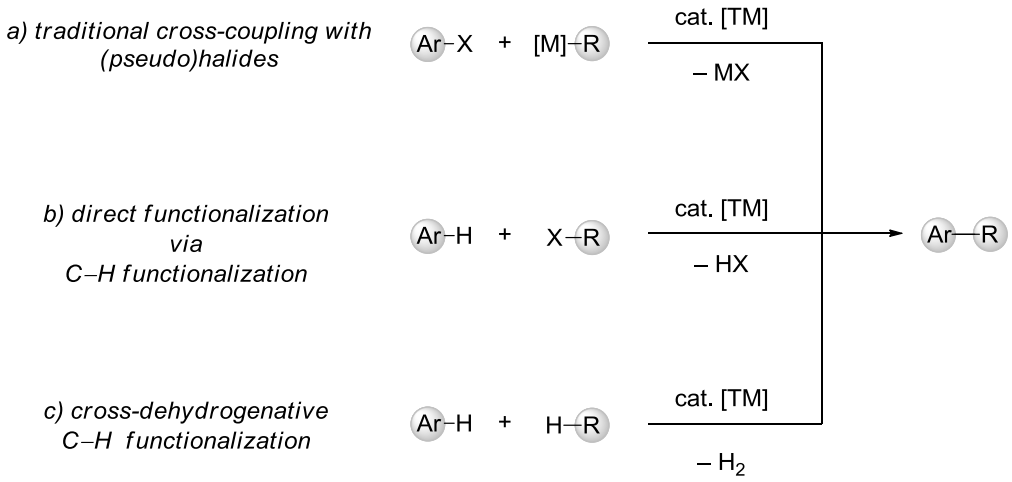
1.1 Transition Metal-Catalyzed C–H Bond Functionalization

During the last decades, C–C bond forming reactions have been established as one of the most important tools for modern organic synthesis for the functionalization of otherwise difficult to activate compounds.[1-3] One prominent example was awarded for the Nobel Prize of Chemistry in 2010 for the palladium-catalyzed formation of C–C single bond formation *via* cross-coupling chemistry for *Heck*, *Negishi* and *Suzuki*.[1, 4-6] The series of classical cross-coupling processes, such as *Kumada-Corriu*, *Negishi*, *Migita-Stille* and *Suzuki-Miyaura* reactions, is largely based upon participation of palladium catalysts, which are costly. In general, the common catalytic cycle for cross-coupling reactions involves a (pseudo)halide as an electrophile and an organometallic species as a nucleophile, as presented in Scheme 1. The key steps are the oxidative addition of the (pseudo)halide, followed by a transmetalation with the organometallic species and a final reductive elimination affording the cross-coupled product.



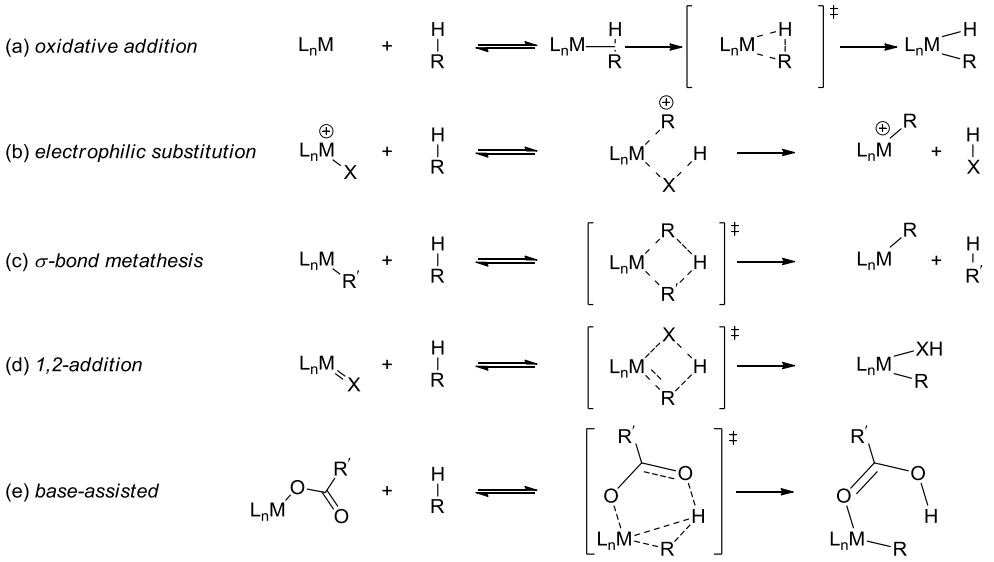
Scheme 1: General catalytic cycle for the transition metal-catalyzed cross-coupling reaction.

Significant drawbacks of these reactions are the required prefunctionalization of starting materials and potential side reactions, such as *ß*-hydride elimination and the formation of stoichiometric metal salts as undesired byproducts (Scheme 2a). Therefore, more economically and environmental friendly alternatives are needed to circumvent these disadvantages. To avoid unnecessary and expensive prefunctionalization steps, unfunctionalized (hetero)arenes can be used in transition metal-catalyzed direct C–H bond functionalizations, as shown in Scheme 2b. Another pathway is the cross-dehydrogenative coupling, presented in Scheme 2c. In this context, the use of an external oxidant is required.



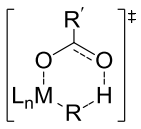
Scheme 2: Comparison of classical cross-coupling and transition metal-catalyzed C–H transformations.

Although a great number of published reactions are described as C–H bond activations, the term "C–H activation" should only be applied to a limited number of reactions.[7, 8] True C–H activation involves an elementary C–H metalation step by the active metal species ML_n.[9-11] First elaborations on the stoichiometric cyclometalations were performed by the groups of *Shaw*[12] and *Reutov*,[13] relating to base-promoted metalation reactions. Generally five different main mechanisms are widely accepted up to now (Scheme 3a–e). For example, an oxidative addition can occur if electron-rich, low-valent, late-transition metal complexes of iron, ruthenium, rhenium, osmium, iridium or platinum are employed as the catalysts (Scheme 3a). Electrophilic substitution is more likely occurring when late- or post-transition metals (Pd^{2+}, Pt^{2+}, Pt^{4+}, Hg^{2+}) are used. The reaction starts with an electrophilic attack of the metal complex, acting in this case as a *Lewis* acid (LA) (Scheme 3b). Early transition metals with d^0 electronic configuration of the groups 3 and 4 as well as the lanthanoids can undergo *σ*-bond metathesis, highlighting a concerted formation and cleavage of bonds. Herein, usually an alkyl or hydride complex is involved (Scheme 3c). With unsaturated M=X bonds the C–H activation can occur through a 1,2-addition, where a heteroatom-based group bearing a lone electron pair acts as a H-acceptor (Scheme 3d).[9, 11] This mechanism is related to the *σ*-bond metathesis with the constraint that the cleaved proton still remains in the structure of metalated product. This type of reactions can take place with imido and alkylidene complexes of early to middle transition metals. Experimental and theoretical analyses have offered a further type of C–H activation *via* "base-assisted" metalation (Scheme 3e).[9] The proton is abstracted by a carboxylate or carbonate ligand, which can act as an intramolecular base.



Scheme 3: Possible mechanisms for the C–H metalation step by transition metal complexes.

The carboxylate-assisted C–H transformations proceed *via* concerted base-assisted deprotonations. The corresponding possible six-membered transition state is shown in Figure 1, resulting from a concerted metalation-deprotonation pathway (CMD, *Fagnou*)[14] or from the amphiphilic metal ligand activation (AMLA, *Davies*, *Macgregor*).[11]



CMD/ AMLA TS

Figure 1: Possible transition state (TS) for the base-assisted metalation.

In the case of hydroxo or alkoxy ligands, DFT calculations by *Goddard* as well as *Gunnoe* support an internal electrophilic substitution (IES)[15, 16] as an possible pathway. The newly formed O–H bond is based on different orbital interactions than the cleaved O–M bond. In this case, an additional lone pair from the heteroatomic ligand is available for interactions with the metal. In an IES transition state (Figure 2), the O–H bond is formed from one of the lone pair of the M–O bond orbital,[15, 16] whereas in a traditional *σ*-bond metathesis the formerly bonding C–H orbital, which forms the new C–M bond orbital, is delocalized in the transition state.

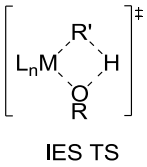


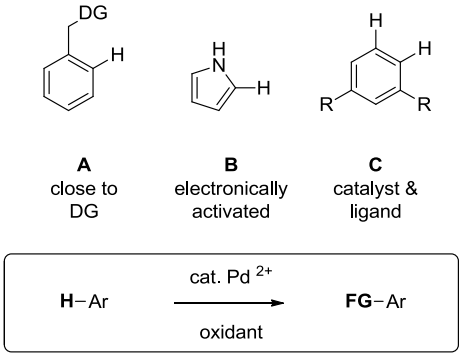
Figure 2: Possible transition state (TS) for the IES pathway.

1.2 Site-Selectivity in C–H Bond Functionalization

While elaborating on the functionalization of C–H bonds, one important issue is the selective functionalization of these bonds. For example, the conversion of methane to methanol is of significant interest for the petrochemical industry for the refinement of a fuel. The chemoselective oxidation of these "inert alkanes" is problematic due to a facile overoxidation of the methanol to the corresponding carboxylic acid.[17] Early and recent examples by *Shilov*[7] and *Periana*[15, 18] presented catalytic systems for the oxidation of methane or higher aliphatic homologues. As a bioengineering approach, enzymes like methane monooxygenase (MMO) with a di-iron oxo cluster as active site or heme-based systems like cytochrome P450 have been taking into account for methane oxidation.[7, 19]

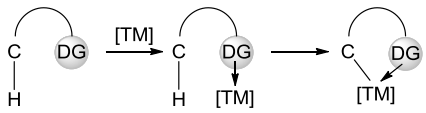
In comparison to C(sp^3)–H bond functionalizations in alkanes, the selective functionalization of inherently stronger C(sp^2)–H bonds in arenes can be promoted due to pre-coordination of the aromatic π-system to the metal catalyst. Enthalpies of bond formation in organic molecules are undoubtedly of crucial importance for their reactivity,[20] and the C–H bond cleavage in arenes is generally believed to be difficult because of their enhanced strength. Indeed, benzene has a bond dissociation energy of 113 kcal/mol[21] and a pK_a value of 43.0–44.7,[21] the C–H bonds are of equal substitution and according to this of equal reactivity. The C–H bonds in heterocycles contain different electronic properties and marginal acidities within the molecule. The resulting pK_a values of C–H bonds of heterocycles are taking a significant influence on the reactivity of the aromatic molecules.[21] This approach was applicable for several functionalizations of heteroarenes with palladium, copper or rhodium catalysts.[2, 22] In the past two decades, different strategies have been developed to improve the site-selectivity towards C–H bonds. For instant, *Sanford* classified three basic approaches involving substrate- or catalyst-control to achieve the site-selectivities in oxidative palladium-catalyzed transformations, as shown in Scheme 4: (**A**) Substrate-based control

through a directing group (DG) to a proximal site, (**B**) substrate-based direction through electronic properties of the C–H bond, (**C**) catalyst-based control through design of ligand.[23]



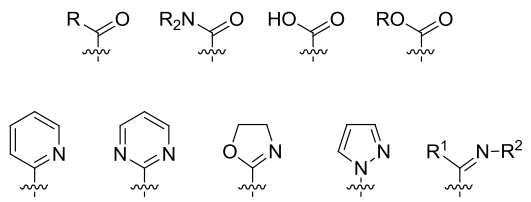
Scheme 4: Possible approaches to achieve site-selectivities in oxidative palladium-catalyzed functionalizations by *Sanford*.

The most common strategy to achieve site-selectivity relies on the chelation of a transition metal through a *Lewis* basic directing group, bearing a heteroatom with a lone pair that can coordinate to the metal catalyst (Scheme 5). One of the earliest examples of a stoichiometric metalation of a C–H bond was presented by *Kleiman* and *Dubeck* with an dicyclopentadienylnickel complex in the presence of diazobenzene.[24] The site-selectivity is induced through a cyclometalation step employing a directing group which can be potentially modified.[25] Usually the C–H functionalization takes place in *ortho*-position. By varying the moiety of the construct of the directing group and the metal interaction, *meta*-substitution was achieved by *Yu* and coworkers through a palladium-catalyzed end-on coordinating template.[26] In general, the directing group approach is related to the stoichiometric direct *ortho*-metalation reaction (D*o*M), in which deprotonation by a strong base occurs *ortho* to a heteroatom containing directing group.[27, 28]



Scheme 5: Strategy for the site-selective functionalization through a proximal directing group.

A large variety of these directing groups (Scheme 6) have successfully been applied for palladium-, rhodium-, ruthenium-, nickel-, iridium- and iron-catalyzed direct alkylations, alkenylations, arylations or alkynylations. The directing group is mostly incorporated in the target molecule structure or can ideally be removed to release the final desired product.[3, 9, 29, 30]

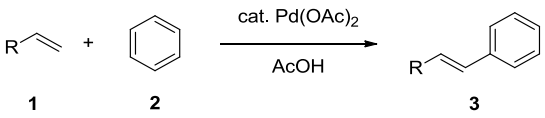


Scheme 6: Selected examples of directing groups for the transition metal-catalyzed *ortho*-functionalization.

1.3 Transition Metal-Catalyzed Oxidative Couplings

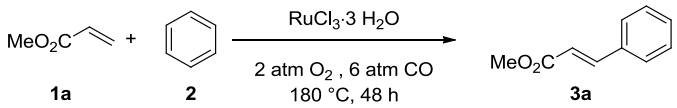
Factors, such as site-selectivity and diversity of a reaction are determining the success of C–H transformations. To incorporate a variety of functional groups, oxidative couplings and oxidative annulation reactions have been developed. Undoubtedly, the low waist production and the exclusion of prefunctionalization are the main advantages of these processes.

Pioneering studies by *Fujiwara* and *Moritani* (Scheme 7) in the field of direct oxidative palladium-catalyzed coupling set the stage for the use of various alkenes **1** and arenes **2** as coupling partners.[31] Further development was realized by *Mizoroki* and *Heck* of aryl (pseudo)halides with alkenes led to the synthesis of diverse styrenes **3**.[32]



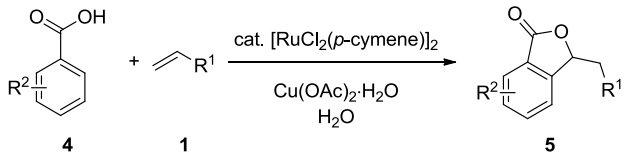
Scheme 7: The *Fujiwara-Moritani* oxidative alkenylation.

Based on the innovative work of *Fujiwara* and *Moritani*, a number of useful protocols for oxidative palladium-catalyzed alkenylation reactions were recently elaborated and described by the groups of *Miura* and *Satoh*,[33, 34] *Yu*[35, 36] and *Georg*.[36] In 2001, *Milstein* reported on a ruthenium-catalyzed oxidative coupling of arenes for the synthesis of styrene derivatives using *Michael*-acceptors **1a** and simple arenes, such as benzene **2** (Scheme 8).[37] Molecular oxygen was used as a terminal oxidant in this reaction, while high pressure was required. Simple arenes such as toluene or anisole were used with *Michael* acceptors, while the yields with non-activated alkenes were rather low. Formation of predominantly *para*- and *meta*-substituted products indicated the absence of a directing group effect in the arene, whereas formations of the ortho-products were significantly retarded due to steric hindrance.



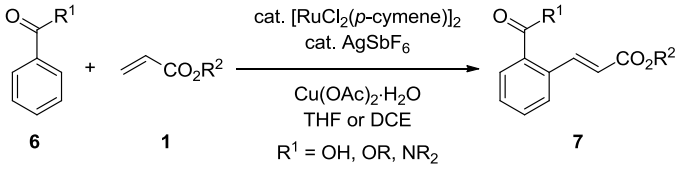
Scheme 8: Ruthenium-catalyzed oxidative coupling by *Milstein*.

Since then, numerous examples on C–H bond functionalization with ruthenium catalysts have been reported.[38, 39] Significant progress have been accomplished by the group of *Ackermann* with weakly coordinating acids.[39] The use of simple carboxylic acids have successfully been used as the directing groups in several C–H bond functionalization reactions. The ability to undergo facile decarboxylation[40] or transformation turned the carboxylic group to be a removable directing group and a versatile synthon in organic chemistry. Taking this into account, *Ackermann et al.* presented ruthenium-catalyzed cross-dehydrogenative direct alkenylations with benzoic acids **4** in water as the reaction medium, under exceedingly mild reaction conditions, using copper acetate as the oxidant (Scheme 9).[41] After the alkenylation, a subsequent cyclization occurred *via* an intramolecular oxa-*Michael* addition.[41] *Satoh* and *Miura* reported the synthesis of butenolides through rhodium-catalyzed oxidative coupling.[42] By changing the oxidant to silver acetate, the direct annulations with rhodium complexes as catalysts led to the synthesis of non-cyclized styrene derivatives.[43] Furthermore, benzamides, benzanilides and aldimines were successfully converted, delivering the oxidative annulation products *via* C–H/C–Het bond functionalizations.[44]



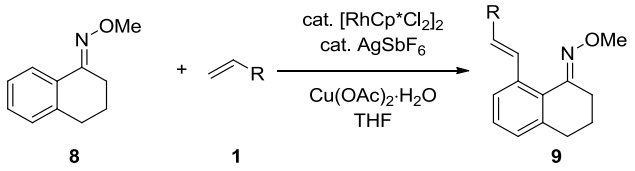
Scheme 9: Ruthenium(II)-catalyzed annulations reaction.

Further, *Ackermann* disclosed weakly coordinating esters and ketones **2** for the direct oxidative coupling in the synthesis of styrene derivatives **7** (Scheme 10).[45, 46] The reactions were conveniently performed under air with substoichiometric amounts of copper acetate as cooxidant. Previously reported studies by *Chang* disclosed a similar olefination of aromatic esters employing a more expensive rhodium catalyst.[47]



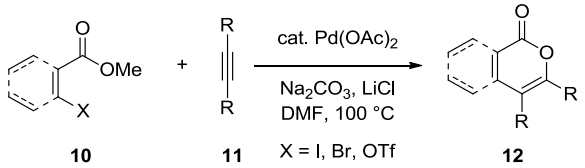
Scheme 10: Ruthenium-catalyzed oxidative olefination reaction.

The rhodium-catalyzed oxidative couplings were not restricted to acrylates. *Bergman* and *Ellman* described the oxidative alkenylation of *O*-methyl phenonoximes **8** with an extensive selection of alkenes **1** using relative expensive rhodium catalysts (Scheme 11).[48] Besides electron-poor arenes, electron-rich anilides or aryl carbamates could also be used for oxidative alkenylations.[49, 50] The direct alkenylations of heterocyclic compounds have been reported as well.[51]



Scheme 11: Rhodium-catalyzed alkenylation of aryl *O*-methyl oximes **8**.

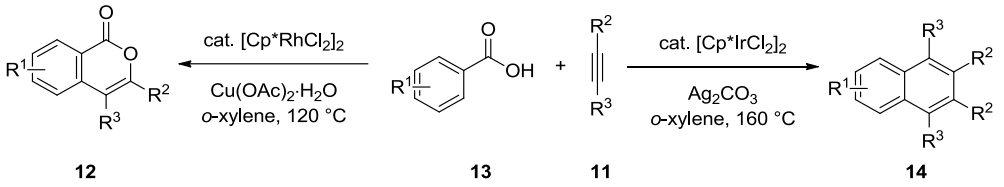
Transition metal-catalyzed oxidative annulation reactions of alkynes are important methods for the synthesis of heterocyclic compounds. Early achievements were reported by *Larock*, using *ortho*-iodoanilides for a palladium-catalyzed synthesis of indoles with internal alkynes.[52] Modified versions of *Larock*-type cross-coupling reactions and further investigations revealed valuable protocols for the synthesis of indoles and other important heterocycles.[34, 53] The use of prefunctionalized esters **10** in palladium-catalyzed annulation reactions was also described by the group of *Larock*, which provided the synthesis of isocoumarins **12** and *α*-pyrones (Scheme 12).[54] Later on, an intramolecular variation was presented by the use of differently substituted esters and alkynes.[55]



Scheme 12: Palladium-catalyzed annulation of alkynes using prefunctionalized esters **10**.

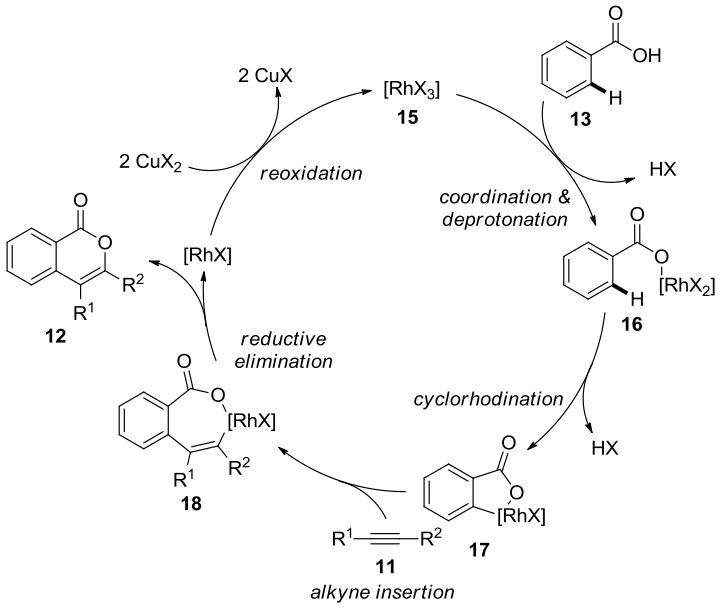
Satoh und *Miura* developed a rhodium(II)-catalyzed method for the synthesis of isocoumarins **12** using copper acetate as the oxidant (Scheme 13).[56, 57] By switching to an iridium complex as the catalyst and silver carbonate as the oxidant, the substrate **13**

underwent decarboxylation followed by an oxidative coupling with two molecules of alkyne **11**, affording naphthalene derivatives **14** (Scheme 13).[56, 57]



Scheme 13: Rhodium- and iridium-catalyzed annulation reactions.

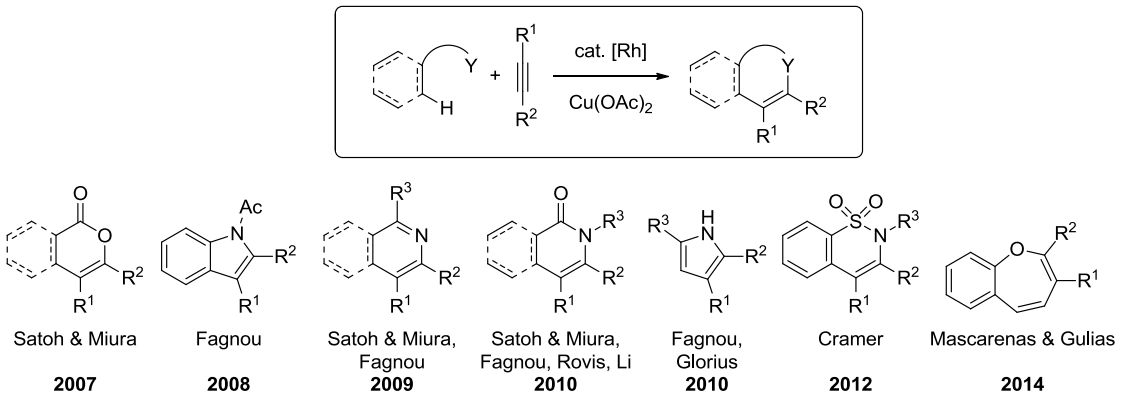
The proposed mechanism for the formation of isocoumarins through oxidative coupling by rhodium(III)-catalysis is presented in Scheme 14.[57] The first step involves a coordination of a rhodium(III) species **15** by the benzoate **13** followed by formation of rhodium benzoate **16**. The subsequent cyclometalation takes place, affording intermediate **17**. First precoordination and then insertion of the alkyne **11** into the rhodacycle **17** leads to the seven-membered intermediate **18**, which undergoes reductive elimination to release the final product **12**.



Scheme 14: Proposed catalytic cycle for the rhodium(III)-catalyzed annulation reaction.

Further syntheses by using *N*-phenylanthranillic acid or other heteroaromatic carboxylic acids afforded the corresponding annulated heterocycles as well.[58]

Subsequently, a series of rhodium-catalyzed annulations reactions appeared, thus delivering a set of new synthetic methods for the preparation of different types of heterocycles, which are summarized in Scheme 15.[59-61]

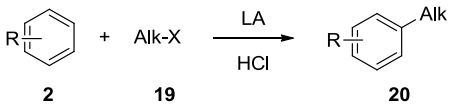


Scheme 15: Selected examples of oxidative rhodium-catalyzed annulation reactions.

1.4 Transition Metal Catalyzed Alkylation and Arylation Reactions

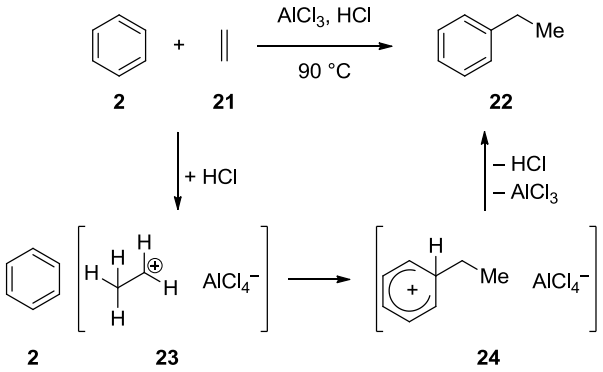
Friedel-Crafts Chemistry

Regioselective alkylation reactions of substituted aromatic substrates remain a challenge, even though significant progress have been achieved in direct alkylations and arylations of (hetero)arenes.[62, 63] Traditional alkylation reactions still belong to the numerous processes in chemical industry, for example, with the production of ethylbenzol (27 Mt/a) or substituted *o*-alkylated anilides (3 t/a), through *Friedel-Crafts*[64] chemistry (Scheme 16).[65]



Scheme 16: Generalized *Friedel-Crafts* alkylation.

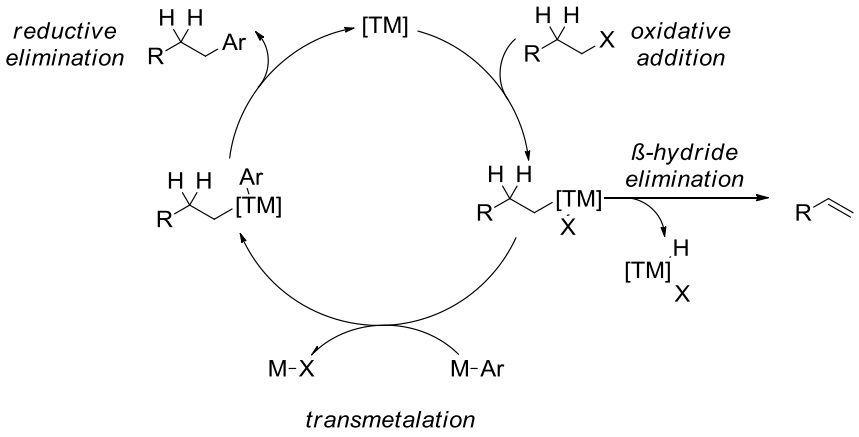
The general mechanism for this type of reaction is shown in Scheme 17, for the ethylation of benzene, which leads to ethylbenzol **22** as an intermediate in the styrene production. Ethylene is converted into a carbocation by protonation. The formed product is more reactive than the reagent itself and therefore prone to overalkylation, which can be partly avoided by using large excess of benzene or by using zeolites as heterogeneous catalyst. Besides $AlCl_3$, other *Lewis* acids, such as $FeCl_3$, $TiCl_4$ or BF_3 and strong *Brønsted* acids (HF or H_2SO_4) have been described for *Friedel-Crafts* reactions.[63] In addition, the *Wagner-Meerwein* rearrangement is leading to decreased chemoselectivity, to form the most stable alkylated carbocation. Furthermore, corrosive reagents, waste disposal, harsh reaction conditions and undesired overalkylation are the main disadvantages.



Scheme 17: *Friedel-Crafts* alkylation of benzene.

Cross-Coupling Chemistry

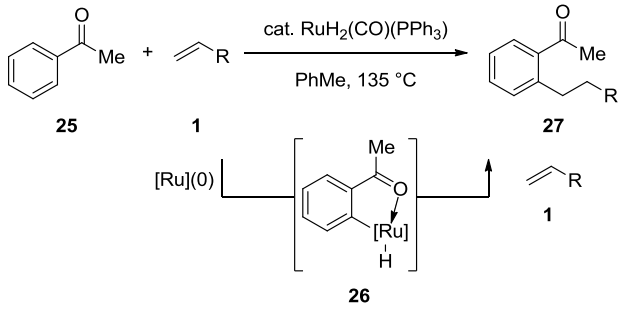
Transition metal-catalyzed cross-coupling reactions can be an alternative way for the alkylation of arenes.[5, 66] The regioselectivity is controlled by the use of prefunctionalized substrates. Cationic rearrangements are avoided and the milder reaction conditions allow for a broader functional group tolerance, as compared to *Friedel-Crafts* alkylations. However, unactivated alkyl (pseudo)halides, that bear a *ß*-hydrogen atom, can undergo *ß*-hydride elimination as an undesired side reaction (Scheme 18).



Scheme 18: General mechanism for the transition metal-catalyzed cross-coupling of alkyl halides bearing a *ß*-hydrogen.

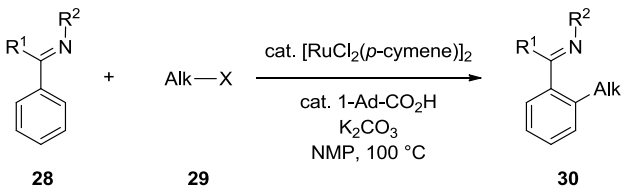
1.4.1 Transition Metal-Catalyzed Alkylation through C–H Functionalization

To overcome the drawbacks of classical cross-coupling reactions, the formation of C–C bonds by activation of otherwise inert C–H bonds provides an atom-economical pathway for the construction of functionalized molecules.[67] Although there are many examples of stoichiometric transition metal-mediated reactions for C–H activation, catalytic C–H activation is obviously superior.[68] A notable innovative groundbreaking research for the synthesis of alkylated substrates is the transition metal-catalyzed hydroarylation of alkenes. The *Murai*-reaction is a ruthenium-catalyzed addition of phenones onto olefins (Scheme 19).[69] This achievement started with pioneering work by *Lewis* and *Smith* on ruthenium-catalyzed hydroarylations.[70] Further development was performed by the groups of *Genet* and *Ackermann*.[71, 72] Continuing progress by using diverse *Lewis*-basic directing groups and various ruthenium complexes enabled highly effective hydroarylations of different types of alkenes **1**, including the unactivated ones, gaining access to novel C–H transformations.[23, 72, 73]



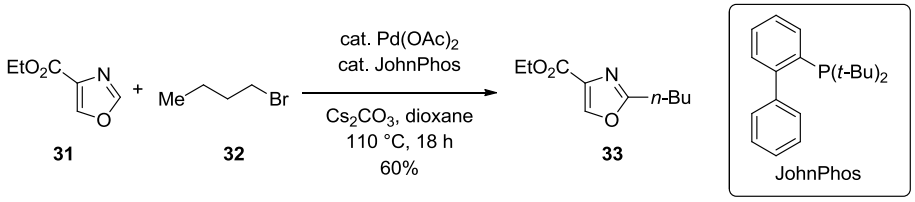
Scheme 19: Ruthenium(0)-catalyzed hydroarylation.

Notably, only a few useful protocols for the direct alkylation, alkenylation, alkynylation, and benzylation of (hetero)arenes have been described.[74] A prominent work was developed by the group of *Ackermann* for the ruthenium-catalyzed direct alkylation of arenes **28** with unactivated alkyl halides **29** bearing *ß*-hydrogen atoms (Scheme 20).[75] In this way, a variety of heteroarenes **30**, such as pyridine, pyrazole or ketimine derivatives were alkylated with primary and secondary alkyl halides.



Scheme 20: Ruthenium-catalyzed direct alkylation with unactivated alkyl halides.

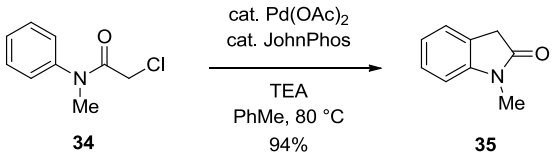
In 2009, *Hoarau* reported a palladium-catalyzed reaction between oxazole **31** and *n*-butyl bromide (**32**) (Scheme 21).[76] The use of methyl iodide as electrophile resulted in product formation in 41% yield.



Scheme 21: Palladium-catalyzed alkylation of oxazole **31** with alkyl halide **32**.

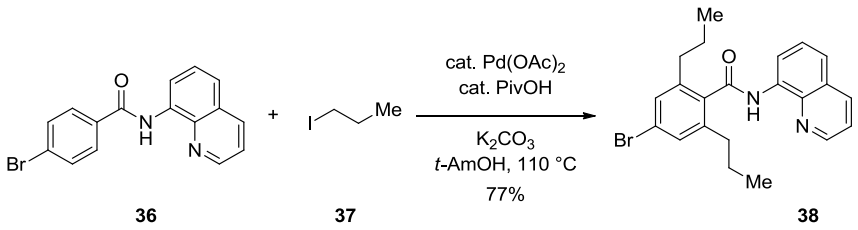
Further prominent examples of alkylation reactions of somewhat acidic C–H bonds were reported by *Hu*.[77] The combination of a nickel complex and a copper salt was efficient for the coupling of electron-rich and electron-deficient heterocycles with alkyl halides. Further contributions were described by *Satoh* and *Miura* with an example of palladium-catalyzed alkylation reactions.[78] Since then a variety of transition metals has been described for the monoalkylation of C–H bonds in heterocycles.[79]

An example of an intramolecular direct alkylation with alkyl halides as electrophiles for the synthesis of oxindoles **35** was reported by *Hennessy* and *Buchwald* (Scheme 22).[80] The oxidative addition of the *α*-chloroacetanilides **34** was proposed to be the rate-determining step. No kinetic isotope effect was observed in the competitive reaction of *α*-chloroacetanilide **34** and $[D]_5$-**34**, whereas an intramolecular primary isotope effect (KIE) of k_H/k_D = 4 was detected in the cyclization of the *ortho*-monodeuterated substrate. Among several proposed mechanistic scenarios, one viable pathway might be through an *σ*-bond metathesis.



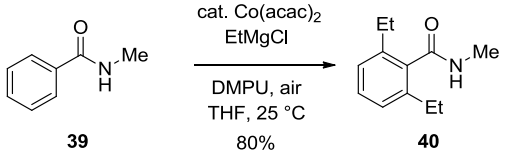
Scheme 22: Palladium-catalyzed direct alkylation for the synthesis of oxindoles **35**.

A more applicable approach for direct alkylations reactions with catalytic amounts of palladium was achieved by *Shabashov* and *Daugulis* through the use of an 8-aminoquinoline auxiliary (Scheme 23).[116] Examples of direct alkylation reactions by bidentate chelation assistance were reported by *Chatani* and *Ackermann et al*. with earth abundant nickel complexes as catalysts.[81]



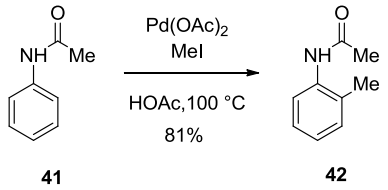
Scheme 23: Palladium-catalyzed direct alkylation using 8-aminoquinoline as auxiliary.

Ortho-ethylation was achieved by *Nakamura* and coworkers through a cobalt-catalyzed C–H activation of alkyl *Grignard* reagents with benzamide **39** or 2-phenylpyridine derivatives (Scheme 24).[82] In this case, DMPU was used to stabilize the alkyl cobalt intermediate, thus avoiding a *ß*-hydride elimination and isomerizations, which were detected previously when using *i*-PrMgCl.[83]



Scheme 24: Cobalt-catalyzed ethylation.

Early examples for direct arene methylation reactions were reported in 1984 by *Rahman* and *Tremont*.[84] The *ortho*-methylation of acetanilides **41** and *N*-benzylidenaniline was mediated by $Pd(OAc)_2$ by the use of methyl iodide in stoichiometric amounts (Scheme 25).



Scheme 25: Stoichiometric palladium-catalyzed methylation of acetanilides.

Higher turnover numbers (TONs) were more recently accomplished by the use of AgOAc as additive.[85] In recent years the C–H alkylation reactions evolved employing other transition metals, such as nickel, iridium, cobalt or rhodium with different alkyl sources.[82, 86, 87] For comparison, the classical methods for the direct transformation of a C–H into C–Alk bonds included initial stoichiometric deprotonation through direct *ortho*-metalation (D*o*M) and required stoichiometric quantities of strong bases.[28, 88]

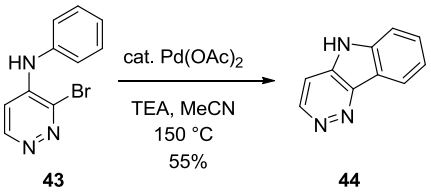
As the methyl group is one of the most common substituents in biologically active compounds, the introduction of a small carbon fragment can diversify the biological activity

and physical properties in pharmacologically active drug molecules.[89] Thus, a methyl group increases the hydrophobic character of a molecule and its affinity to bind to biomolecules.[90] This so-called "magic methyl effect" is not only a result of solvation effects, but also generates a favorable conformational change in a hydrophobic pocket of the active site.[91] Hence, a single methyl group can increase the potency of a potential drug molecule, resulting in a significant increase of the IC_{50} value.[92]

1.4.2 Transition Metal-Catalyzed Arylation through C–H Functionalization

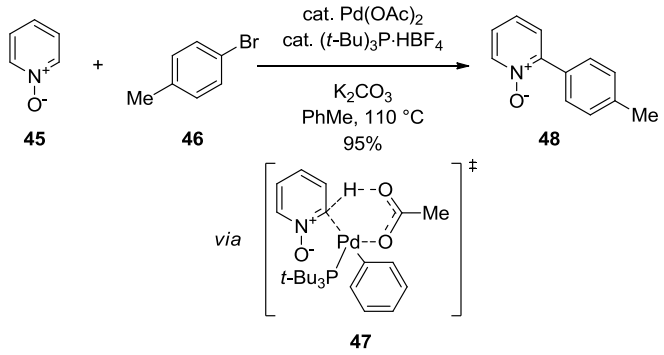
Biaryls are important structural motifs in complex molecules, such as natural products or bioactive compounds and widely applied in medical chemistry, crop protection or material sciences.[93] The preparation of biaryls is normally accomplished by transitions metal-catalyzed cross-coupling reactions for the formations of $C(sp^2)$–$C(sp^2)$ bonds. In general, (pseudo)halides as electrophiles and organometallic species as nucleophiles are involved. Keeping in mind the drawbacks of cross-coupling reactions (*vide supra*), direct C–H arylations represent a more attractive route for the synthesis of biaryls. Thereby, an unfunctionalized (hetero)arene is directly used as substrate.

The earliest example of a direct arylation reaction was reported by *Ames* in 1982 and *Ohta* in 1989.[94] The C–H functionalization proceeded through the intramolecular cyclization of 3-bromo-4-phenylaminocinnoline (**43**) (Scheme 26). Thereby, a variety of useful polycyclic aromatic compounds could be synthesized.[95] In 2004, *Fagnou* reported on an elegant synthetic route for the synthesis of six- and seven-membered cycles through intramolecular C–H arylation with a low catalyst loading.[96] Moreover, indoles, pyrroles, furans and thiophenes could be arylated in a chemo- and site-selective fashion.[97] Proposed mechanisms include precoordination of the palladium to the heteroatom, as well as an electrophilic mechanism involving ArPd(+II) species. The selectivity of the C–H arylations strongly depends on the electronic properties of the electrophiles and substrates, on the nature of the palladium catalyst, as well as the additives in the reaction.



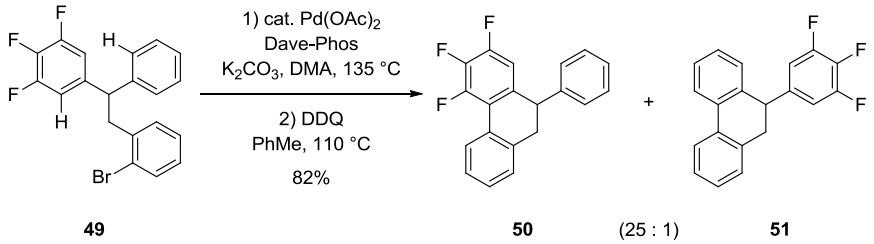
Scheme 26: Early example of an intramolecular palladium-catalyzed direct arylation.

Electron-rich heteroarenes were amenable for palladium-catalyzed direct arylations, whereas their electron-deficient analogs were more difficult to address due to their less reactivity and instability of substrates. Arylation reactions of electron-deficient pyridines continued to be challenging. Arylpyridines could be obtained by traditional cross-couplings of prefunctionalized pyridines,[98] whereas direct C–H bond functionalizations were achieved only in recent years.[99] In 2005, *Fagnou* presented C–H functionalizations of pyridine *N*-oxides **45** *via* palladium-catalyzed direct arylations (Scheme 27).[100] Ongoing progress in the field and mechanistic studies illustrated that an acetate-assisted CMD pathway was a possible mechanism.[101]



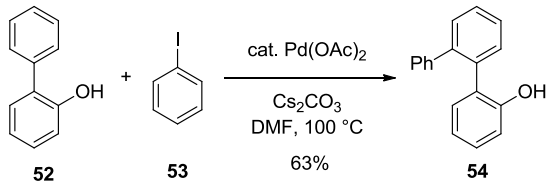
Scheme 27: Carboxylate-assisted palladium-catalyzed direct arylation of pyridine *N*-oxide **45**.

Intramolecular competition experiments with fluorinated arenes were accomplished by the group of *Echavarren*.[102] The experiments revealed that the functionalization takes place at the most acidic C–H bond in the substrate **49** (Scheme 28). The effect of the substituents and the resulting substitution pattern on the aryl excluded an electrophilic aromatic substitution as the mechanism. Additional computational studies supported a CMD-type mechanism. Independently, the group of *Fagnou* reported the direct arylation of perfluoroarenes with similar results.[103]



Scheme 28: Intramolecular competition experiment by *Echavarren.*

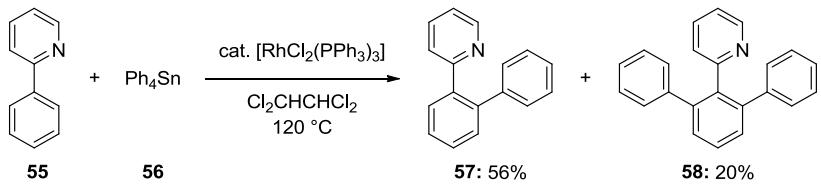
An early example was presented by *Satoh* and *Miura* for the direct arylation of 2-phenylphenols **52** with aryl iodides **53** (Scheme 29).[104] The inorganic base Cs_2CO_3 was of crucial importance for the reaction. Monoarylated products were more favored by the use of $Pd(OAc)_2$ as the catalyst, while more diarylated product formation was observed with $PdCl_2$.



Scheme 29: Palladium-catalyzed arylation of 2-phenyl phenol (**52**).

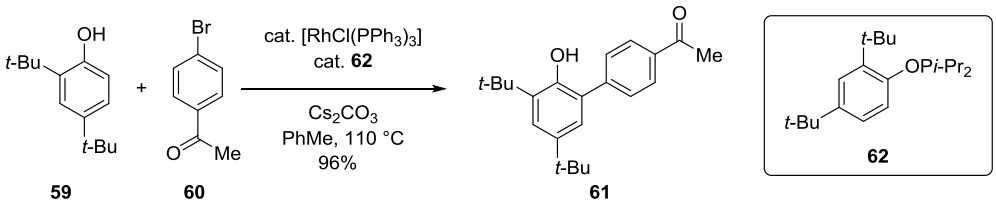
Intensive studies on the heteroatom-substituted secondary phosphine (HASPO) ligands have been done by the group of *Ackermann* for direct C–H arylations.[105] The air-stable and easily accessible preligands provided access to several substituted aryl moieties, such as C-3 substituted indoles and pyridines through palladium catalysis.[106]

Rhodium-catalyzed direct arylations of 2-arylpyridines **55** with arylstannanes **56** were accomplishes by *Oi* and *Inoue* (Scheme 30).[107] Later on, less-toxic aryl boranes could be used as arylating agents by *Satoh* and *Miura*.[108]



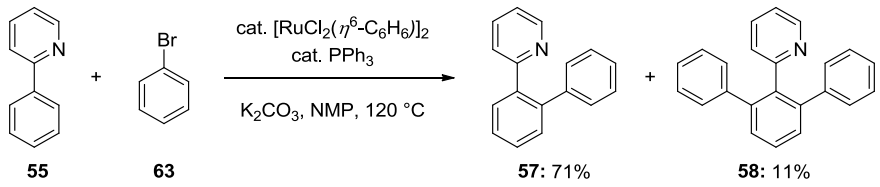
Scheme 30: Rhodium-catalyzed arylation of 2-phenylpyridine (**55**).

Bedford and coworkers showed that phenols **59** could be used for the rhodium-catalyzed arylation (Scheme 31).[109] In the presence of the *Wilkinson* catalyst, the reaction proceeded *via* an *ortho*-metalation through chelation-assistance of the corresponding *in situ* formed phosphite. Several 2-arylated phenols, such as **61** could be synthesized by this elegant method.



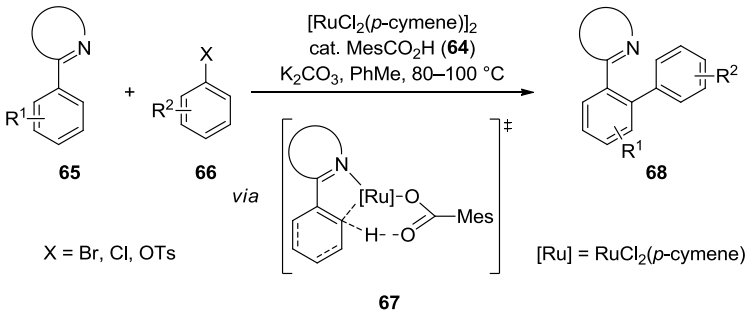
Scheme 31: Phosphine-assisted direct arylation by *Bedford*.

An early ruthenium-catalyzed direct arylation was reported by *Oi* and *Inoue* with phenylpyridines **55** and aryl bromides **63** (Scheme 32).[30] Considerable progress in this area was accomplished by the group of *Ackermann,*[87, 110] among others when using phenylpyridines **55** and aryl chlorides[111] or aryl tosylates[112] as electrophiles.



Scheme 32: Ruthenium-catalyzed arylation of pyridine **55**.

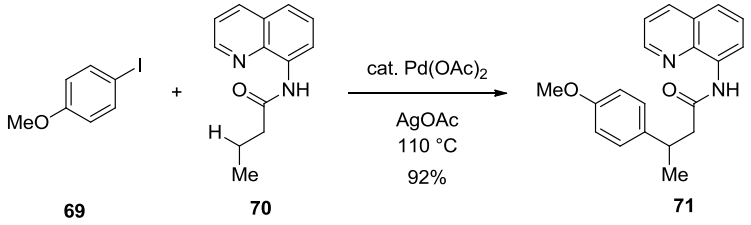
In palladium chemistry, the addition of carboxylic acid facilitates the direct arylation *via* a concerted deprotonation/metalation mechanism.[9] Carboxylate assistance was also useful in ruthenium-catalyzed arylation reactions.[113, 114] The addition of various acids, such as mesitylcarboxylic acid (**64**), allowed *inter alia* for the direct arylation of triazoles, pyridines, pyrazoles or oxazolines with aryl halides **66** (Scheme 33).[113] A mechanism *via* concerted metalation-deprotonation was suggested.



Scheme 33: Carboxylate-assisted ruthenium-catalyzed C–H arylation.

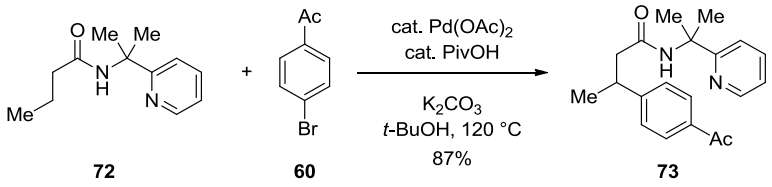
Transition metal-catalyzed direct arylations have been studied in great detail, and a number of synthetically useful protocols was devised for the synthesis of bi(hetero)aryls. In contrast, the direct functionalization of unactivated C(sp^3)–H bonds is a more difficult problem and therefore remains a challenge. In regard to the unsaturated hydrocarbons like alkanes, orbital interactions between the substrate and the metal center are unlikely to occur. An

alternative example of such cross-coupling chemistry for the arylation and alkylation of *O*-methyl hydroxamic acids with arylboronic reagents by the use of monodentate directing groups was reported by *Yu*.[115] Only a few direct arylations of unactivated C(sp^3)–H bonds[116] could mechanistically be rationalized in terms of agostic three-center two-electron interactions, between the C–H bond and the metal atom.[6, 116] One of the earliest examples using the 8-aminoquinoline as a bidentate directing group was presented by the group of *Daugulis* (Scheme 34).[117, 118] Later on, with 2-methylthioaniline as an auxiliary, *Daugulis* achieved selective monoarylations of primary C(sp^3)–H bonds.[119]



Scheme 34: 8-Aminoquinoline-assisted palladium-catalyzed direct arylation by *Daugulis.*

A pyridine containing bidentate directing group, such as substrate **72**, for arylation reactions with aryl bromides **60** and iodides under palladium catalysis, was recently reported by *B.-F. Shi* (Scheme 35).[120] Furthermore, nickel-catalyzed functionalizations of 2,2-disubstituted propionamides were performed using aryl iodides and aryl bromides as the electrophiles.[121]

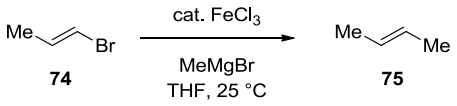


Scheme 35: Direct arylation of unactivated C(sp^3)–H bonds by *B.-F. Shi*.

1.5 Iron-Catalyzed Alkylation and Arylation Cross-Coupling Reactions

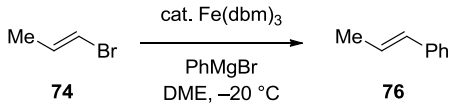
The use of non-precious first row transition-metals for C–C bond forming reactions continuous to be attractive.[122, 123] Their low price and earth abundance make them endearing catalysts for industrial transformations.[65, 124] Especially iron offers significant advantages compared to other metals, since it is the 4th most abundant metal in the earth crust. In the field of iron catalysis, a number of impressive examples demonstrate the potential of these cost-efficient and nontoxic iron complexes.[122, 125] Besides, iron takes place in manifold essential biological processes. Facile interconversion of its oxidation states and *Lewi*s acidity allows a broad range of versatile reactions, such as additions, reductions or oxidations. Respectable advances in traditional cross-coupling chemistry have been accomplished with iron complexes.[126]

Since *Kharasch*[127] studied the reaction of aryl *Grignard* reagents in the presence of metallic halides focusing on iron-catalyzed couplings with *Grignard* reagents, examples of iron-catalyzed cross-coupling reactions have been reported. Probably, the effect of iron catalysts upon cross-couplings was most significantly clarified by the investigations of reactions with alkenyl and aryl halides by *Kochi et al*.[128, 129] According to this, alkenyl halides **74** reacted with excess amounts of organomagnesium halides in the presence of catalytic amounts of $FeCl_3$ (Scheme 36).[130]



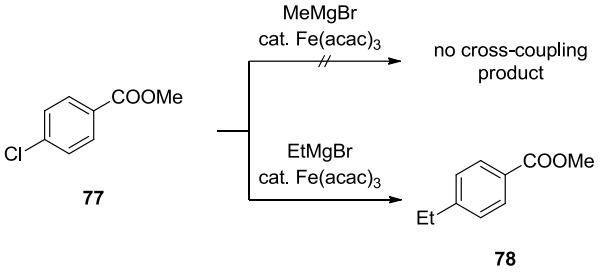
Scheme 36: Iron-catalyzed cross-coupling by *Kochi et al.*

Molander improved the yield of coupling product **76** by using equimolar amounts of reactants in 1,2-dimethoxyethan as the solvent and by lowering the reaction temperature (Scheme 37).[131] Further development was accomplished by *Cahiez,* who used a mixture of polar solvents, such as THF and *N*-methylpyrrolidinone (NMP).[132] Especially NMP was important because of its stabilizing effect as a ligand for the catalytically active iron species, thus avoiding *ß*-hydride elimination.



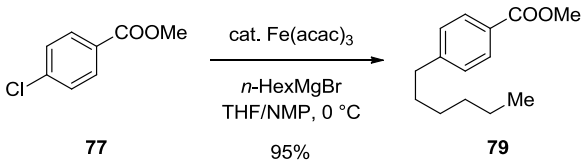
Scheme 37: Iron-catalyzed cross-coupling by *Molander et al.*

Unfortunately, iron-catalyzed cross-coupling reactions suffer from major limitations. Thus, the methyl *Grignard* reagents were efficient in alkylations of alkenyl halides but not capable to methylate aryl chlorides **77** (Scheme 38).[133] In contrast, EtMgBr or higher alkyl *Grignard* reagents afforded the desired products, such as **78** and **79**.



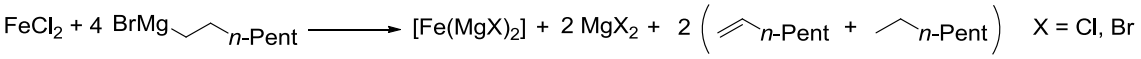
Scheme 38: Different behavior of MeMgBr and EtMgBr in iron-catalyzed coupling reactions.

The reaction was widely applicable for a variety of aryl chlorides and tosylates with alkyl or alkenyl *Grignard* reagents (Scheme 39).



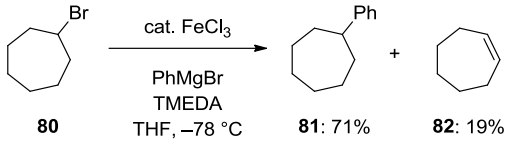
Scheme 39: Iron-catalyzed cross-coupling with *Grignard* reagents.

These observations are in accordance with the findings of *Bogdanović* and coworkers.[134] Iron(+II) can be reduced *in situ* by the *Grignard* reagent to form a highly nucleophilic species of the formal composition $[Fe(MgX)_2]_n$ (Scheme 40), with a formal negative oxidation state and a d^{10} electron configuration. In this example the alkyl *Grignard* is able to undergo *ß*-hydride elimination.



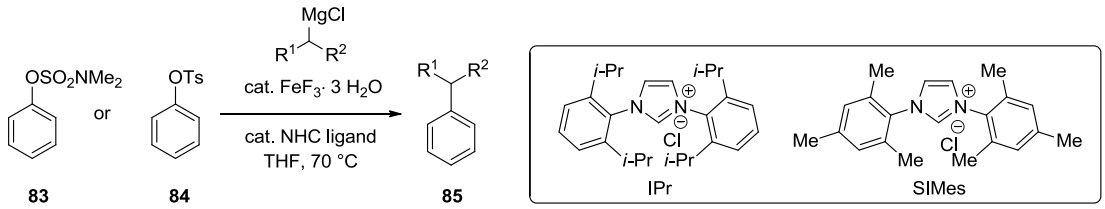
Scheme 40: Formation of inorganic *Grignard* reagents.

In 2004, *Nakamura* discovered the influence of TMEDA as an additional *Lewis*-basic additive on suppressing the *ß*-hydride elimination (Scheme 41).[135] In the absence of TMEDA, the reaction of cycloheptyl bromide **80** with PhMgBr resulted in the formation of cycloheptene **82** as the major product.



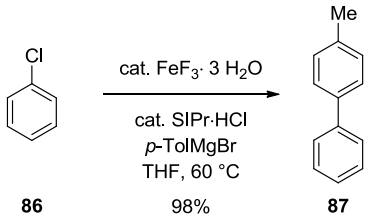
Scheme 41: Effect of the additive TMEDA on the cross-coupling reaction of alkyl halide **80**.

Additionally, iron complexes can be used for the introduction of branched alkyl chains. In the recently reported reactions by *Cook*[136] and *Garg,*[137] coupling of sulfamates **83** and tosylates **84** with several primary and secondary alkyl *Grignard* reagents in the presence of NHCs as ligands have successfully been utilized for the alkylation of arenes in the *Kochi*-type[130]couplings (Scheme 42).



Scheme 42: Iron-catalyzed alkylating cross-coupling.

In contrast, aryl-aryl bond formations were more sensible in iron-catalyzed cross-coupling reactions. The homo-coupling of the *Grignard* reagent was the primary problem. Moreover, these reactions appeared to be mostly limited to electron-deficient haloarenes **86**.[138] The homo-coupling could be avoided by addition of KF or FeF_3 in combination with NHC ligands (Scheme 43).[139]

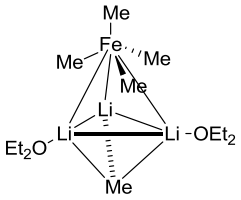


Scheme 43: FeF_3 catalyzed cross-coupling.

Mechanistic Insights in Iron-Catalyzed Cross-Coupling Chemistry

In spite of the rapid development of iron-catalyzed cross-coupling chemistry, the true nature of the catalytic cycle is thus far poorly understood due to the fact, that the active catalyst species is usually generated *in situ*. Depending on the ability of the *Grignard* reagent to reduce iron species, three oxidation states of the operating iron species will be presented, enclosing three different catalytic cycles with Fe(+I)/Fe(+III), Fe(0)/Fe(+II) or Fe(-II)/Fe(0).

The early studies by *Kochi et al.* reported on "a reduced form of soluble iron", that served as the active catalytic species presuming a Fe(+I)/Fe(+III) catalytic cycle, but did not exclude a Fe(0)/Fe(+II) manifold to be involved.[130] The canonic mechanism included an oxidative addition, transmetalation and reductive elimination, similar to the mechanism of the *Kumada-Corriu* coupling.[140] Several reports indicate a homoleptic nonstabilized alkyliron or organoferrat species of FeX_n (n = 2,3).[141] Merely the reduction of $FeCl_3$ to $FeCl_2$ with one equivalent of MeLi has been proven.[142] In the reaction of $FeCl_3$ with 5 portions of MeLi, the formation of $Li_2[FeMe_4]$ has been postulated, but the latter was not isolated.[143] However, *Fürstner* and coworkers synthesized a similar tetrahedral homoleptic ferrate $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$ (**88**) with an iron(+II) atom surrounded by four methyl groups (Figure 3).[144]

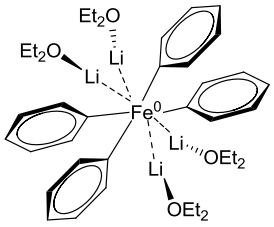


88

Figure 3: Structure of the "super ate" iron-complex $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$.

The treatment of $FeCl_3$ with a large excess of PhLi resulted in the thermally unstable planar-rectangular $[Ph_4Fe][Li(OEt_2)]_4$ (**89**) with an iron(0) center (Figure 4).[145, 146] The reaction of $FeCl_2$ with four equivalents of PhLi led to the comparable tetraphenylferrate complex $[Ph_4Fe][Li(Et_2O)_2][Li(1,4\text{-dioxane})]$ **90** with an iron(+II) center. Both complexes **89** and **90** can thermally decompose to generate biphenyl as the major product. The undesired homo-coupling, which was also observed in cross-coupling reactions with PhMgBr, indicated that decomposition was faster than the transfer of an aryl group to an electrophilic partner.[146]

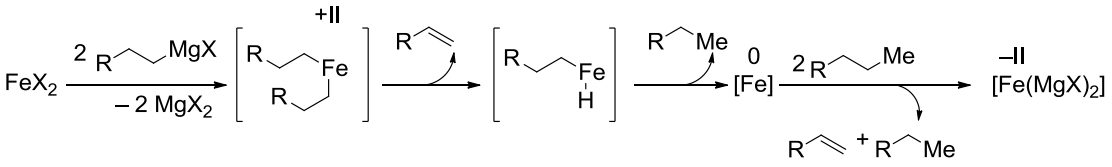
Fürstner and coworkers proposed that the complexes are intermediates, which are formed through several catalytic cycles, thus explaining the formation of homocoupled byproducts.



89

Figure 4: Schematic presentation of planar-rectangular $[Ph_4Fe][Li(OEt_2)]_4$.

As indicated above, MeMgBr and PhMgBr are unable to undergo *ß*-hydride elimination, whereas EtMgBr and higher homologues form inorganic *Grignard* reagents displaying low-valent iron bimetallic cluster species of the formal composition $[Fe(MgX)_2]_n$ or $[Fe(MgX_2)_2]_n$, first suggested by *Bogdanović* and coworkers.[134, 147] Four equivalents of RMgX reacted with FeX_2 (X = Cl, Br) to produce complexes with a formally negative d^{10} electron configuration of iron (Scheme 44). The catalytic cycle involves an activation of the aryl halide by the low valent iron cluster species *via σ*-bond metathesis rather than oxidative insertion, following by additional alkylation with RMgX instead of transmetalation. The resulting bisorganoiron intermediate undergoes reductive elimination to form the alkylated product and regenerate the catalyst.



Scheme 44: Reduction of iron to "inorganic *Grignard* reagent".

These *in situ* generated low valent iron complexes have been used in alkyl-aryl and aryl-alkyl cross-coupling reactions with good results.[146, 148, 149] *Jonas* and coworkers demonstrated the replacement of Cp^*-ligands in ferrocene-type half-sandwich and sandwich complexes with ethylene[150] and TMEDA as substituted ligands, thus creating an iron(–II) center (Figure 5).[150] Examination of this structurally defined complex **91,** resulted in similar effects on the yield, towards alkyl and aryl *Grignard* reagents to mimic cross-coupling reactions with the *in situ* generated low valent iron species.[146, 149]

91

Figure 5: Low-valent iron(–II) complex **91**.

The spin state of iron strongly depends on the nature of the ligands and the ability of the *Grignard* reagents to reduce iron. Therefore, several oxidation states for iron catalysts are feasible, even allowing simultaneous operating of several mechanisms. These detailed investigations in the last decades demonstrate that iron-catalyzed cross-coupling reactions are able to pass through more than one catalytic pathway, indicating many conceivable events of potentially connected catalytic cycles (Figure 6).[146]

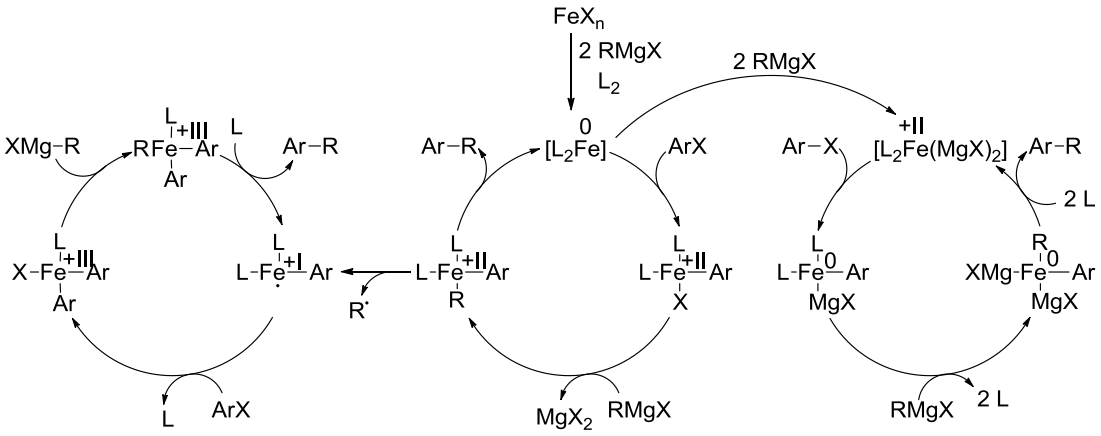
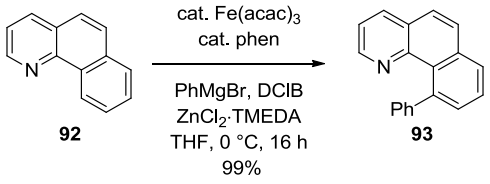


Figure 6: Interconnected catalytic cycles of iron-catalyzed cross-coupling reactions.

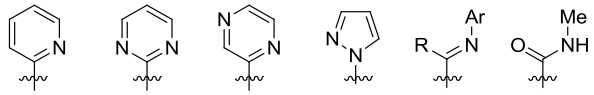
1.6 Iron-Catalyzed Direct C–H Bond Functionalizations

Among direct C–H functionalizations direct alkylations and arylations catalyzed by efficient, versatile and inexpensive iron complexes remain underexploited. However, a few examples of iron-catalyzed C–H functionalizations have been reported thus far.[151, 152] Pioneering work on iron-catalyzed arylations of arenes of the type **92** with a nitrogen-containing directing group have been accomplished by *Nakamura et al*. (Scheme 45).[152]



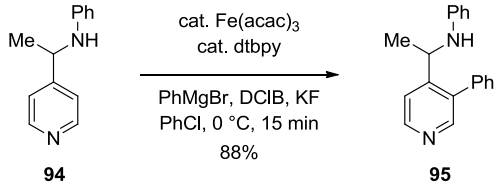
Scheme 45: Iron-catalyzed phenylation of benzo[*h*]quinolone (**92**).

The scope of this reaction was successfully probed by *Nakamura* and coworkers employing alkenes and arenes bearing a number of directing groups (Scheme 46).[153] Later, this reaction could be improved by the *in situ* formation of the *Grignard* reagent.[154] In general, these arylations were not limited to the reaction profile described for iron-catalyzed cross-coupling reactions.[155]



Scheme 46: Different directing groups employed in iron-catalyzed arylations according to *Nakamura et al*.

An additional contribution to iron-catalyzed C–C bond transformations was made by *DeBoef* and coworkers who presented the arylation of heteroarenes **94** through directed C–H bond activation (Scheme 47).[156] The use of DMPU or KF as additives minimized the homo-coupling of the *Grignard* reagents.[136, 139]



Scheme 47: Pyridine arylation by *DeBoef et al*.

In contrast to C(sp^2)–H bond functionalizations, the chemoselective direct alkylation and arylation of unactivated C(sp^3)–H bonds remains challenging. Albeit, benzylic C(sp^3)–H bonds in *α*-position to a heteroatom undergo such transformations easily. The introduction of bidentate directing groups set the stage for new strategies of C(sp^3)–H functionalizations (*vide supra*).[157, 158] Thus, employment of 8-aminoquinoline **70** or picolinamide **96** as bidentate directing groups (Figure 7) allowed for the first time palladium-catalyzed arylations and alkylations of C(sp^3)–H in a highly site-selective fashion, as reported by *Daugulis* and coworkers.[117, 119]

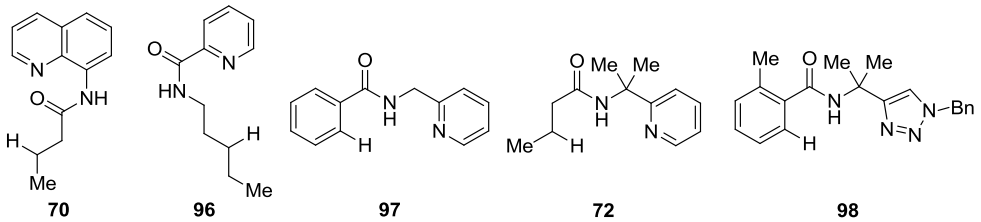
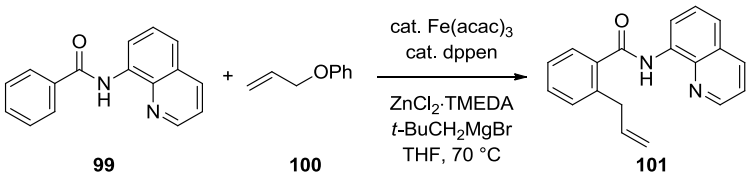


Figure 7: *N*-containing bidentate directing groups for C(sp^3)–H and C(sp^2)–H bond functionalizations.

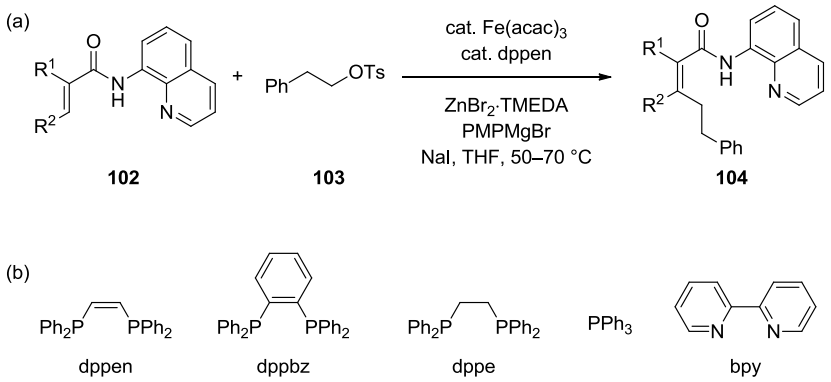
Recently, a few publications on the direct C(sp^3)–H functionalization involving transition metals, like palladium,[159] nickel[160, 161] and others[162] were released. *Chatani* and coworkers explored the influence of the substitution pattern on diversely substituted benzamides.[163] The aromatic amide **97** (Figure 7) was used as an effective directing group for the synthesis of phthalimides using $Ru_3(CO)_{12}$ as the catalyst. Moreover, the contribution by *B.-F. Shi et al*. was succeeded through the 2-(pyridine-2-yl)isopropylamine **72** as new directing group by palladium catalysis.[120] In 2014, *Ackermann et al.* reported on a triazole-assisted ruthenium-catalyzed arylation of aromatic amides **98** (Figure 7).[164] Additionally, ruthenium-catalyzed alkylations of C(sp^2)–H and C(sp^3)–H bonds could be achieved *via* additions of C–H bonds onto alkenes by the groups of *Chatani*[165] and *Ackermann*,[166, 167] through chelation assistance. Further substantial contributions by *Nakamura*[168-170] and coworkers established iron-catalyzed direct functionalizations. for the direct *ortho*-allylation of *N*-(quinolin-8yl)carboxamide derivatives **99** with allylic ether **100** (Scheme 48).[169]



Scheme 48: Iron-catalyzed *ortho*-allylation of carboxamide **101**.

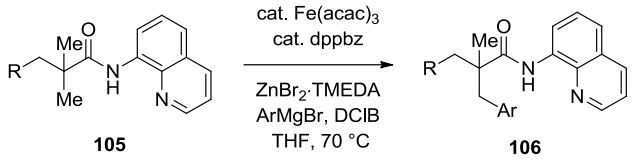
Through continuous work on exploring the bidentate directing group, alkylations of aromatic and olefinic carboxamides **102** with alkyl tosylates **103**, mesylates and halides were accomplished (Scheme 49a).[171] The effect of the ligand and the directing group is crucial for the iron-catalyzed reaction. The employment of diphosphine ligands, such as dppen and dppbz, possessing a rigid π-bridge were successful, while using dppe, monophosphines or bipyridyl ligands was ineffective (Scheme 49b). Recently, *Cook et al.* reported on an iron-catalyzed arylation and alkylation reaction by directly using aryl and alkyl chlorides as an

unified strategy for the direct functionalization of aromatic and heteroaromatic benzamides.[172]



Scheme 49: Iron-catalyzed directed alkylation and the applied ligands.

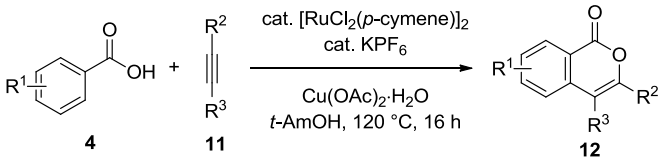
As the C(sp^3)–H bond functionalization is of special importance in direct iron-catalyzed functionalizations, *Nakamur*a presented an arylation of *ß*-methyl group in 2,2-disubstituted propionamides **105** (Scheme 50).[168] The structure of the directing group, the ligand and the substrate were very important for the success of the reaction. The torsion angle between the *ß*-H atom and the amide moiety in the substrate is crucial for the effective formation of a chelated intermediate with the iron catalyst. Furthermore, the higher reactivity of the methyl group over a benzylic group excluded a radical pathway and thereby implied an organoiron species as the key intermediate.



Scheme 50: Iron-catalyzed arylation of the *ß*-methyl group of 2,2-disubstituted propionamides **105**.

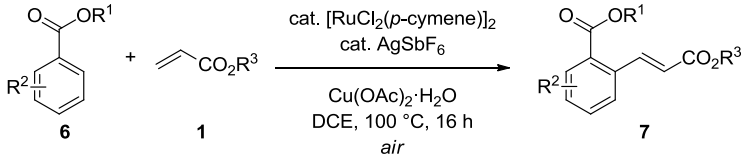
2 Objectives

In recent years, the research group of *Ackermann* developed versatile, useful protocols for oxidative ruthenium-catalyzed annulations for the synthesis of heteroarenes.[41, 173] *Satoh* and *Miura* reported on analogous rhodium-catalyzed reactions for C–H/O–H bond functionalization.[56] However, ruthenium-catalyzed annulation reactions with benzoic acids **4** for the synthesis of isocoumarins **12** were thus far unprecedented. Therefore, the development of such an alkyne annulations as well as investigations on the substrate scope and detailed mechanistic studies were highly attractive objectives (Scheme 51).



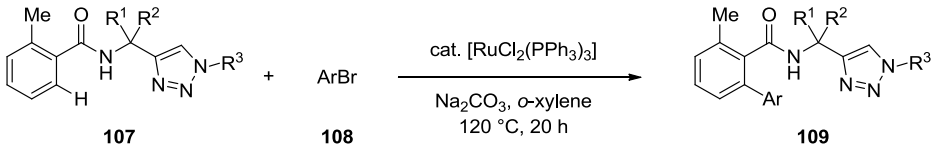
Scheme 51: Ruthenium(II)-catalyzed oxidative alkyne annulation of **4** via C–H/O–H functionalization.

Furthermore, the developed catalytic system with the rather inexpensive ruthenium(II) complexes should be applicable for oxidative olefinations of benzoates **6**. The use of substrates with such a weakly coordinating group as an ester would give a facile access to styrene derivatives **7** (Scheme 52).



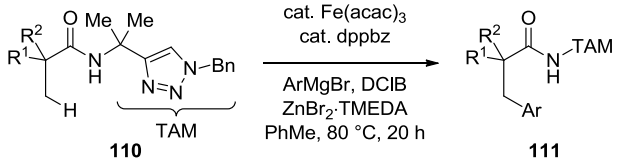
Scheme 52: Ruthenium(II)-catalyzed oxidative alkenylation of benzoates **6**.

The introduction of bidentate directing groups enabled new strategies of C–H functionalizations.[158, 165, 174] The work of *Daugulis*[117, 119] and further contribution by *Nakamura*[168, 169] provided new C(sp^2)–H and C(sp^3)–H disconnection reactions. Further contributions to ruthenium- and nickel-catalyzed C(sp^3)–H bond arylation and alkylation reactions were provided by *Chatani,*[161] *Ackermann*[178] and *Ge*.[160] To meet the requirements for this challenge, new concepts in bidentate directing groups have to be developed. A novel family of directing groups was developed by the group of *Ackermann* and applied for ruthenium-catalyzed C(sp^2)–H arylations of aromatic amides (Scheme 53).[164]



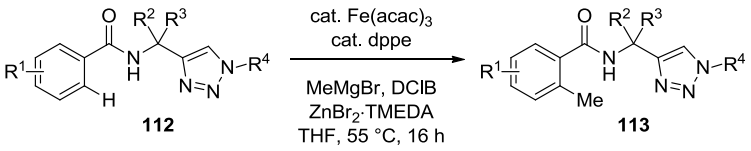
Scheme 53: Triazole-assisted ruthenium-catalyzed C(sp^2)–H arylations of aromatic amides.

However, the corresponding iron-catalyzed arylation of unactivated C(sp^3)–H bonds remains a challenging transformation. Hence, the major focus in this work was set on the use of the bidentate triazolyldimethylmethyl (TAM) directing group (**110**) for the C(sp^3)–H arylation (Scheme 54).



Scheme 54: Triazole-assisted iron-catalyzed C(sp^3)–H arylation of aromatic amides.

Known methylation methods (D*o*M) or inefficient palladium-mediated methylation protocols have limited functional group tolerance or high waste production. Therefore, the development of new methylation methods using the less expensive iron catalyst is in high demand. Exploiting the novel bidentate TAM directing group, we became interested in the direct methylation reaction of unactivated arenes **112** (Scheme 55).



Scheme 55: Triazole-assisted iron-catalyzed methylation.

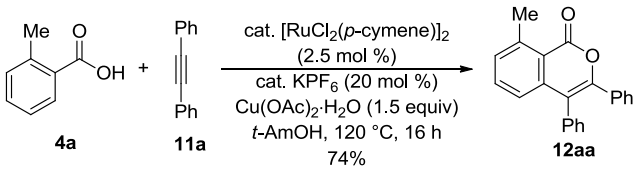
3 Ruthenium(II)-Catalyzed Oxidative C–H Bond Functionalization

3.1 Ruthenium(II)-Catalyzed Oxidative Annulation Reaction

Transition metal-catalyzed oxidative direct annulation reactions of alkynes have attracted significant interest in recent years. The most benefit of these sustainable strategies for C–H bond functionalization are the omitted prefunctionalization of starting materials and employment of environmentally friendly oxidants such as oxygen or air under mild conditions.[61, 175] Pioneering works using expensive rhodium(III) catalysts were accomplished by *Miura*, *Satoh* and *Fagnou* for C–H/O–H and C–H/N–H annulation reactions.[56, 60] Otherwise, analogous ruthenium-catalyzed cyclizations have not been completely explored and elaborated very recently by *Ackermann*[49, 173, 176] and, subsequently by *Jeganmohan*.[177]

Preliminary Studies

An alternative ruthenium catalytic system was examined by *Ackermann*, *Pospech* and *Graczyk* towards the synthesis of isocoumarins **12**.[178] Extensive optimization studies with the benzoic acid **4a** revealed the most efficient conditions for this reaction as described in Scheme 56.



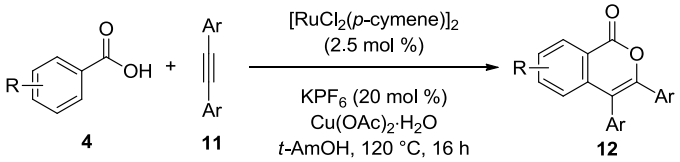
Scheme 56: Optimized reaction conditions for the ruthenium(II)-catalyzed oxidative synthesis of isocoumarin **12aa**.

Notably, the use of KPF_6 as additive formed a cationic ruthenium(II) complex,[179] which is able to operate in water as the reaction medium, to obtain isocoumarin **12aa**, albeit in lower yield (52%). Whereas other cocatalytic additives, such as $AgSbF_6$, $AgBF_4$, AgOTf, CsOAc or HOPiv were not as effective as was KPF_6. $Cu(OAc)_2 \cdot H_2O$ was the oxidant of choice and even the performance of the reaction under air did not limit its efficacy (87% yield). Alternative oxidants, such as silver acetate or cupric(II) bromide, appeared to be less productive.

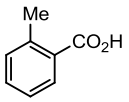
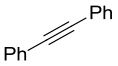
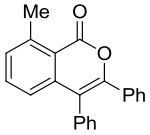
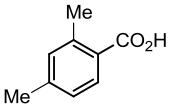
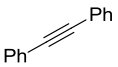
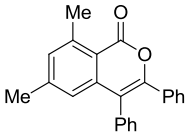
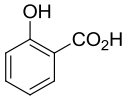
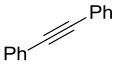
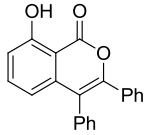
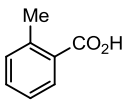
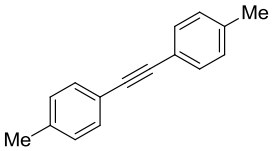
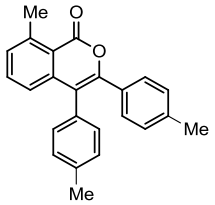
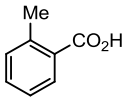
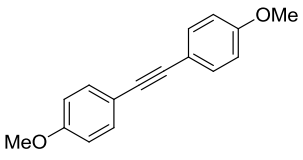
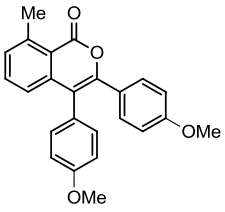
3.1.1 Scope and Limitation

Variously decorated aromatic acids **4** were treated with several symmetrically substituted aromatic alkynes **11** under the optimized reaction conditions (Table 1). The annulation of tolane (**11a**) by *o*-toluic (**4a**) and 2,4-dimethylbenzoic acids (**4b**) bearing electron-donating substituents afforded the corresponding isocoumarins **12aa** and **12ba**, respectively, in very good yields (entries 1 and 2). Even salicylic acid (**4c**) with a free *ortho*-hydroxyl substituent was well tolerated (entry 3). Furthermore, different substitution patterns on the aromatic moieties of tolanes **11b** and **11c** were amenable for the synthesis of isocoumarins **12ab** and **12ac** (entries 4 and 5).

Table 1: Substrate scope for the ruthenium(II)-catalyzed annulations of diarylalkynes **11** by aromatic acids **4**.[a]



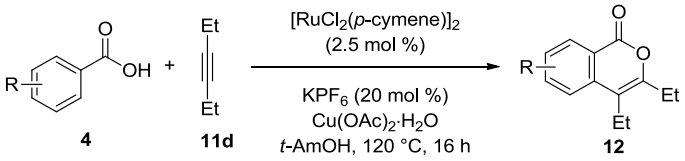
4 **11** **12**

entry	substrate	alkyne	product	yield [%][b]
1	 **4a**	 **11a**	 **12aa**	74
2	 **4b**	 **11a**	 **12ba**	84
3	 **4c**	 **11a**	 **12ca**	62
4	 **4a**	 **11b**	 **12ab**	74
5	 **4a**	 **11c**	 **12ac**	78

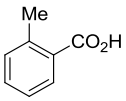
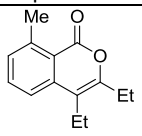
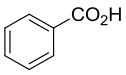
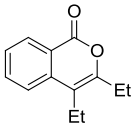
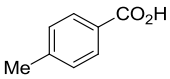
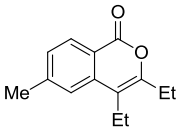
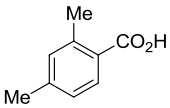
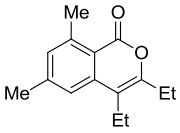
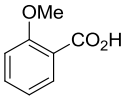
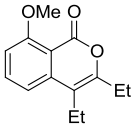
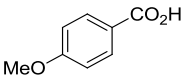
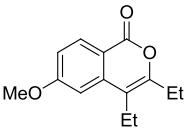
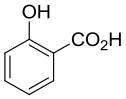
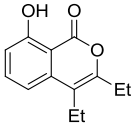
[a] Reaction conditions: **4a**-**4c** (2.0 mmol), **11a**-**11c** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), *t*-AmOH (3.0 mL), 120 °C, 16 h; under N_2. [b] Isolated yields.

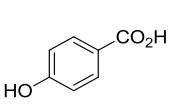
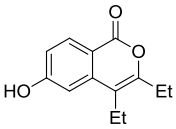
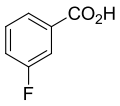
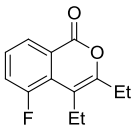
The substrate scope was not restricted to aromatic alkynes **11a**-**11c** but also included dialkylalkynes **11d**-**11e**. Thus, a variety of aromatic acids entered the oxidative annulation reaction with internal acetylene hex-3-yne (**11d**) (Table 2). Substrates **4a,b** and **4d-g** with electron-donating substituents were efficiently converted in good yields (entries 1–6). In the presence of functional groups, such as free hydroxyl groups **4c** and **4h** (entries 7 and 8) or fluorine substituents **4i** (entry 9), isocoumarins could be obtained as well.

Table 2: Substrate scope for the ruthenium(II)-catalyzed annulation reactions of hex-3-yne (**11d**) with aromatic acids **4**.[a]



4 **11d** **12**

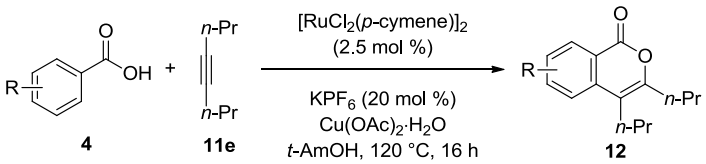
entry	substrate	product	yield [%][b]
1	 **4a**	 **12ad**	76
2	 **4d**	 **12dd**	93
3	 **4e**	 **12ed**	97
4	 **4b**	 **12bd**	78
5	 **4f**	 **12fd**	58
6	 **4g**	 **12gd**	67
7	 **4c**	 **12cd**	85

8	 **4h**	 **12hd**	52
9	 **4i**	 **12id**	36

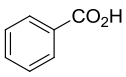
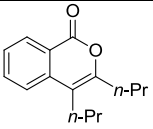
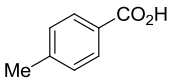
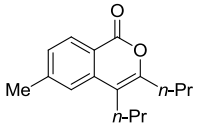
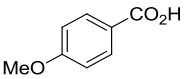
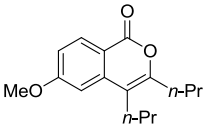
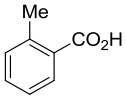
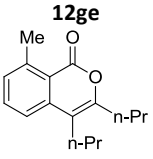
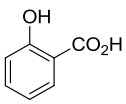
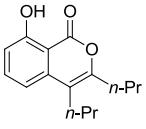
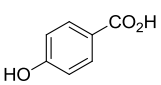
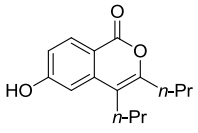
[a] Reaction conditions: **4** (2.0 mmol), **11d** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv), *t*-AmOH (3.0 mL), 120 °C, 16 h; under N_2. [b] Isolated yields.

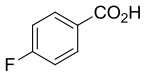
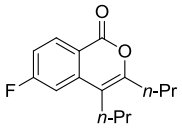
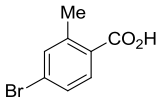
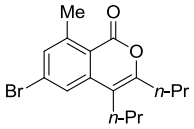
Furthermore, the substrate scope could be extended by the use of oct-4-yne (**11e**) as an internal alkyne (Table 3). Tolerance of valuable functional groups was observed (entries 1–7). Notably, the bromo substituent on the aromatic ring was tolerated by the ruthenium(II) catalyst as well (entry 8).

Table 3: Substrate scope for the ruthenium(II)-catalyzed annulation of oct-4-yne (**11e**) by aromatic acids **4**.[a]



4 **11e** **12**

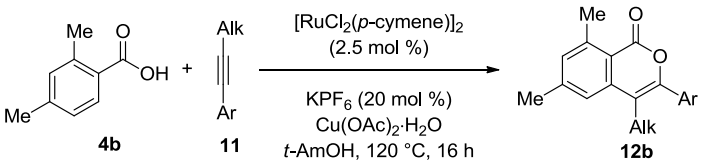
entry	substrate	product	yield [%][b]
1	 **4d**	 **12de**	78
2	 **4b**	 **12be**	85
3	 **4g**	 **12ge**	80
4	 **4a**	 **12ae**	66
5	 **4c**	 **12ce**	81
6	 **4h**	 **12he**	70

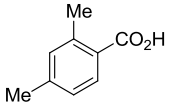
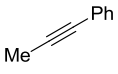
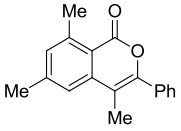
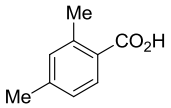
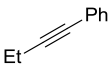
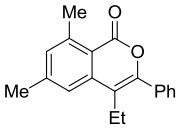
7	 **4j**	 **12je**	67
8	 **4k**	 **12ke**	60

[a] Reaction conditions: **4** (2.0 mmol), **11e** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv), *t*-AmOH (3.0 mL), 120 °C, 16 h; under N_2. [b] Isolated yields.

With the stable ruthenium(II)-based catalytic system for oxidative annulation reactions in hand, examinations of unsymmetrically substituted alkynes **11** were carried out (Table 4). Isocoumarins **12bf** and **12bg** were obtained from 2,4-dimethylbenzoic acid (**4b**) in a highly regioselective fashion, delivering in each case only a single regioisomeric product (entries 1 and 2). In these products, the aromatic moiety of the internal alkyne favored the position proximal to the heteroatom. It is noteworthy, that in analogous rhodium-catalyzed annulations, mixtures of 3- and 4-arylsubstituted regioisomers with ratios of 6 : 1 to 8 : 1.5 were obtained.[56, 57]

Table 4 Annulation of unsymmetrically substituted alkynes **11** by 2,4-dimethylbenzoic acid (**4b**).[a]



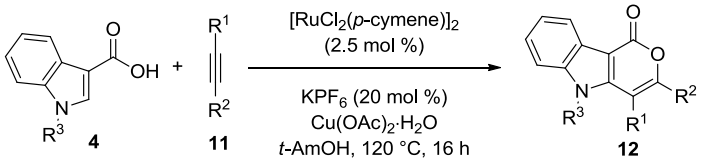
entry	substrate	alkyne	product	yield [%][b]
1	 **4b**	 **11f**	 **12bf**	59
2	 **4b**	 **11g**	 **12bg**	57

[a] Reaction conditions: **4b** (2.0 mmol), **11** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1.5 equiv), *t*-AmOH (3.0 mL), 120 °C, 16 h; under N_2. [b] Isolated yields.

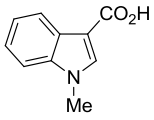
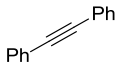
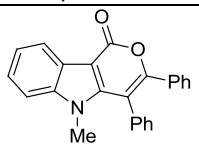
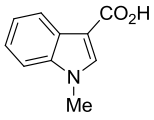
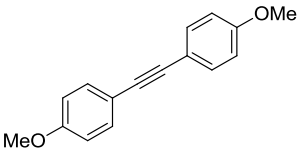
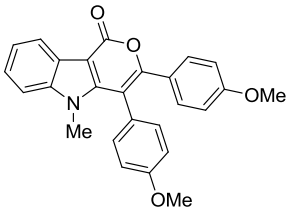
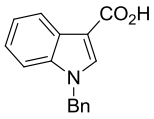
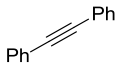
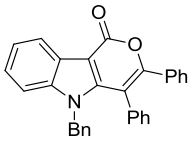
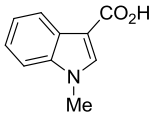
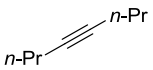
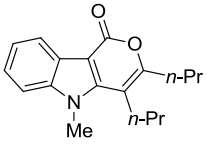
Under these reaction conditions, also heteroaromatic carboxylic acids were suitable for the ruthenium(II)-catalyzed annulations process (Table 5). Thereby, *N*-methyl- (**4l**) and *N*-benzyl-1*H*-indole-3-carboxylic acid (**4m**) were successfully converted into *N*-protected 3,4-

disubstituted pyrano[4,3-*b*]indol-1-ones **12l** and **12m** through a successful oxidative C–H/O–H bond functionalization.

Table 5: Annulation reactions of alkynes with *N*-protected indole-3-carboxylic acids **4** and **11**.[a]

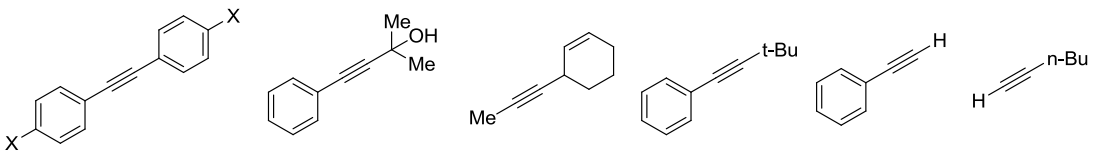


4 **11** **12**

entry	substrate	alkyne	product	yield [%][b]
1	 **4l**	 **11a**	 **12la**	65
2	 **4l**	 **11c**	 **12lc**	52
3	 **4m**	 **11a**	 **12ma**	77
4	 **4l**	 **11e**	 **12le**	82

[a] Reaction conditions: **4** (2.0 mmol), **11** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), *t*-AmOH (3.0 mL), 120 °C, 16 h; under N_2. [b] Isolated yields.

Among the limitations of this synthetic method, unsuccessful oxidative ruthenium-catalyzed annulations of halo- (**11h**) and hydroxyl-substituted (**11i**) acetylenes, alkynes of the type **11j** and **11k** with unsaturated and sterically demanding substituents as well as terminal alkynes **11l** and **11m** (Figure 8) should be pointed out.



11h **11i** **11j** **11k** **11l** **11m**

X = Br, Cl, CF_3

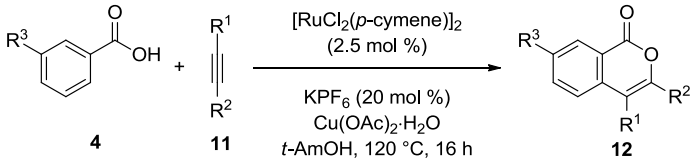
Figure 8: Unsymmetrically substituted alkynes with insufficient reactivity.

3.1.2 Mechanistic Studies

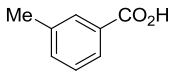
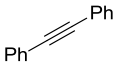
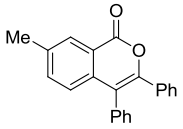
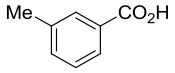
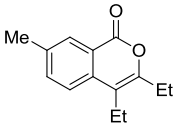
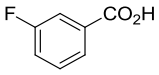
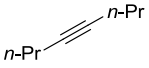
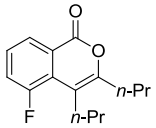
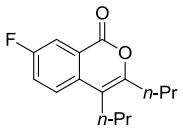
Intramolecular Competition Experiments

Intramolecular competition experiments were performed to gain insights in the catalysts mode of action (Table 6). Both tolane (**11a**) and hex-3-yne (**11d**) were annulated with *m*-toluic acid (**4n**), affording only the less sterically congested regioisomers **12na** and **12nd** in moderate yields (entries 1 and 2). In contrast, *meta*-fluorosubstituted acid **4n** furnished the sterically more demanding 5-fluoroisocoumarin **12ie** as a major product and only 5% of its 7-fluoro regioisomer **12ie'** (entry 3). Such a different kinetic acidity of the two *ortho*-C–H bonds in the arene **4i** can be interpreted as a result of concerted action of the well-known *ortho*-fluoro effect[180] and a carboxy directing group.

Table 6: Annulations of alkynes **11** by *meta*-substituted benzoic acids **4**.[a]



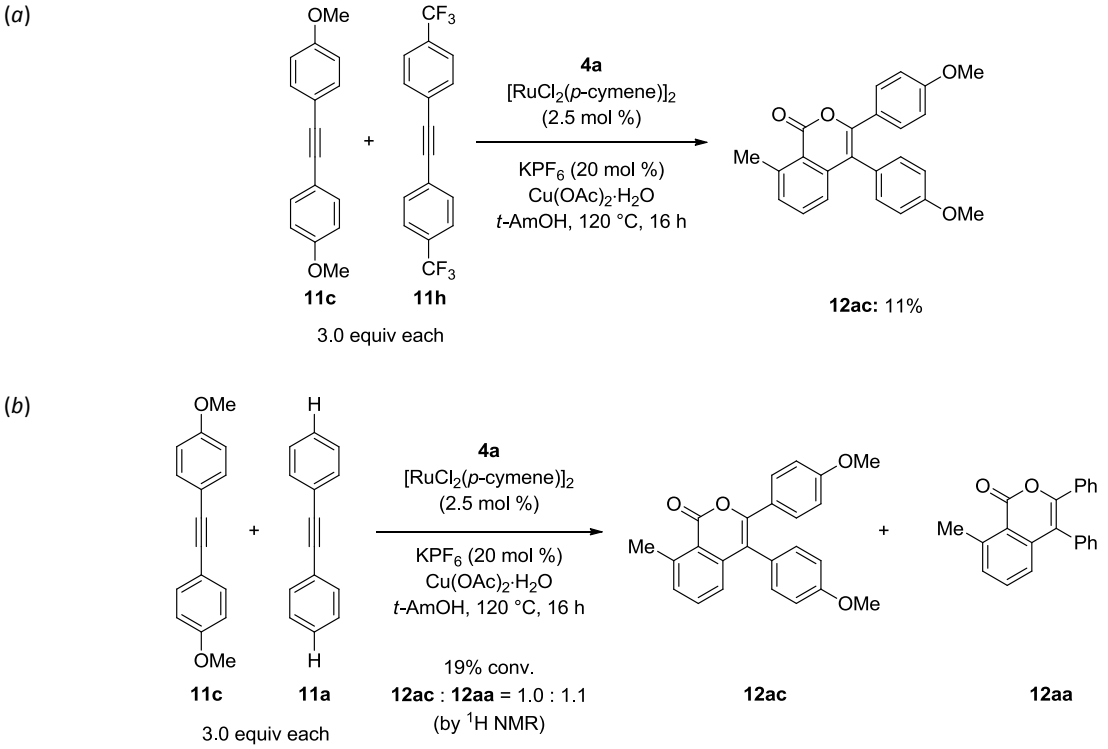
4 **11** **12**

entry	substrate	alkyne	product	yield [%][b]
1	 **4n**	 **11a**	 **12na**	32
2	 **4n**	 **11d**	 **12nd**	50
3	 **4i**	 **11e**	 **12ie**	32
			 **12ie'**	5

[a] Reaction conditions: **4** (2.0 mmol), **11** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), *t*-AmOH (3.0 mL), 120 °C, 16 h; under N_2. [b] Isolated yields.

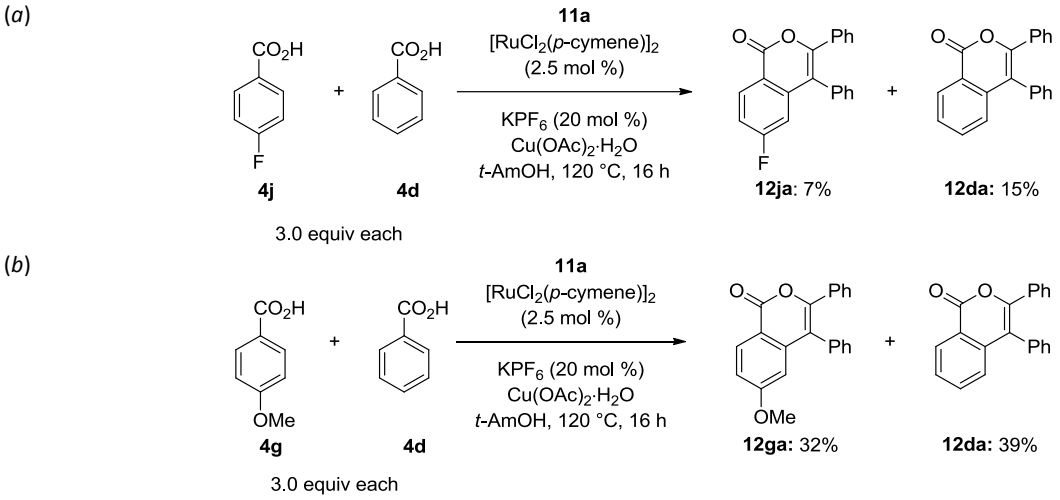
Intermolecular Competition Experiments

Intermolecular competition experiments were performed with two pairs of differently substituted internal aromatic alkynes **11** in annulation reactions with *o*-toluic acid (**4a**) (Scheme 57). Competition of electron-rich (**11c**) and electron-poor alkyne **11h** demonstrated the preferential conversion to the isocoumarin **12ac** as a sole product (Scheme 57a). Whereas, cyclizations of alkynes **11c** and **11a** showed no essential predominant formation of either the products **12ac** or **12aa** (Scheme 57b).



Scheme 57: Intermolecular competition experiments with two pairs of alkynes **11**.

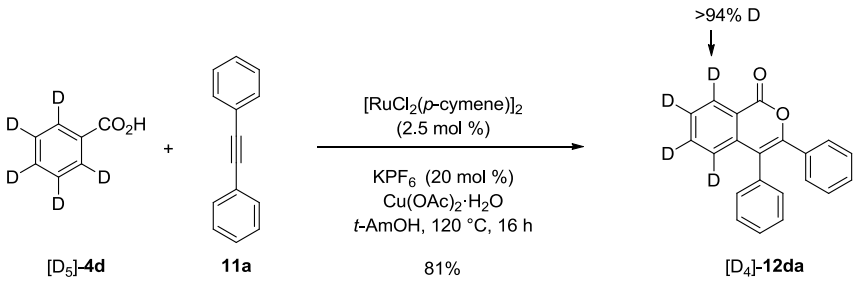
Moreover, intermolecular competition experiments between differently substituted benzoic acids **4** were performed (Scheme 58). Electron-deficient aromatic acid **4j** was less reactive, as compared to the parent benzoic acid (**4d**) (Scheme 58a). The almost equal conversion of the non-substituted acid **4d** and the methoxy-substituted one **4j** was observed in the second intermolecular competitive cyclization with tolane (**11a**) (Scheme 58b).



Scheme 58: Intermolecular competition experiments with two pairs of benzoic acids **4**.

Experiments with Isotopically Labeled Substrates

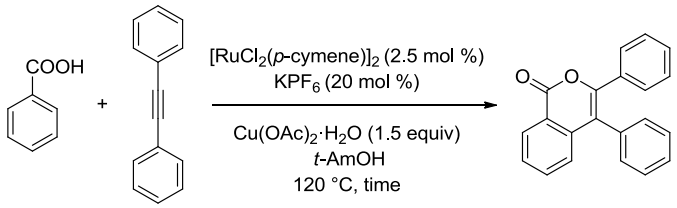
The study of the reaction mechanism means determination of the elementary steps of a catalytic cycle. Determination of the rate-determining step is of prime importance in mechanistic studies on transition metal-catalyzed C–H bond functionalization reactions. Estimation of the KIE values as a common method in organic chemistry can differentiate the rate-determining and the product-determining steps [181, 182] As shown in Scheme 59, in the annulation reaction of tolane (**11a**) with deuterated benzoic acid [D_5]-**4d** no significant H/D exchange in the *ortho*-position was observed, thus indicating an irreversible cyclometalation step right.



Scheme 59: Experiment with isotopically labeled substrate [D_5]-**4d**.

Before experiments with the isotopically labeled substrates [D_5]-**4d** were performed, the indicatory time for stopping the reaction mixture had to be determined. These experiments revealed a time-dependent linear regression for the yield with a complete conversion of the substrate **4d** already after 1 h when using a sixfold excess of the acid **4d** (Table 7).

Table 7: Reaction times for the annulations by benzoic acid (**4d**).

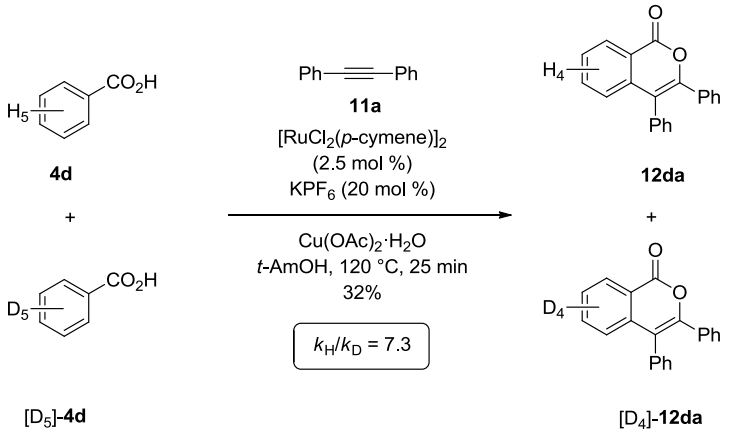


4d **11a** **12da**

entry	time [min]	yield [%][a]
1	10	10
2	15	27
3	30	43
4	60	90

[a] Reaction conditions: **4d** (6.0 mmol), **11a** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv), *t*-AmOH, 120 °C, under N_2. [b] Isolated yields.

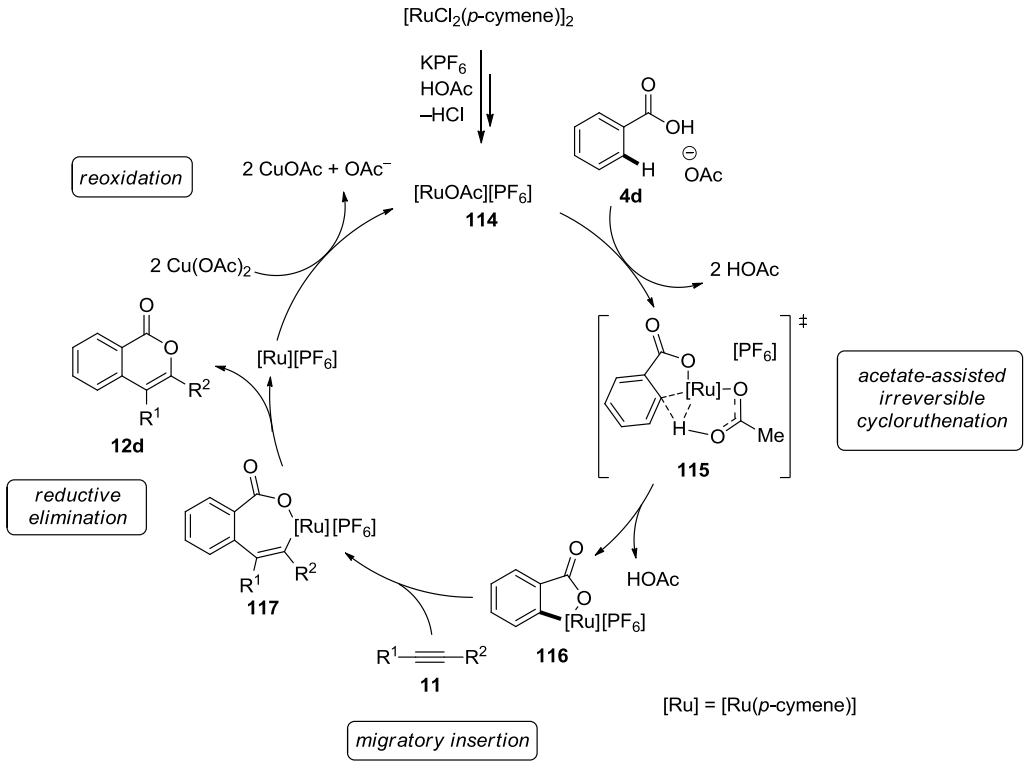
On the basis of this observation, an intermolecular competition experiment with benzoic acid (**4d**) and its isotopically labeled analog [D_5]-**4d** was conducted (Scheme 60). A significant primary KIE value of 7.3 was confirmed indicating a rate-determining C–H metalation step through an acetate-assisted metalation with ruthenium.[9]



Scheme 60: KIE-determining experiment with isotopically labeled substrate [D_5]-**4d**.

Proposed Catalytic Cycle

Based on these experimental data, a catalytic cycle for the oxidative ruthenium-catalyzed C–H/O–H bond functionalization can be proposed, as presented in Scheme 61. The *in situ* formed cationic ruthenium(II)-complex **114** with PF_6^- as the counterion caused an irreversible, acetate-assisted cycloruthenation of benzoic acid (**4d**) *via* transition state **115**, thus delivering the intermediate **116** and acetic acid. Coordination of the alkyne **11** and subsequent migratory insertion furnished the seven-membered key ruthenacycle **117**. Subsequent reductive elimination in **117** afforded product **12d** and ruthenium(0) species, further reoxidation to ruthenium(II) complex occurred by copper(II) acetate.



Scheme 61: Proposed catalytic cycle for the ruthenium(II)-catalyzed oxidative C–H/O–H functionalization.

According to this mechanism, the regiochemistry-determining step in annulations of unsymmetrically substituted arylalkyl alkynes (see above, Table 4) is the migratory insertion of alkyne **11** into the ruthenium–carbon bond of key intermediate **116** to give the seven-membered ruthenacycle **117**. Thus, the observed regioselectivities can be rationalized by the enhanced kinetic stability of **117**, in which the aryl substituent R^2 is in the neighboring position to the ruthenium.

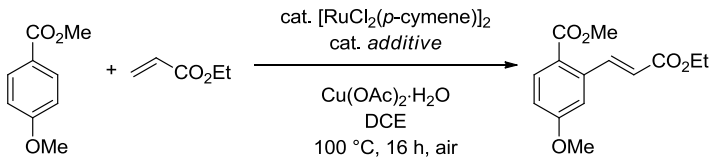
3.2 Ruthenium(II)-Catalyzed Alkenylation Reaction

Since the 1960´s several cross-coupling methods for C–C bond formations involving palladium compounds as the catalyst have been reported. Important approaches for the synthesis of styrene derivatives are the palladium-catalyzed *Mizoroki-Heck*[186,187] and *Fujiwara-Moritani*[188–191] reactions. Efficient and selective, yet relatively expensive rhodium catalysts have also been developed in recent years. For example, *Chang* reported on a versatile protocol using rhodium-catalyzed dehydrogenative cross-couplings.[47] Significantly less expensive ruthenium complexes have only recently been exploited as catalysts for oxidative C–H bond alkenylations on arenes.[46, 183]

3.2.1 Optimization Studies

Initially, the aromatic ester **6a** and ethyl acrylate (**1b**) were used for the screening experiments upon searching for optimal reaction conditions (Table 8). The catalytic system consisting of the versatile ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ and the copper(II) acetate as oxidant in DCE was used for the oxidative coupling reaction under air. First, a variety of additives were tested. The additive KPF_6 (entry 1), which was suitable for oxidative annulations of alkynes **11**, was not efficient in the reaction. Different carboxylates (entries 2–5) could not furnish the desired product **7ab** as well. Silver(I) salts as additives (entries 6–8) increased the conversion of this oxidative ruthenium-catalyzed coupling reaction. Notably, $AgSbF_6$ turned out to be ideal (entry 6).

Table 8: Optimization studies: additive effect.[a]



6a **1b** **7ab**

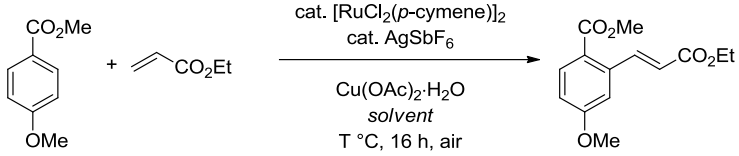
entry	additive	GC-conv.	yield [%][b]
1	KPF_6	---	0
2	CsOAc	---	0
3	$MesCO_2K$	---	0
4	NaOAc	---	0
5	AgOAc	---	0
6	$AgSbF_6$	67	62

7	$AgSO_3CF_3$	63	48
8	$AgBF_4$	30	---

[a] Reaction conditions: **6a** (0.5 mmol), **1b** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), DCE (2.0 mL), 100 °C, 16 h, under air. [b] Isolated yields.

In order to find the optimal solvent, different milieus were examined (Table 9). A variety of polar and apolar solvents were inefficient for the catalytic reaction (entries 1–8), whereas DCE was found to be optimal (entry 9). AcOH as the co-solvent did not improve the yield (entry 10). By the attempted reduction of the catalyst loading or amount of additive the yields slightly dropped (entries 11 and 12).

Table 9: Solvent effect in the twofold C–H functionalization.[a]



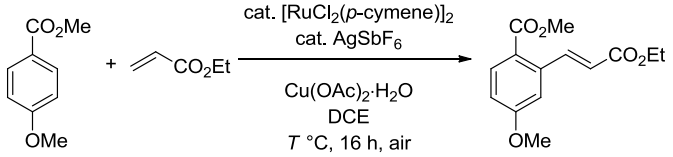
6a **1b** **7ab**

entry	solvent	T [°C]	GC-conv.	yield [%][b]
1	H_2O	120	1	0
2	*t*-AmOH	120	42	13
3	DMF	120	---	0
4	*o*-xylene	120	---	0
5	1,4-dioxane	100	27	0
6	AcOH	100	8	0
7	THF	80	20	11
8	neat	100	70	40
9	DCE	100	67	62
10	DCE/AcOH	100	40	19
11	DCE	100	64	55[c]
12	DCE	100	76	60[d]

[a] Reaction conditions: **6a** (0.5 mmol), **1b** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), solvent (2.0 mL), 16 h, under air. [b] Isolated yields. [c] $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %). [d] Under N_2.

Performing the reaction at elevated temperatures did not result in a higher-yielding product formation (Table 10).

Table 10: Optimization studies: reaction temperature.[a]



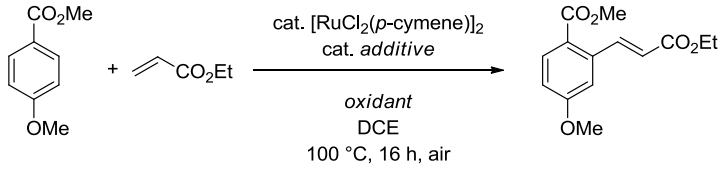
6a **1b** **7ab**

entry	*T* [°C]	GC-conv.	yield [%][b]
1	120	80	50[c]
2	140	75	45[c]
3	140	65	43[d]
4	200	35	0[c]

[a] Reaction conditions: **6a** (0.5 mmol), **1b** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), DCE (2.0 mL), 16 h, under air. [b] Isolated yields. [c] Sealed tube. [d] Microwave irradiation, 1 h.

Furthermore, several combinations of different additives and oxidants were examined to identify the optimal reaction conditions (Table 11). The presence of external oxidant is of crucial importance for the reaction (entry 1). Cupric acetate as oxidant was found to be the best one (entries 2–4), whereas the other copper(II) salts appeared to be inefficient (entries 6–9).

Table 11: Optimization studies: oxidants and additives.[a]



6a **1b** **7ab**

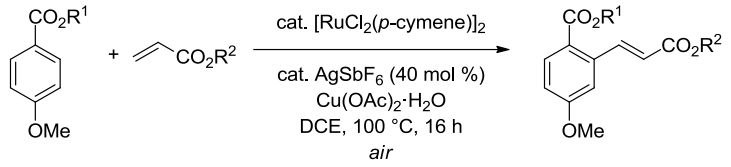
entry	oxidant (equiv)	additive	GC-conv.	yield [%][b]
1	---	$AgSbF_6$	---	0[c]
2	$Cu(OAc)_2 \cdot H_2O$ (1.5)	$AgSbF_6$	77	56
3	$Cu(OAc)_2 \cdot H_2O$ (1.0)	$AgSbF_6$	75	61
4	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgSbF_6$	78	55[d]
5	$K_2S_2O_8$ (4.0)	---	---	0
6	$CuBr_2$ (2.0)	---	---	0
7	$CuBr_2$ (2.0)	CsOAc	---	0
8	$CuBr_2$ (2.0)	NaOAc	---	0
9	$CuBr_2$ (2.0)	KOAc	---	0

[a] Reaction conditions: **6a** (0.5 mmol), **1b** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (40 mol %), oxidant (2.0 equiv), DCE (2.0 mL), 100 °C, 16 h, under air. [b] Isolated yields. [c] $AgSbF_6$ (1.5 equiv). [d] $AgSbF_6$ (20 mol %).

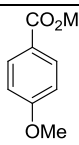
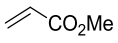
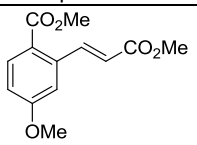
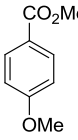
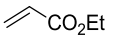
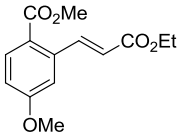
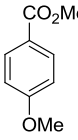
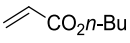
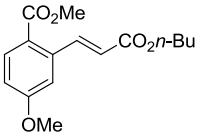
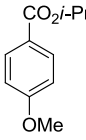
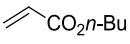
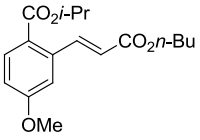
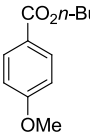
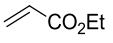
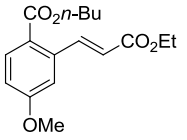
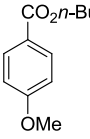
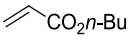
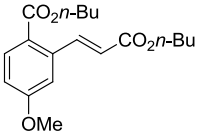
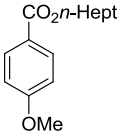
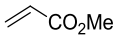
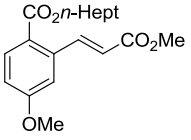
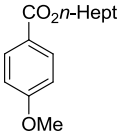
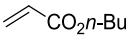
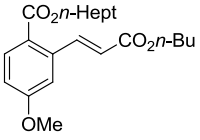
3.2.2 Scope and Limitation

Initially, the scope of the alkyl substituents in ester functionalities on substrates **6** and acrylates **1** was explored by using the *para*-methoxy-substituted benzoates **6a** (Table 12). Methyl, ethyl and *n*-butyl acrylates were accessible for the oxidative alkenylation (entries 1–3). Diversifying the ester group in benzoates with *iso*-propyl or *n*-butyl substituents has no significant effect on the isolated yields (entries 3–6), whereas substrate **6d** with a longer alkyl chained afforded the corresponding products **7da** and **7dc** in slightly increased yields (entries 7 and 8).

Table 12: Substrate scope for the oxidative alkenylation of *p*-anisates **6a**-**6d** with acrylates **1a**-**1c**.[a]



6 **1** **7**

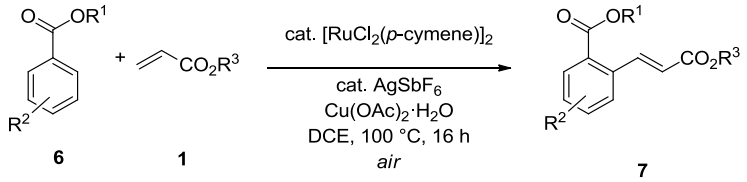
entry	substrate	acrylate	product	yield [%][b]
1				62
	6a	**1a**	**7aa**	
2				62
	6a	**1b**	**7ab**	
3				59
	6a	**1c**	**7ac**	
4				63
	6b	**1c**	**7bc**	
5				56
	6c	**1b**	**7cb**	
6				57
	6c	**1c**	**7cc**	
7				68
	6d	**1a**	**7da**	
8				61
	6d	**1c**	**7dc**	

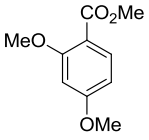
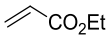
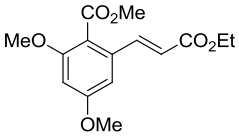
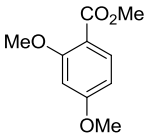
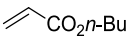
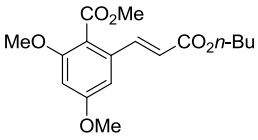
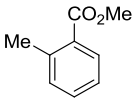
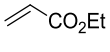
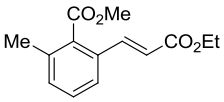
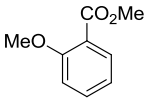
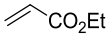
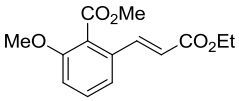
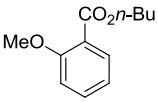
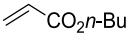
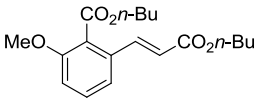
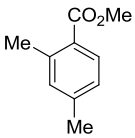
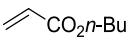
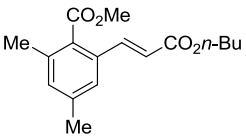
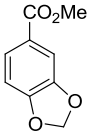
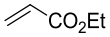
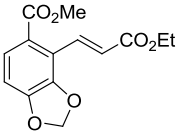
[a] Reaction conditions: **6a**-**6d** (0.5 mmol), **1a**-**1c** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), DCE (2.0 mL), 100 °C, 16 h, under air. [b] Isolated yields.

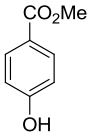
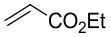
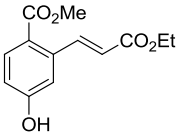
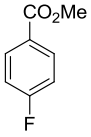
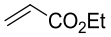
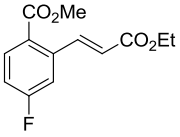
A number of differently decorated aromatic esters were suitable for the ruthenium-catalyzed oxidative coupling (Table 13). Methoxy- and methyl-substitutes arenes were well

tolerated in this reaction (entries 1–6). As a consequence of the secondary chelating effect, 4-alkenylated benzo[*d*]dioxole **7jb** was obtained as the major product in good yield (entry 7). Notably, the other 6-alkenylated regioisomer was formed in only 6% yield, as determined by ^{1}H NMR spectroscopy of the crude product. In contrast, the styrene derivatives **7kb** and **7lb** bearing unprotected free hydroxyl or fluoro substituent were obtained in poorer yields (entries 8 and 9). In general, the scope was mostly amenable for electron-rich aromatic esters **6e**-**6j**, while electron-deficient arenes **6l** were not completely converted under these catalytic conditions. Importantly, no twofold alkenylations of the esters **6** occurred in any of these reactions.

Table 13: Substrate scope for the oxidative alkenylation of substituted benzoates **6** with acrylates **1**.[a]



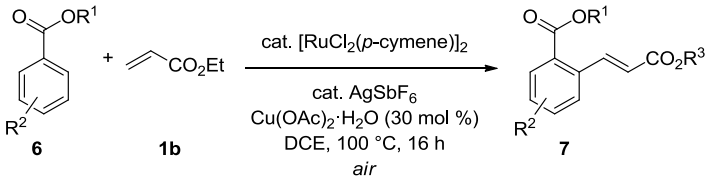
entry	substrate	acrylate	product	yield [%][b]
1	 **6e**	 **1b**	 **7eb**	54
2	 **6e**	 **1c**	 **7ec**	56
3	 **6f**	 **1b**	 **7fb**	48
4	 **6g**	 **1b**	 **7gb**	52
5	 **6h**	 **1c**	 **7hc**	62
6	 **6i**	 **1c**	 **7ic**	57
7	 **6j**	 **1b**	 **7jb**	74

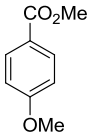
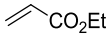
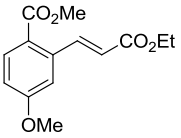
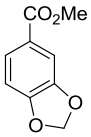
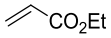
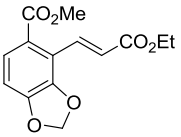
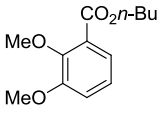
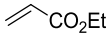
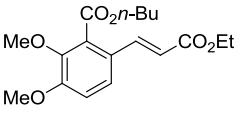
8	 **6k**	 **1b**	 **7kb**	36
9	 **6l**	 **1b**	 **7lb**	37

[a] Reaction conditions: **6** (0.5 mmol), **1** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (40 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv), DCE (2.0 mL), 100 °C, 16 h, under air. [b] Isolated yields.

With regard of sustainable chemistry, the quantity of copper(II) salt could be reduced to cocatalytic amounts under an atmosphere of ambient air (Table 14). Under these conditions, alkenylated *p*-anisate **6a** and benzo[*d*]dioxole **6j** could be obtained in a slightly decreased yield as compared to the reaction with stoichiometric amounts of cupric acetate (entries 1 and 2). Particularly, styrene derivative **7mb** was obtained in a good yield (entry 3).

Table 14: Substrate scope using catalytic amounts of $Cu(OAc)_2{\cdot}H_2O$.[a]



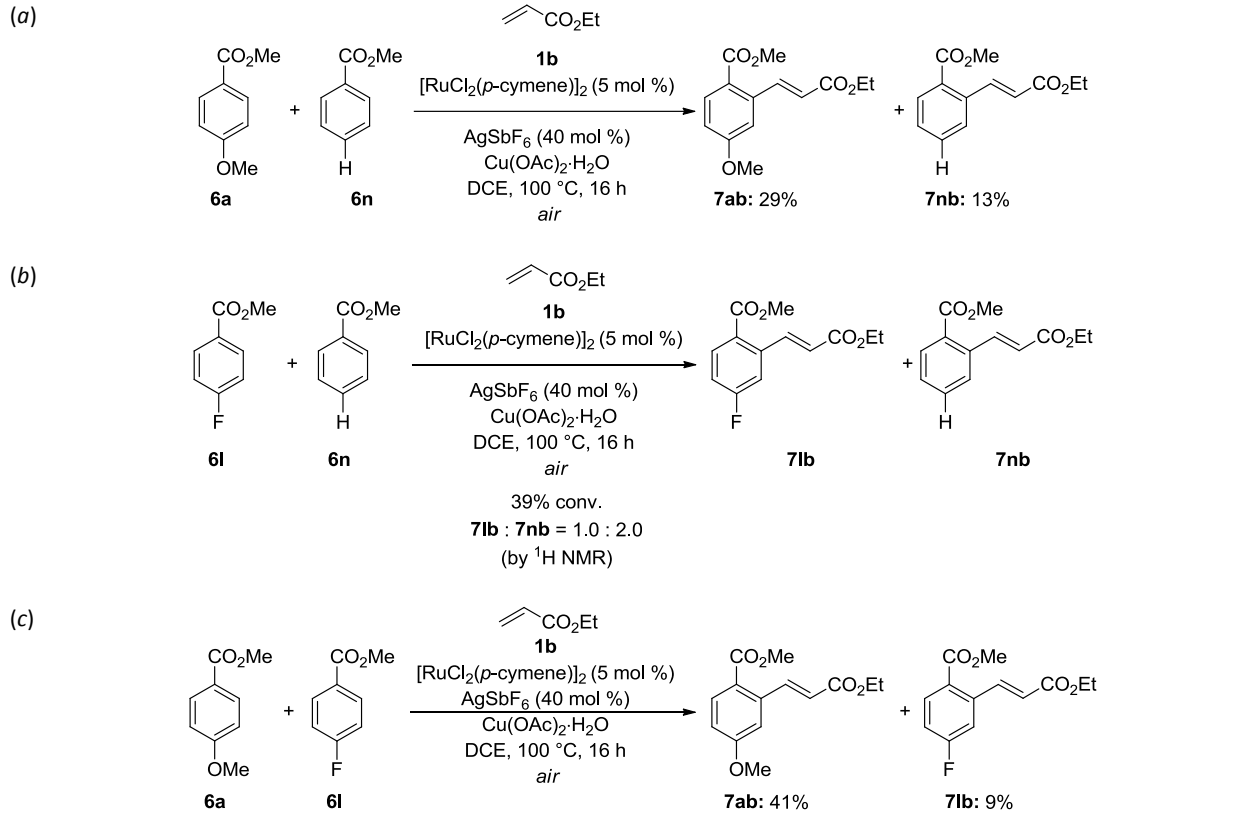
entry	substrate	acrylic ester	product	yield [%][b]
1	 **6a**	 **1b**	 **7ab**	55
2	 **6j**	 **1b**	 **7jb**	61
3	 **6m**	 **1b**	 **7mb**	72

[a] Reaction conditions: **6** (0.5 mmol), **1b** (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (30 mol %), DCE (2.0 mL), 100 °C, 16 h, under air. [b] Isolated yields.

3.2.3 Mechanistic Studies

Intermolecular Competition Experiments

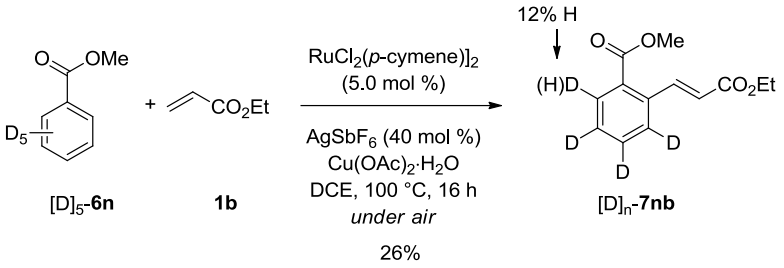
As in the previously discussed projects, intermolecular competition experiments with diversely substituted aromatic esters **6** have been performed to gain insights into the order of reactivity in this reaction (Scheme 62). By comparing the reactivity of methoxy-substituted *p*-anisate **6a** and unsubstituted methyl benzoate (**6n**), the electron-rich styrene **7a** was formed predominantly (Scheme 62a). The second experiment disclosed the electron-poor fluoro-substituted arene **6l** to be less reactive than the unsubstituted methyl benzoate (**6n**) (Scheme 62b). In accordance with the previous experiments, the third experiment (Scheme 62c) confirmed the following relative reactivity trend for substituted benzoates: OMe >H > F.



Scheme 62: Intermolecular competition experiments with diversely substituted aromatic esters **6**.

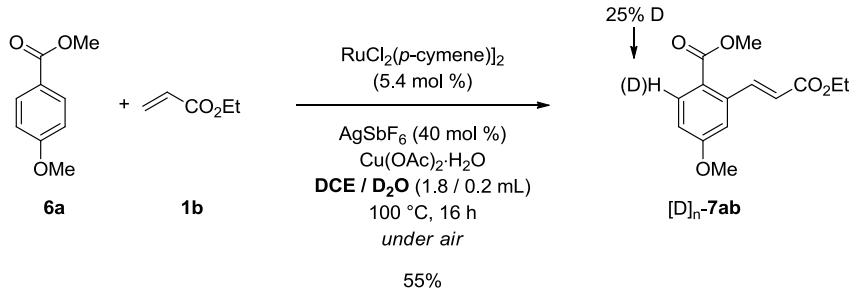
Experiments with Isotopically Labeled Substrates

Mechanistic studies with isotopically labeled methyl benzoate [D_5]-**6n** indicated a D/H scrambling of 12% in the *ortho*-position (Scheme 63).



Scheme 63: Experiment with isotopically labeled substrate [D_5]-**6n**.

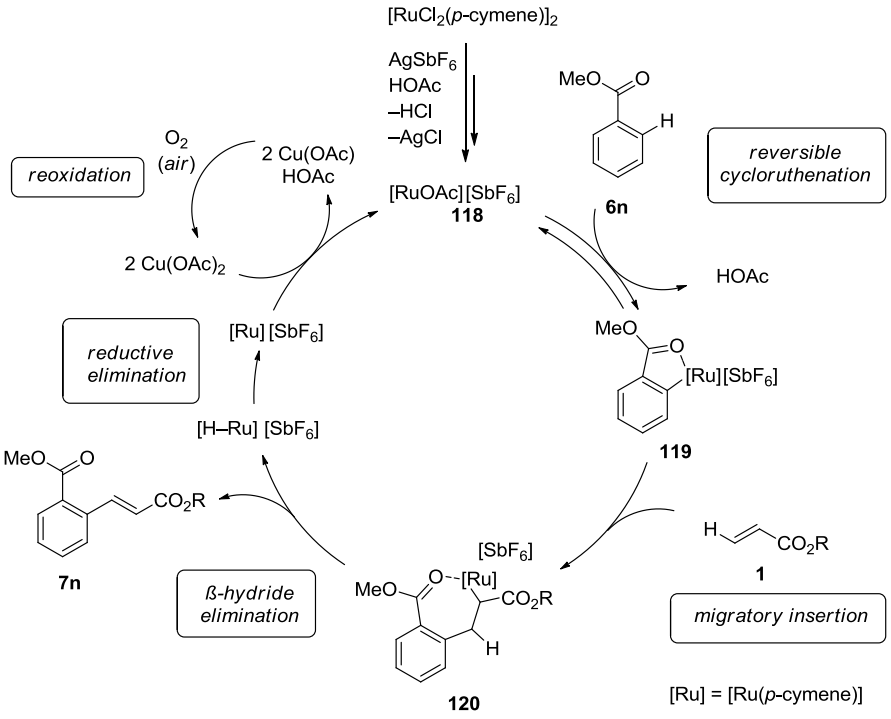
A significantly higher H/D exchange was observed for unlabeled *p*-anisate **6a** by performing the reaction in the presence of D_2O as a cosolvent (Scheme 64). Here, up to 25% H/D scrambling was observed according to analysis by ^{1}H NMR spectrum of the product [D_n]-**7ab**. These observations indicated a reversible C–H ruthenation step in the *ortho*-position.



Scheme 64: Experiment in the presence of D_2O.

Proposed Catalytic Cycle

Based on these mechanistic studies, a catalytic cycle for the ruthenium-catalyzed oxidative alkenylation of aromatic esters **6n** can be proposed (Scheme 65). The acetate-containing ruthenium(II) complex with SbF_6^- as the counterion was formed *in situ* (**118**). A reversible acetate-assisted C–H cycloruthenation step took place to form intermediate **119**. Subsequent migratory insertion of acrylate **1** afforded ruthenacycle **120**. Consecutive *ß*-hydride elimination and reductive elimination furnish the desired product **7n**, whereas reoxidation by $Cu(OAc)_2$ regenerates the catalytically active cationic species. When using cocatalytic amounts of copper(II) acetate, air acts as the sacrificial oxidant for the reoxidation of copper(I) to copper(II).

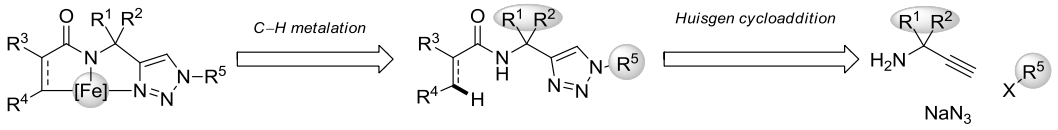


Scheme 65: Proposed catalytic cycle for the ruthenium(II)-catalyzed oxidative alkenylation of aromatic esters **6n**.

4 Iron-Catalyzed C–H Bond Functionalization

4.1 Iron-Catalyzed C(sp^3)–H Arylation by Triazole Assistance

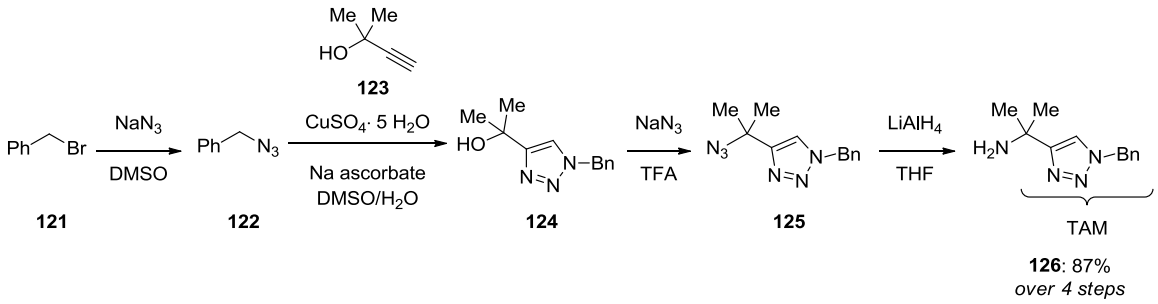
The easily accessible bidentate *N*-[(1-alkyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamide auxiliary with a 1,2,3-triazole moiety was previously developed in the *Ackermann* research group.[176] This novel family of directing groups for C–H activation is available in a modular fashion through copper(I)-catalyzed 1,3-dipolar *Huisgen* cycloaddition (Scheme 66).[184]



Scheme 66: Strategy for C–H activation through triazole assistance.

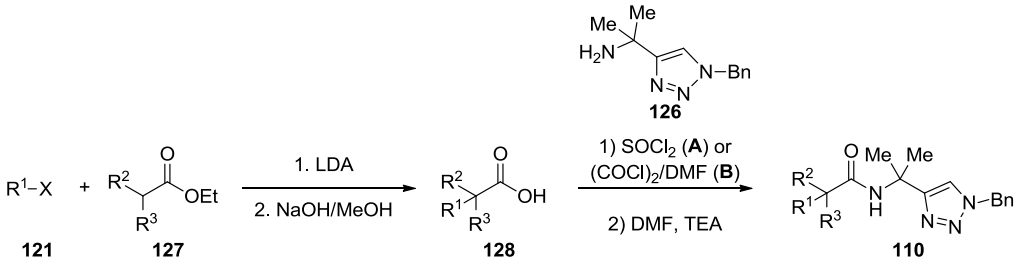
4.1.1 Synthesis of Starting Materials

The new directing group is accessible from inexpensive and easily available starting materials. Starting with the azidation of benzyl bromide **121**, further reaction *via* the 1,3-dipolar cycloaddition and repeated azidation furnished the azide **125** in quantitative yields. The reduction of the azide **125** gave the desired product 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) in 87% overall yield (Scheme 67).



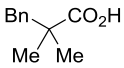
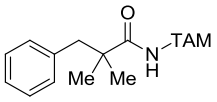
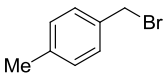
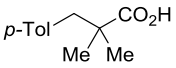
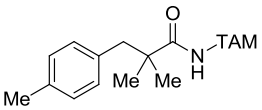
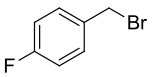
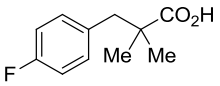
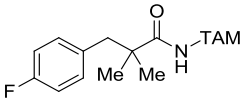
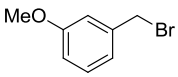
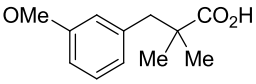
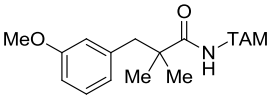
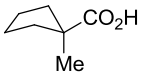
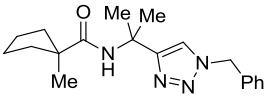
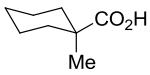
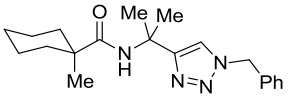
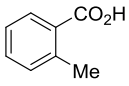
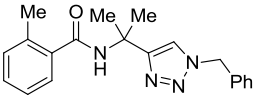
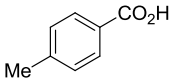
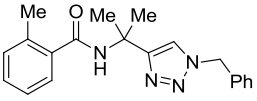
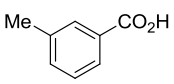
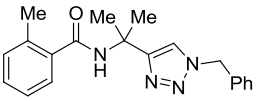
Scheme 67: Synthesis of the bidentate TAM directing group.

Substituted acids **128** were synthesized according to published protocols.[182] Further reactions provided the corresponding novel benzamides **110** and **112**, which were synthesized adopting the known literature procedures in good yields without further optimization of the reaction conditions (Scheme 68 and Table 15).[163, 164, 182]



Scheme 68: Synthesis of the benzamides **110**.

Table 15: Synthesis of the bidentate benzamides **110** and **112** from the corresponding acids **128**.[a]

entry	R^1-X	acid	method	product	yield [%][b]
1			A		67
	121a	**128a**		**110a**	
2			A		68
	121b	**128b**		**110b**	
3			B		73
	121c	**128c**		**110c**	
4			B		57
	121d	**128d**		**110d**	
5	MeI		B		80
	121e	**128e**		**110e**	
6	MeI		B		65
	121e	**128f**		**110f**	
7	---[c]		B		75
		128g		**112**	
8	---[c]		B		98
		128h		**112h**	
9	---[c]		B		90
		128o		**112o**	

[a] Reaction conditions: see supporting information. [b] Isolated yields over three steps. [c] Commercially available acid.

4.1.2 Optimization Studies of the C(sp^3)–H Arylation

Preliminary screening of the reaction conditions for the C(sp^2)–H and C(sp^3)–H arylation of benzamides **110** has been performed by Dr. *Gu* in the *Ackermann* research group. The optimal reaction conditions highlighted a combination of $Fe(acac)_3$ as the pre-catalyst, dppbz as the ligand and $ZnBr_2$·TMEDA additive and appeared to be most efficient for the C(sp^3)–H arylation (Table 16, entry 1). Further optimization studies illustrated the possible use of further low-cost iron catalysts (Table 16, entries 2 and 3). The use of ligand-free $ZnCl_2$ as an additive did not lead to product formation (entry 6). Other alternative phosphine and amine ligands were completely ineffective in this reaction (entries 7–9).

Table 16: Optimization studies for the C(sp^3)–H arylation of benzamide **110c**.[a]

entry	[Fe]	ligand	zinc salt	recovery of **110c**	yield [%][b]
1	$Fe(acac)_3$	dppbz	$ZnBr_2$·TMEDA	16	74
2	$FeCl_3$	dppbz	$ZnBr_2$·TMEDA	24	68
3	$FeBr_3$	dppbz	$ZnBr_2$·TMEDA	0	65
4	---	dppbz	$ZnBr_2$·TMEDA	75	0
5	$Fe(acac)_3$	dppbz	$ZnCl_2$·TMEDA	21	74
6	$Fe(acac)_3$	dppbz	$ZnCl_2$	80	0
7	$Fe(acac)_3$	(±)-DPEN	$ZnBr_2$·TMEDA	99	0
8	$Fe(acac)_3$	dppe	$ZnBr_2$·TMEDA	80	0
9	$Fe(acac)_3$	PPh_3	$ZnBr_2$·TMEDA	84	0

[a] Reaction conditions: **110c** (0.2 mmol), PhMgBr (1.40 mmol), DClB (0.40 mmol), PhMe (5.0 mL), 80 °C, 20 h. [b] Yields of isolated product.

The structural peculiarities of the ligands are illustrated in Figure 9. The ligands dppe und dppbz are structurally closely related. The bite angle of dppe is slightly larger and possesses a more flexible backbone as compared to dppbz.[185]

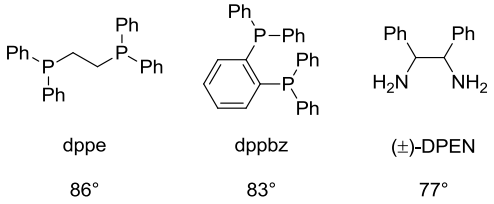
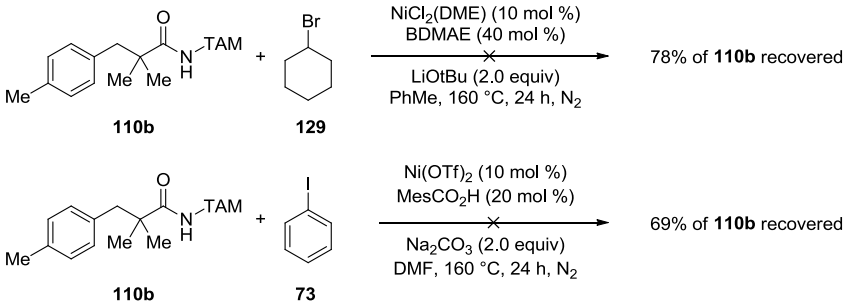


Figure 9: Representative ligands and their bite angles $ß_n$.

(*R*,*R*)-1,2-Diphenyl-1,2-diaminoethane [(*R*,*R*)-DPEN] has previously been used for the enantioselective synthesis of chiral vitamin K antagonist warfarin.[186] The prochiral nature of

the substrate **110c** bears potential for accessing to the enantioselective transformations by iron-catalyzed arylation reactions. Unfortunately, the bidentate ligand (±)-DPEN[187] with smaller bite angle and a more flexible backbone as well as the monodentate ligand PPh_3 were both ineffective.

Attempted nickel-catalyzed alkylation and arylation of the substrate **110b** under previously established reaction conditions[166] were inefficient (Scheme 69).



Scheme 69: Attempted nickel-catalyzed C(sp^3)–H alkylation and arylation of the substrate **110b**.

The specific structure of the directing group and the properties of the ligand have a strong influence on the iron-catalyzed arylation reaction. Figure 10 illustrates the alternatively probed benzamides for the C(sp^3)–H arylation. The simple primary and the secondary *tert*-butyl-substituted benzamides **129** and **130** were not able to enter the reaction. Therefore, the role of the second *Lewis*-basic nitrogen is of crucial importance. Indeed, in the absence of the second nitrogen as in phenyl-substituted substrate **131** the C–H functionalization did not occur. Also the pyridyl-substituted amide **132** was not an appropriate substrate.

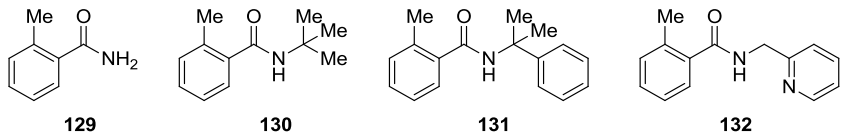


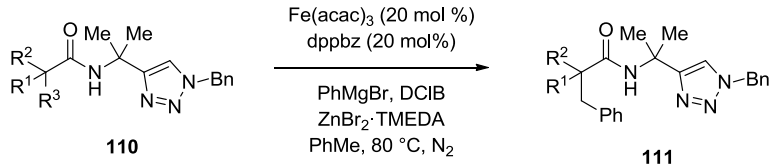
Figure 10: Unreactive substrates for the iron-catalyzed C–H arylation.

4.1.3 Scope and Limitation of the C(sp^3)–H Arylation

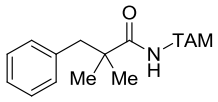
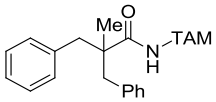
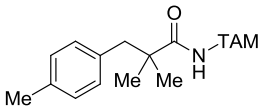
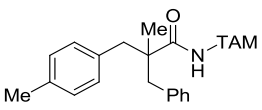
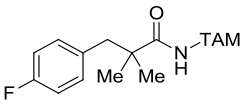
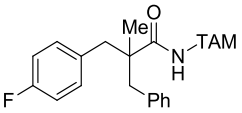
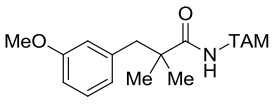
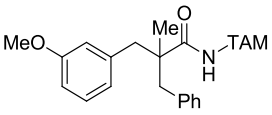
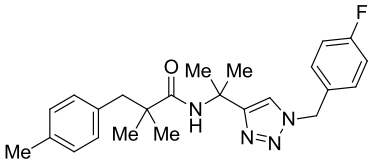
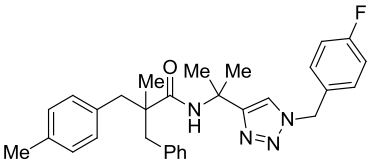
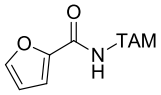
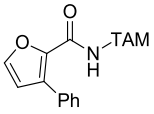
Under the optimized reaction conditions, representative benzamides **110** were subjected to the iron-catalyzed direct C(sp^3)–H arylation (Table 17). Notably, both electron-poor and electron-rich benzamides **110a**-**110d** were successfully converted with very good yields (entries 1–4). Substitution on these substrates occurred exclusively on one of the two methyl

groups. Variation of the benzylic group on the 1,2,3-triazole auxiliary by substitution with an electron-deficient fluoro-substituent, resulted in a drop of the yield (entry 5) due to the altered electronic properties of the triazole group in **110g**. Additionally, one example of C(sp^2)–H arylation reaction on a furan **110i** moiety could be accomplished, albeit in lower yield (entry 6).

Table 17: Scope for the direct iron-catalyzed C(sp^3)–H arylations with PhMgBr.[a]



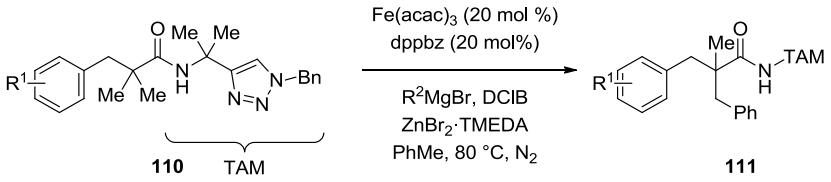
110 **111**

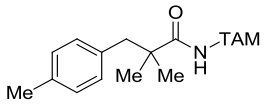
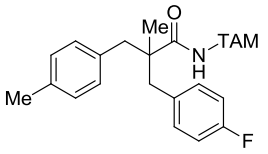
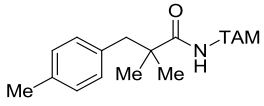
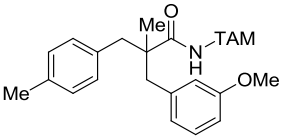
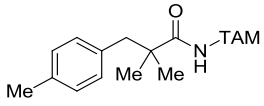
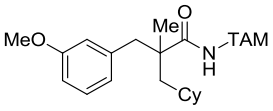
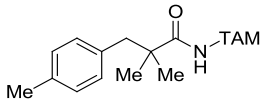
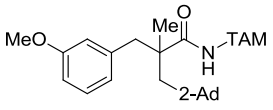
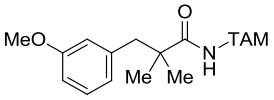
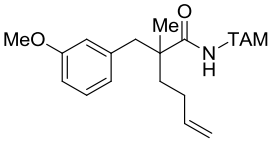
entry	substrate	product	yield [%][b]
1	 **110a**	 **111a**	92
2	 **110b**	 **111b**	63
3	 **110c**	 **111c**	75
4	 **110d**	 **111d**	87
5	 **110g**	 **111g**	48
6	 **110i**	 **111i**	35

[a] Reaction conditions: **110** (0.2 mmol), PhMgBr (1.40 mmol), $ZnCl_2$·TMEDA (0.6 mmol), $Fe(acac)_3$ (20 mol %), dppbz (20 mol %), DClB (0.40 mmol), PhMe (5.0 mL), 80 °C, 20 h. [b] Yields of isolated product.

Fluoro- and methoxy-substituted arylmagnesium bromides (**133** and **134**) entered the reaction as well, furnishing the desired products (Table 18, entries 1 and 2), whereas the use of alkyl- or allyl-substituted *Grignard* reagents **135**-**137** did not lead to product formation (entries 3–5).

Table 18: Scope for the direct iron-catalyzed C(sp^3)–H arylation with different *Grignard* reagents.[a]

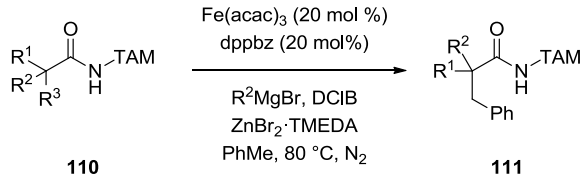


entry	substrate	R^2MgBr	product	yield [%][b]
1	 **110b**	4-FC_6H_4MgBr **133**	 **111bb**	57
2	 **110b**	3-$MeOC_6H_4MgBr$ **134**	 **111bc**	57
3	 **110b**	CyMgBr **135**	 **111bd**	0
4	 **110b**	2-AdMgBr **136**	 **111be**	0
5	 **110d**	AllylMgBr **137**	 **111bf**	0

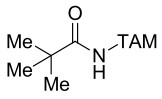
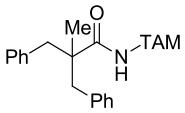
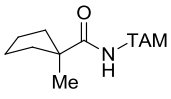
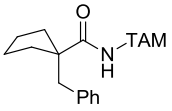
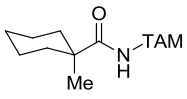
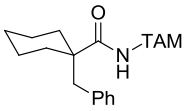
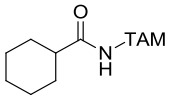
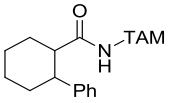
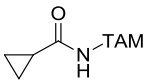
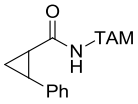
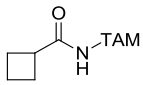
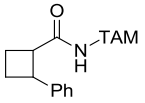
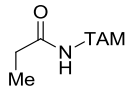
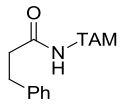
[a] Reaction conditions: **110** (0.2 mmol), R^2MgBr (1.40 mmol), $ZnCl_2$·TMEDA (0.6 mmol), $Fe(acac)_3$ (20 mol %), dppbz (20 mol %), DClB (0.40 mmol), PhMe (5.0 mL), 80 °C, 20 h. [b] Yields of isolated product.

Pivalamide **110j** gave a mixture of difficult to separate mono- and diarylated products, likely due to the entropic factor, *i. e.* enhanced number of reactive hydrogen atoms in the substrate **111j** (Table 19, entry 1). Cyclopentane- and cyclohexanecarboxamides **110e** and **110f** (entries 2 and 3) reacted exclusively at the *α*-methyl group. In the absence of available methyl groups no product formation was observed (entries 4–6). All substrates were completely recovered from the reaction mixtures. Interestingly, no ring opening of the cyclopropyl moiety occurred in the reisolated substrate **110l**. The bond angle and the resulting interatomic distance between the *ß*-hydrogen and the nitrogen atoms are of crucial importance. The angle compression of the *ß*-H to the reactive site of the reaction, due to the *Thorpe-Ingold* effect,[188] is a plausible explanation for the inert behavior of propionamide **110n** (entry 7).

Table 19: Iron-catalyzed arylation of 2,2-disubstituted propionamides.[a]



110 **111**

entry	substrate	product	yield [%][b]
1	 **110j**	 **111j**	30[c]
2	 **110e**	 **111e**	83
3	 **110f**	 **111f**	52
4	 **110k**	 **111k**	0
5	 **110l**	 **111l**	0
6	 **110m**	 **111m**	0
7	 **110n**	 **111n**	0

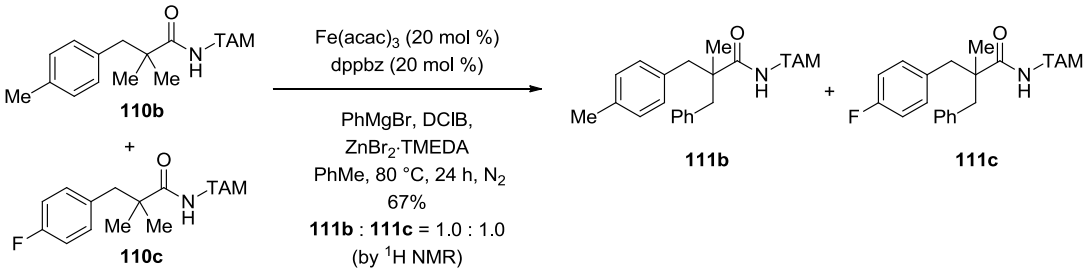
[a] Reaction conditions: **110** (0.2 mmol), PhMgBr (1.40 mmol), $ZnCl_2$·TMEDA (0.6 mmol), $Fe(acac)_3$ (20 mol %), dppbz (20 mol %), DClB (0.40 mmol), PhMe (5.0 mL), 80 °C, 20 h. [b] Yields of isolated product. [c] 40% of monoarylated product by ^{1}H NMR.

4.1.4 Mechanistic Studies of the C(sp^3)–H Arylation

Mechanistic rationalization of the selective functionalization of the primary aliphatic C–H bonds in substrates **110** in the presence of the more labile C–H bonds in the benzylic position is a rather intriguing problem. A priori, an iron-catalyzed C–H metalation step should be rather preferred than a radical mechanism. Therefore, intermolecular competition

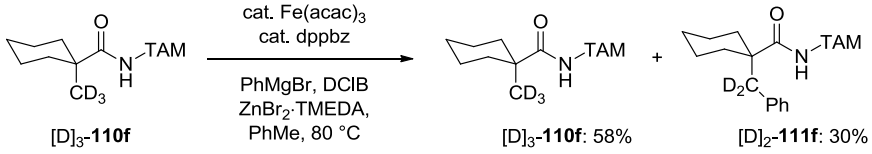
experiments between differently substituted propionamides and reactions with isotopic labeled substrates were performed.

First, to establish the qualitative relative reactivity, intermolecular competition experiments with electron-rich and electron-deficient substituted propionamides **110b** and **110c**, respectively, were conducted (Scheme 70). No significant discrimination between these two differently substituted arenes **111b** and **111c** was observed.



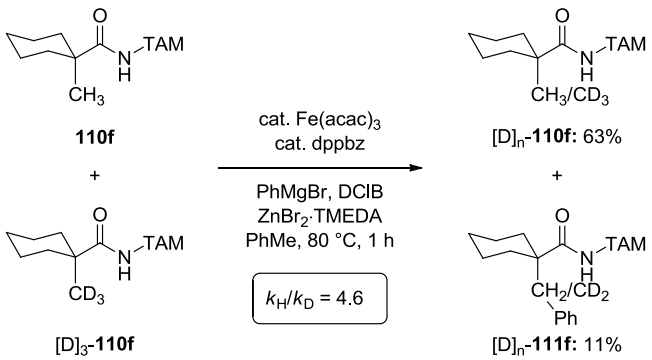
Scheme 70: Intermolecular competition experiment.

Second, the α-D_3-methylsubstituted propionamide [D]$_3$-**110f** was synthesized and subjected to the optimized reaction conditions. The recovered starting material [D]$_3$-**110f** and the deuterated product [D]$_2$-**111f** were isolated without significant D/H scrambling (Scheme 71).



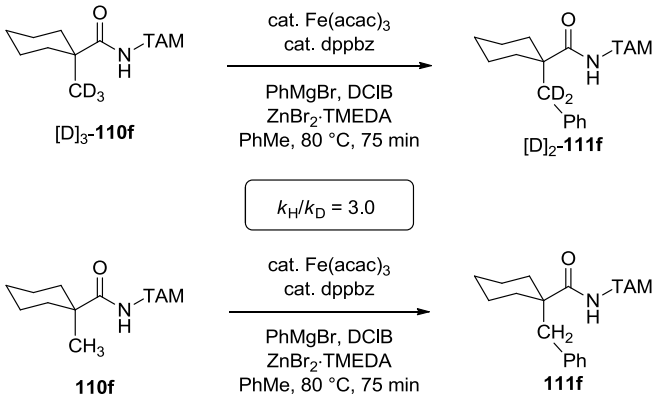
Scheme 71: Experiment with isotopically labeled substrate [D]$_3$-**110f**.

Third, an intermolecular competition experiment between [D]$_3$-**110f** and **110f** showed a primary kinetic isotope effect (KIE) of k_H/k_D = 4.6 at 11% conversion (Scheme 72), suggesting the C–H cleavage as the rate-determining step of the functionalization.



Scheme 72: Intermolecular competition experiment with participation of isotopically labeled substrate [D]$_3$-**110f**.

Kinetic measurements of the two independent reactions with deuterated and undeuterated substrates $[D]_3$-**110f** and **110f**, respectively, disclosed a KIE of 3.0 (Scheme 73). These significant findings suggest that the C–H bond cleavage appears to be the rate-determining step.[181]

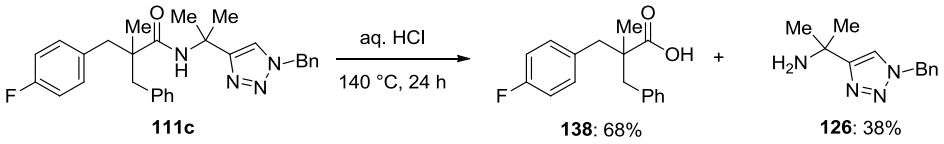


Scheme 73: Determination of KIE in two parallel experiments.

The proposal of a plausible mechanism for the iron-catalyzed direct arylation of benzamides **110** is not a simple task. The high sensitivity towards the ligand and the particular reactivity of a methyl group over a benzylic one excluded a radical pathway. Based on our preliminary mechanistic studies, an initial rate-determining C–H activation by the iron catalyst can be postulated. However, it is still an open question, which of the two possible catalytic scenarios – the one including a low-valent iron(–II) species or alternatively, with participation of a hypervalent iron(0) species – is involved.

Removal of the TAM Directing Group

Finally, the cleavage of the TAM directing group could be easily accomplished in a traceless fashion under acidic reaction conditions, furnishing the arylated product **138** in good yield (Scheme 74). Furthermore, the reisolation of the TAM directing group could be achieved, as an example of an economical and reusable directing group for C–H functionalization reactions.



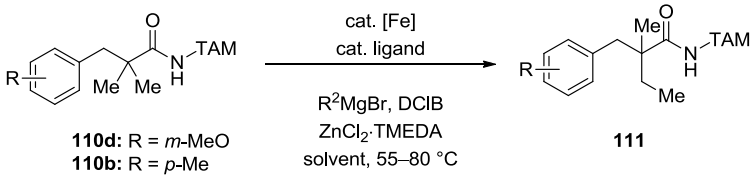
Scheme 74: Removal of the TAM directing group.

4.2 Iron-Catalyzed C(sp^2)–H Methylation by Triazole Assistance

Preliminary Experiments on C(sp^3)–H Bond Methylation

As outlined above, alkylations of unactivated C(sp^3)–H bonds still remain a major challenge. No synthetically useful robust protocol for methylation reactions through C–H activation with metals other than expensive palladium has been reported so far. During this research, the group by *Nakamura* observed the methylation of a C(sp^2)–H bond as a side reaction.[171] Nevertheless, our attemts to adopt these reaction conditions towards the iron-catalyzed methylation of C(sp^3)–H bonds in 2,2-substituted propionamides of the type **110**, but with the 8-aminoquinoline (Q) auxiliary, were unsuccessful. Since the direct methylation on such 2,2-substituted propionamides **110** could not be optimized, alternative substrates could offer novel access to this homologation strategy. Fortunately, in the presence of the modular TAM auxiliary the versatile iron catalyst allowed for the direct methylation of the otherwise inert C(sp^3)–H bonds in substrates **110b** and **110d** with THF as the solvent, as presented in Table 20 (entries 1, 4–6). Interestingly, neither methylation (entries 2 and 7) nor benzylation (entry 3) occurred in toluene or diethyl ether.

Table 20: Iron-catalyzed C(sp^3)–H methylation with TAM-substituted amides **110b** and **110d**.[a]



entry	substrate	[Fe]	ligand	solvent	R^2MgBr	T [°C]	product	yield [%][b]
1		$FeCl_3$	dppe	THF	MeMgBr	55		80 (61)
2		$Fe(acac)_3$	dppbz	PhMe	MeMgBr	80		0
	110d						**111dg**	
3		$Fe(acac)_3$	dppbz	PhMe	BnMgBr	80		0
							111dh	
4		$FeCl_3$	dppbz	THF	MeMgBr	80		70 (27)
5		$Fe(acac)_3$	dppbz	THF	MeMgBr	80		42
6	**110b**	$FeCl_3$	dppe	THF	MeMgBr	80		30
7		$FeCl_3$	dppe	Et_2O	MeMgBr	55		0
							111bg	

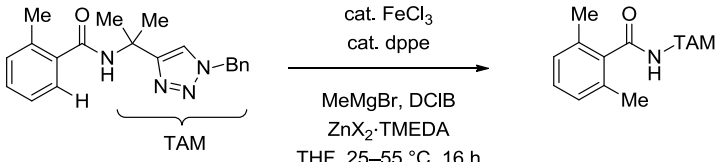
[a] Reaction conditions: **110d** or **110b** (0.2 mmol), R'MgBr (1.40 mmol), $ZnCl_2$·TMEDA (0.6 mmol), FeX_3 (20 mol %), ligand (20 mol %), DClB (0.40 mmol), PhMe or THF (5.0 mL), 55–80 °C, 20 h. [b] Conversion as determined by GC-MS with *n*-dodecane as internal standard; yields of isolated product are in parentheses.

4.2.1 Optimization Studies of the C(sp^2)–H Methylation

Subsequently, a detailed screening was performed with benzamide **112a** as the standard substrate to reveal the best reaction conditions for the iron-catalyzed C(sp^2)–H bonds methylation reaction (Table 21). The use of iron salts as the catalyst and zinc salts as the additives is of crucial importance for the success of the reactions (entries 1 and 2). Fortunately, the use of inexpensive $FeCl_3$ as the iron source and dppe as the ligand was the most efficient for the methylation under mild reaction conditions (entry 3). Other iron sources were also suitable for these transformations even at ambient temperature (entries 4 and 5). No preference is observed when comparing $ZnCl_2$·TMEDA and $ZnBr_2$·TMEDA (entries 6 and 7). The reaction can be performed even with the ligand-free $ZnCl_2$ (entry 8), while the use of $ZnEt_2$ was not successful (entries 9 and 10). The right choice of the ligand is crucial for the iron-catalyzed methylation reaction. The use of other bidentate phosphine ligands, such as dppp, dppf or the monodentate ligand PPh_3, gave no product formation (entries 11–13).

Reducing the amount of MeMgBr had an detrimental effect (entry 14). When the reaction was performed with iron(III) chloride of high purity (99.99%), quantitative product formation was observed (entry 15). Employment of palladium, nickel or copper catalysts was completely ineffective (entries 16–19). The reaction proceeded very fast after 1.5 h (entry 20) and can be run even with a low catalyst loading of 3 mol % of $FeCl_3$ (entry 21).

Table 21: Optimization of iron-catalyzed C(sp^2)–H bond methylation.[a]



112a **113a**

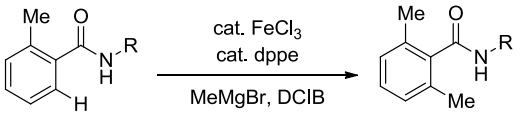
entry	catalyst (mol %)	ligand (mol %)	T [°C]	zinc salt (equiv)	yield [%][b]
1	---	dppe (20)	55	$ZnBr_2$·TMEDA (3.0)	0
2	$FeCl_3$ (20)	dppe (20)	55	---	0
3	$FeCl_3$ (20)	dppe (20)	55	$ZnBr_2$·TMEDA (3.0)	85
4	$FeBr_3$ (10)	dppe (10)	25	$ZnCl_2$·TMEDA (3.0)	80
5	$FeCl_2$ (10)	dppe (10)	25	$ZnCl_2$·TMEDA (3.0)	90
6	$FeCl_3$ (20)	dppe (10)	55	$ZnBr_2$·TMEDA (3.0)	84
7	$FeCl_3$ (20)	dppe (20)	55	$ZnCl_2$·TMEDA (3.0)	93
8	$FeCl_3$ (20)	dppe (20)	55	ZnCl2 (3.0)	84
9	$FeCl_3$ (10)	dppe (10)	55	$ZnEt_2$, $MgBr_2$ (3.0)	0
10	$FeCl_3$ (10)	dppe (10)	55	$ZnEt_2$ (3.0)	0
11	$FeCl_3$ (20)	dppp (20)	55	$ZnCl_2$·TMEDA (3.0)	0
12	$FeCl_3$ (20)	dppf (20)	55	$ZnCl_2$·TMEDA (3.0)	0
13	$FeCl_3$ (20)	PPh_3 (40)	55	$ZnCl_2$·TMEDA (3.0)	0
14	$FeCl_3$ (20)	dppe (10)	55	$ZnCl_2$·TMEDA (3.0)	0[c]
15	$FeCl_3$ (10)	dppe (10)	25	$ZnCl_2$·TMEDA (3.0)	99[d]
16	$Pd(OAc)_2$ (10)	dppe (10)	25	$ZnCl_2$·TMEDA (3.0)	0
17	$NiCl_2$ (10)	dppe (10)	25	$ZnCl_2$·TMEDA (3.0)	0
18	Cu_2O (10)	dppe (10)	25	$ZnCl_2$·TMEDA (3.0)	0
19	$CuCl_2$ (20)	dppe (20)	55	$ZnBr_2$·TMEDA (3.0)	0
20	$FeCl_3$ (20)	dppe (20)	55	$ZnCl_2$·TMEDA (3.0)	85[e]
21	$FeCl_3$ (3)	dppe (3)	55	$ZnCl_2$·TMEDA (3.0)	65

[a] Reaction conditions: **112** (0.20 mmol), [TM] (10–20 mol %), ligand (10–40 mol %), MeMgBr (1.4 mmol), DClB (0.4 mmol), THF (5.0 mL), 25–55 °C, 16 h. [b] Yields of isolated product. [c] MeMgBr (3.5 equiv). [d] [Fe] (99.9% metal basis). [e] Reaction time: 1.5 h.

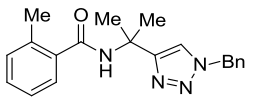
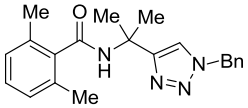
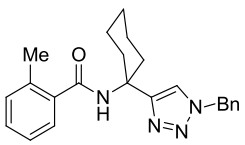
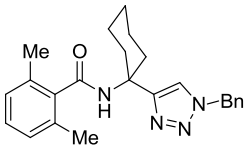
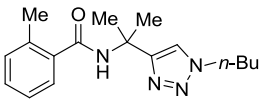
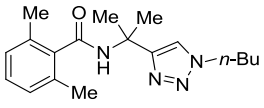
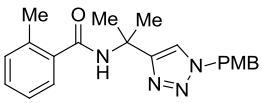
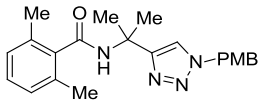
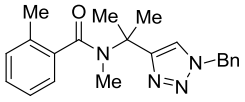
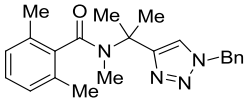
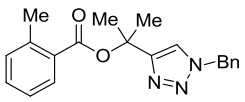
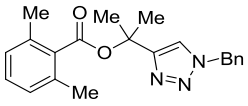
4.2.2 Scope and Limitation of the C(sp^2)–H Methylation

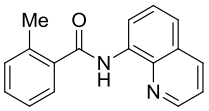
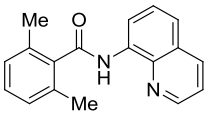
With the optimized catalytic reaction conditions in hand, the influence of the substitution pattern of the directing group was studied (Table 22). The TAM group tolerated variations in the form of either spiroannulation in the benzylic position as in substrate **112b** (entry 2) or substitution on the nitrogen atom in triazole moieties of compounds **113c** and **113d** (entries 3 and 4). For comparison, the conversion of the substrate displaying the 8-aminoquinoline auxiliary, was considerably lower (entry 7). In contrast, blocking the amide NH position by a methyl group in **112e** or replacing the benzamide moiety by an ester (**112f**), inhibited the product formation entirely (entries 5 and 6), thus demonstrating the importance of the mono-anionic bidentate auxiliary for the C–H methylation.

Table 22: Influence of the substitution pattern on the directing group.[a]



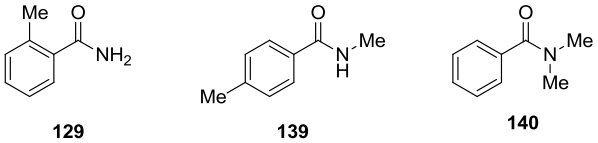
112 **113**

entry	substrate	product	yield [%][b]
1	 **112a**	 **113a**	93
2	 **112b**	 **113b**	95
3	 **112c**	 **113c**	93
4	 **112d**	 **113d**	91
5	 **112e**	 **113e**	0
6	 **112f**	 **113f**	0

7	 **112g**	 **113g**	40[c]

[a] Reaction conditions: **112** (0.2 mmol), $FeCl_3$ (20 mol %), dppe (20 mol %), $ZnCl_2$·TMEDA (0.6 mmol), MeMgBr (1.40 mmol), DClB (0.40 mmol), THF (5.0 mL), 25–55 °C, 16 h. [b] Yields of isolated product. [c] Conversion was determined by ^{1}H NMR spectroscopy.

Indeed, benzamide **129**, *N*-methylbenzamide **139** and *N*,*N*-dimethylbenzamide **140** did also not react at all (Figure 11).

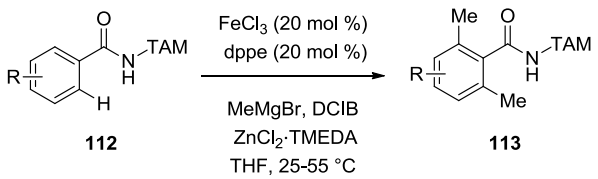


129 **139** **140**

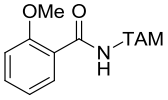
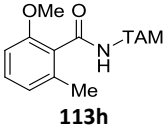
Figure 11: Attempted methylation of benzamides **129**, **139** and **140**.

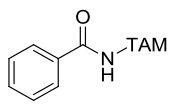
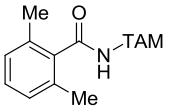
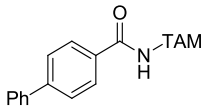
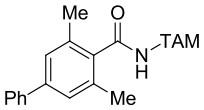
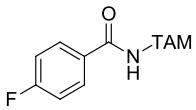
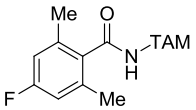
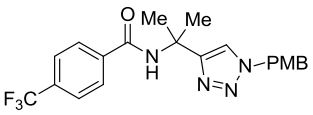
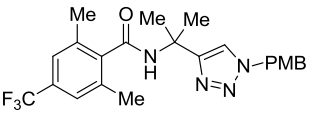
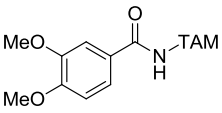
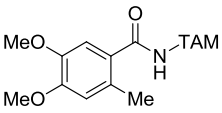
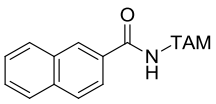
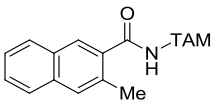
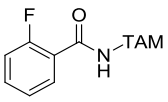
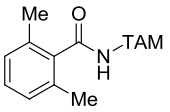
As the TAM group appeared to be a perfect tool to accomplish the challenging C–H methylation, the scope was expanded to diversely substituted benzamides **112h**-**112o** (Table 23). The *ortho*-methoxybenzamide **112h** (entry 1) was converted in a highly site-selective fashion. Unsubstituted benzamide **112i** (entry 2) or its *para*-substituted derivatives **112j**-**112l** (entries 3–5) were efficiently transformed into the twofold-methylated products **113j**, **113k**, and **113l**, respectively. Benzamides **112m** and **112n** reacted in a highly site-selective fashion (entries 6 and 7), whereas the transformation of the *ortho*-fluoro-substituted benzamide **112o** (entry 8) resulted in a twofold methylation through iron-catalyzed C–H and C–F bond functionalization (**113o**).[189] Generally it can be concluded, that both the electron-donating and electron-poor benzamides **112h**-**112o** could be methylated with similarily high efficacy. These results demonstrate the remarkable synthetic power of C–H methylation with the versatile iron-catalyst.

Table 23: Scope of the iron-catalyzed C(sp^2)–H methylation reactions.[a]



112 **113**

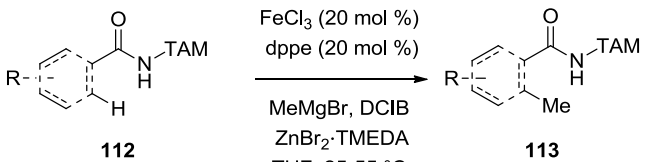
entry	substrate	product	yield [%][b]
1	 **112h**	 **113h**	80

2	 **112i**	 **113i**	83
3	 **112j**	 **113j**	97
4	 **112k**	 **113k**	76
5	 **112l**	 **113l**	87
6	 **112m**	 **113m**	74
7	 **112n**	 **113n**	95
8	 **112o**	 **113o**	91

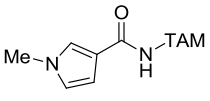
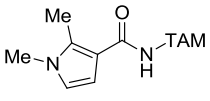
[a] Reaction conditions: **112** (0.2 mmol), $FeCl_3$ (20 mol %), dppe (20 mol %), $ZnCl_2$·TMEDA (0.6 mmol), MeMgBr (1.40 mmol), DClB (0.40 mmol), THF (5.0 mL), 25–55 °C, 16 h. [b] Yields of isolated product.

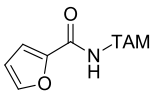
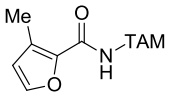
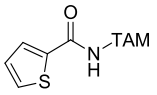
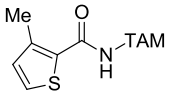
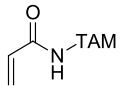
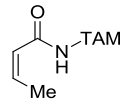
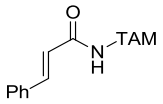
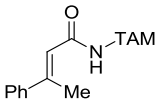
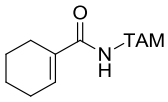
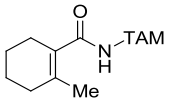
The methodology of iron-catalyzed C–H bond methylations was successfully applied to aromatic heteroamides **112p**, **110i** and **112q** (Table 24, entries 1–3). Intriguingly, the methylation of acryl amide **112r** and cinnamamide **112s** occurred with excellent diastereoselectivity, exclusively delivering the thermodynamically less stable *Z*-olefin as the sole product with an vicinal coupling constant of ^3J = 11.5 Hz for the substrate **113r** (entries 4 and 5).

Table 24: Scope of heteroarenes and acrylamide derivatives in the iron-catalyzed C(sp^2)–H methylation reactions.[a]



112 **113**

entry	substrate	product	yield [%][b]
1	 **112p**	 **113p**	53

2	 **110i**	 **113ia**	50
3	 **112q**	 **113q**	60
4	 **112r**	 **113r**	57
5	 **112s**	 **113s**	43
6	 **112t**	 **113t**	90

[a] Reaction conditions: **112** (0.2 mmol), $FeCl_3$ (20 mol %), dppe (20 mol %), $ZnBr_2$·TMEDA (0.6 mmol), MeMgBr (1.40 mmol), DClB (0.40 mmol), THF (5.0 mL), 25–55 °C, 16 h. [b] Yields of isolated product.

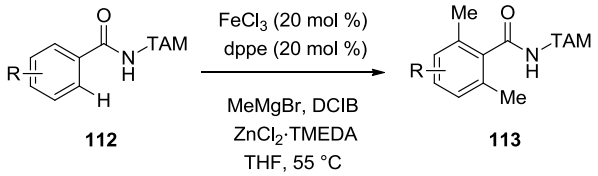
4.2.3 Mechanistic Studies of the the C(sp^2)–H Methylation

Intramolecular Competition Experiments

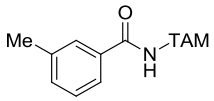
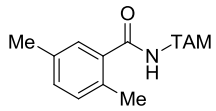
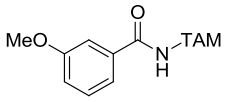
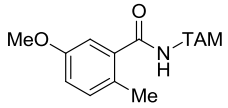
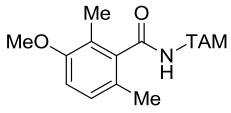
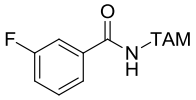
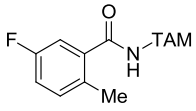
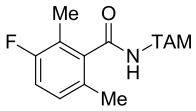
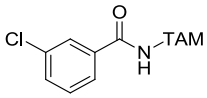
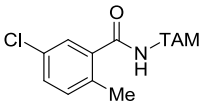
Competitive reactions of substrates with various steric and electronic properties can provide valuable information about the mechanism of the iron-catalyzed methylation reaction. To this end, intramolecular competition experiments with *meta*-substituted benzamides **112u**-**112x** as the substrates were performed (Table 25). The *meta*-methyl substituted benzamide **112u** (entry 1) was methylated at the less sterically hindered position, delivering compound **113u** as the sole product. The substrates **112v** and **112w** with a *meta*-methoxy and a *meta*-fluoro substituents gave the twofold methylated products **113v'** and **113w'** through the initial formation of sterically less hindered 2-substituted benzamides **113v** and **113w** (entries 2 and 3). The formation of the dimethylated products **113v'** and **113w'** were presumably a consequence of the secondary chelating effect caused by the methoxy group and in line with well-known *ortho*-fluoro effect.[180] The site-selectivity of the intramolecular competition experiment with the *meta*-chlorine substituent **112x**, was controlled by sterical interactions as well, delivering the sterically less hindered product (entry 4). To our delight, the product **113x** obtained from chlorobenzamide **112x** did not enter the traditional cross-coupling reactions under iron catalysis, which opened perspectives for its further transformations. In

all reactions, electron-donating and electron-deficient substrates afforded the products in good yields.

Table 25: Intramolecular competition experiments with *meta*-substituted benzamides **112**.



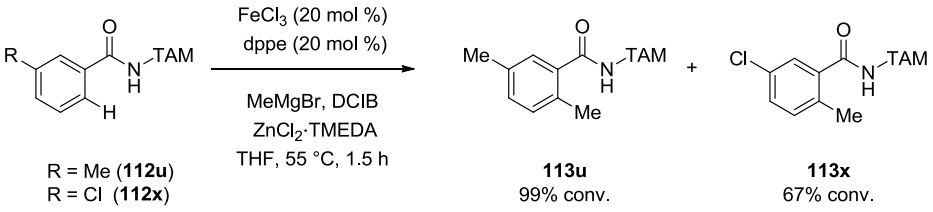
112 **113**

entry	substrate	product	yield [%][b]
1	 **112u**	 **113u**	81
2	 **112v**	 **113v**	20
		 **113v'**	65
3	 **112w**	 **113w**	15
		 **113w'**	71
4	 **112x**	 **113x**	81

[a] Reaction conditions: **112** (0.2 mmol), MeMgBr (1.40 mmol), $FeCl_3$ (20 mol %), dppe (20 mol %), $ZnCl_2$·TMEDA (0.6 mmol), DClB (0.40 mmol), THF (5.0 mL), 55 °C, 16 h. [b] Yields of isolated product.

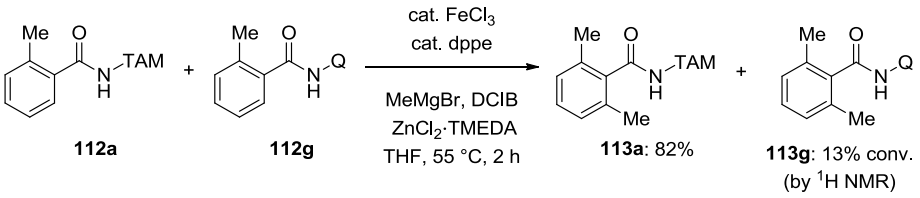
Intermolecular Competition Experiments

To gain more insight into the reaction mechanism, intermolecular competition experiments were performed between differently substituted arenes (Scheme 75). Substrate **112u** bearing an electron-donating group was preferably converted to the product.



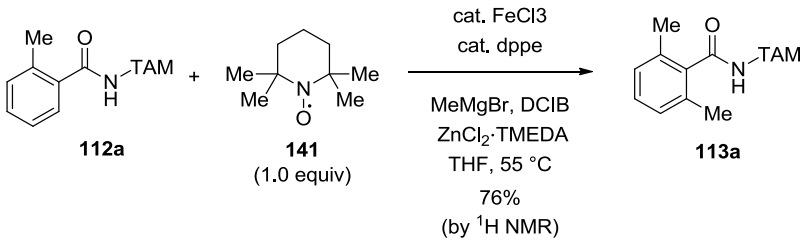
Scheme 75: Intermolecular competition experiment on iron-catalyzed methylation. Conversion as determined by ^{1}H NMR and GC-MS with *n*-dodecane as internal standard.

Intermolecular competition between starting materials **112a** and **112g** with different auxiliaries as directing groups showed that the benzamide **112a** with the TAM moiety, in contrast to Q-substituted one **112g**, reacted predominantly under the optimized reaction conditions (Scheme 76).



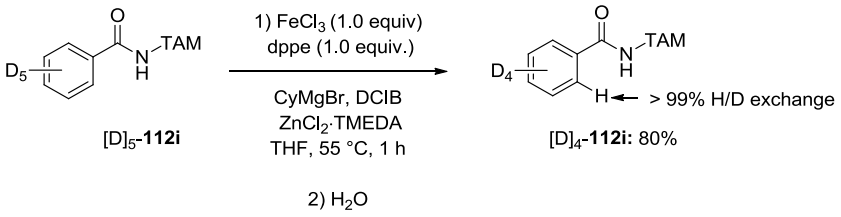
Scheme 76: Intermolecular competition experiment with compounds bearing the TAM- and the Q-auxiliary.

Furthermore, the possible participation of radical intermediates was tested by carrying out the methylation in the presence of TEMPO as a radical scavenger (Scheme 77). The conversion of the benzamide **112a** was 76%, which suggests a non-radical character of the reaction.



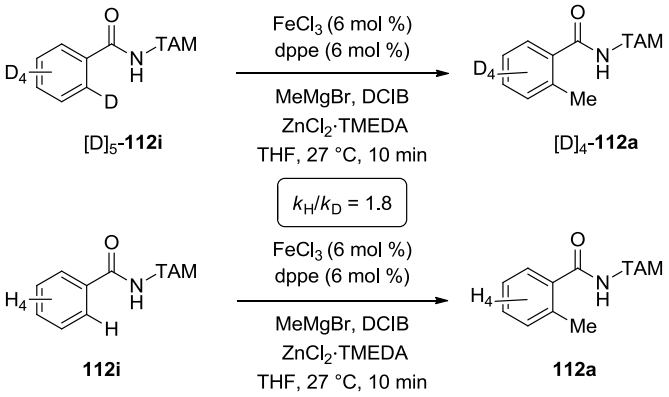
Scheme 77: Experiment with radical scavenger TEMPO.

The reaction of isotopically labeled substrate [D]$_5$-**112b** with stoichiometric amounts of the iron salt followed by aqueous treatment, disclosed virtually quantitative D/H exchange exclusively in *ortho*-position of [D]$_4$-**112b** (Scheme 78). This experiment indicated the participation of a C–H metalation caused by the iron catalyst as an indispensable reaction step.



Scheme 78: Iron-mediated H/D exchange through C–H metalation step.

Additional kinetic studies of two parallel independent reactions with deuterated and undeuterated substrates [D]$_5$-**112b** and **112b** were performed and revealed a kinetic isotope effect (KIE) of $k_H/k_D \approx 1.8$ (Scheme 79). Hence, the C–H bond breaking process appeared to be the rate-determining step of the reaction.



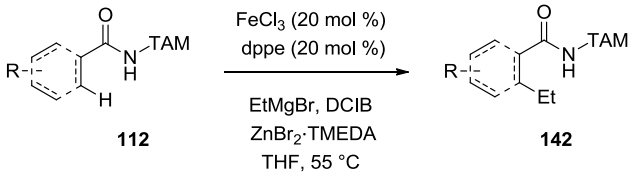
Scheme 79: KIE study of independent experiments. Reaction conditions: [D]$_n$-**112b** (0.2 mmol), MeMgBr (1.4 mmol), $ZnCl_2$·TMEDA (0.6 mmol), $FeCl_3$ (6 mol %), dppe (6 mol %), THF (10 mL), 27 °C, 10 min.

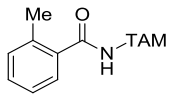
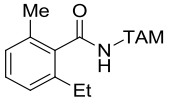
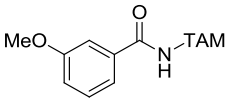
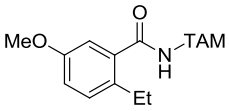
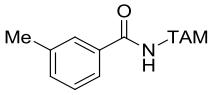
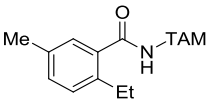
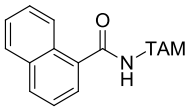
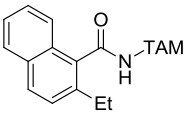
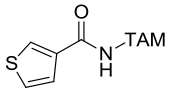
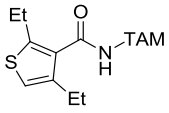
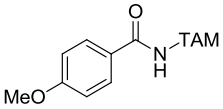
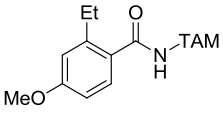
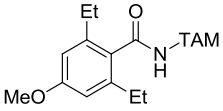
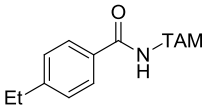
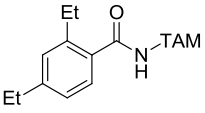
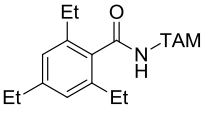
4.3 Iron-Catalyzed C(sp^2)–H Ethylation by Triazole Assistance

The synthetic utility of the inexpensive iron catalyst was not limited to the methylation reactions of benzamides **112**. Surprisingly, the ethylation of these substrates could be accomplished as well with the same catalytic system (Table 26). Thus, the desired ethylated benzamide **142a** was obtained in very good yields, whereas no *ß*-hydride elimination occured employing the iron catalyst (entry 1). Similar to methylation (Table 25, entry 2), ethylation of the substrate **112v** with a *meta*-methoxy substituent occurred at the C-6-position (Table 26, entry 2). However, only the monoethylated product **142b** was isolated. Furthermore, ethylation of the *meta*-methylbenzamide **112u** furnished the less sterically

hindered product **142c** (entry 3). Thiophenamide **112z** as well as *para*-substituted benzamides **112aa** and **112ab** were ethylated twice (entries 6-9). Comparatively to methylation, the ethylation reactions afforded products in slightly lower, but still good yields.

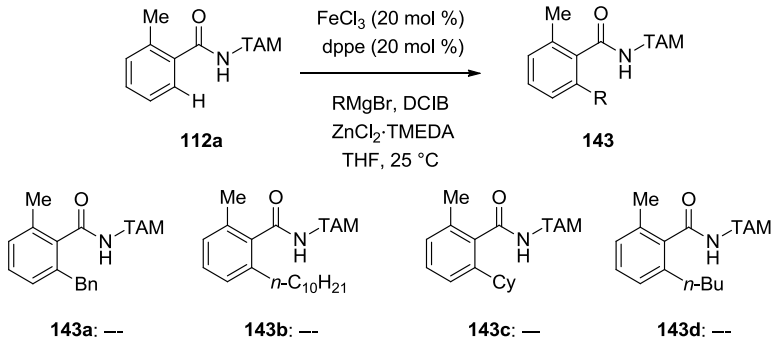
Table 26: Scope of iron-catalyzed C(sp^2)–H ethylations.[a]



entry	substrate	product	yield [%][b]
1	 **112a**	 **142a**	78
2	 **112v**	 **142b**	74
3	 **112u**	 **142c**	69
4	 **112y**	 **142d**	92[c]
5	 **112z**	 **142e**	46
6	 **112aa**	 **142f**	30
7		 **142f'**	54
8	 **112ab**	 **142g**	25
9		 **142g'**	54

[a] Reaction conditions: **112** (0.2 mmol), EtMgBr (1.40 mmol), $ZnBr_2$·TMEDA (0.6 mmol), $FeCl_3$ (20 mol %), dppe (20 mol %), DClB (0.40 mmol), THF (5.0 mL), 55 °C, 16 h. [b] Yields of isolated product. [c] Reaction on 3.0 mmol scale.

Attempted use of further *Grignard* reagents did not deliver any products (Scheme 80). For cyclohexylmagnesium bromide this can be explained by the increased steric hindrance, whereas the strain parameters for ethyl, *n*-butyl, *n*-decyl and benzyl substituents are very close to one another,[180] and the result with benzylmagnesium bromide excludes *ß*-hydride elimination as a possible reason. It is still an open question, if different degrees of association of these *Grignard* reagents and the solubility can play any role.[180]

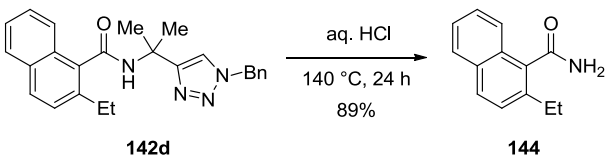


Scheme 80: Attempted alkylations.

Interestingly, in all attempted reactions the color of the reaction mixture remained yellow, while in the successful methylations or ethylations the reaction mixture turned dark-red or brownish in the initial phase. Upon the completion of the reaction, the color turned to yellow. These observations are in accordance with previous studies of *Fürstner* and *Kochi*.[129, 190]

Removal of the TAM Directing Group

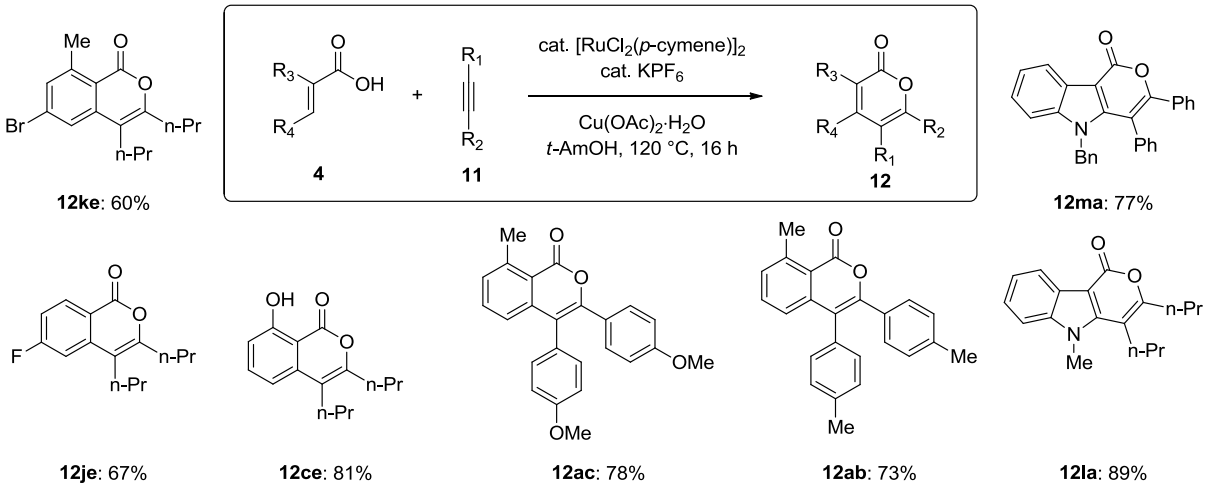
Finally, the TAM group could be cleaved in a traceless fashion by treatment with aqueous hydrochloric acid, affording the unprotected *ortho*-ethylated benzamide **144** (Scheme 81).



Scheme 81: Cleavage of the TAM group.

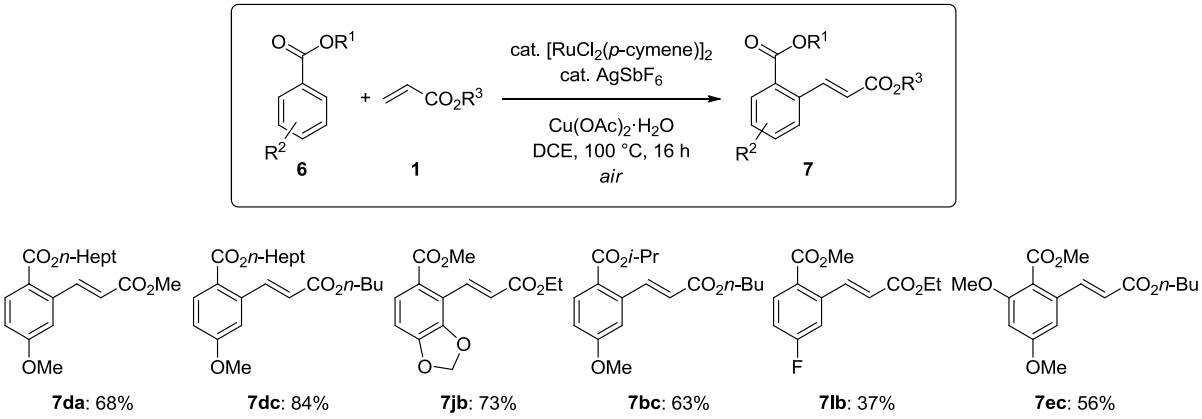
5 Summary and Outlook

The synthesis of functionally substituted heterocycles is of crucial importance for agrochemical and pharmaceutical industries as well as material sciences. In the first part of the thesis, the research focused on ruthenium-catalyzed oxidative C–H functionalizations. An effective protocol for the synthesis of isocoumarins **12** was established through the direct C–H/O–H functionalization *via* ruthenium(II)-catalyzed alkyne annulation reactions by aromatic acids **4** (Scheme 82). The reaction tolerated a broad range of functional groups and displayed an excellent regioselectivity. Mechanistic studies revealed an irreversible C–H bond ruthenation. Further investigations should focus on the application of functionally substituted and terminal alkynes.



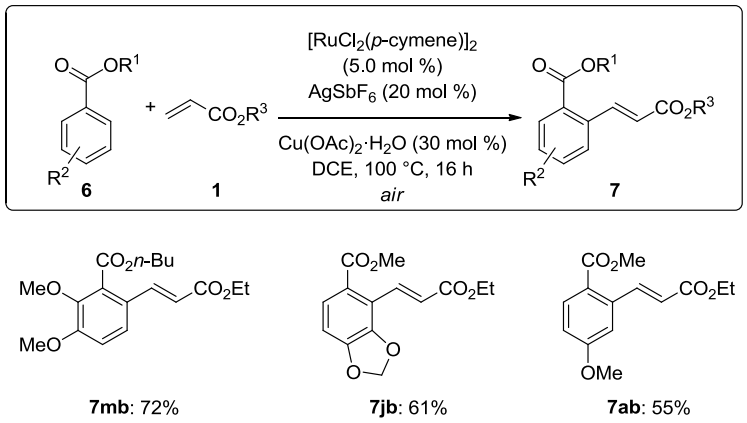
Scheme 82: Ruthenium(II)-catalyzed annulation of alkynes **11** by (hetero)aromatic acids **4**.

Moreover, the versatile ruthenium catalyst was applicable to twofold C–H functionalizations, directly employing benzoates **6** and acrylates **1** for the synthesis of styrene derivatives **7** (Scheme 83).



Scheme 83: Ruthenium(II)-catalyzed oxidative coupling of aromatic esters **6** with acrylates **1**.

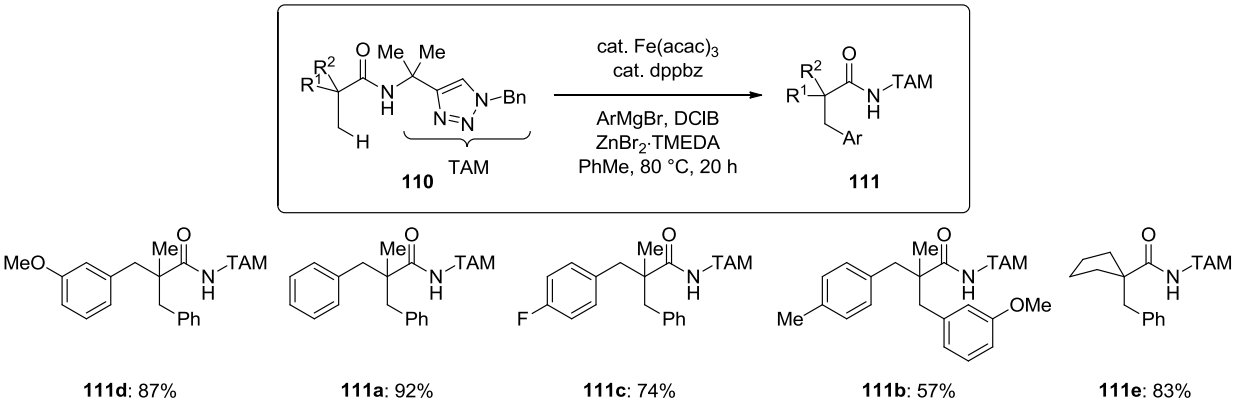
The environmentally-friendly protocol for the sustainable synthesis of styrenes **7** through the use of air as the ideal terminal oxidant proved also viable with weakly-coordinating esters (Scheme 84).



Scheme 84: Ruthenium(II)-catalyzed aerobic, twofold C–H functionalization.

Detailed mechanistic studies were indicative of a reversible C–H metalation step. Further explorations of electron-deficient and heteroaromatic esters for oxidative C–H alkenylations are of great interest, as well as alkenylations with the use of unactivated, simple olefins.

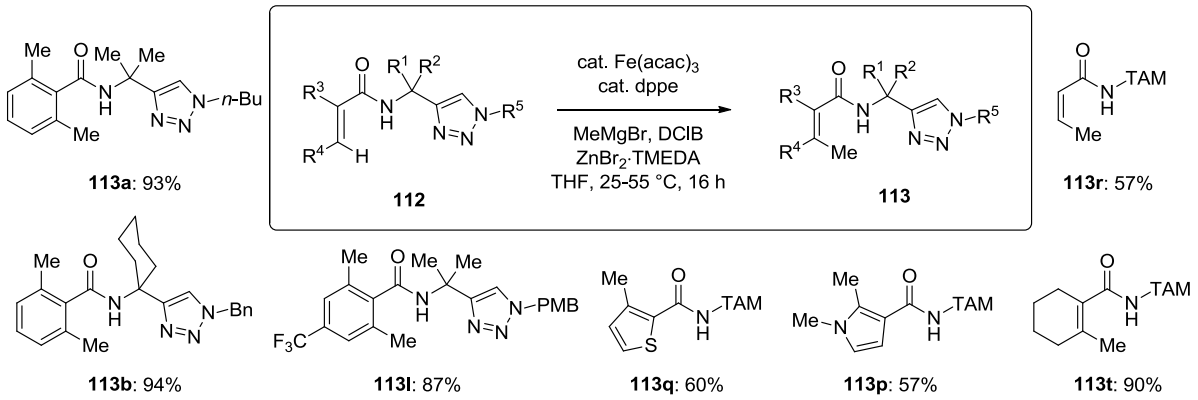
The second part of the thesis focused on the development of new versatile protocols for atom- and step-economical C–H functionalizations as an alternative for traditional cross-coupling chemistry. The novel bidentate TAM directing group was applied for site-selective iron-catalyzed C–H activations. The use of the inexpensive iron catalyst provided access to new strategies for the cleavage of C(sp^2)–H and (Csp^3)–H bonds. Specifically, the arylation of substituted propionamides **110** could be accomplished through triazole-assisted iron-catalyzed C–H bond functionalization (Scheme 85). A variety of functional groups on the propionamide derivatives was tolerated, and both electron-rich and electron-deficient substituents were efficiently converted. The preferred arylation of the *ß*-methyl group over the benzylic position rendered a radical pathway as less likely to be operative. Experiments with isotopically labeled substrates revealed the C–H bond cleavage to be the rate-determining step. With respect to future developments, the functionalization of prochiral substrates, such as 2,2-substituted propionamide derivatives **111** should be probed for enantio-selective C–H functionalizations.



Scheme 85: Iron-catalyzed direct C(sp^3)–H arylations by triazole assistance.

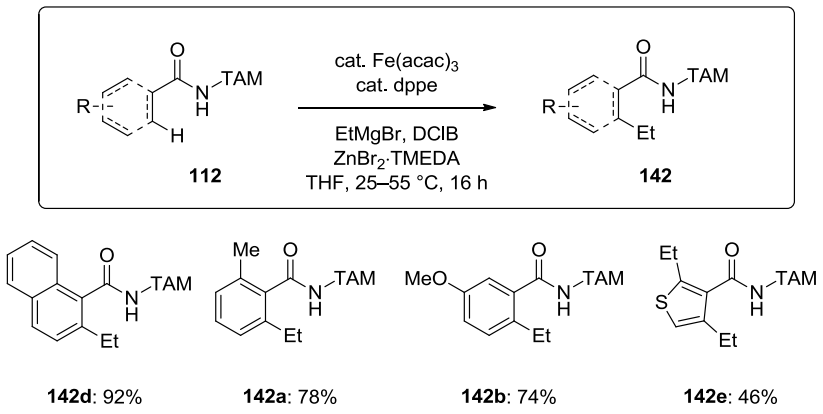
Since the methyl group is a common structural motive in natural products and pharmaceutical drugs, the development of modern methylation reactions is of crucial importance. Methylated products were obtained through iron-catalyzed C–H functionalizations of various arenes and heteroarenes bearing electron-rich and electron-deficient substituents (Scheme 86). The methylation of acrylamide **113r** proceeded in a diastereo-selective fashion, leading to the *Z*-olefin as the sole product. Mechanistic studies were supportive of an organometallic, turnover-determining C–H breaking process.

Regarding future efforts, useful methylation protocols for unactivated C(sp^3)–H bonds are in high demand.



Scheme 86: Iron-catalyzed C–H methylation.

Remarkably, the ethylation was accomplished employing the versatile and inexpensive iron salt (Scheme 87). The employment of higher homologues of alkyl *Grignard* reagents and secondary alkyl *Grignard* reagents would be highly desirable, to enable novel practicable protocols for iron-catalyzed direct C–H functionalizations in the future. To conclude, development of more reactive catalyst with lower catalyst loadings are constitutive promising objectives.



Scheme 87: Iron-catalyzed C–H ethylation of benzamides **112**.

6 Experimental Section

6.1 General Remarks

All catalytic reactions involving air- or moisture-sensitive reagents or products were performed under an atmosphere of dry N_2 using standard Schlenk techniques and predried glassware. Syringes for handling of dry solvents or liquids were flushed with dry N_2 threefold prior to use. Analytical data of the known substances were in accordance with the ones previously reported in the chemical literature.

Solvents

All solvents for reactions involving moisture-sensitive reagents were distilled and stored under inert atmosphere according to the following standard procedures or alternatively purified by using a solvent purification system (SPS-800) from MBRAUN.

Dichloromethane (DCM) was purified using a solvent purification system (SPS-800) from MBRAUN.

1,2-Dichloroethane (DCE) was dried over CaH_2 for 8 h at 100 °C and subsequently distilled under ambient pressure.

Toluene was purified using a solvent purification system (SPS-800) from MBRAUN.

Tetrahydrofurane was purified using a solvent purification system (SPS-800) from MBRAUN.

Diethyl ether was purified using a solvent purification system (SPS-800) from MBRAUN.

Methanol was stirred over magnesium turnings at 65 °C for 3 h prior to distillation from $Mg(OMe)_2$.

***t*-Amyl alcohol** was stirred over sodium chips at 103 °C for 5 h prior to distillation.

***t*-Butyl alcohol** was stirred over sodium chips 83 °C for several hours at prior to distillation.

Triethylamine was stirred over CaH_2 at 90 °C for 4 h prior to distillation.

Water was degassed before its use, applying repeated Freeze-Pump-Thaw degassing procedure.

1,4-Dioxane was distilled from sodium benzophenone ketyl.

1,2-Dimethoxyethane (DME) was distilled from sodium benzophenone ketyl.

***N*-Methyl-2-pyrrolidone** was stirred over CaH_2 at 200 °C for 4 h and subsequently distilled under reduced pressure.

Vacuum

The following pressures were measured on the used vacuum pumps and were not corrected: membrane pump vacuum (MPV): 0.5 mbar, oil pump vacuum (OPV): 0.1 mbar.

Melting points

Melting points were measured on the *Stuart® Melting Point Apparatus SMP3* from BARLOWORLD SCIENTIFIC. Reported values are uncorrected.

Chromatography

Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60F plates (MACHEREY-NAGEL) with 254 nm fluorescent indicator from MERCK. Plates were either visualized under ultraviolet light or developed by treatment with a $KMnO_4$ solution followed by careful warming with a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on GEDURAN® silica gel 60 - MERCK MILLIPORE, grade 60 (40–63 µm and 63–200 µm, 70–230 mesh estimated).

High Performance Liquid Chromatography

Preparative and analytical separations were performed on a HPLC-System from KNAUER (*Smartline Pump 100*, Dynamic Mixing Chamber, Injection- and Control-Valve , *Smartline UV Detector 2500*). Separation column VP C18 ec (NP) (250 × 16 mm, Nucleodur, 100-10) from MACHEREY-NAGEL was used. Organic solvents of HPLC-grade were employed. All samples were filtered through Polytetrafluorethylen Filter from ROTH (Ø 13 mm, 0.2 µm) prior to separation.

Gas Chromatography

Monitoring of the reaction process *via* coupled gas chromatography-mass spectrometry was performed using *G1800C GCDplus* with mass detector *HP 5971, 5890 Series II* with mass detector *HP 5972* from HEWLETT-PACKARD and *7890A* GC-System with mass detector *5975C* (*Triplex-Axis-Detector*) from AGILENT TECHNOLOGIES. *HP-5MS* columns (30 m × 0.25 mm, film 0.25 µm) were used.

Mass Spectrometry

EI and EI-HRMS spectra were measured on a Time-of-Flight mass spectrometer *AccuTOF* from JOEL. ESI mass spectra were recorded on an Ion-Trap mass spectrometer *LCQ* from FINNIGAN or on a Time-of-Flight mass spectrometer *microTOF* from BRUKER. ESI-HRMS spectra were recorded on a BRUKER *APEX IV* or a BRUKER *Daltonic* (7T, Transform Ion Cyclotron Resonance (FTICR)) mass spectrometer. The ratios of mass to charge are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectra were recorded at 300 or 600 MHz (^{1}H NMR), at 75 or 125 MHz [^{13}C NMR and APT (Attached Proton Test)] and at 285 MHz (^{19}F NMR) on VARIAN *Unity-300*, *AMX 300*, *Inova-500* and *Inova-600* instruments. Chemical shifts are

reported as δ values in ppm relative to the residual proton peak or the carbon peak of the deuterated solvent. For characterization of the observed resonance multiplicities the following abbreviations were applied: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), hept (heptet), m (multiplet). The coupling constants *J* are reported in Hertz (Hz). Analysis of the recorded spectra was carried out using *MestReNova 7.1* software.

	^{1}H NMR	^{13}C NMR
$CDCl_3$	7.26 ppm	77.0 ppm
DMSO-d_6	2.50 ppm	49.5 ppm

Infrared Spectroscopy

Infrared spectra were recorded on a BRUKER *Alpha-P ATR* spectrometer. Liquid samples were measured as film and solid samples neat. Analysis of the spectral data was carried out using *OPUS 6*. Absorption is given in wave numbers (cm^{-1}). Spectra were recorded in the range from 4000 to 400 cm^{-1}.

Reagents

Chemicals obtained from commercial sources (purity > 95%) were used without further purification. The following compounds are known and were synthesized according to previously described literature protocols:

Alkynes (**11b**, **11c** and **11h**),[191] 2,3,4,5,6-pentadeuterobenzoic acid ([D5]-**4d**),[192] esters (**6**),[193] benzamides (**112**)[164] benzamides (**110**).[163, 182]

The following compounds were obtained by the courtesy of the persons named below: B. Sc. F. Chrobak: Esters (**6d**), (**6j**), (**6m**). Dr. H. H. Al Mamari: benzamides (**112a-112c**). Dr. Q. Gu: benzamides (**111a-112h**). Dr. E. Diers: benzamides (**110i**), (**112k**). B. Sc. Julian Köhler: benzamide (**110g**). Karten Rauch: $[RuCl_2(p\text{-cymene})]_2$.

The *Grignard* reagents were prepared from the corresponding bromides or iodides and magnesium turnings in anhydrous THF or anhydrous Et_2O, and were titrated threefold prior to use.[194]

6.2 General Procedures

General Procedure A: Ruthenium-Catalyzed Annulations of Alkynes 11 with Benzoic Acids 4

A suspension of benzoic acid (**4**) (2.0 equiv), alkyne (**11**) (1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), KPF_6 (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv) in *t*-AmOH (3.0 mL) was stirred at 120 °C for 16 h. At ambient temperature, the reaction mixture was diluted with saturated aq. NH_4Cl/NH_3 solution (1:1, 50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 25/1) to yield the corresponding product **12**.

General Procedure B: Ruthenium-Catalyzed Oxidative Alkenylations of Aromatic Esters 6

A suspension of the benzoate **6** (1.0 equiv), acrylate **1** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (40 mol %) and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) in DCE (2.0 mL) was stirred at ambient temperature for 5 min and then at 100 °C for 16 h under an atmosphere of ambient air. At ambient temperature, the reaction mixture was diluted with saturated aq. NH_4Cl/NH_3 solution (1:1, 10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 50/1→25/1) to yield the desired product **7**.

General Procedure C: Ruthenium-Catalyzed Oxidative Aerobic Alkenylations of Aromatic Esters with Cocatalytic Amounts of $Cu(OAc)_2 \cdot H_2O$

A suspension of the benzoate **6** (1.0 equiv), acrylate **1** (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2 \cdot H_2O$ (30 mol %) in DCE (2.0 mL) was pre-stirred at ambient temperature for 5 min under N_2. Thereafter, the reaction mixture was stirred at 100 °C for 16 h under an atmosphere of ambient air. At ambient temperature, the reaction mixture was diluted with saturated aq. NH_4Cl/NH_3 solution (1:1, 10 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and

evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 50/1→25/1) to yield the corresponding product **7.**

General Procedure D: Synthesis of Amides 110: Method A

A solution of carboxylic acid **128** (1.0 equiv) in $SOCl_2$ (10 equiv) was stirred for 3 h at 85 °C, then the excess $SOCl_2$ was removed under vacuum to give the crude acid chloride. The crude acid chloride was taken up with dry CH_2Cl_2 (15 mL). The 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (1.0 equiv) and Et_3N (1.1 equiv) were successively added to this solution at 0 °C. The resulting reaction mixture was allowed to warm to ambient temperature, then stirred overnight at this temperature, diluted with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel.

General Procedure E: Synthesis of Amides 110 and 112: Method B

Oxalyl chloride (1.1 equiv) was added dropwise to a stirred solution of the respective carboxylic acid **128** (1.0 equiv) and DMF (0.2 equiv) in dry CH_2Cl_2 under a N_2 atmosphere at 0°C. The reaction mixture was stirred at the same temperature for 5 h, upon which it was allowed to warm up to ambient temperature. The crude acid chloride solution was cooled to 0 °C and then added dropwise to a solution of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (1.0 equiv) and Et_3N (3.0 equiv) in dry CH_2Cl_2 at 0 °C. The resulting reaction mixture was stirred at the same temperature for 10 min and then at ambient temperature for 12 h. The reaction was diluted with saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with aq. 1 M HCl (30 mL), brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel.

General Procedure F: Iron-Catalyzed C(sp^3)–H Bond Arylations of Amides 110

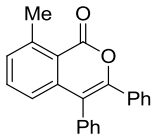
A solution of the *Grignard* reagent (1.0 M in THF, 7.0 equiv) was slowly added to a mixture of amide **110** (1.0 equiv) and $ZnBr_2$·TMEDA (3.0 equiv) in anhydrous toluene (1.5 mL) under N_2. The resulting reaction mixture was stirred at ambient temperature for 10 min, then a solution of $Fe(acac)_3$ (20 mol %) and dppbz (40 mol %) in dry toluene (1.0 mL) was added. The black mixture was stirred at ambient temperature for 10 min, and then DCIB (2.0 equiv) was added. The reaction mixture was stirred at 80 °C for 24 h. After cooling to ambient temperature, the mixture was diluted with a saturated NH_4Cl solution (5.0 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), then dried over Na_2SO_4 and filtered. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel to yield the product **111**.

General Procedure G: Iron-Catalyzed C(sp^2)–H Bond Methylations of Amides 112

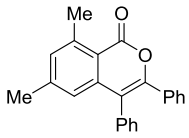
A solution of the *Grignard* reagent (3.0 M or 1.0 M in Et_2O or THF, 7.0 equiv) was slowly added to a mixture of amide **112** (1.0 equiv) and $ZnCl_2$·TMEDA (3.0 equiv) in anhydrous THF (2.5 mL) under N_2. The resulting mixture was stirred at ambient temperature for 5 min, then a solution of $FeCl_3$ (20 mol %) and dppe (20 mol %) in dry THF (2.5 mL) was added. The dark-red reaction mixture was stirred at ambient temperature for 5 min and then DCIB (2.0 equiv) was added. The mixture was stirred at 55 °C for 16 h. After cooling to ambient temperature, the mixture was diluted with saturated NH_4Cl solution (5.0 mL). The solution was extracted with EtOAc (2 × 20 mL), then dried over Na_2SO_4 and filtered. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel to yield the product **113**.

6.3 Experimental Procedures and Analytical Data

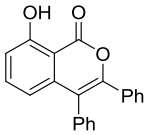
6.3.1 Analytical Data for the Ruthenium(II)-Catalyzed Oxidative Annulation Reaction



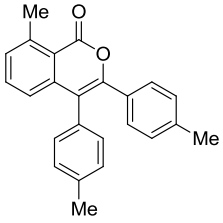
8-Methyl-3,4-diphenyl-1*H*-isochromen-1-one (12aa): The general procedure **A** was followed using 2-methylbenzoic acid (**4a**) (272 mg, 2.00 mmol) and diphenylacetylene (**11a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12aa** (231 mg, 74%) as a colorless solid. M. p. = 142−143 °C (lit.: [56] 142–143 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51–7.36 (m, 4H), 7.33-7.30 (m, 3H), 7.28–7.14 (m, 5H), 7.01 (d, *J* = 8.0 Hz, 1H), 2.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.4 (C_q), 150.6 (C_q), 143.4 (C_q), 140.5 (C_q), 135.0 (C_q), 133.6 (CH), 133.0 (C_q), 131.3 (CH), 131.0 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 123.6 (CH), 118.9 (C_q), 116.9 (C_q), 23.5 (CH_3). IR (neat): 1721, 1466, 1444, 1202, 1087, 1027, 1013, 762, 694 cm^{-1}. MS (EI): *m/z* (relative intensity) 312 ([M]$^+$ 100), 284 (26), 235 (20), 179 (13), 105 (50), 77 (57). HR-MS (ESI) *m/z* calcd for $C_{22}H_{16}O_2^+$ [M]$^+$ 312.1150, found 312.1144. The analytical data are in accordance with those reported in the literature.[56]



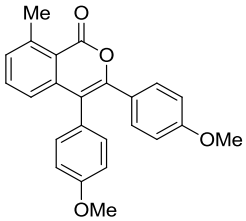
6,8-Dimethyl-3,4-diphenyl-1*H*-isochromen-1-one (12ba): The general procedure **A** was followed using 2,4-dimethylbenzoic acid (**4b**) (300 mg, 2.00 mmol) and diphenylacetylene (**11a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12ba** (275 mg, 84%) as a pale yellow solid. M. p. = 157−158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46−7.36 (m, 3H), 7.28 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.24–7.14 (m, 5H), 7.11 (m, 1H), 6.77 (d, *J* = 0.6 Hz, 1H), 2.86 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (C_q), 150.6 (C_q), 144.6 (C_q), 143.3 (C_q), 140.5 (C_q), 135.0 (C_q), 133.1 (C_q), 132.4 (CH), 131.3 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 123.6 (CH), 116.8 (C_q), 116.5 (C_q), 23.4 (CH_3), 21.8 (CH_3). IR (neat): 1720, 1600, 1443, 1215, 1027, 766, 694, 670 cm^{-1}. MS (EI): *m/z* (relative intensity) 326 ([M]$^+$ 100), 311 (17), 298 (18), 294 (17), 193 (18), 105 (33), 77 (36). HR-MS (ESI) *m/z* calcd for $C_{23}H_{18}O_2^+$ [M]$^+$ 326.1307, found 326.1308.



8-Hydroxy-3,4-diphenyl-1*H*-isochromen-1-one (12ca): The general procedure **A** was followed using salicylic acid (**4c**) (277 mg, 2.00 mmol) and diphenylacetylene (**11a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12ca** (195 mg, 62%) as a pale yellow solid. M. p. = 149−151 °C (lit.: [58] 150–153 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.36 (s, 1H), 7.59 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.51–7.42 (m, 3H), 7.41–7.20 (m, 7H), 7.07 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.69 (dd, *J* = 8.0, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.1 (C_q), 161.7 (C_q), 150.3 (C_q), 139.4 (C_q), 137.1 (CH), 134.1 (C_q), 132.3 (C_q), 131.0 (CH), 129.1 (CH), 129.1 (CH), 129.0 (CH), 128.2 (CH), 127.9 (CH), 118.0 (C_q), 116.1 (CH), 115.3 (CH), 105.9 (C_q). IR (neat): 3024, 1686 1193, 1167, 813, 760, 690, 465 cm^{-1}. MS (EI): *m/z* (relative intensity) 314 ([M]$^+$ 100), 237 (31), 181 (23), 152 (35), 105 (69), 77 (50), 51 (26). HR-MS (ESI) *m/z* calcd for $C_{21}H_{14}O_3^+$ [M]$^+$ 314.0943, found 314.0940. The analytical data are in accordance with those reported in the literature.[58]

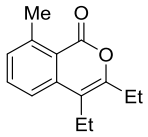


8-Methyl-3,4-di-*p*-tolyl-1*H*-isochromen-1-one (12ab): The general procedure **A** was followed using 2-methylenzoic acid (**4a**) (272 mg, 2.00 mmol) and 1,2-di-*p*-tolylethyne (**11b**) (206 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12ab** (251 mg, 74%) as a yellow solid. M. p. = 165−169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.31–7.19 (m, 5H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.06–6.96 (m, 3H), 2.91(s, 3H), 2.42 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.5 (C_q), 150.5 (C_q), 143.2 (C_q), 140.7 (C_q), 138.6 (C_q), 137.5 (C_q), 133.5 (CH), 131.9 (C_q), 131.0 (CH), 130.7 (CH), 130.1 (CH), 129.7 (CH), 128.8 (CH), 128.4 (CH), 123.5 (CH), 118.7 (C_q), 116.2 (C_q), 23.4 (CH_3), 21.2 (CH_3), 21.2 (CH_3). IR (neat): 2920, 1726, 1089, 1021, 799, 784, 727, 499 cm^{-1}. MS (EI): *m/z* (relative intensity) 340 ([M]$^+$ 85), 312 (42), 193 (23), 119 (100), 91 (69), 65 (26), 43 (46). HR-MS (ESI) *m/z* calcd for $C_{24}H_{20}O_2^+$ [M]$^+$ 340.1463, found 340.1463.

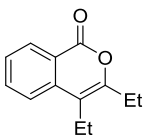


3,4-Bis(4-methoxyphenyl)-8-methyl-1*H*-isochromen-1-one (12ac): The general procedure **A** was followed using 2-methylbenzoic acid (**4a**) (273 mg, 2.00 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (**11c**) (239 mg,

1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12ac** (293 mg, 78%) as a yellow solid. M. p. = 186−192 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.33–7.25 (m, 3H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 2.91 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.6 (C_q), 159.7 (C_q), 159.1 (C_q), 150.4 (C_q), 143.2 (C_q), 141.0 (C_q), 133.5 (CH), 132.3 (CH), 130.5 (CH), 130.4 (CH), 127.2 (C_q), 125.4 (C_q), 123.3 (CH), 118.6 (C_q), 115.3 (C_q), 114.4 (CH), 113.2 (CH), 55.2 (CH_3), 55.1 (CH_3), 23.5 (CH_3). IR (neat): 2928, 2838, 1720, 1506, 1247, 1173, 1023, 805, 544 cm^{-1}. MS (EI): *m/z* (relative intensity) 372 ($[M]^+$ 93), 344 (74), 256 (21), 165 (21), 135 (100), 77 (19), 43 (28). HR-MS (ESI) *m/z* calcd for $C_{24}H_{20}O_4^+$ $[M]^+$ 372.1362, found 372.1368.

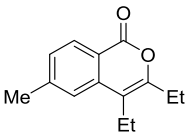


3,4-Diethyl-8-methyl-1*H*-isochromen-1-one (12ad): The general procedure **A** was followed using 2-methylbenzoic acid (**4a**) (273 mg, 2.00 mmol) and hex-3-yne (**11d**) (83.8 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded **12ad** (168 mg, 76%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 7.9, 7.4 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 2.79 (s, 3H), 2.58 (q, *J* = 7.2 Hz, 2H)2.56 (q, *J* = 7.2 Hz, 2H), 1.24 (t, 7.5 Hz, 3H), 1.14 (t, 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.0 (C_q), 154.6 (C_q), 143.6 (C_q), 139.2 (C_q), 133.5 (CH), 130.0 (CH), 120.3 (CH), 119.4 (C_q), 112.8 (C_q), 23.9 (CH_3), 23.4 (CH_2), 19.5 (CH_2), 14.1 (CH_3), 12.3 (CH_3). IR (neat): 2970, 2935, 1715, 1469, 1072, 1023, 805, 786 cm^{-1}. MS (EI): *m/z* (relative intensity) 216 ($[M]^+$ 87), 201 (82), 175 (46), 145 (100), 115 (65), 91 (42), 57 (85). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_2^+$ $[M]^+$ 216.1150, found 216.1148.

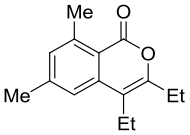


3,4-Diethyl-1*H*-isochromen-1-one (12dd): The general procedure **A** was followed using benzoic acid (**4d**) (244 mg, 2.00 mmol) and hex-3-yne (**11d**) (81.1 mg, 0.99 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded isocoumarin **12dd** (187 mg, 93%) as a colorless solid. M. p. = 59−64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.0 Hz, 1H), 7.73 (dd, *J* = 7.6, 7.6, Hz, 1H), 7.54 (d, *J* = 8.0, Hz, 1H), 7.46 (dd, *J* = 7.6, 7.6 Hz, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.64 (q, 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.20 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0 (C_q), 155.0 (C_q), 137.7

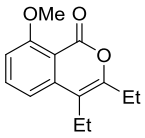
(C_q), 134.5 (CH), 129.9 (CH), 127.0 (CH), 122.4 (CH), 120.9 (C_q), 113.0 (C_q), 24.1 (CH_2), 19.3 (CH_2), 14.3 (CH_3), 12.5 (CH_3). IR (neat): 2964, 2870, 1698, 1639, 1472, 1074, 773, 703. S (EI): m/z (relative intensity) 202 ([M]$^+$ 86), 187 (100), 159 (29), 131 (97), 115 (38), 91 (34), 57 (24), 43 (37). HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}O_2^+$ [M]$^+$ 202.0994, found 202.0994. The analytical data are in accordance with those reported in the literature.[195]



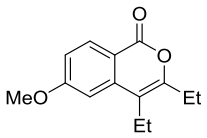
3,4-Diethyl-6-methyl-1*H*-isochromen-1-one (12ed): The general procedure **A** was followed using *p*-toluic acid (**4e**) (273 mg, 2.00 mmol) and hex-3-yne (**11d**) (81.6 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12ed** (209 mg, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.1 Hz, 1H), 7.24 (s, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 2.56 (q, *J* = 7.5 Hz, 2H), 2.54 (q, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 1.20 (t, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (C_q), 154.5 (C_q), 145.1 (C_q), 137.3 (C_q), 129.3 (CH), 127.9 (CH), 122.1 (CH), 117.9 (C_q), 112.5 (C_q), 23.6 (CH_3), 21.9 (CH_2), 18.8 (CH_2), 13.9 (CH_3), 12.1 (CH_3). IR (neat): 2970, 2874, 1716, 1638, 1609, 1074, 1057, 782 cm^{-1}. MS (EI): *m/z* (relative intensity) 216 ([M]$^+$ 87), 201 (100), 145 (98), 115 (50), 91 (37), 57 (36), 43 (44). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_2^+$ [M]$^+$ 216.1150, found 216.1142. The analytical data are in accordance with those reported in the literature.[195]



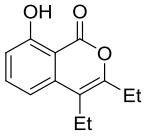
3,4-Diethyl-6,8-dimethyl-1*H*-isochromen-1-one (12bd): The general procedure **A** was followed using 2,4-dimethylbenzoic acid (**4b**) (300 mg, 2.00 mmol) and hex-3-yne (**11d**) (83.1 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12bd** (182 mg, 78%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (s, 1H), 7.04 (s, 1H), 2.76 (s, 3H), 2.57 (q, *J* = 7.4 Hz, 2H), 2.55 (q, *J* = 7.4 Hz, 2H) 2.40 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.15 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2 (C_q), 154.7 (C_q), 144.3 (C_q), 143.6 (C_q), 139.3 (C_q), 131.3 (CH), 120.6 (CH), 116.9 (C_q), 112.7 (C_q), 24.0 (CH_2), 23.5 (CH_3), 22.0 (CH_3), 19.5 (CH_2), 14.2 (CH_3), 12.5 (CH_3). IR (neat): 2968, 1713, 1646, 1604, 1465, 1303, 1140, 1073, 1029, 851 cm^{-1}. MS (EI): *m/z* (relative intensity) 230 ([M]$^+$ 100), 215 (82), 187 (33), 173 (34), 159 (68), 128 (25), 115 (21). HR-MS (ESI) *m/z* calcd for $C_{15}H_{18}O_2^+$ [M]$^+$ 230.1307, found 230.1308.



3,4-Diethyl-8-methoxy-1*H*-isochromen-1-one (12fd): The general procedure **A** was followed using 2-methoxybenzoic acid (**4f**) (304 mg, 2.00 mmol) and hex-3-yne (**11d**) (83.2 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 3/2) yielded isocoumarin **12fd** (137 mg, 58%) as a colorless solid. M. p. = 87–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 8.3, 8.1 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 3.97 (s, 3H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.55 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.15 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.9 (C_q), 159.6 (C_q), 155.5 (C_q), 140.6 (C_q), 135.3 (CH), 114.3 (CH), 112.4 (C_q), 109.7 (CH), 108.9 (C_q), 56.2 (CH_3), 24.0 (CH_2), 19.6 (CH_2), 14.1 (CH_3), 12.5 (CH_3). IR (neat): 2965, 2934, 1713, 1566, 1253, 1190, 1044, 811 cm^{-1}. MS (EI): *m/z* (relative intensity) 232 ([M]$^+$ 100), 217 (45), 203 (52), 175 (36), 161 (72), 115 (29), 57 (51), 43 (50). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_3^+$ [M]$^+$ 232.1099, found 232.1100.

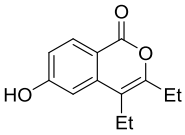


3,4-Diethyl-6-methoxy-1*H*-isochromen-1-one (12gd): The general procedure **A** was followed using *p*-anisic acid (**4g**) (311 mg, 2.04 mmol) and hex-3-yne (**11d**) (84.2 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded isocoumarin **12gd** (157 mg, 67%) as a colorless solid. M. p. = 62–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 1H), 3.90 (s, 3H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.17 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6 (C_q), 162.6 (C_q), 155.5 (C_q), 139.9 (C_q), 132.1 (CH), 114.2 (CH), 114.0 (C_q), 112.8 (C_q), 105.8 (CH), 55.5 (CH_3), 24.1 (CH_2), 19.3 (CH_2), 14.1 (CH_3), 12.5 (CH_3). IR (neat): 2933, 1704, 1601, 1228, 1058, 1029, 778, 683 cm^{-1}. MS (EI): *m/z* (relative intensity) 232 ([M]$^+$ 62), 217 (83), 175 (23), 161 (50), 115 (15), 77 (13), 57 (29), 43 (100). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_3^+$ [M]$^+$ 232.1099, found 232.1095.

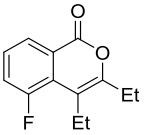


3,4-Diethyl-8-hydroxy-1*H*-isochromen-1-one (12cd): The general procedure **A** was followed using salicylic acid (**4c**) (276 mg, 2.00 mmol) and hex-3-yne (**11d**)

(83.1 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12cd** (188 mg, 85%) as a colorless solid. M. p. = 68−69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.33 (s, 1H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.00–6.80 (m, 2H), 2.59 (q, 7.5 Hz, 2H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6 (C_q), 162.0 (C_q), 154.4 (C_q), 138.2 (C_q), 137.0 (CH), 114.4 (C_q), 114.2 (CH), 112.7 (CH), 106.2 (C_q), 23.8 (CH_2), 19.5 (CH_2), 14.0 (CH_3), 12.4 (CH_3). IR (neat): 2967, 2931, 1675, 1450, 1236, 1174, 813, 742 cm^{-1}. MS (EI): *m/z* (relative intensity) 218 ([M]$^+$ 100), 203 (67), 175 (42), 161 (34), 147 (79), 57 (38), 43 (54). HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}O_3^+$ [M]$^+$ 218.0943, found 218.0946.

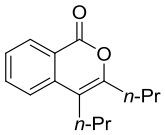


3,4-diethyl-6-hydroxy-1*H*-isochromen-1-one (12hd): The general procedure **A** was followed using 4-hydroxybenzoic acid (**4h**) (276 mg, 2.00 mmol) and hex-3-yne (**11d**) (80.2 mg, 0.98 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12hd** (111 mg, 52%) as a colorless solid. M. p. = 258−261 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.71 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 6.96–6.86 (m, 2H), 2.54 (q, *J* = 7.5 Hz, 2H), 2.48 (q, *J* = 7.5 Hz, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 1.09 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 163.4 (C_q), 161.2 (C_q), 154.7 (C_q), 139.5 (C_q), 131.7 (CH), 116.2 (CH), 112.3 (C_q), 111.7 (C_q), 107.3 (CH), 23.3 (CH_2), 18.6 (CH_2), 14.0 (CH_3), 12.2 (CH_3). IR (neat): 3076, 2965, 1672, 1613, 1340, 1209, 1106, 786 cm^{-1}. MS (EI): *m/z* (relative intensity) 218 ([M]$^+$ 82), 203 (100), 175 (18), 161 (27), 147 (85), 57 (31). HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}O_3^+$ [M]$^+$ 218.0943, found 218.0944.

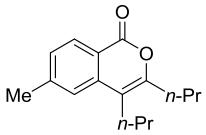


3,4-Diethyl-5-fluoro-1*H*-isochromen-1-one (12id): The general procedure **A** was followed using 3-fluorobenzoic acid (**4i**) (280 mg, 2.00 mmol) and hex-3-yne (**11d**) (83.1 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 500/1 → 50/1) yielded isocoumarin **12id** (80 mg, 36%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22–8.10 (m, 1H), 7.48–7.33 (m, 2H), 2.75 (qd, *J* = 7.4, 2.8 Hz, 2H), 2.63 (q, *J* = 7.4 Hz, 2H), 1.28 (t, *J* = 7.4, 3H), 1.21 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7 (d, $J_{C–F}$ = 3 Hz, C_q), 157.8 (d, $J_{C–F}$ = 253 Hz, C_q), 155.5 (d, $J_{C–F}$ = 2 Hz, C_q), 127.9 (d, $J_{C–F}$ = 9 Hz, CH), 126.5 (d, $J_{C–F}$ = 11 Hz, C_q), 126.1 (d, $J_{C–F}$ = 4 Hz, CH), 123.2 (d, $J_{C–F}$ = 5 Hz,

C_q), 121.9 (d, $J_{C–F}$ = 25 Hz, CH), 111.2 (d, $J_{C–F}$ = 5 Hz, C_q), 23.9 (CH_2), 21.4 (d, $J_{C–F}$ = 11 Hz, CH_2), 15.1 (d, $J_{C–F}$ = 4 Hz, CH_3), 12.6 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$) δ = -115.6 (t, J = 8.6 Hz). IR (neat): 2966, 2932, 1711, 1630, 1463, 1243, 1168, 768 cm^{-1}. MS (EI): *m/z* (relative intensity) 220 ([M]$^+$ 84), 205 (80), 177 (35), 149 (100), 133 (50), 109 (37), 57 (64). HR-MS (ESI) *m/z* calcd for $C_{13}H_{13}FO_2^+$ [M]$^+$ 220.0900, found 220.0902.

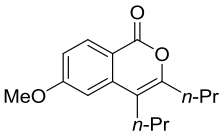


3,4-Di-*n*-propyl-1*H*-isochromen-1-one (12de): The general procedure **A** was followed using benzoic acid (**4d**) (245 mg, 2.00 mmol) and oct-4-yne (**11e**) (112 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12de** (181 mg, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (dd, J = 7.9, 1.4 Hz, 1H), 7.71 (ddd, J = 8.4, 7.2, 1.5 Hz, 1H), 7.51 (dd, J = 7.9, 1.0 Hz, 1H), 7.44 (ddd, J = 8.3, 7.2, 1.1 Hz, 1H), 2.63–2.50 (m, 4H), 1.84–1.66 (m, 2H), 1.66–1.48 (m, 2H), 1.09–0.93 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.9 (C_q), 154.1 (C_q), 137.9 (C_q), 134.5 (CH), 129.7 (CH), 127.0 (CH), 122.6 (CH), 120.7 (C_q), 112.2 (C_q), 32.6 (CH_2), 28.1 (CH_2), 22.8 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3). IR (neat): 2960, 2872, 1719, 1638, 1079, 1026, 767, 690 cm^{-1}. MS (EI): *m/z* (relative intensity) 230 ([M]$^+$ 58), 201 (100), 173 (12), 145 (19), 131 (84), 115 (18), 43 (67). HR-MS (ESI) *m/z* calcd for $C_{15}H_{18}O_2^+$ [M]$^+$ 230.1307, found 230.1305. The analytical data are in accordance with those reported in the literature.[196]

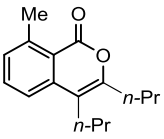


6-Methyl-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12be): The general procedure **A** was followed using *p*-toluic acid (**4b**) (273 mg, 2.00 mmol) and oct-4-yne (**11e**) (111 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded isocoumarin **12be** (209 mg, 85%) as a colorless solid. M. p. = 110−116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.0 Hz, 1H), 7.32–7.16 (m, 2H), 2.61−2.50 (m, 4H), 2.47 (s, 3H), 1.81–1.64 (m, 2H), 1.64–1.48 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9 (C_q), 154.1 (C_q), 145.4 (C_q), 138.0 (C_q), 129.8 (CH), 128.4 (CH), 122.7 (CH), 118.3 (C_q), 112.1 (C_q), 32.7 (CH_2), 28.1 (CH_2), 22.9 (CH_2), 22.3 (CH_3), 21.2 (CH_2), 14.1 (CH_3), 13.8 (CH_3). IR (neat): 2960, 2871, 1712, 1638, 1608, 1080, 842, 786 cm^{-1}. MS (EI): m/z (relative intensity) 244 ([M]$^+$ 47),

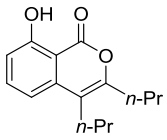
215 (100), 187 (11), 159 (22), 145 (72), 115 (30), 43 (27). HR-MS (ESI) *m/z* calcd for $C_{16}H_{20}O_2^+$ $[M]^+$ 244.1463, found 244.1467. The analytical data are in accordance with those reported in the literature.[196]



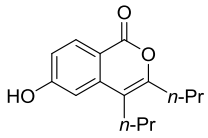
6-Methoxy-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12ge): The general procedure **A** was followed using draconic acid (**4g**) (310 mg, 2.04 mmol) and oct-4-yne (**11e**) (110 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded isocoumarin **12ge** (208 mg, 80%) as a colorless solid. M. p. = 81−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.8 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 3.92 (s, 3H), 2.60–2.46 (m, 4H), 1.83–1.50 (m, 4H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6 (C_q), 162.7 (C_q), 154.8 (C_q), 140.2 (C_q), 132.2 (CH), 114.1 (CH), 114.1 (C_q), 112.0 (C_q), 106.2 (CH), 55.5 (CH_3), 32.8 (CH_2), 28.3 (CH_2), 22.7 (CH_2), 21.1 (CH_2), 14.2 (CH_3), 13.8 (CH_3). IR (neat): 2930, 2871, 1708, 1599, 1234, 1080, 1018, 856 cm^{-1}. MS (EI): m/z (relative intensity) 260 ($[M]^+$ 46), 231 (100), 203 (7), 175 (22), 161 (62), 133 (8), 43 (46). HR-MS (ESI) *m/z* calcd for $C_{16}H_{20}O_3^+$ $[M]^+$ 260.1412, found 260.1408. The analytical data are in accordance with those reported in the literature.[196]



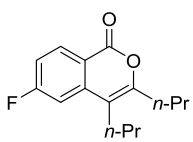
8-Methyl-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12ae): The general procedure **A** was followed using 2-methylbenzoic acid (**4a**) (273 mg, 2.00 mmol) and oct-4-yne (**11e**) (111 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12ae** (162 mg, 66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 2.81 (s, 3H), 2.59–2.49 (m, 4H), 1.80–1.64 (m, 2H), 1.64–1.45 (m, 2H), 1.07−0.94 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.1 (C_q), 153.8 (C_q), 143.6 (C_q), 139.4 (C_q), 133.6 (CH), 130.0 (CH), 120.6 (CH), 119.2 (C_q), 112.0 (C_q), 32.5 (CH_2), 28.5 (CH_2), 23.6 (CH_3), 22.7 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3). IR (neat): 2962, 2873, 1718, 1469, 1080, 1024, 805, 786 cm^{-1}. MS (EI): m/z (relative intensity) 244 ($[M]^+$ 17), 215 (41), 189 (36), 161 (26), 145 (60), 91 (24), 43 (100). HR-MS (ESI) *m/z* calcd for $C_{16}H_{20}O_2^+$ $[M]^+$ 244.1463, found 244.1467. The analytical data are in accordance with those reported in the literature.[196]



8-Hydroxy-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12ce): The general procedure **A** was followed using salicylic acid (**4c**) (278 mg, 2.01 mmol) and oct-4-yne (**11e**) (113 mg, 1.03 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded isocoumarin **12ce** (201 mg, 81%) as a colorless solid. M. p. = 44−49 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.38 (s, 1H), 7.60 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.05−6.85 (m, 2H), 2.65–2.45 (m, 4H), 1.74 (sx, *J* = 7.4 Hz, 2H) 1.57 (sx, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7 (C_q), 162.0 (C_q), 153.6 (C_q), 138.5 (C_q), 137.0 (CH), 114.3 (CH), 113.6 (C_q), 113.0 (CH), 106.3 (C_q), 32.4 (CH_2), 28.4 (CH_2), 22.7 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.7 (CH_3). IR (neat): 2965, 2871, 1674, 1456, 1234, 1170, 816, 751 cm^{-1}. MS (EI): *m/z* (relative intensity) 246 ([M]$^+$ 54), 217 (81), 189 (13), 161 (15), 147 (100), 91 (12), 43 (44). HR-MS (ESI) *m/z* calcd for $C_{15}H_{18}O_3^+$ [M]$^+$ 246.1256, found 246.1256.

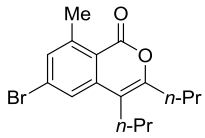


6-Hydroxy-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12he): The general procedure **A** was followed using 4-hydroxybenzoic acid (**4h**) (278 mg, 2.01 mmol) and oct-4-yne (**11e**) (112 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 5/1) yielded isocoumarin **12he** (175 mg, 70%) as a colorless solid. M. p. = 133−135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.6 Hz, 1H), 7.34 (s, 1H), 7.02 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 2.60–2.45 (m, 4H), 1.82–1.43 (m, 4H), 1.06–0.90 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.6 (C_q), 162.2 (C_q), 154.6 (C_q), 140.8 (C_q), 132.4 (CH), 116.2 (CH), 113.3 (C_q), 112.5 (C_q), 108.0 (CH), 32.7 (CH_2), 28.3 (CH_2), 22.7 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3). IR (neat): 3130, 2961, 1673, 1470, 1261, 1104, 782, 691 cm^{-1}. MS (EI): m/z (relative intensity) 246 ([M]$^+$ 50), 217 (100), 189 (12), 161 (22), 147 (67), 89 (9), 43 (59). HR-MS (ESI) *m/z* calcd for $C_{15}H_{18}O_3^+$ [M]$^+$ 246.1256, found 246.1265.

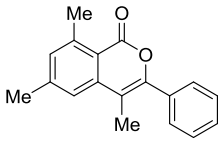


6-Fluoro-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12je): The general procedure **A** was followed using 4-fluorobenzoic acid (**4j**) (286 mg, 2.04

mmol) and oct-4-yne (**11e**) (110 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded isocoumarin **12je** (166 mg, 67%) as a colorless solid. M. p. = 39−45 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44–8.18 (m, 1H), 7.19–7.10 (m, 2H), 2.63–2.43 (m, 4H), 1.86–1.49 (m, 4H), 1.09–0.95 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.6 (C_q), 163.6 (d, J_{C-F} = 246 Hz, C_q), 155.6 (C_q), 141.0 (d, J_{C-F} = 10 Hz, C_q), 133.1 (d, J_{C-F} = 10 Hz, CH), 117.2 (d, J_{C-F} = 2 Hz, C_q), 115.3 (d, J_{C-F} = 23 Hz, CH), 111.9 (d, J_{C-F} = 3 Hz, C_q), 108.7 (d, J_{C-F} = 23 Hz, CH), 32.7 (s, CH_2), 28.3 (CH_2), 22.7 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3). ^{19}F NMR (283 MHz, $CDCl_3$) δ = – 102.0 (ddd, *J* = 10.2, 8.5, 6.0 Hz). IR (neat): 3074, 2962, 1723, 1611, 1230, 1074, 865, 781 cm^{-1}. MS (EI): *m/z* (relative intensity) 248 ([M]$^+$ 44), 219 (100), 191 (12), 163 (18), 149 (67), 133 (16), 43 (68). HR-MS (ESI) *m/z* calcd for $C_{15}H_{17}FO_2^+$ [M]$^+$ 248.1213, found 248.1216.

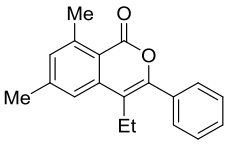


6-Bromo-8-methyl-3,4-di-*n*-propyl-1*H*-isochromen-1-one (12ke): The general procedure **A** was followed using 4-bromo-2-methylbenzoic acid (**4k**) (444 mg, 2.06 mmol) and oct-4-yne (**11e**) (113 mg, 1.03 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 100/1) yielded isocoumarin **12ke** (201 mg, 60%) as a colorless solid. M. p. =55−60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H), 7.38 (s, 1H), 2.78 (s, 3H), 2.52 (q, *J* = 7.5 Hz, 4H), 1.83–1.47 (m, 4H), 1.12–0.91 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.5 (C_q), 155.2 (C_q), 145.8 (C_q), 141.0 (C_q), 132.8 (CH), 129.1 (C_q), 123.6 (CH), 118.0 (C_q), 111.3 (C_q), 32.7 (CH_2), 28.4 (CH_2), 23.5 (CH_3), 22.6 (CH_2), 21.0 (CH_2), 14.1 (CH_3), 13.8 (CH_3). IR (neat): 2956, 2869, 1713, 1644, 1571, 1133, 1023, 857 cm^{-1}. MS (EI): *m/z* (relative intensity) 324/322 ([M]$^+$ 56/56), 295/293 ([M–Et]$^+$ 97/98), 223/221 ([M–2Pr–Me]$^+$ 85/85), 144 (19), 129 (23), 115 (37), 43 (100). HR-MS (ESI) *m/z* calcd for $C_{16}H_{19}BrO_2^+$ [M]$^+$ 322.0568, found 322.0563.

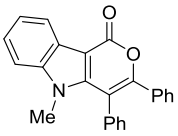


4,6,8-Trimethyl-3-phenyl-1*H*-isochromen-1-one (12bf): The general procedure **A** was followed using 2,4-dimethylbenzoic acid (**4b**) (307 mg, 2.04 mmol) and prop-1-yn-1-ylbenzene (**11f**) (116 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12bf** (156 mg, 59%) as a colorless solid. M. p. = 153−158 °C. ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 7.62–7.55 (m, 2H), 7.51–7.39 (m, 3H), 7.26 (s, 1H), 7.16 (s, 1H), 2.84 (s, 3H), 2.47 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8 (C_q), 151.0 (C_q), 144.6 (C_q), 143.5 (C_q), 140.3 (C_q), 133.5 (C_q), 132.1 (CH), 129.4 (CH), 129.1 (CH), 128.1 (CH), 121.6 (CH), 116.8 (C_q), 108.8 (C_q), 23.4 (CH_3), 22.0 (CH_3), 14.0 (CH_3). IR (neat): 2958, 2919, 1713, 1604, 1052, 848, 775, 697, 658 cm^{-1}. MS (EI): *m/z* (relative intensity) 264 ([M]$^+$ 66), 236 (100), 115 (15), 105 (46), 77 (49), 51 (15), 43 (23). HR-MS (ESI) *m/z* calcd for $C_{18}H_{16}O_2^+$ [M]$^+$ 264.1150, found 264.1151.

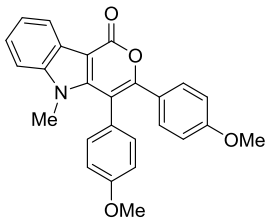


4-Ethyl-6,8-dimethyl-3-phenyl-1*H*-isochromen-1-one (12bg): The general procedure **A** was followed using 2,4-dimethylbenzoic acid (**4b**) (307 mg, 2.04 mmol) and but-1-yn-1-ylbenzene (**11g**) (128 mg, 0.98 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12bg** (156 mg, 57%) as a colorless solid. M. p. = 110−116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.52 (m, 2H), 7.49–7.40 (m, 3H), 7.29 (s, 1H), 7.15 (s, 1H), 2.84 (s, 3H), 2.67 (q, *J* = 7.4 Hz, 2H), 2.48 (s, 3H), 1.26 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7 (C_q), 151.1 (C_q), 144.5 (C_q), 143.7 (C_q), 139.1 (C_q), 133.7 (C_q), 132.1 (CH), 129.1 (CH), 128.9 (CH), 128.2 (CH), 121.6 (CH), 117.3 (C_q), 114.9 (C_q), 23.5 (CH_3), 22.1 (CH_3), 20.3 (CH_2), 14.7 (CH_3). IR (neat): 2924, 2874, 1703, 1601, 1065, 1034, 769, 663 cm^{-1}. MS (EI): *m/z* (relative intensity) 278 ([M]$^+$ 100), 263 (45), 250 (22), 235 (74), 173 (23), 105 (42), 77 (57), 43 (16). HR-MS (ESI) *m/z* calcd for $C_{19}H_{18}O_2^+$ [M]$^+$ 278.1307, found 278.1310.

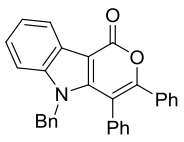


5-Methyl-3,4-diphenylpyrano[4,3-*b*]indol-1(5*H*)-one (12la): The general procedure **A** was followed using 1-methyl-1*H*-indole-3-carboxylic acid (**4l**) (350 mg, 2.00 mmol) and diphenylacetylene (**11a**) (180 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1 → 16/1) yielded isocoumarin **12la** (229 mg, 65%) as a pale yellow solid. M. p. = 206−209 °C (lit.:[227] 228–234 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41–8.27 (m, 1H), 7.51–7.10 (m, 13H), 3.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4 (C_q), 155.8 (C_q), 144.8 (C_q), 139.9 (C_q), 133.4 (C_q), 133.1 (C_q), 131.7 (CH), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 127.8 (CH), 124.7 (CH), 123.8 (C_q), 122.8 (CH), 121.5 (CH), 110.5 (C_q), 109.4 (CH), 100.8 (C_q), 32.1 (CH_3). IR (neat): 3055, 2943, 1715, 1461,

1444, 9445, 751, 708, 688 cm^{-1}. MS (EI): *m/z* (relative intensity) 351 ($[M]^+$ 100), 274 (25), 246 (27), 217 (25), 105 (36), 77 (37), 51 (14). HR-MS (ESI) *m/z* calcd for $C_{24}H_{17}NO_2^+$ $[M]^+$ 351.1259, found 351.1272. The analytical data are in accordance with those reported in the literature.[58]

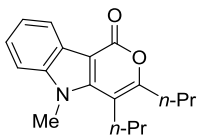


3,4-Bis(4-methoxyphenyl)-5-methylpyrano[4,3-*b*]indol-1(5*H*)-one (12lc): The general procedure **A** was followed using 1-methyl-1*H*-indole-3-carboxylic acid (**4l**) (351 mg, 2.00 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (**11c**) (240 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1 → 5/1) yielded isocoumarin **12lc** (215 mg, 52%) as an orange solid. M. p. = 235−240 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (m, 1H), 7.42–7.19 (m, 7H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 3.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.9 (C_q), 159.8 (C_q), 159.5 (C_q), 155.8 (C_q), 145.5 (C_q), 139.9 (C_q), 132.8 (CH), 130.9 (CH), 125.7 (C_q), 125.5 (C_q), 124.5 (CH), 123.9 (C_q), 122.6 (CH), 121.4 (CH), 114.6 (CH), 113.2 (CH), 109.3 (CH), 109.1 (C_q), 100.4 (C_q), 55.3 (CH_3), 55.2 (CH_3), 32.1 (CH_3). IR (neat): 2834, 1701, 1504, 1242, 1171, 1021, 835, 750 cm^{-1}. MS (EI): *m/z* (relative intensity) 411 ($[M]^+$ 14), 369 (100), 338 (8), 248 (11), 121 (16). HR-MS (ESI) *m/z* calcd for $C_{26}H_{21}NO_4^+$ $[M]^+$ 411.1471, found 411.1465.



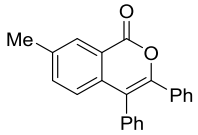
5-Benzyl-3,4-diphenylpyrano[4,3-*b*]indol-1(5*H*)-one (12ma): The general procedure **A** was followed using 1-benzyl-1*H*-indole-3-carboxylic acid (**4m**) (503 mg, 2.00 mmol) and diphenylacetylene (**11a**) (181 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1 → 10/1) yielded isocoumarin **12ma** (331 mg, 77%) as an orange solid. M. p. = 165−172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46–8.36 (m, 1H), 7.46–7.03 (m, 16H), 6.53 (dd, *J* = 7.3, 2.4 Hz, 2H), 4.94 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3 (C_q), 156.1 (C_q), 144.6 (C_q), 139.7 (C_q), 136.3 (C_q), 133.0 (C_q), 132.5 (C_q), 131.4 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.7 (CH), 127.2 (CH), 125.1 (CH), 125.0 (CH), 123.9 (C_q), 123.0 (CH), 121.5 (CH), 110.6 (C_q), 110.1 (CH), 101.4 (C_q), 47.6 (CH_2). IR (neat): 3028, 1715, 1452, 1139, 943, 751, 714, 693 cm^{-1}. MS (EI): *m/z*

(relative intensity) 427 ([M]$^+$ 95), 336 (62), 308 (27), 278 (20), 105 (78), 91 (100), 77 (63), 65 (20). HR-MS (ESI) *m/z* calcd for $C_{30}H_{21}NO_2^+$ [M]$^+$ 427.1572, found 427.1586.



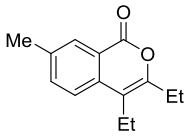
5-Methyl-3,4-di-*n*-propylpyrano[4,3-*b*]indol-1(5*H*)-one (12le): The general procedure **A** was followed using 1-methyl-1*H*-indole-3-carboxylic acid (**4l**) (351 mg, 2.00 mmol) and oct-4-yne (**11e**) (120 mg, 1.09 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1 → 5/1) yielded isocoumarin **12le** (253 mg, 82%) as a pale yellow solid. M. p. = 151−158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 7.3 Hz, 1H), 7.41–7.30 (m, 3H), 4.00 (s, 3H), 2.82–2.73 (m, 2H), 2.68–2.59 (m, 2H), 2.70–2.58 (m, 2H), 1.88–1.55 (m, 2H), 1.10 (t, *J* = 7.4 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.0 (C_q), 159.4 (C_q), 145.8 (C_q), 139.5 (C_q), 124.3 (C_q), 124.1 (CH), 122.5 (C_q), 121.3 (CH), 109.1 (CH), 107.2 (C_q), 101.2 (C_q), 32.8 (CH_2), 31.9 (CH_3), 28.1 (CH_2), 24.6 (CH_2), 21.7 (CH_2), 13.9 (CH_3), 13.9 (CH_3). IR (neat): 2955, 2866, 1706, 1464, 1067, 969, 751, 739 cm^{-1}. MS (EI): *m/z* (relative intensity) 283 ([M]$^+$ 58), 254 (100), 226 (12), 184 (16), 168 (10), 155 (9), 43 (15). HR-MS (ESI) *m/z* calcd for $C_{18}H_{21}NO_2^+$ [M]$^+$ 283.1572, found 283.1583.

Intramolecular Competition Experiments



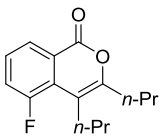
7-Methyl-3,4-diphenyl-1*H*-isochromen-1-one (12na): The general procedure **A** was followed using 3-methylbenzoic acid (**4n**) (278 mg, 2.04 mmol) and diphenylacetylene (**11a**) (178 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12na** (100 mg, 32%) as a colorless solid. M. p. = 176–177 °C (Lit.:[226] 171–176 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (m, 1H), 7.46–7.35 (m, 4H), 7.31 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.25–7.13 (m, 5H), 7.08 (d, *J* = 8.2 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (C_q), 150.1 (C_q), 138.4 (C_q), 136.4 (C_q), 135.9 (CH), 134.5 (C_q), 133.0 (C_q), 131.2 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 125.3 (CH), 120.3 (C_q), 116.8 (C_q), 21.2 (CH_3). IR (neat): 3058, 1722, 1494, 1073, 835, 692, 556, 496 cm^{-1}. MS (EI): *m/z* (relative intensity) 312 ([M]$^+$ 100), 284 (24), 235 (36), 207 (12), 178 (23), 105 (61), 77 (39). HR-MS (ESI) *m/z* calcd for $C_{22}H_{16}O_2^+$

$[M]^+$ 312.1150, found 312.1153. The analytical data are in accordance with those reported in the literature.[196]



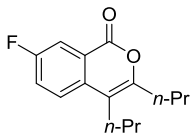
3,4-Diethyl-7-methyl-1*H*-isochromen-1-one (12nd): The general procedure **A** was followed using 3-methylbenzoic acid (**4n**) (278 mg, 2.04 mmol) and hex-3-yne (**11d**) (79.8 mg, 0.97 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarin **12nd** (105 mg, 50%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (m, 1H), 7.54 (dd, J = 8.3, 2.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 2.62 (q, J = 7.5 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.45 (s, 3H), 1.27 (t, J = 7.5 Hz, 3H), 1.19 (t, J = 7.5 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (C_q), 150.1 (C_q), 138.4 (C_q), 136.4 (C_q), 135.9 (CH), 134.5 (C_q), 133.0 (C_q), 131.2 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 125.3 (CH), 120.3 (C_q), 116.8 (C_q), 21.2 (CH_3). IR (neat): 2972, 1713, 1641, 1172, 1111, 833, 789, 495 cm^{-1}. MS (EI): *m/z* (relative intensity) 216 ($[M]^+$ 100), 201 (84), 175 (79), 159 (33), 145 (82), 115 (51), 91 (40). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_2^+$ $[M]^+$ 216.1150, found 216.1156.

5-Fluoro-3,4-dipropyl-1*H*-isochromen-1-one (12ie) and 7-Fluoro-3,4-dipropyl-1*H*-isochromen-1-one (12ie'): The general procedure **A** was followed using 3-fluorobenzoic acid (**4i**) (286 mg, 2.04 mmol) and oct-4-yne (**11e**) (110 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 10/1) yielded isocoumarins **12ie** (80.6 mg, 32%) and **12ie'** (11.9 mg, 5%) as colorless oils.



(**12ie**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (m, 1H), 7.43–7.33 (m, 2H), 2.66 (td, J = 8.1, 3.0 Hz, 2H), 2.56 (t, 2H), 1.73 (h, J = 7.4 Hz, 2H), 1.56 (h, J = 7.3 Hz, 2H), 1.00 (td, J = 7.4, 4.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (d, $J_{C–F}$ = 253 Hz, C_q), 154.5 (d, $J_{C–F}$ = 2 Hz, C_q), 127.9 (d, $J_{C–F}$ = 9 Hz, CH), 126.5 (d, $J_{C–F}$ = 10 Hz, C_q), 126.0 (d, $J_{C–F}$ = 4 Hz, CH), 123.0 (d, $J_{C–F}$ = 4 Hz, C_q), 121.9 (d, $J_{C–F}$ = 24 Hz, CH), 110.3 (C_q), 110.3 (C_q), 32.5 (d, $J_{C–F}$ = 11 Hz, CH_2), 30.1 (d, $J_{C–F}$ = 11 Hz, CH_2), 23.9 (d, $J_{C–F}$ = 4 Hz, CH_2), 21.5 (CH_2), 14.1 (CH_3), 13.7 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$): −115.31 (s). IR (neat): 2962, 2872, 1725, 1630, 1463, 1172, 1064, 757 cm^{-1}. MS (EI): *m/z* (relative intensity) 248 ($[M]^+$ 45), 219 (100), 163

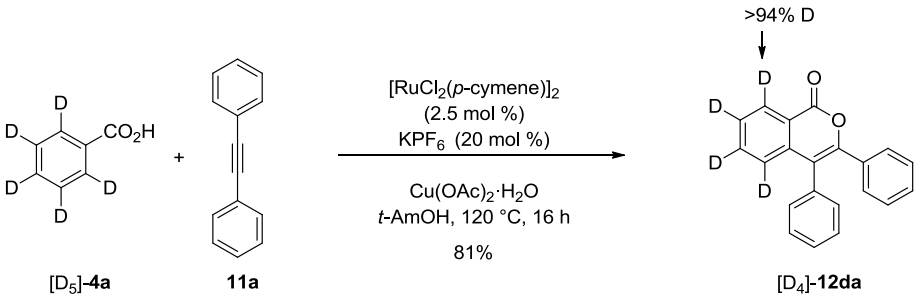
(15), 149 (84), 133 (18), 120 (16), 43 (42). HR-MS (ESI) *m/z* calcd for $C_{15}H_{17}FO_2^+$ $[M]^+$ 248.1213, found 248.1213.



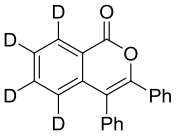
(12ie'): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (m, 1H), 7.43–7.35 (m, 2H), 2.66 (td, *J* = 8.1, 3.0 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 1.73 (h, *J* = 7.4 Hz, 2H), 1.56 (h, *J* = 7.4 Hz, 2H), 1.00 (td, *J* = 7.4, 4.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8 (d, $J_{C–F}$ = 249 Hz, C_q), 154.5 (d, $J_{C–F}$ = 2 Hz, C_q), 127.9 (d, $J_{C–F}$ = 9 Hz, CH), 126.5 (d, $J_{C–F}$ = 10 Hz, C_q), 125.1 (d, $J_{C–F}$ = 8 Hz, CH), 122.7 (d, $J_{C–F}$ = 23 Hz, CH), 115.2 (d, $J_{C–F}$ = 23 Hz, CH), 111.7 (C_q), 111.7 (C_q), 32.5 (CH_2), 28.3 (CH_2), 22.9 (CH_2), 21.1 (CH_2), 14.1 (CH_3), 13.8 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$): –112.92 (td, *J* = 8, 5 Hz). IR (neat): 2962, 2872, 1717, 1493, 1266, 1085, 831, 544 cm^{-1}. MS (EI): *m/z* (relative intensity) 248 ($[M]^+$ 52), 219 (90), 191 (27), 163 (15), 149 (100), 133 (18), 120 (16), 43 (65). HR-MS (ESI) *m/z* calcd for $C_{15}H_{17}FO_2^+$ $[M]^+$ 248.1213, found 248.1214.

Mechanistic Studies

Experiments with Isotopically-Labeled Substrates

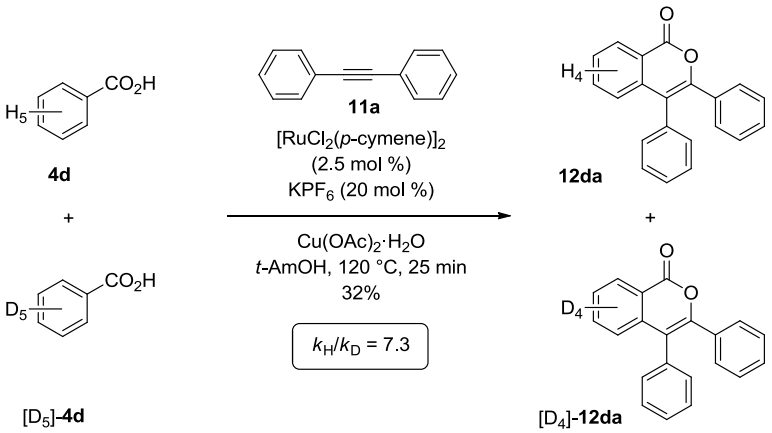


A mixture of 1,2,3,4,5-pentadeuteriobenzoic acid ([D_5]-**4a**) (254 mg, 2.00 mmol), diphenylacetylene (**11a**) (180 mg, 1.01 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 25.2 µmol, 2.5 mol %), KPF_6 (37.2 mg, 0.20 mmol, 20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.00 mmol) in *t*-AmOH (3.0 mL) was stirred at 120 °C for 16 h. At ambient temperature, the reaction mixture was diluted with a solution of saturated aq. NH_4Cl/NH_3 (1:1, 20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel to yield [D_4]-**12da** (247 mg, 81%) as a colorless solid.



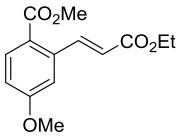
([D_4]-**12da**)**:** M. p. = 174−178 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.61–7.13 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 160.9 (C_q), 150.3 (C_q), 137.9 (C_q), 134.7 (t, $J_{C–D}$ = 24 Hz, CD), 133.6 (C_q), 132.6 (C_q), 131.0 (CH), 129.0 (CH), 128.8 (CH), 128.8 (CH), 128.4 (t, $J_{C–D}$ = 24 Hz, CD), 128.3 (t, $J_{C–D}$ = 24 Hz, CD), 128.0 (CH), 127.8 (CH), 124.5 (t, $J_{C–D}$ = 24 Hz, CD), 119.5 (C_q), 116.4 (C_q). IR (neat): 3047, 1729, 1307, 1075, 690, 584 cm^{-1}. MS (EI): *m/z* (relative intensity) 302 ([M]$^+$ 100), 274 (34), 224 (33), 169 (30), 105 (67), 77 (55), 51 (14). HR-MS (ESI) *m/z* calcd for $C_{21}H_{10}D_4O_2^+$ [M]$^+$ 302.1245, found 302.1243.

Intermolecular Competition Experiment between Substrates 4d and [D_5]-4d

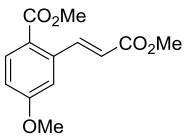


A mixture of benzoic acid (**4d**) (357 mg, 2.92 mmol), 1,2,3,4,5-pentadeuteriobenzoic acid ([D_5]-**4d**) (371 mg, 2.92 mmol), diphenylacetylene (**11a**) (180 mg, 1.01 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (15.8 mg, 25.8 µmol, 2.5 mol %), KPF_6 (37.0 mg, 0.20 mmol, 20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.00 mmol) in *t*-AmOH (3.0 mL) was stirred at 120 °C. After 25 min, a solution of saturated aq. NH_4Cl/NH_3 (1:1, 20 mL) was added, and the reaction mixture was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with aq. NH_4Cl/NH_3 solution (1:1, 2 × 20 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel to yield [D_n]-**12da** (96 mg, 32%) as a colorless solid. The ratio of **12da**/[D_4]-**12da** was determined to be 88/12 by ^{1}H NMR spectroscopy.

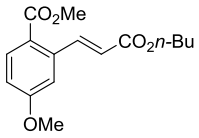
6.3.2 Analytical Data for the Ruthenium(II)-Catalyzed Alkenylation Reaction



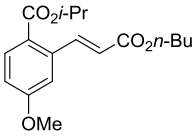
Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-methoxybenzoate (7ab): The general procedure **B** was followed using methyl 4-methoxybenzoate (**6a**) (83.3 mg, 0.50 mmol) and ethyl acrylate (**1b**) (110 mg, 1.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded styrene **7ab** (81.9 mg, 62%) as a colorless solid. The general procedure **C** was followed using methyl 4-methoxybenzoate (**6a**) (83.3 mg, 0.50 mmol) and ethyl acrylate (**1b**) (110 mg, 1.10 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded styrene **7ab** (72.6 mg, 55%) as a colorless solid. M. p. = 44−48 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 15.9 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7 (C_q), 166.5 (C_q), 162.5 (C_q), 144.2 (CH), 139.0 (C_q), 133.1 (CH), 121.8 (C_q), 121.2 (CH), 114.6 (CH), 113.0 (CH), 60.6 (CH_2), 55.5 (CH_3), 52.1 (CH_3), 14.3 (CH_3). IR (neat): 2950, 2844, 1701, 1234, 1173, 1123, 1021, 974, 849 cm^{-1}. MS (EI): *m/z* (relative intensity) 264 ($[M]^+$ 7), 219 (9), 191 (99), 177 (8), 161 (12), 159 (8) 148 (14), 77 (4). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_5^+$ $[M]^+$ 264.0998, found 264.0999.



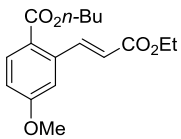
Methyl (*E*)-4-Methoxy-2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (7aa): The general procedure **B** was followed using methyl 4-methoxybenzoate (**7aa**) (83.8 mg, 0.50 mmol) and methyl acrylate (**1a**) (87.7 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded styrene **7aa** (78.0 mg, 62%) as a colorless solid. M. p. = 68−70 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.51 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.9 (C_q), 166.7 (C_q), 162.5 (C_q), 144.5 (CH), 139.0 (C_q), 133.1 (CH), 121.8 (C_q), 120.8 (CH), 114.6 (CH), 113.1 (CH), 55.5 (CH_3), 52.1 (CH_3), 51.8 (CH_3). IR (neat): 2954, 1708, 1253, 1175, 1123, 1019, 851, 780 cm^{-1}. MS (EI): *m/z* (relative intensity) 250 ($[M]^+$ 5), 219 (7), 191 (99), 176 (8), 160 (12), 148 (16), 89 (17), 77 (5). HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}O_5^+$ $[M]^+$ 250.0841, found 250.0842.



Methyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-4-methoxybenzoate (7ac): The general procedure **B** was followed using methyl 4-methoxybenzoate (**6a**) (83.8 mg, 0.50 mmol) and *n*-butyl acrylate (**1c**) (133 mg, 1.04 mmol). Purification by column chromatography (*n*-pentane/EtOAc: 50/1) yielded styrene **7ac** (86.6 mg, 59%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.6 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.77−1.63 (m, 2H), 1.51−1.37 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7 (C_q), 166.6 (C_q), 162.5 (C_q), 144.2 (CH), 139.0 (C_q), 133.1 (CH), 121.9 (C_q), 121.2 (CH), 114.6 (CH), 113.0 (CH), 64.5 (CH_2), 55.5 (CH_3), 52.1 (CH_3), 30.7 (CH_2), 19.2 (CH_2), 13.8 (CH_3). IR (neat): 2957, 1708, 1599, 1254, 1168, 1126, 1088, 1032 cm^{-1}. MS (EI): *m/z* (relative intensity) 292 ([M]$^+$ 3), 219 (6), 191 (99), 177 (8), 161 (7), 148 (11), 89 (5), 77 (4). HR-MS (ESI) *m/z* calcd for $C_{16}H_{20}O_5^+$ [M]$^+$ 292.1311, found 292.1313.

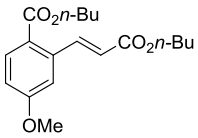


***iso*-Propyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-4-methoxybenzoate (7bc):** The general procedure **B** was followed using *iso*-propyl 4-methoxybenzoate (**6b**) (98.9 mg, 0.51 mmol) and *n*-butyl acrylate (**1c**) (132 mg, 1.03 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 100/1→50/1) yielded styrene **7bc** (102 mg, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 15.9 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 5.24 (tq, *J* = 6.3 Hz, 1H), 4.22 (t, *J* = 6.7 Hz, 2H), 3.87 (s, 3H), 1.70 (q, *J* = 7.4 Hz, 2H), 1.44 (q, J = 7.4 Hz, 2H), 1.37 (d, *J* = 6.3 Hz, 6H), 0.96 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.5 (C_q), 165.8 (C_q), 162.2 (C_q), 144.3 (CH), 138.5 (C_q), 132.9 (CH), 122.8 (C_q), 120.8 (CH), 114.6 (CH), 112.9 (CH), 68.7 (CH), 64.5 (CH_2), 55.5 (CH_3), 30.8 (CH_2), 22.0 (CH_3), 19.3 (CH_2), 13.8 (CH_3). IR (neat): 2960, 2873, 1704, 1254, 1169, 1135, 1104, 1031 cm^{-1}. MS (EI): *m/z* (relative intensity) 320 ([M]$^+$ 4), 278 (4), 219 (13), 205 (6), 178 (16), 177 (99) 161 (14), 77 (3). HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}O_5^+$ [M]$^+$ 320.1624, found 320.1629.

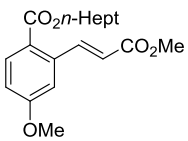


***n*-Butyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-methoxybenzoate (7cb):** The general procedure **B** was followed using *n*-butyl 4-methoxybenzoate (**6c**) (106 mg, 0.51 mmol) and ethyl acrylate (**1b**) (99.5 mg, 0.99 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7cb**

(87.5 mg, 56%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 15.8 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 4.35−4.10 (m, 4H), 3.85 (s, 3H), 1.83−1.65 (m, 2H), 1.53−1.39 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4 (C_q), 166.4 (C_q), 162.3 (C_q), 144.4 (CH), 138.8 (C_q), 133.0 (CH), 122.2 (C_q), 121.0 (CH), 114.6 (CH), 113.0 (CH), 65.0 (CH_2), 60.5 (CH_2), 55.5 (CH_3), 30.7 (CH_2), 19.3 (CH_2), 14.3 (CH_3), 13.7 (CH_3). IR (neat): 2960, 2935, 1706, 1251, 1251, 1171, 1126, 1086, 1031 cm^{-1}. MS (EI): *m/z* (relative intensity) 306 ($[M]^+$ 4), 233 (35), 203 (10), 177 (99), 161 (20), 118 (5), 89 (6), 77 (5). HR-MS (ESI) *m/z* calcd for $C_{17}H_{22}O_5^+$ $[M]^+$ 306.1467, found 306.1466.

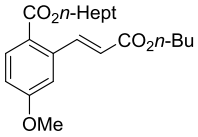


***n*-Butyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-4-methoxybenzoate (7cc):** The general procedure **B** was followed using *n*-butyl 4-methoxybenzoate (**6c**) (107 mg, 0.51 mmol) and *n*-butyl acrylate (**1c**) (128 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7cc** (97.4 mg, 57%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 4.30 (t, *J* = 6.6 Hz, 2H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.87 (s, 3H), 1.80−1.62 (m, 4H), 1.54−1.33 (m, 4H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6 (C_q), 166.4 (C_q), 162.4 (C_q), 144.4 (CH), 138.9 (C_q), 133.1 (CH), 122.4 (C_q), 121.1 (CH), 114.6 (CH), 113.0 (CH), 65.0 (CH_2), 64.5 (CH_2), 55.5 (CH_3), 30.8 (CH_2), 30.7 (CH_2), 19.3 (CH_2), 19.2 (CH_2), 13.7 (CH_3), 13.7 (CH_3). IR (neat): 2959, 2873, 1707, 1599, 1251, 1169, 1126, 1085, 1032 cm^{-1}. MS (EI): *m/z* (relative intensity) 334 ($[M]^+$ 3), 261 (4), 233 (36), 203 (7), 178 (13), 177 (99) 161 (21), 77 (4). HR-MS (ESI) *m/z* calcd for $C_{19}H_{26}O_5^+$ $[M]^+$ 334.1780, found 334.1784.

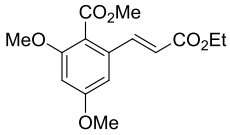


***n*-Heptyl (*E*)-4-Methoxy-2-(3-methoxy-3-oxoprop-1-en-1-yl)benzoate (7da):** The general procedure **B** was followed using *n*-heptyl 4-methoxybenzoate (**6d**) (134 mg, 0.54 mmol) and methyl acrylate (**1a**) (87 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7da** (121 mg, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.25 (d, *J* = 15.9 Hz,

1H), 4.28 (t, *J* = 6.7 Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 1.82−1.64 (m, 2H), 1.49−1.18 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.9 (C_q), 166.3 (C_q), 162.4 (C_q), 144.6 (CH), 138.8 (C_q), 133.0 (CH), 122.2 (C_q), 120.6 (CH), 114.6 (CH), 113.0 (CH), 65.3 (CH_2), 55.5 (CH_3), 51.7 (CH_3), 31.7 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 26.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3). IR (neat): 2929, 2856, 1707, 1251, 1192, 1168, 1126, 1033 cm^{-1}. MS (EI): *m/z* (relative intensity) 334 ($[M]^+$ 7), 275 (26), 203 (7), 191 (7), 178 (15) 177 (99), 161 (8), 77 (2). HR-MS (ESI) *m/z* calcd for $C_{19}H_{26}O_5^+$ $[M]^+$ 334.1780, found 334.1781.

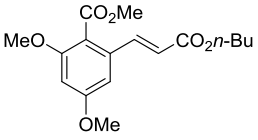


***n*-Heptyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-4-methoxybenzoate (7dc):** The general procedure **B** was followed using *n*-heptyl 4-methoxybenzoate (**6d**) (115 mg, 0.46 mmol) and *n*-butyl acrylate (**1c**) (131 mg, 1.02 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded styrene **7dc** (106 mg, 61%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 15.9 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 4.29 (t, *J* = 6.7 Hz, 2H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.87 (s, 3H), 1.79−1.61 (m, 4H), 1.52 – 1.25 (m, 10H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.5 (C_q), 166.4 (C_q), 162.4 (C_q), 144.4 (CH), 138.9 (C_q), 133.0 (CH), 122.4 (C_q), 121.1 (CH), 114.6 (CH), 113.0 (CH), 65.3 (CH_2), 64.5 (CH_2), 55.5 (CH_3), 31.7 (CH_2), 30.8 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 26.0 (CH_2), 22.6 (CH_2), 19.2 (CH_2), 14.0 (CH_3), 13.7 (CH_3). IR (neat): 2956, 2929, 2857, 1708, 1252, 1169, 1126, 10832 cm^{-1}. MS (EI): *m/z* (relative intensity) 376 ($[M]^+$ 2), 275 (32), 203 (17), 178 (14, 177 (99), 161 (22) 43 (9), 44 (16). HR-MS (ESI) *m/z* calcd for $C_{22}H_{32}O_5^+$ $[M]^+$ 376.2250, found 376.2249.

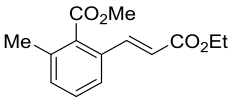


Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4,6-dimethoxybenzoate (7eb): The general procedure **B** was followed using methyl 2,4-dimethoxybenzoate (**6e**) (102 mg, 0.52 mmol) and ethyl acrylate (**1b**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded styrene **7eb** (82.5 mg, 54%) as a colorless solid. M. p. = 88−90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 15.9 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 1.32 (t, *J* = 7.1 Hz,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.5 (C_q), 166.3 (C_q), 161.6 (C_q), 158.4 (C_q), 141.4 (CH), 134.8 (C_q), 121.3 (CH), 117.1 (C_q), 102.2 (CH), 100.2 (CH), 60.6 (CH_2), 56.0 (CH_3), 55.5 (CH_3), 52.5 (CH_3), 14.2 (CH_3). IR (neat): 2962, 1703, 1267, 1202, 1157, 1096, 1045, 979 cm^{-1}. MS (EI): *m/z* (relative intensity) 294 ([M]$^+$ 7), 263 (5), 249 (6), 233 (5), 222 (15), 221 (99), 207 (10), 191 (13). HR-MS (ESI) *m/z* calcd for $C_{15}H_{18}O_6^+$ [M]$^+$ 294.1103, found 294.1101.

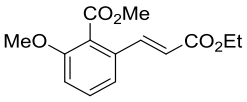


Methyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-4,6-dimethoxybenzoate (7ec): The general procedure **B** was followed using methyl 2,4-dimethoxybenzoate (**6e**) (98.3 mg, 0.50 mmol) and *n*-butyl acrylate (**1c**) (130 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1) yielded styrene **7ec** (90.2 mg, 56%) as a colorless solid. M. p. = 69−71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 15.8 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 1.76−1.59 (m, 2H), 1.51−1.32 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.5 (C_q), 166.4 (C_q), 161.6 (CH), 158.4 (C_q), 141.4 (CH), 134.8 (C_q), 121.3 (CH), 117.1 (C_q), 102.2 (CH), 100.2 (CH), 64.6 (CH_2), 56.1 (CH_3), 55.5 (CH_3), 52.5 (CH_3), 30.7 (CH_2), 19.2 (CH_2), 13.7 (CH_3). IR (neat): 2984, 2841, 1711, 1266, 1235, 1202, 1041, 832 cm^{-1}. MS (EI): *m/z* (relative intensity) 322 ([M]$^+$ 4), 249 (5), 222 (16), 221 (99), 207 (15), 191 (15) 178 (6), 41 (11). HR-MS (ESI) *m/z* calcd for $C_{17}H_{22}O_6^+$ [M]$^+$ 322.1416, found 322.1415.

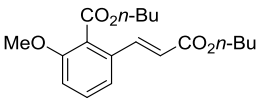


Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-6-methylbenzoate (7fb): The general procedure **B** was followed using methyl 2-methylbenzoate (**6f**) (75.2 mg, 0.50 mmol) and ethyl acrylate (**1b**) (103 mg, 1.03 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7fb** (59.8 mg, 48%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 15.8 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 7.6, 7.4, Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 2.33 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.2 (C_q), 166.4 (C_q), 141.6 (CH), 135.8 (C_q), 134.0 (C_q), 132.3 (C_q), 131.6 (CH), 129.7 (CH), 123.9 (CH), 120.7 (CH), 60.5 (CH_2), 52.3 (CH_3), 19.6 (CH_3), 14.2 (CH_3). IR (neat): 2983, 2953, 1711, 1267, 1229, 1165, 1116, 1072 cm^{-1}. MS (EI): *m/z* (relative intensity)

248 ([M]$^+$ 5), 203 (12), 189 (35), 175 (99), 161 (32), 147 (80) 132 (18), 115 (37). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_4^+$ [M]$^+$ 248.1049, found 248.1048. The analytical data are in accordance with those reported in the literature.[47]

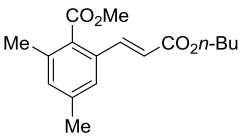


Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-6-methoxybenzoate (7gb): The general procedure **B** was followed using methyl 2-methoxybenzoate (**6g**) (88.9 mg, 0.53 mmol) and ethyl acrylate (**1b**) (103 mg, 1.03 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1→17/1) yielded styrene **7gb** (73.5 mg, 52%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 15.9 Hz, 1H), 7.37 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.22 (dd, *J* = 8.2, 7.8 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 3.85 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6 (C_q), 166.3 (C_q), 156.7 (C_q), 140.9 (CH), 133.3 (C_q), 130.8 (CH), 124.1 (C_q), 121.4 (CH), 118.6 (CH), 112.3 (CH), 60.6 (CH_2), 56.1 (CH_3), 52.6 (CH_3), 14.3 (CH_3). IR (neat): 2981, 2951, 1709, 1258, 1173, 1113, 1066, 1030 cm^{-1}. MS (EI): *m/z* (relative intensity) 264 ([M]$^+$ 7), 219 (7), 203 (9), 191 (99), 177 (19), 161 (13) 89 (6), 77 (5). HR-MS (ESI) *m/z* calcd for $C_{14}H_{16}O_5^+$ [M]$^+$ 264.0998, found 264.1001.

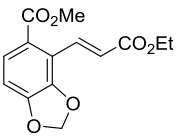


***n*-Butyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-6-methoxybenzoate (7hc):** The general procedure **B** was followed using *n*-butyl 2-methoxybenzoate (**6h**) (106 mg, 0.51 mmol) and *n*-butyl acrylate (**1c**) (200 mg, 1.56 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1→10/1→6/1) yielded styrene **7hc** (106 mg, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 15.9 Hz, 1H), 7.35 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 4.37 (t, *J* = 6.7 Hz, 2H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.84 (s, 3H), 1.87−1.55 (m, 4H), 1.54−1.30 (m, 4H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.2 (C_q), 166.3 (C_q), 156.6 (C_q), 140.9 (CH), 133.3 (C_q), 130.6 (CH), 124.5 (C_q), 121.4 (CH), 118.6 (CH), 112.3 (CH), 65.5 (CH_2), 64.5 (CH_2), 56.0 (CH_3), 30.7 (CH_2), 30.6 (CH_2), 19.2 (CH_2), 19.1 (CH_2), 13.7 (CH_3), 13.6 (CH_3). IR (neat): 2959, 2935, 2873, 1713, 1260, 1168, 1112, 1066 cm^{-1}. MS (EI): *m/z* (relative intensity) 334 ([M]$^+$ 5), 261 (8), 233

(35), 203 (8), 178 (14), 177 (99), 161 (18), 41 (14). HR-MS (ESI) *m/z* calcd for $C_{19}H_{26}O_5^+$ $[M]^+$ 334.1780, found 334.1781.

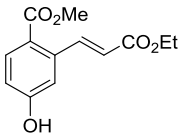


Methyl (*E*)-2-(3-*n*-Butoxy-3-oxoprop-1-en-1-yl)-4,6-dimethylbenzoate (7ic): The general procedure **B** was followed using methyl 2,4-dimethylbenzoate (**6i**) (82.9 mg, 0.50 mmol) and *n*-butyl acrylate (**1c**) (129 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7ic** (83.3 mg, 57%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 15.9 Hz, 1H), 7.27 (s, 1H), 7.05 (s, 1H), 6.35 (d, *J* = 15.9 Hz, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 3.93 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 1.77−1.60 (m, 2H), 1.52−1.37 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.4 (C_q), 166.6 (C_q), 142.0 (CH), 139.7 (C_q), 136.0 (C_q), 132.6 (CH), 132.5 (C_q), 131.3 (C_q), 124.6 (CH), 120.4 (CH), 64.4 (CH_2), 52.2 (CH_3), 30.7 (CH_2), 21.2 (CH_3), 19.7 (CH_3), 19.2 (CH_2), 13.7 (CH_3). IR (neat): 2957, 2873, 1711, 1258, 1165, 1083, 975, 853 cm^{-1}. MS (EI): *m/z* (relative intensity) 290 ($[M]^+$ 5), 231 (15), 189 (99), 175 (46), 159 (14), 146 (13) 115 (12), 77 (5). HR-MS (ESI) *m/z* calcd for $C_{17}H_{22}O_4^+$ $[M]^+$ 290.1518, found 290.1516.

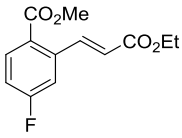


Methyl (*E*)-4-(3-Ethoxy-3-oxoprop-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate (7jb): The general procedure **B** was followed using methyl benzo[*d*][1,3]dioxole-5-carboxylate (**6j**) (90.9 mg, 0.50 mmol) and ethyl acrylate (**1b**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7jb** (103 mg, 74%) as a colorless solid. The general procedure **C** was followed using methyl benzo[*d*][1,3]dioxole-5-carboxylate (**6j**) (90.9 mg, 0.50 mmol) and ethyl acrylate (**1b**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrene **7jb** (84.9 mg, 61%) as a colorless solid. M. p. = 84−85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 16.3 Hz, 1H), 7.58 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.80 (dd, *J*=8.3, 0.8 Hz, 1H), 6.72 (dd, *J* = 16.3, 0.8 Hz, 1H), 6.12 (d, *J* = 0.8 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.89 (d, *J* = 0.8 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (C_q), 166.7 (C_q), 150.7 (C_q), 147.2 (C_q), 137.3 (CH), 126.5 (CH), 123.9 (CH), 123.8 (C_q) 118.2 (C_q), 108.2 (CH), 102.1 (CH_2), 60.5 (CH_2), 52.2 (CH_3), 14.3

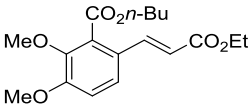
(CH_3). IR (neat): 2980, 2954, 1706, 1447, 1255, 1121, 1025, 778 cm^{-1}. MS (EI): *m/z* = 278 ($[M]^+$ 17), 233 (11), 217 (17), 206 (20), 205 (100), 190 (12), 173 (13), 162 (12), 87 (8). HR-MS (ESI) *m/z* calcd for $C_{14}H_{14}O_6^+$ $[M]^+$ 278.0790, found 279.0792.



Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-hydroxybenzoate (7kb): The general procedure **B** was followed using methyl 4-hydroxybenzoate (**6k**) (76.2 mg, 0.50 mmol) and ethyl acrylate (**1b**) (106 mg, 1.06 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded styrene **7kb** (45.1 mg, 36%) as a colorless solid. M. p. = 91−94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 15.9 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 6.88 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.74 (s, 1H), 6.21 (d, *J* = 15.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.2 (C_q), 166.9 (C_q), 159.6 (C_q), 144.6 (CH), 139.0 (C_q), 133.4 (CH), 121.5 (C_q), 120.9 (CH), 116.5 (CH), 114.7 (CH), 61.0 (CH_2), 52.2 (CH_3), 14.2 (CH_3). IR (neat): 3360, 3317, 1694, 1185, 1119, 972, 857, 788 cm^{-1}. MS (EI): *m/z* (relative intensity) 250 ($[M]^+$ 4), 205 (10), 177 (100), 147 (9), 134 (12), 43 (21). HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}O_5^+$ $[M]^+$ 250.0841, found 250.0836.



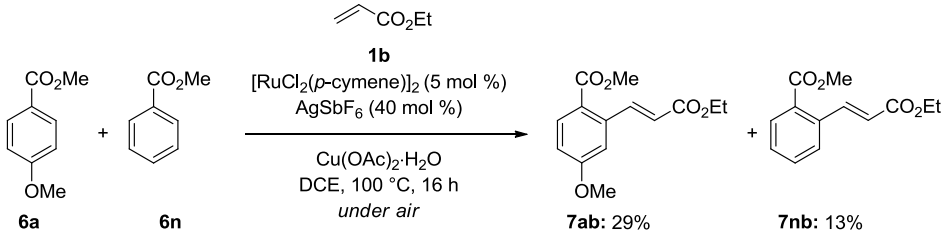
Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-fluorobenzoate (7lb): The general procedure **B** was followed using methyl 4-fluorobenzoate (**6l**) (79.0 mg, 0.51 mmol) and ethyl acrylate (**1b**) (100 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded styrene **7lb** (47.1 mg, 37%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, *J* = 15.9 Hz, 1H), 8.01 (dd, *J* = 8.7, 5.8 Hz, 1H), 7.30−7.21 (m, 1H), 7.11 (ddd, *J* = 8.7, 7.7, 2.6 Hz, 1H), 6.28 (dd, *J* = 15.9, 0.9 Hz, 1H), 4.28 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.92 (d, *J* = 1.0 Hz, 3H), 1.34 (td, *J* = 7.1, 1.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2 (C_q), 166.2 (C_q), 164.7 (d, J_{C-F} = 254 Hz, C_q), 142.5 (d, J_{C-F} = 2 Hz, CH), 139.6 (d, J_{C-F} = 9 Hz, C_q), 133.5 (d, J_{C-F} = 9 Hz, CH), 125.8 (d, J_{C-F} = 3 Hz, C_q), 122.2 (CH), 116.3 (d, J_{C-F} = 22 Hz, CH), 114.8 (d, J_{C-F} = 23 Hz, CH), 60.7 (CH_2), 52.4 (CH_3), 14.3 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$) δ = -106.15 (dddd, *J* = 9.4, 7.4, 5.8, 1.5 Hz). IR (neat): 2984, 2955, 1711, 1251, 1213, 1176, 1117, 1077 cm^{-1}. MS (EI): *m/z* (relative intensity) 264 ($[M]^+$ 7), 252 (3), 207 (12), 180 (26), 179 (99), 151 (19) 136 (12), 94 (9). HR-MS (ESI) *m/z* calcd for $C_{13}H_{13}FO_4^+$ $[M]^+$ 252.0798, found 252.0800.



(*E*)-*n*-Butyl-6-(3-Ethoxy-3-oxoprop-1-en-1-yl)-2,3-dimethoxybenzoate (7mb): The general procedure **C** was followed using *n*-butyl 2,3-dimethoxybenzoate (**6m**) (124.0 mg, 0.52 mmol) and ethyl acrylate (**1b**) (103 mg, 1.03 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 20/1→15/1→8/1) yielded styrene **7mb** (126 mg, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 15.9 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.27 (d, *J* = 15.9 Hz, 1H), 4.39 (t, *J* = 6.7 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 1.84−1.65 (m, 2H), 1.54−1.38 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.8 (C_q), 166.6 (C_q), 154.0 (C_q), 146.0 (C_q), 140.6 (CH), 130.2 (C_q), 124.8 (C_q), 123.0 (CH), 118.8 (CH), 113.4 (CH), 65.6 (CH_2), 61.6 (CH_3), 60.4 (CH_2), 56.0 (CH_3), 30.6 (CH_2), 19.1 (CH_2), 14.3 (CH_3), 13.6 (CH_3). IR (neat): 2960, 2938, 1709, 1490, 1246, 1176, 1158, 1055 cm^{-1}. MS (EI): *m/z* (relative intensity) 336 ([M]$^+$ 13), 263 (29), 235 (19), 233 (49), 207 (99), 192 (24) 176 (9), 147 (9). HR-MS (ESI) *m/z* calcd for $C_{18}H_{24}O_6^+$ [M]$^+$ 336.1573, found 336.1585.

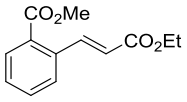
Mechanistic Studies

Intermolecular Competition Experiments



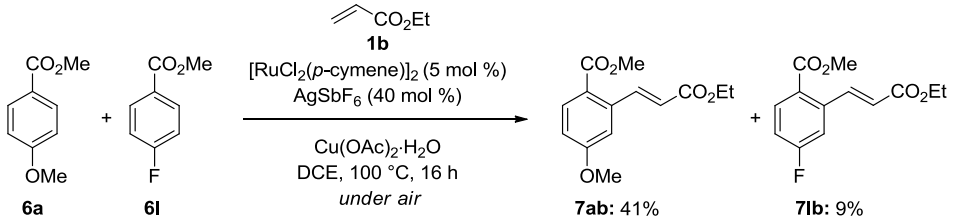
The general procedure **B** was followed. A suspension of methyl 4-methoxybenzoate (**6a**) (250 mg, 1.50 mmol), methyl benzoate (**6n**) (208 mg, 1.53 mmol), ethyl acrylate (**1b**) (103 mg, 1.03 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31.5 mg, 51.5 µmol, 5.0 mol %), $AgSbF_6$ (141.6 mg, 0.41 mmol, 40 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in DCE (2.0 mL) was pre-stirred at ambient temperature for 5 min. Thereafter, the reaction mixture was stirred at 100 °C for 16 h under an atmosphere of ambient air. The reaction mixture was diluted with sat. aq. NH_4Cl/NH_3 (1:1, 10 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers

were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude products were purified by column chromatography on silica gel (*n*-hexane/EtOAc: 60/1→30/1→15/1) to yield **7ab** (79.7 mg, 29%) and **7nb** (31.6 mg, 13%) as colorless oils.



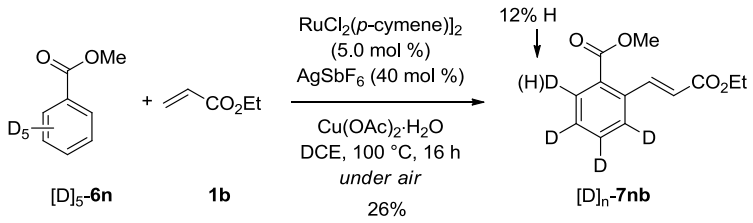
Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)benzoate (7nb):

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.42 (d, *J* = 15.9 Hz, 1H), 7.95 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 7.8, 7.5, 1.4 Hz, 1H), 7.42 (ddd, *J* = 7.8, 7.5, 1.5 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.1 (C_q), 166.5 (C_q), 143.6 (CH), 136.4 (C_q), 132.3 (CH), 130.7 (CH), 129.8 (C_q), 129.3 (CH), 127.9 (CH), 121.1 (CH), 60.5 (CH_2), 52.3 (CH_3), 14.3 (CH_3). IR (neat): 2983, 2953, 1710, 1255, 1175, 1129, 1076, 763 cm^{-1}. MS (EI): *m/z* (relative intensity) 234 ([M]$^+$ 3), 173 (10), 161 (99), 147 (8), 129 (9), 118 (8) 101 (8), 76 (7). HR-MS (ESI) *m/z* calcd for $C_{13}H_{14}O_4^+$ [M]$^+$ 234.0892, found 234.0890. The analytical data are in accordance with those reported in the literature.[197]

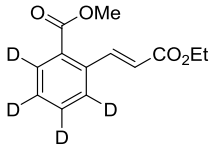


The general procedure **B** was followed using methyl 4-methoxybenzoate (**6a**) (250 mg, 1.50 mmol), methyl 4-fluorobenzoate (**6l**) (236 mg, 1.53 mmol), ethyl acrylate (**1b**) (105 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (32.2 mg, 52.5 µmol, 5.0 mol %), $AgSbF_6$ (141.6 mg, 0.41 mmol, 40 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (201 mg, 1.01 mmol). Purification by column chromatography (*n*-hexane/EtOAc: 50/1→25/1) yielded styrenes **7ab** (113 mg, 41%) and **7lb** (23.4 mg, 9%) as colorless oils.

Experiments with Isotopically Labeled Substrate

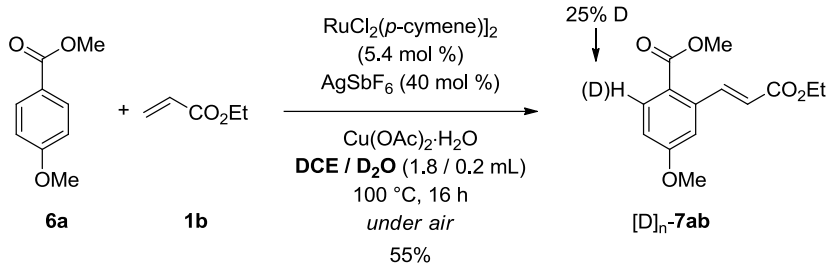


A mixture of methyl 1,2,3,4,5-pentadeuteriobenzoate ([D]$_5$-**6n**) (75.1 mg, 0.53 mmol), ethyl acrylate (**1b**) (107 mg, 1.07 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (16.1 mg, 26.2 µmol, 5.0 mol %), $AgSbF_6$ (72.8 mg, 0.21 mmol, 40 mol %) and $Cu(OAc)_2 \cdot H_2O$ (200 mg, 1.00 mmol) in DCE (2.0 mL) was stirred at ambient temperature for 5 min. Thereafter, the reaction mixture was stirred at 100 °C for 16 h under an atmosphere of ambient air. The reaction mixture was diluted with a solution of saturated aq. NH_4Cl/NH_3 (1:1, 20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 60/1→30/1→10/1) to yield [D]$_n$-**7nb** (32.6 mg, 26%) as a colorless oil. The H-incorporation in [D]$_n$-**7nb** was estimated by ^{1}H NMR spectroscopy.



Methyl (*E*)-2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-3,4,5,6-tetradeuteriobenzoate ([D]$_n$-7nb): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, *J* = 15.9 Hz, 1H), 6.30 (d, *J* = 15.9 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.0 (C_q), 166.4 (C_q), 143.5 (CH), 136.2 (C_q), 131.7 (t, J_{C-D} = 24 Hz, CD), 130.3 (t, J_{C-D} = 24 Hz, CD), 129.6 (C_q), 128.7 (t, J_{C-D} = 24 Hz, CD), 127.4 (t, J_{C-D} = 24 Hz, CD), 121.1 (CH), 60.6 (CH_2), 52.4 (CH_3), 14.4 (CH_3). IR (neat): 2982, 2954, 1710, 1264, 1218, 1174, 1151, 1075 cm^{-1}. MS (EI): *m/z* (relative intensity) 302 ([M]$^+$ 100), 274 (34), 224 (33), 169 (30), 105 (67), 77 (55), 51 (14). HR-MS (ESI) *m/z* calcd for $C_{13}H_{10}D_4O_4^+$ [M]$^+$ 238.1143, found 238.1153.

Ruthenium(II)-Catalyzed H/D Exchange in 6a with D_2O as a Cosolvent



The general procedure **B** was followed using methyl 4-methoxybenzoate (**6a**) (85.4 mg, 0.51 mmol), ethyl acrylate (**1b**) (105 mg, 1.05 mmol), $[RuCl_2(p\text{-cymene})]_2$ (16.8 mg, 27.4 µmol, 5.4 mol %), $AgSbF_6$ (69.0 mg, 0.20 mmol, 40 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in a solvent mixture of DCE and D_2O (1.8/0.2 mL). Purification by column chromatography (*n*-hexane/EtOAc: 25/1) yielded $[D]_n$-**7ab** (74.1 mg, 55%) as a colorless oil. The D-incorporation in $[D]_n$-**7ab** was estimated by ^{1}H NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (d, J = 15.8 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 6.91 (dd, J = 8.8, 2.6 Hz, 1H), 6.25 (d, J = 15.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7 (C_q), 166.5 (C_q), 162.5 (C_q), 144.2 (CH), 139.0 (C_q), 133.1 (CH), 121.8 (C_q), 121.2 (CH), 114.6 (CH), 113.0 (CH), 60.6 (CH_2), 55.5 (CH_3), 52.1 (CH_3), 14.3 (CH_3). MS (EI): *m/z* (relative intensity) 302 ($[M]^+$ 100), 274 (34), 224 (33), 169 (30), 105 (67), 77 (55), 51 (14). IR (neat): 2981, 2952, 1255, 1172, 1126, 1089, 1031 cm^{-1}. HR-MS (ESI) *m/z* calcd for $C_{14}H_{15}DO_5^+$ $[M]^+$ 265.1061, found 265.1073.

6.4. Analytical Data for the Iron-Catalyzed C–H Functionalization

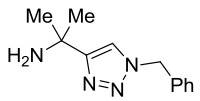
6.4.1 Analytical Data for Starting Materials

Synthesis of the TAM–NH_2:

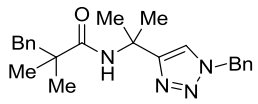
Benzyl bromide **121** (17.1 g, 100 mmol, 1.00 equiv) and NaN_3 (7.22 g, 111 mmol, 1.11 equiv) were dissolved in DMSO (150 mL). The reaction mixture was stirred for 48 h at ambient temperature. $CuSO_4{\cdot}5H_2O$ (4.99 g, 20.0 mmol, 20 mol %), sodium ascorbate (1.98 g, 10.0 mmol, 10 mol %) and 2-methylbut-3-yn-2-ol **123** (8.41 g, 100 mmol, 1.00 equiv) were dissolved in H_2O (100 mL) in a separate flask. The solution of the crude (azidomethyl)benzene (**122**) was transferred *via* a cannula to the aqueous phase, while the

color of the resulting mixture turned from orange to blue. The reaction mixture was stirred for 24 h at ambient temperature, diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to give 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (**124**) as a viscous oil, which was used without further purification. The complete conversion to the product **124** was verified by ^{1}H NMR spectroscopy.

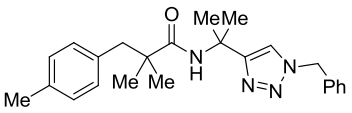
To the stirred mixture of crude 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (**124**) and NaN_3 (13.0 g, 200 mmol, 2.00 equiv) in $CHCl_3$ (150 mL), TFA (59.52 g, 40.0 mL, 522 mmol, 5.22 equiv) was added slowly at –10 °C, and the reaction mixture was stirred at ambient temperature for 24 h. The reaction was diluted with ice-cold H_2O (50 mL) and conc. aq. NH_3 solution (50 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over brine and Na_2SO_4. The filtrate was concentrated under reduced pressure affording 4-(2-azidopropan-2-yl)-1-benzyl-1*H*-1,2,3-triazole (**125**) which was used further without purification. The complete conversion to the product **125** was verified by ^{1}H NMR spectroscopy.



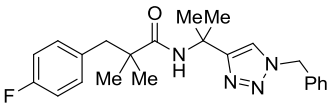
2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (TAM–NH_2) (126): $LiAlH_4$ (7.97 g, 210 mmol, 2.10 equiv) was dissolved in anhydrous THF (50 mL), and the oily crude azide **125** (dissolved in 50 mL THF), was added slowly at 0 °C. After the addition, the mixture was allowed to warm to ambient temperature and stirred for 24 h. To the resulting mixture, $Na_2SO_4 \cdot 10\ H_2O$ was added. The precipitate was filtered off and washed with CH_2Cl_2 (3 × 200 mL). The combined filtrates were concentrated under reduced pressure. The crude amine **126** was purified by Kugelrohr-distillation affording product **126** (18.8 g, 87%; average yield from 3 preparations) as a colorless solid. M. p. = 62–67 °C (lit.:[198] 32–34 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 6H), 5.43 (s, 2H), 1.92 (s, 2H), 1.45 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5 (C_q), 134.7 (C_q), 129.0 (CH), 128.6 (CH), 128.0 (CH), 118.3 (CH), 53.9 (CH_2), 48.5 (C_q), 31.3 (CH_3). IR (ATR): 3364, 2965, 1586, 1496, 1455, 1077, 877, 503 cm^{-1}. HR-MS (ESI) *m/z* calcd for $C_{12}H_{17}N_4^+$ $[M+H]^+$ 217.1448, found 217.1450. The analytical data are in accordance with those reported in the literature.[198]



***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,2-dimethyl-3-phenylpropanamide (110a):** The representative procedure **D** was followed using 2,2-dimethyl-3-phenylpropanoic acid (**128a**) (1.25 g, 7.00 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (1.51 g, 7.00 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **110a** (1.76 g, 67%) as a colorless solid. M. p. = 79–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 4H), 7.30–7.19 (m, 2H), 7.19–7.10 (m, 3H), 7.10–6.99 (m, 2H), 6.25 (s, 1H), 5.46 (s, 2H), 2.78 (s, 2H), 1.71–1.60 (m, 6H), 1.12 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2 (C_q), 153.8 (C_q), 138.1 (C_q), 134.6 (C_q), 130.2 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH) 126.2 (CH), 120.3 (CH), 54.1 (C_q), 51.2 (CH_2), 46.5 (CH_2), 43.6 (C_q), 27.7 (CH_3), 25.2 (CH_3). IR (neat): 3327, 2975, 1641, 1525, 1452, 1222, 1028, 723, 702 cm^{-1}. MS (EI) *m/z* (relative intensity): 376 (15) $[M]^+$, 333 (22), 201 (33), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{23}H_{28}N_4O^+$ $[M]^+$ 376.2263, found 376.2264.

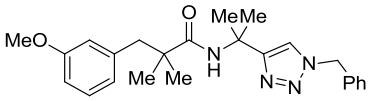


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,2-dimethyl-3-(*p*-tolyl)propanamide (110b):** The representative procedure **D** was followed using 2,2-dimethyl-3-(*p*-tolyl)propanoic acid (**128b**) (1.92 g, 10.0 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (2.16 g, 10.0 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **110b** (2.66 g, 68%) as a colorless solid. M. p. = 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.15 (m, 6H), 7.13–6.82 (m, 4H), 6.26 (s, 1H), 5.49 (s, 2H), 2.76 (s, 2H), 2.29 (s, 3H), 1.68 (s, 6H), 1.12 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3 (C_q), 153.8 (C_q), 135.6 (C_q), 134.9 (C_q), 134.6 (C_q), 130.1 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 120.3 (CH), 54.2 (CH_2), 51.2 (C_q), 46.2 (CH_2), 43.7 (C_q), 27.9 (CH_3), 25.3 (CH_3), 21.1 (CH_3). IR (neat): 3320, 2970, 1639, 1524, 1509, 1214, 721, 694 cm^{-1}. MS (EI) *m/z* (relative intensity): 390 (23) $[M]^+$, 347 (14), 201 (66), 105 (37), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{24}H_{30}N_4O^+$ $[M]^+$ 390.2420, found 390.2406.

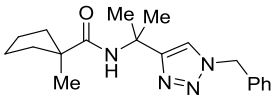


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-(4-fluorophenyl)-2,2-dimethylpropanamide (110c):** The

representative procedure **E** was followed using 3-(4-fluorophenyl)-2,2-dimethylpropanoic acid (**128c**) (1.98 g, 10.0 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (2.16 g, 10.0 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **110c** (2.87 g, 73%) as a colorless solid. M. p. = 99–100 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.32 (m, 4H), 7.30–7.25 (m, 2H), 7.03 (dd, J = 8.6, 5.5 Hz, 2H), 6.94–6.80 (m, 2H), 6.33 (s, 1H), 5.49 (s, 2H), 2.76 (s, 2H), 1.67 (s, 6H), 1.13 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.9 (C_q), 161.8 (d, $J_{C–F}$ = 245 Hz, C_q), 153.8 (C_q), 134.5 (C_q), 134.0 (d, $J_{C–F}$ = 4 Hz, C_q), 131.7 (d, $J_{C–F}$ = 8 Hz, CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 120.2 (CH), 114.7 (d, $J_{C–F}$ = 21 Hz, CH), 54.2 (CH_2), 51.3 (C_q), 45.8 (CH_2), 43.7 (C_q), 27.8 (CH_3), 25.3 (CH_3). ^{19}F NMR (500 MHz, $CDCl_3$): δ = –117.07 (d, J = 5.5 Hz). IR (neat): 3317, 2968, 1640, 1508, 1214, 802, 715, 495 cm^{-1}. MS (EI) *m/z* (relative intensity): 394 (23) $[M]^+$, 351 (23), 201 (49), 109 (43), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{23}H_{27}FN_4O^+$ $[M]^+$ 394.2169, found 394.2169.

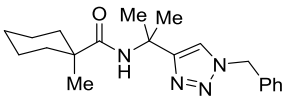


_N_-[2-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-3-(3-methoxyphenyl)-2,2-dimethylpropanamide (110d): The representative procedure **E** was followed using 3-(3-methoxyphenyl)-2,2-dimethylpropanoic acid (**128d**) (1.10 g, 5.28 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (1.19 g, 5.50 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **110d** (1.23 g, 57%) as a colorless solid. M. p. = 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 4H), 7.29–7.23 (m, 2H), 7.15–7.07 (m, 1H), 6.77–6.65 (m, 3H), 6.30 (s, 1H), 5.49 (s, 2H), 3.75 (s, 3H), 2.78 (s, 2H), 1.68 (s, 6H), 1.15 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.3 (C_q), 159.1 (C_q), 153.9 (C_q), 139.8 (C_q), 134.7 (C_q), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 122.8 (CH), 120.2 (CH), 116.1 (CH), 111.6 (CH), 55.0 (CH_3), 54.1 (CH_2), 51.2 (C_q), 46.5 (CH_2), 43.6 (C_q), 27.8 (CH_3), 25.4 (CH_3). IR (neat): 3315, 3123, 2953, 1645, 1508, 1150, 1047, 726 cm^{-1}. MS (EI) *m/z* (relative intensity): 406 (10) $[M]^+$, 363 (6), 201 (35), 121 (45), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{24}H_{30}N_4O_2^+$ $[M]^+$ 406.2369, found 406.2351.

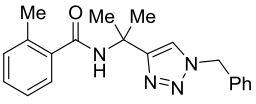


_N_-[2-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-1-methylcyclopentanecarboxamide (110e): The representative procedure **E**

was followed using 1-methylcyclopentanecarboxylic acid (**128e**) (380 mg, 2.96 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (324 mg, 1.50 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **110e** (392 mg, 80%) as a colorless solid. M. p. = 91–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 1H), 7.35–7.29 (m, 3H), 7.27–7.20 (m, 2H), 6.34 (s_{br}, 1H), 5.46 (s, 2H), 2.01–1.89 (m, 2H), 1.69 (s, 6H), 1.67–1.59 (m, 4H), 1.47–1.37 (m, 2H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8 (C_q), 154.0 (C_q), 134.6 (C_q), 128.9 (CH), 128.5 (CH), 127.9 (CH), 120.1 (CH), 54.1 (C_q), 51.1 (CH_2), 50.3 (C_q) , 37.7 (CH_2), 28.0 (CH_3), 25.5 (CH_3), 24.9 (CH_2). IR (neat): 3339, 2957, 1645, 1519, 1214, 1050, 719 cm^{-1}. MS (EI) *m/z* (relative intensity): 326 (3) $[M]^+$, 333 (22), 298 (12), 283 (54), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{19}H_{26}N_4O^+$ $[M]^+$ 326.2107, found 326.2101.

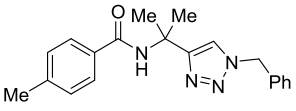


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-1-methylcyclohexanecarboxamide (110f):** The representative procedure **E** was followed using 1-methylcyclohexanecarboxylic acid (**128f**) (142 mg, 1.00 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (2.16 mg, 1.00 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **110f** (221 mg, 65%) as a colorless solid. M. p. = 78–79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 1H), 7.36–7.29 (m, 3H), 7.26–7.20 (m, 2H), 6.42 (s_{br}, 1H), 5.46 (s, 2H), 1.90–1.76 (m, 2H), 1.69 (s, 6H), 1.52–1.20 (m, 8H), 1.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.8 (C_q), 154.0 (C_q), 134.6 (C_q), 128.9 (CH), 128.5 (CH), 127.9 (CH), 120.1 (CH), 54.1 (C_q), 51.1 (CH_2), 43.0 (C_q), 35.7 (CH_2), 28.0 (CH_3), 25.9 (CH_2), 23.0 (CH_3). IR (neat): 3382, 2928, 1655, 1469, 1048, 717 cm^{-1}. MS (EI) *m/z* (relative intensity): 340 (10) $[M]^+$, 297 (47), 201 (20), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{20}H_{28}N_4O^+$ $[M]^+$ 340.2263, found 340.2259.

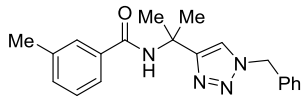


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methylbenzamide (112a):** The representative procedure **E** was followed using 2-methylbenzoic acid (**128g**) (708 mg, 5.20 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (1.13 g, 5.20 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded product **112a** (1.31 g, 75%) as a colorless solid. M. p. = 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.36–7.27 (m,

4H), 7.25–7.19 (m, 3H), 7.15–7.05 (m, 2H), 6.51 (s, 1H), 5.46 (s, 2H), 2.33 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5 (C_q), 153.6 (C_q), 137.0 (C_q), 135.6 (C_q), 134.5 (C_q), 130.7 (CH), 129.5 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 126.5 (CH), 125.5 (CH), 120.3 (CH), 54.0 (CH_2), 51.7 (C_q), 27.8 (CH_3), 19.5 (CH_3). IR (ATR): 3239, 1639, 1531, 1496, 1343, 1215, 1157, 1048, 959, 903, 861 cm^{-1}. MS (EI) *m/z* (relative intensity): 334 (14) $[M]^+$, 306 (13), 291 (60), 200 (11), 119 (64), 91 (100), 65 (18); HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}N_4O^+$ $[M]^+$ 334.1794, found 334.1792.



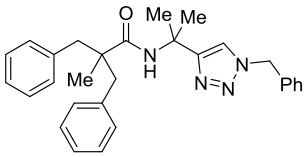
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-4-methylbenzamide (112h):** The representative procedure **E** was followed using 4-methylbenzoyl chloride (**128h**) (230 mg, 1.50 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (238 mg, 1.10 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) yielded product **112h** (359 mg, 98%) as a colorless solid. M. p. = 133–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 7.39–7.22 (m, 5H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 5.47 (s, 2H), 2.34 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (C_q), 153.9 (C_q), 141.6 (C_q), 134.5 (C_q), 132.3 (C_q), 129.0 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 126.7 (CH), 120.2 (CH), 54.1 (CH_2), 51.6 (C_q), 27.9 (CH_3), 21.3 (CH_3). IR (ATR): 3246, 1650, 1505, 1360, 1228, 1214, 1193, 1057, 861 cm^{-1}. MS (EI) *m/z* (relative intensity): 334 (1) $[M]^+$, 306 (19), 291 (65), 215 (5), 171 (6), 119 (63), 91 (100), 65 (20). HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}N_4O^+$ $[M]^+$ 334.1794, found 334.1795.



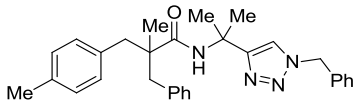
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-methylbenzamide (112u):** The representative procedure **E** was followed using 3-methylbenzoyl chloride (**128u**) (340 mg, 2.20 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (**126**) (368 mg, 1.70 mmol). Purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) yielded product **112u** (510 mg, 90%) as a colorless solid. M. p. = 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.49 (m, 2H), 7.48 (s, 1H), 7.39–7.21 (m, 7H), 7.02 (s, 1H), 5.48 (s, 2H), 2.34 (s, 3H), 1.83 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 153.8 (C_q), 138.1 (C_q), 135.1 (C_q), 134.5 (C_q), 131.9 (CH), 129.0 (CH),

128.6 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 123.8 (CH), 120.2 (CH), 54.1 (CH_2), 51.6 (C_q), 27.9 (CH_3), 21.2 (CH_3). IR (ATR): 1647, 1585, 1484, 1385, 1365, 1222, 1190, 1171, 1150, 1117, 1053, 1015, 918, 896, 851 cm^{-1}. MS (EI) *m/z* (relative intensity): 334 (2) $[M]^+$, 306 (27), 291 (76), 215 (53), 171 (8), 119 (84), 91 (100), 65 (20). HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}N_4O^+$ $[M]^+$ 334.1794, found 334.1795.

6.4.2 Analytical Data for C(sp^3)–H Arylation

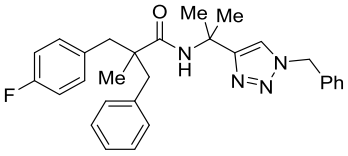


2-Benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methyl-3-phenylpropanamide (111a): The representative procedure **F** was followed using amide **110a** (79.2 mg, 0.21 mmol) and PhMgBr (1.4 mL, 1 M, 1.4 mmol). The reaction mixture was stirred at 80 °C for 48 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111a** (87.3 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 3H), 7.31 (s, 1H), 7.27–7.22 (m, 2H), 7.18–7,13 (m, 6H), 7.09–7.02 (m, 4H), 5.96 (s, 1H), 5.46 (s, 2H), 3.29 (d, *J* = 12.0 Hz, 2H), 2.49 (d, *J* = 12.0 Hz, 2H), 1.57 (s, 6H), 0.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (C_q), 153.4 (C_q), 137.6 (C_q), 134.6 (C_q), 130.4 (C_q), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.3 (CH), 120.4 (CH), 54.1 (C_q), 51.4 (CH_2), 48.6 (C_q), 46.8 (CH_2), 27.6 (CH_3), 19.5 (CH_3). IR (neat): 3344, 2979, 1641, 1495, 1224, 1030, 912, 723 cm^{-1}. MS (EI) *m/z* (relative intensity): 452 (2) $[M]^+$, 409 (15), 361 (57), 318 (5), 200 (27), 172 (18), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{29}H_{32}N_4O^+$ $[M]^+$ 452.2576, found 452.2584.

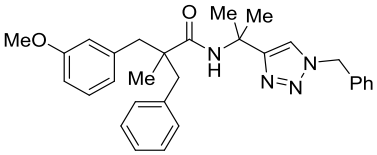


2-Benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methyl-3-(*p*-tolyl)propanamide (111b): The representative procedure **F** was followed using amide **110b** (75.2 mg, 0.20 mmol) and PhMgBr (1M, 1.4 mL, 1.4 mmol). The reaction mixture was stirred at 80 °C for 48 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111b** (58.6 mg, 63%) as a white solid. M. p. = 140–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 4H), 7.28–7.20 (m, 2H), 7.16–7.14 (m, 3H), 7.09–7.02 (m, 2H), 6.97–6.95 (m, 4H), 5.97 (s, 1H), 5.46 (s, 2H), 3.26 (d, *J* = 12.0 Hz, 2H), 2.46 (d, *J* = 12.0 Hz, 2H), 2.26 (s, 3H), 1.59 (s, 6H), 0.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6 (C_q), 153.5 (C_q), 137.7 (C_q), 135.7 (C_q), 134.7 (C_q),

134.5 (C_q), 130.4 (CH), 130.3 (CH), 129.0 (CH), 128.6 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.3 (CH), 120.6 (CH), 54.1 (C_q), 51.3 (CH_2), 48.5 (C_q), 46.7 (CH_2), 46.3 (CH_2), 27.6 (CH_3), 21.0 (CH_3), 19.4 (CH_3). IR (neat): 3420, 2974, 1653, 1495, 1453, 1381, 1224, 700 cm^{-1}. MS (EI) *m/z* (relative intensity): 466 (2) [M^+], 423 (5), 375 (45), 200 (38), 172 (22), 118 (11), 105 (25), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{30}H_{34}N_4O^+$ [M^+] 466.2733, found 466.2732.

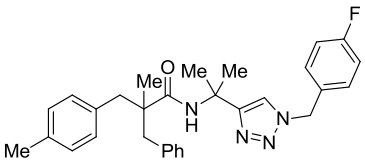


2-Benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-(4-fluorophenyl)-2-methylpropanamide (111c): The representative procedure **F** was followed using amide **110c** (199 mg, 0.50 mmol) and PhMgBr (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111c** (176 mg, 75%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 4H), 7.30–7.23 (m, 2H), 7.22–7.14 (m, 3H), 7.11–6.98 (m, 4H), 6.85 (t, *J* = 8.7 Hz, 2H), 6.08 (s, 1H), 5.47 (s, 2H), 3.29 (dd, *J* = 13.0, 2.9 Hz, 2H), 2.47 (dd, *J* = 14.5, 13.1 Hz, 2H), 1.59 (s, 6H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3 (C_q), 161.6 (d, J_{C-F} = 243 Hz, C_q), 153.4 (C_q), 137.4 (C_q), 134.5 (C_q), 133.3 (C_q, d, J_{C-F} = 3 Hz), 131.7 (d, J_{C-F} = 8 Hz, CH), 130.3 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.3 (CH), 120.3 (CH), 114.6 (d, J_{C-F} = 21 Hz, CH), 54.0 (CH_2), 51.3 (CH_2), 48.5 (C_q), 46.7 (CH_2), 45.7 (C_q), 27.5 (CH_3), 27.4 (CH_3), 19.2 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$): δ = –116.8 (tt, *J* = 9, 6 Hz). IR (neat): 3410, 2971, 1656, 1507, 1453, 1219, 721 cm^{-1}. MS (EI) *m/z* (relative intensity): 470 (2) [$M]^+$, 427 (10), 379 (28), 361 (13), 200 (22), 172 (18), 109 (23), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{29}H_{31}FN_4O^+$ [$M]^+$ 470.2482, found 470.2479.

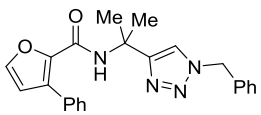


2-Benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-(3-methoxyphenyl)-2-methylpropanamide (111d): The representative procedure **F** was followed using amide **110d** (205 mg, 0.50 mmol) and PhMgBr (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111d** (211 mg, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 4H), 7.29–7.21 (m, 2H), 7.20–7.13 (m, 3H),

7.13–7.05 (m, 3H), 6.84–6.47 (m, 3H), 6.08 (s, 1H), 5.45 (s, 2H), 3.73 (s, 3H), 3.30 (d, *J* = 12.9 Hz, 2H), 2.51 (dd, *J* = 12.9, 5.6 Hz, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5 (C_q), 159.1 (C_q), 153.6 (C_q), 139.2 (C_q), 137.5 (C_q), 134.6 (C_q), 130.4 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 126.3 (CH), 122.9 (CH), 120.3 (CH), 116.3 (CH), 111.5 (CH), 54.9 (CH_3), 53.8 (CH_2), 51.3 (C_q), 48.3 (C_q), 46.6 (CH_2), 46.5 (CH_2), 27.5 (CH_3), 27.4 (CH_3), 19.3 (CH_3). IR (neat): 3411, 2933, 1654, 1453, 1261, 1047, 722 cm^{-1}. MS (EI) *m/z* (relative intensity): 482 (2) $[M]^+$, 439 (5), 391 (35), 200 (32), 172 (21), 121 (17), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{30}H_{34}N_4O_2^+$ $[M]^+$ 482.2682, found 482.2693.

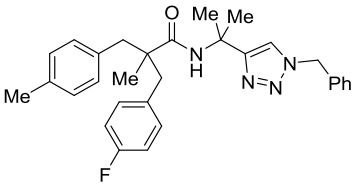


2-Benzyl-*N*-{2-[1-(4-fluorobenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-2-methyl-3-(*p*-tolyl)propanamide (111g): The representative procedure **F** was followed using amide **110g** (196 mg, 0.48 mmol) and PhMgBr (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 30 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111g** (112 mg, 48%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (s, 1H), 7.27–7.20 (m, 2H), 7.16 (d, *J* = 1.5 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 2H), 7.07–7.01 (m, 4H), 7.00–6.90 (m, 4H), 5.92 (s, 1H), 5.43 (s, 2H), 3.27 (d, *J* = 6.9 Hz, 1H), 3.23 (d, *J* = 6.9 Hz, 1H), 2.48 (d, *J* = 4.4 Hz, 1H), 2.44 (d, *J* = 4.4 Hz, 1H), 2.26 (s, 3H), 1.58 (s, 6H), 0.95 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7 (C_q), 162.8 (d, $J_{C–F}$ = 247 Hz, C_q), 153.4 (C_q), 137.8 (C_q), 135.8 (C_q), 134.5 (C_q), 130.5 (d, $J_{C–F}$ = 3 Hz, C_q), 130.4 (CH), 130.3 (CH), 129.8 (d, $J_{C–F}$ = 8 Hz, CH), 128.6 (CH), 127.8 (CH), 126.3 (CH), 120.6 (CH), 116.0 (d, *J* = 22 Hz, CH), 91.4 (CH), 53.3 (CH_2), 51.2 (CH_2), 48.5 (CH_2), 46.7 (C_q), 46.3 (C_q), 27.6 (CH_3), 21.0 (CH_3), 19.4 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$): δ = –-112.9 (s). IR (neat): 3245, 2689 1583, 1544, 1288, 704, 695 cm^{-1}. MS (EI) *m/z* (relative intensity): 484 (4) $[M]^+$, 441 (8), 375 (44), 200 (35), 172 (30), 109 (28), 105 (50), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{30}H_{33}FN_4O^+$ $[M]^+$ 484.2638, found 484.2643.

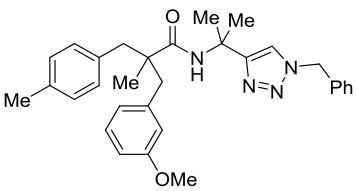


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-phenylfuran-2-carboxamide (111i):** The representative procedure **F** was followed using amide **110i** (155 mg, 0.50 mmol) and PhMgBr (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 30 h. Purification by column

chromatography on silica gel (*n*-pentane/EtOAc 2:1) yielded product **111i** (66.9 mg, 35%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.3 Hz, 2H), 7.43 (s, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.39–7.29 (m, 6H), 7.25 (d, *J* = 4.4 Hz, 1H), 7.25 (d, *J* = 4.4 Hz, 1H), 6.92 (s, 1H), 6.55 (d, *J* = 1.8 Hz, 1H), 5.47 (s, 2H), 1.77 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (C_q), 153.7 (C_q), 142.6 (CH), 141.9 (C_q), 134.8 (C_q), 132.0 (C_q), 130.4 (C_q), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 120.6 (CH), 114.5 (CH), 54.0 (CH_2), 51.4 (C_q), 28.0 (CH_3). IR (neat): 3145, 1656, 1535, 1503, 1057, 832, 751, 715, 694 cm^{-1}. MS (EI) *m/z* (relative intensity): 386 (1) $[M]^+$, 343 (29), 200 (29), 171 (37), 115 (26), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{23}H_{23}N_4O_2^+$ $[M+H]^+$ 387.1816, found 387.1820.

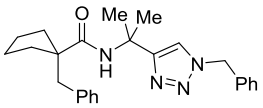


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-(4-fluorobenzyl)-2-methyl-3-(*p*-tolyl)propanamide (111bb):** The representative procedure **F** was followed using amide **110b** (196 mg, 0.50 mmol) and 4-FC_6H_4MgBr **133** (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111bb** (137 mg, 57%) as a colorless solid. M. p. = 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 4H), 7.28–7.22 (m, 2H), 7.03–6.91 (m, 6H), 6.84 (t, *J* = 8.7 Hz, 2H), 6.04 (s, 1H), 5.46 (s, 2H), 3.23 (dd, *J* = 13.1, 9.6 Hz, 2H), 2.43 (dd, *J* = 13.1, 10.0 Hz, 2H), 2.26 (s, 3H), 1.58 (s, 6H), 0.95 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (C_q), 161.5 (d, J_{C-F} = 242 Hz, C_q), 153.4 (C_q), 135.8 (C_q), 134.5 (C_q), 134.3 (C_q), 133.3 (d, J_{C-F} = 3 Hz, C_q), 131.7 (d, J_{C-F} = 8 Hz, CH), 130.2 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 120.4 (CH), 114.7 (d, J_{C-F} = 21 Hz, CH), 54.2 (CH_2), 51.4 (C_q), 48.6 (C_q), 46.4 (CH_2), 45.8 (CH_2), 27.7 (CH_3), 27.6 (CH_3), 21.1 (CH_3), 19.4 (CH_3).^{19}F NMR (285 MHz, $CDCl_3$): δ = –116.9 (tt, *J* = 9, 6 Hz). IR (neat): 3346, 2978, 1642, 1507, 1224, 803, 720 cm^{-1}. MS (EI) *m/z* (relative intensity): 484 (2) $[M]^+$, 441 (4), 375 (38), 200 (36), 172 (23), 109 (22), 105 (27), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{30}H_{33}FN_4O^+$ $[M]^+$ 484.2638, found 484.2644.

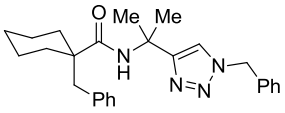


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-(3-methoxybenzyl)-2-methyl-3-(*p*-tolyl)propanamide (111bc):**

The representative procedure **F** was followed using amide **110b** (195 mg, 0.50 mmol) and 3-$MeOC_6H_4MgBr$ **134** (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→3:2) yielded product **111bc** (137 mg, 70%) as a colorless solid. M. p. = 108–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 4H), 7.27–7.21 (m, 2H), 7.07 (dd, *J* = 9.1, 7.3 Hz, 1H), 6.99–6.91 (m, 4H), 6.70 (m, 1H), 6.66 (d, *J* = 8.0 Hz, 2H) 6.03 (s, 1H), 5.45 (s, 2H), 3.72 (s, 3H), 3.24 (dd, *J* = 13.0, 7.3 Hz, 2H), 2.47 (d, *J* = 13.0 Hz, 2H), 2.26 (s, 3H), 1.59 (s, 6H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5 (C_q), 158.9 (C_q), 153.4 (C_q), 139.2 (C_q), 135.6 (C_q), 134.6 (C_q), 134.4 (C_q), 130.2 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 127.9 (CH), 122.8 (CH), 120.4 (CH), 116.3 (CH), 111.5 (CH), 55.1 (CH_3), 54.0 (CH_2), 51.4 (CH_2), 48.5 (CH_2), 46.6 (C_q), 46.3 (C_q), 27.7 (CH_3), 27.7 (CH_3), 21.1 (CH_3), 19.6 (CH_3). IR (neat): 3419, 2924, 1654, 1511, 1453, 1047, 722, 697 cm^{-1}. MS (EI) *m/z* (relative intensity): 496 (2) $[M]^+$, 453 (2), 391 (16), 375 (26), 200 (38), 172 (22), 105 (30), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{31}H_{36}N_4O_2^+$ $[M]^+$ 496.2838, found 496.2846.



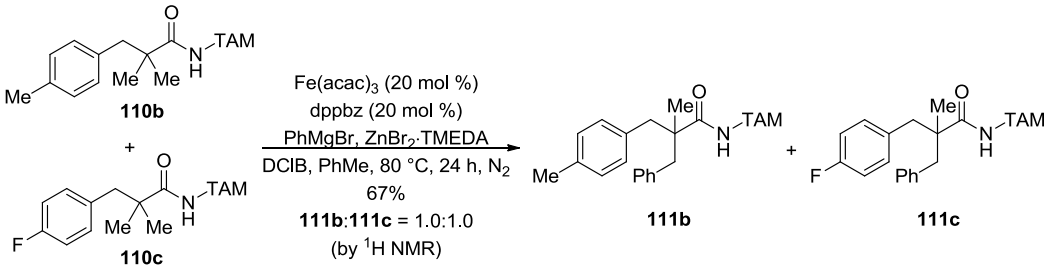
1-Benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-cyclopentane-1-carboxamide (111e): The representative procedure **F** was followed using amide **110e** (164 mg, 0.50 mmol) and PhMgBr (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 48 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1) yielded product **111e** (166 mg, 83%) as a colorless solid. M. p. = 90–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 3H), 7.32 (s, 1H), 7.28–7.20 (m, 2H), 7.19–7.10 (m, 3H), 7.07–7.04 (m, 2H), 6.00 (s, 1H), 5.46 (s, 2H), 2.85 (s, 2H), 1.94–1.81 (m, 2H), 1.61 (s, 6H), 1.72–1.50 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (C_q), 153.8 (C_q), 138.6 (C_q), 134.7 (C_q), 129.9 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH) 127.9 (CH), 126.2 (CH), 120.4 (CH), 56.3 (C_q), 54.1 (CH_2), 51.1 (C_q), 43.9 (CH_2), 35.5 (CH_2), 27.7 (CH_3), 23.6 (CH_2). IR (neat): 3297, 2939, 1651, 1272, 1053, 729, 703 cm^{-1}. MS (EI) *m/z* (relative intensity): 402 (15) $[M]^+$, 359 (22), 201 (30), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{25}H_{30}N_4O^+$ $[M]^+$ 402.2420, found 402.2428.



1-Benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]cyclohexanecarboxamide (111f): The representative procedure **F** was followed using amide **110f** (68.0 mg, 0.20 mmol) and PhMgBr (3.50 mL, 1 M, 3.50 mmol). The reaction mixture was stirred at 80 °C for 48 h. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) yielded product **111f** (43.1 mg, 52%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 1H), 7.35–7.32 (m, 3H), 7.26–7.20 (m, 2H), 7.17–7.11 (m, 3H), 7.04–6.98 (m, 2H), 6.00 (s_{br}, 1H), 5.46 (s, 2H), 2.71 (s, 2H), 1.92–1.82 (m, 2H), 1.63 (s, 6H), 1.61–1.44 (m, 4H), 1.38–1.26 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5 (C_q), 153.8 (C_q), 137.3 (C_q), 134.7 (C_q), 130.4 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.7 (CH), 126.2 (CH), 120.6 (CH), 54.1 (C_q), 51.2 (CH_2), 47.8 (C_q), 34.3 (CH_2), 27.7 (CH_3), 25.9 (CH_2), 23.0 (CH_2). IR (neat): 3413, 2928, 1655, 1497, 1452, 1078, 721, 700 cm^{-1}. MS (EI) *m/z* (relative intensity): 416 (22) [M^+], 373 (19), 201 (34), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{26}H_{32}N_4O^+$ [M^+] 416.2576, found 416.2575.

Mechanistic Studies

Intermolecular Competition Experiments

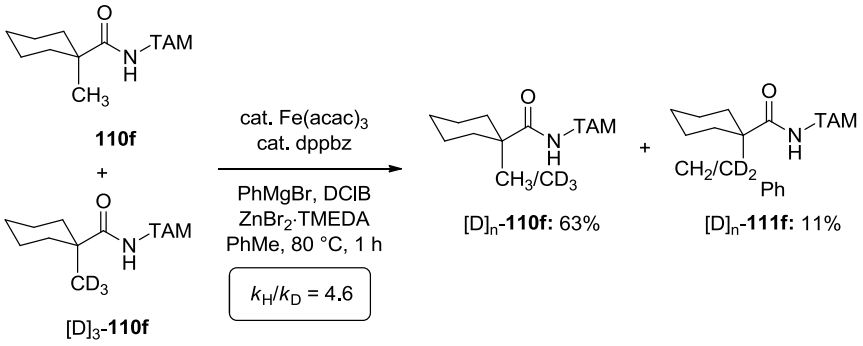


A solution of PhMgBr (3.50 mL, 1 M, 3.50 mmol) in anhydrous THF (2.5 mL) was slowly added to a mixture of amides **110b** (98.5 mg, 0.25 mmol) and **110c** (97.6 mg, 0.25 mmol) as well as $ZnBr_2$·TMEDA (512 mg, 1.50 mmol) under N_2. The resulting mixture was stirred at ambient temperature for 5 min, then a solution of $Fe(acac)_3$ (35.3 mg, 100 µmol, 20 mol %) and dppbz (44.6 mg, 100 µmol, 20 mol %) in anhydrous THF (2.5 mL) was added. The mixture was stirred at ambient temperature for 10 min, and then DCIB (127 mg, 1.00 mmol) was added. The reaction mixture was stirred at 80 °C for 24 h. After cooling to ambient temperature, the reaction was diluted with H_2O (5.0 mL). The filtrate was extracted with EtOAc (2 × 20 mL), then dried over Na_2SO_4 and filtered. After removal of the solvents under reduced pressure,

the residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) to yield a mixture of the products **111b** and **111c** (156 mg, 67%) and a mixture of substrates **110b** and **110c** (53.2 mg, 27%) as colorless solids. The ratio of arylated compounds as well as of reisolated starting material was determined by ^{1}H NMR to be 1.0:1.0 in both cases.

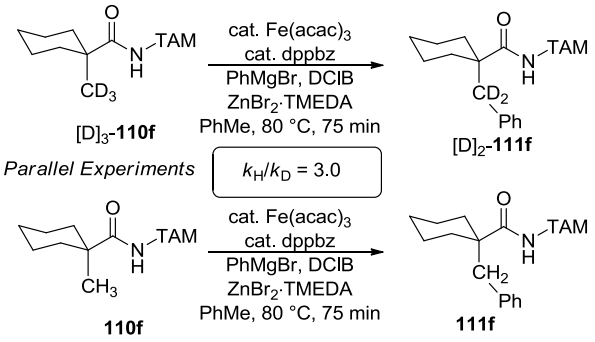
Kinetic Isotope Effect Studies

Intermolecular Competition Experiment



A solution of PhMgBr (3.50 mL, 1 M in THF, 3.50 mmol) was slowly added to a mixture of amides **110f** (85.1 mg, 0.25 mmol), [D]$_3$-**110f** (85.9 mg, 0.25 mmol) and $ZnBr_2$·TMEDA (512 mg, 1.50 mmol) under N_2. The resulting reaction mixture was stirred at ambient temperature for 10 min, then a solution of $Fe(acac)_3$ (35.3 mg, 0.10 mmol) and dppbz (44.6 mg, 0.10 mmol) in dry PhMe (1.0 mL) was added. The black mixture was stirred at ambient temperature for 10 min, and then DCIB (127 mg, 1.00 mmol) was added. The mixture was stirred at 80 °C for 1 h. After cooling to ambient temperature, the reaction was diluted with saturated aq. NH_4Cl solution (5.0 mL), and passed through a short pad of Celite®. The filtrate was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), then dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc 2:1) to yield a mixture [D]$_n$-**111f** (23.1 mg, 11%) as a colorless solid. ^{1}H NMR analysis of this mixture revealed a ratio of [D]$_2$-**111f** and **111f** to be 1.0: 4.6. Therefore, this competition experiment indicated a kinetic isotope effect of $k_H/k_D \approx 4.6$.

Determination of KIE by Two Independant Experiments



Solutions of PhMgBr (1 M in THF, 1.70 mL, 1.70 mmol) were slowly added to the two reaction vessels containing amide [D]$_3$-**110f** (85.8 mg, 0.25 mmol) or undeuterated amide **110f** (85.1 mg, 0.25 mmol), $ZnBr_2$·TMEDA (256 mg, 0.75 mmol) and *n*-dodecane (42.6 mg, 0.25 mmol) as an internal standard in dry PhMe (2.50 mL) in each case under N_2. The resulting mixtures were stirred at ambient temperature for 5 min, then the solutions of $Fe(acac)_3$ (17.7 mg, 50 µmol, 20 mol %) and dppbz (22.3 mg, 50 µmol, 20 mol %) in dry PhMe (2.5 mL) followed by DClB (64 mg, 0.50 mmol) were immediatelly added in each case. The mixtures were stirred at 27 °C for 2 h. Every 15 min 0.2 mL aliquots of the reaction mixtures were collected, filtered through a short pad of silica gel and Na_2SO_4 and directly injected into the GC instrument. The formation of the products was monitored using *n*-dodecane as an internal standard. This experiment with the isotopically labeled and unlabeled substrates [D]$_3$-**111f** and **111f**, respectively, indicated a kinetic isotope effect of $k_H/k_D \approx 3.0$.

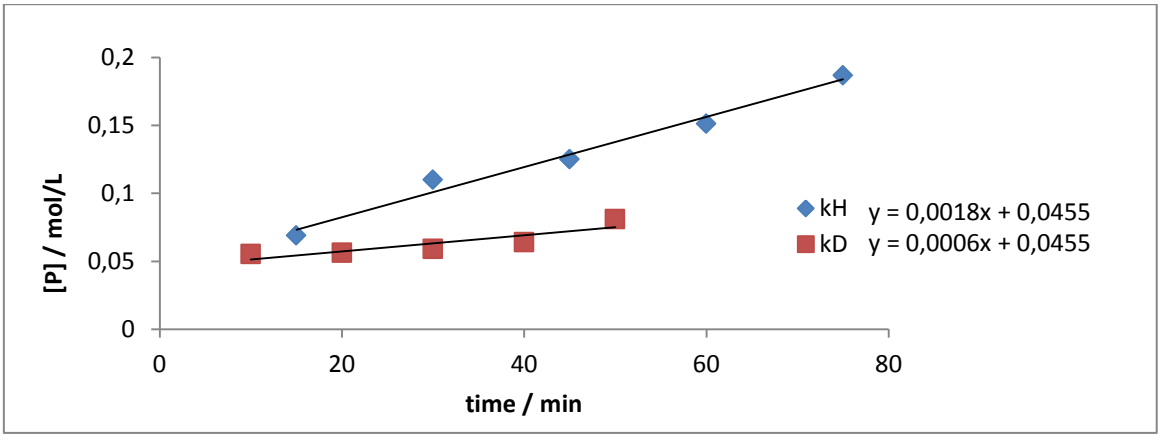
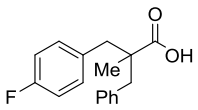


Figure 12: Linear regressions for the iron-catalyzed C–H arylation with substrates [D]$_3$-**110f** and **110f**.

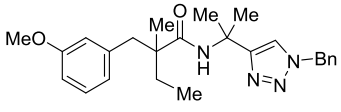
Removal of the TAM Directing Group



2-Benzyl-3-(4-fluorophenyl)-2-methylpropanoic acid (138): HCl (aq. 37%, 3.0 mL) was added to 2-benzyl-*N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-(4-fluorophenyl)-2-methylpropanamide (**111c**) (70.6 mg, 0.15 mmol) in a pressure tube. The reaction mixture was stirred at 140 °C for 24 h and then allowed to cool to ambient temperature. H_2O (20 mL) was carefully added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 1:1) yielded product **138** (27.7 mg, 68%) as a colorless oil and the reisolated NH_2TAM auxiliar **126** (16.4 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.11 (m, 4H), 6.96 (t, *J* = 8.7 Hz, 2H), 3.29–3.08 (m, 3H), 3.22 (dd, *J* = 12.7, 3.4 Hz, 2H), 2.72 (dd, *J* = 12.7, 3.4 Hz, 2H), 1.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 182.7 (C_q), 162.1 (d, J_{C-F} = 245 Hz, C_q), 137.2 (C_q), 133.0 (d, J_{C-F} = 3 Hz, C_q), 131.9 (d, J_{C-F} = 8 Hz, CH), 130.5 (CH) , 128.4 (CH), 127.0 (CH) , 115.2 (d, J_{C-F} = 21 Hz, CH), 49.1 (C_q), 46.1 (CH_2), 45.2 (CH_2), 19.8 (CH_3). IR (neat): 2925, 1697, 1509, 12209, 908, 837, 754, 730, 700 cm^{-1}. MS (EI) *m/z* (relative intensity): 272 (15) $[M]^+$, 181 (27), 109 (100), 91 (98), 43 (22). HR-MS (ESI) *m/z* calcd for $C_{17}H_{17}FO_2^+$ $[M]^+$ 272.1213, found 272.1223.

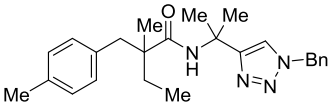
6.4.3 Analytical Data for C(sp^2)–H Methylation

Preliminary Experiments on C(sp^3)–H Methylation



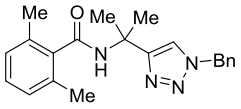
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-(3-methoxybenzyl)-2-methylbutanamide (111dg):** The representative procedure **G** was followed using amide **110d** (58.2 mg, 0.14 mmol), $ZnBr_2$·TMEDA (143 mg, 0.42 mmol) and MeMgBr (0.33 mL, 3 M, 1.0 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **111dg** (15.7 mg,

27%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 3H), 7.30–7.22 (m, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.75–6.65 (m, 3H), 6.26 (s, 1H), 5.49 (s, 2H), 3.74 (s, 3H), 3.05 (d, *J* = 13.0 Hz, 1H), 2.48 (d, *J* = 13.0 Hz, 1H), 1.80 (dq, *J* = 14.7, 7.4 Hz 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.35 (dq, *J* = 14.7, 7.4 Hz 1H), 1.05 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (C_q), 159.2 (C_q), 154.0 (C_q), 139.7 (C_q), 134.8 (C_q), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 122.9 (CH), 120.4 (CH), 116.3 (CH), 111.5 (CH), 55.1 (CH_3), 54.1 (CH_2), 51.3 (C_q), 47.4 (C_q), 45.8 (CH_2), 33.2 (CH_2), 27.8 (CH_3), 27.6 (CH_3), 19.8 (CH_3), 8.8 (CH_3). IR (neat): 2967, 2926, 1657, 1511, 1455, 1261, 1049, 723 cm^{-1}. MS (EI) *m/z* (relative intensity): 420 (25) [M^+], 377 (12), 201 (70), 172 (18), 121 (39), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{25}H_{32}N_4O_2^+$ $[M]^+$ 420.2525, found 420.2529.

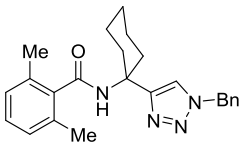


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methyl-2-(4-methylbenzyl)butanamide (111bg):** The representative procedure **G** was followed using amide **110b** (110 mg, 0.28 mmol), $ZnCl_2$·TMEDA (341 mg, 0.84 mmol) and MeMgBr (0.6 mL, 3 M, 1.9 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **111bg** (68.6 mg, 61%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1H), 7.38–7.32 (m, 3H), 7.29–7.22 (m, 2H), 7.03–6.89 (m, 4H), 6.23 (s, 1H), 5.49 (s, 2H), 3.01 (d, *J* = 13.2 Hz, 1H), 2.47 (d, *J* = 13.2 Hz, 1H), 2.28 (s, 3H), 1.78 (dq, *J* = 14.7, 7.7 Hz, 1H), 1.70 (s, 3H), 1.67 (s, 3H), 1.30 (dq, *J* = 14.7, 7.7 Hz, 1H), 1.02 (s, 3H), 0.80 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (C_q), 153.8 (C_q), 135.6 (C_q), 134.9 (C_q), 134.7 (C_q), 130.2 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 120.5 (CH), 54.1 (CH_2), 51.2 (C_q), 47.5 (CH_2), 45.4 (CH_2), 33.1 (C_q), 27.8 (CH_3), 27.6 (CH_3), 21.0 (CH_3), 19.7 (CH_3), 8.9 (CH_3). IR (neat): 3322, 2975, 1641, 1520, 1213, 1046, 717 cm^{-1}. MS (EI) *m/z* (relative intensity): 404 (30) [M^+], 361 (13), 201 (75), 172 (20), 105 (48), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{25}H_{32}N_4O^+$ $[M]^+$ 404.2576, found 404.2577.

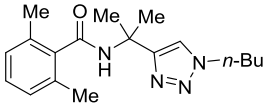
C(sp^2)–H Bond Methylations



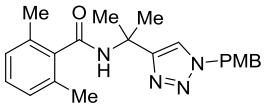
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,6-dimethylbenzamide (113a):** The representative procedure **G** was followed using amide **112a** (68.9 mg, 0.20 mmol), $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 25 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113a** (70.5 mg, 93%) as a colorless solid. M. p. = 135–137 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.38–7.32 (m, 3H), 7.27–7.24 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 6.27 (s, 1H), 5.50 (s, 2H), 2.24 (s, 6H), 1.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C_q), 153.6 (C_q), 138.0 (C_q), 134.7 (C_q), 134.2 (C_q), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.5 (CH), 120.6 (CH), 54.1 (CH_2), 51.8 (C_q), 27.7 (CH_3), 18.9 (CH_3). IR (neat): 3264, 1643, 1544, 1313, 1192, 1048, 717, 695 cm^{-1}. MS (EI) *m/z* (relative intensity): 348 (37) [M^+], 305 (30), 200 (17), 170 (12), 133 (58), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{25}N_4O^+$ $[M+H]^+$ 349.2023, found 349.2029.



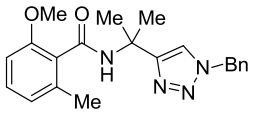
***N*-[1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)cyclohexyl]-2,6-dimethylbenzamide (113b):** The representative procedure **G** was followed using amide **112b** (75.0 mg, 0.20 mmol), $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 25 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113b** (73.8 mg, 95%) as a colorless solid. M. p. = 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (s, 1H), 7.41–7.31 (m, 3H), 7.30–7.23 (m, 2H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.7. Hz, 2H), 5.73 (s, 1H), 5.53 (s, 2H), 2.52 (d, *J* = 13.5 Hz, 2H), 2.23–2.04 (m, 2H) 2.16 (s, 6H), 1.71–1.48 (m, 5H), 1.42 (d, *J* = 13.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9 (C_q), 152.0 (C_q), 138.1 (C_q), 135.0 (C_q), 134.3 (C_q), 129.1 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 122.2 (CH), 54.0 (C_q), 54.0 (CH_2), 35.1 (CH_2), 25.4 (CH_2), 21.9 (CH_2), 19.0 (CH_3). IR (neat): 3286, 2933, 1633, 1538, 1046, 720, 694 cm^{-1}. MS (EI) *m/z* (relative intensity): 388 (22) [M^+], 269 (17), 239 (30), 210 (18), 133 (78), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{24}H_{28}N_4O^+$ $[M+H]^+$ 389.2336, found 389.2345.



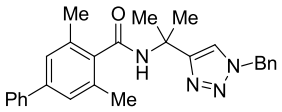
***N*-[2-(1-*n*-Butyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,6-dimethylbenzamide (113c):** The representative procedure **G** was followed using amide **112c** (60.0 mg, 0.20 mmol), $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113c** (58.1 mg, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (s, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.38 (s, 1H), 4.33 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 6H), 1.93–1.83 (m, 2H), 1.88 (s, 6H), 1.35 (q, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C_q), 153.0 (C_q), 138.0 (C_q), 134.1 (C_q), 128.5 (CH), 127.4 (CH), 120.5 (CH), 51.7 (C_q), 50.0 (CH_2), 32.1 (CH_2), 27.7 (CH_3), 19.5 (CH_2), 18.8 (CH_3), 13.3 (CH_3). IR (neat): 3261, 1643, 1542, 1215, 1193, 724, 694, 379 cm^{-1}. MS (EI) *m/z* (relative intensity): 314 (57) $[M]^+$, 271 (52), 166 (38), 133 (100), 105 (45), 84 (27). HR-MS (ESI) *m/z* calcd for $C_{18}H_{27}N_4O^+$ $[M+H]^+$ 315.2179, found 315.2182.



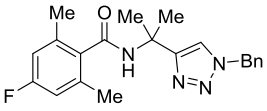
***N*-{2-[1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-2,6-dimethylbenzamide (113d):** The representative procedure **G** was followed using amide **112d** (72.9 mg, 0.20 mmol), $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113d** (69.0 mg, 91%) as a colorless solid. M. p. = 164–165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.28–7.20 (m, 2H), 7.12 (dd, *J* = 8.2, 6.9 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.30 (s, 1H), 5.45 (s, 2H), 3.80 (s, 3H), 2.26 (s, 6H), 1.85 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C_q), 160.0 (C_q), 153.5 (C_q), 138.0 (C_q), 134.2 (C_q), 129.7 (CH), 128.5 (CH), 127.5 (CH), 126.6 (C_q), 120.3 (CH), 114.5 (CH), 55.3 (CH_3), 53.7 (CH_2), 51.8 (C_q), 27.7 (CH_3), 18.9 (CH_3). IR (neat): 3251, 1638, 1538, 1515, 1461, 1251, 1034, 771 cm^{-1}. MS (EI) *m/z* (relative intensity): 378 (20) $[M^+]$, 335 (15), 121 (100), 105 (15), 77 (8). HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O_2^+$ $[M+H]^+$ 379.2129, found 379.2131.



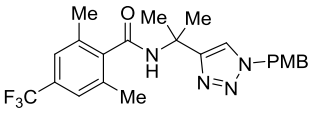
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methoxy-6-methylbenzamide (113h):** The representative procedure **G** was followed using amide **112h** (81.8 mg, 0.23 mmol), $ZnCl_2$·TMEDA (174 mg, 0.69 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 25 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113h** (68.2 mg, 80%) as a colorless solid. M. p. = 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 7.41–7.33 (m, 3H), 7.31–7.23 (m, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.76 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.25 (s, 1H), 5.51 (s, 2H), 3.67 (s, 3H), 2.27 (s, 3H), 1.85 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5 (C_q), 156.1 (C_q), 153.8 (C_q), 136.8 (C_q), 134.9 (C_q), 129.6 (CH), 129.1 (CH), 128.7 (CH), 128.1 (CH), 127.3 (C_q), 122.7 (CH), 120.8 (CH), 108.3 (CH), 55.6 (CH_3), 54.1 (CH_2), 52.1 (C_q), 28.2 (CH_3), 18.8 (CH_3). IR (neat): 2927, 1659, 1548, 1469, 1311, 1255, 774, 722 cm^{-1}. MS (EI) *m/z* (relative intensity): 364 (8) [M^+], 321 (42), 200 (18), 170 (7), 149 (75), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{25}N_4O_2^+$ $[M+H]^+$ 365.1972, found 365.1973.



***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3,5-dimethyl-[1,1'-biphenyl]-4-carboxamide (113j):** The representative procedure **G** was followed using amide **112j** (80.6 mg, 0.20 mmol), $ZnCl_2$·TMEDA (152 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113j** (82.4 mg, 97%) as a colorless solid. M. p. = 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.52 (d, *J* = 1.4 Hz, 1H), 7.51 (d, *J* = 1.1 Hz, 1H), 7.40 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.38–7.34 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.18 (s, 2H), 6.34 (s, 1H), 5.51 (s, 2H), 2.31 (s, 6H), 1.86 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 153.6 (C_q), 141.5 (C_q), 140.8 (C_q), 136.9 (C_q), 134.7 (C_q), 134.7 (C_q), 129.2 (CH), 128.8 (CH), 128.8 (CH), 128.1 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 120.7 (CH), 54.2 (CH_2), 51.8 (C_q), 27.8 (CH_3), 19.0 (CH_3). IR (neat): 3263, 1643, 1544, 1192, 1048, 773, 717, 695 cm^{-1}. MS (EI) *m/z* (relative intensity): 424 (20) [M^+], 381 (13), 281 (12), 208 (73), 165 (28), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{27}H_{29}N_4O^+$ $[M+H]^+$ 425.2336, found 425.2330.

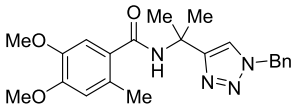


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-4-fluoro-2,6-dimethylbenzamide (113k):** The representative procedure **G** was followed using amide **112k** (68.0 mg, 0.20 mmol), $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113k** (56.0 mg, 76%) as a colorless solid. M. p. = 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.38–7.32 (m, 3H), 7.27–7.24 (m, 2H), 6.66 (d, J_{H-F} = 9.5 Hz, 2H), 6.31 (s, 1H), 5.50 (s, 2H), 2.23 (s, 6H), 1.83 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 162.3 (d, J_{C-F} = 246 Hz, C_q), 153.6 (C_q), 137.0 (d, J_{C-F} = 9 Hz, C_q), 134.7 (C_q), 134.2 (d, J_{C-F}= 3 Hz, C_q), 129.2 (CH), 128.8 (CH), 128.1 (CH), 120.5 (CH), 114.1 (d, J_{C-F} = 21 Hz, CH), 54.2 (CH_2), 51.6 (C_q), 27.7 (CH_3), 19.0 (d, J_{C-F} = 2 Hz, CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.9 (s). IR (neat): 3286, 1643, 1047, 718, 670, 524, 473, 393 cm^{-1}. MS (EI) *m/z* (relative intensity): 366 (38) $[M]^+$, 323 (45), 200 (12), 151 (97), 123 (23), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{24}FN_4O^+$ $[M+H]^+$ 367.1929, found 367.1925.

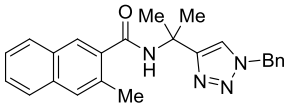


***N*-{2-[1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-2,6-dimethyl-4-(trifluoromethyl)benzamide (113l):** The representative procedure **G** was followed using amide **112l** (83.9 mg, 0.20 mmol), $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113l** (76.9 mg, 87%) as a colorless solid. M. p. = 164–165 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1H), 7.29–7.20 (m, 4H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.41 (s, 1H), 5.45 (s, 2H), 3.81 (s, 3H), 2.32 (s, 6H), 1.85 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3 (C_q), 159.9 (C_q), 153.3 (C_q), 141.0 (C_q), 135.2 (C_q), 130.5 (q, J_{C-F} = 32 Hz, C_q), 129.6 (CH), 126.5 (C_q), 124.2 (q, J_{C-F} = 3.7 Hz, CH), 123.9 (d, *J* = 272 Hz, CF_3), 120.1 (CH), 114.5 (CH), 91.4 (C_q), 55.3 (CH_3), 53.8 (CH_2), 52.1 (C_q), 27.8 (CH_3), 19.0 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ = -62.87 (s). IR (neat): 3289, 1647, 1516, 1345, 1225, 1144, 772, 665 cm^{-1}. MS (EI) *m/z* (relative intensity):

446 (13) $[M]^+$, 403 (22), 201 (28), 173 (12), 121 (100). HR-MS (ESI) *m/z* calcd for $C_{23}H_{26}F_3N_4O_2^+$ $[M+H]^+$ 447.2002, found 447.1997.

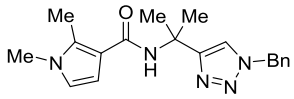


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-4,5-dimethoxy-2-methylbenzamide (113m):** The representative procedure **G** was followed using amide **112m** (76.1 mg, 0.20 mmol), $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113m** (58.2 mg, 74%) as a colorless solid. M. p. = 81–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.39–7.32 (m, 3H), 7.27 (dd, *J* = 7.4, 2.3 Hz, 2H), 6.91 (s, 1H), 6.64 (s, 1H), 6.46 (s, 1H), 5.50 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.35 (s, 3H), 1.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2 (C_q), 153.8 (C_q), 149.9 (C_q), 146.8 (C_q), 134.7 (C_q), 129.1 (CH), 129.1 (C_q), 128.8 (CH), 128.6 (C_q), 128.1 (CH), 120.5 (CH), 113.7 (CH), 110.6 (CH), 56.1 (CH_3), 55.8 (CH_3), 54.1 (CH_2), 51.7 (C_q), 27.9 (CH_3), 19.5 (CH_3). IR (neat): 1509, 1350, 1217, 1085, 1050, 721, 522, 401 cm^{-1}. MS (EI) *m/z* (relative intensity): 394 (22) $[M]^+$, 351 (17), 200 (25), 179 (52), 151 (15), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O_3^+$ $[M+H]^+$ 395.2078, found 395.2079.

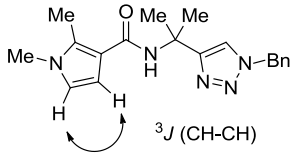


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-methyl-2-naphthamide (113n):** The representative procedure **G** was followed using amide **112n** (76.8 mg, 0.21 mmol), $ZnCl_2$·TMEDA (152 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113n** (76.4 mg, 95%) as a colorless solid. M. p. = 140–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 7.46 (qd, *J* = 7.1, 1.4 Hz, 2H), 7.41–7.34 (m, 3H), 7.32–7.25 (m, 2H), 6.62 (s, 1H), 5.52 (s, 2H), 2.50 (s, 3H), 1.89 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 153.7 (C_q), 136.0 (C_q), 134.7 (C_q), 133.9 (C_q), 133.0 (C_q), 131.2 (C_q), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 127.0 (CH), 126.2 (CH), 125.8 (CH), 120.5 (CH), 54.1 (CH_2), 51.9 (C_q), 27.9 (CH_3), 19.8 (CH_3). IR (neat): 3233, 1625, 1523, 1313, 1216, 1045, 722,

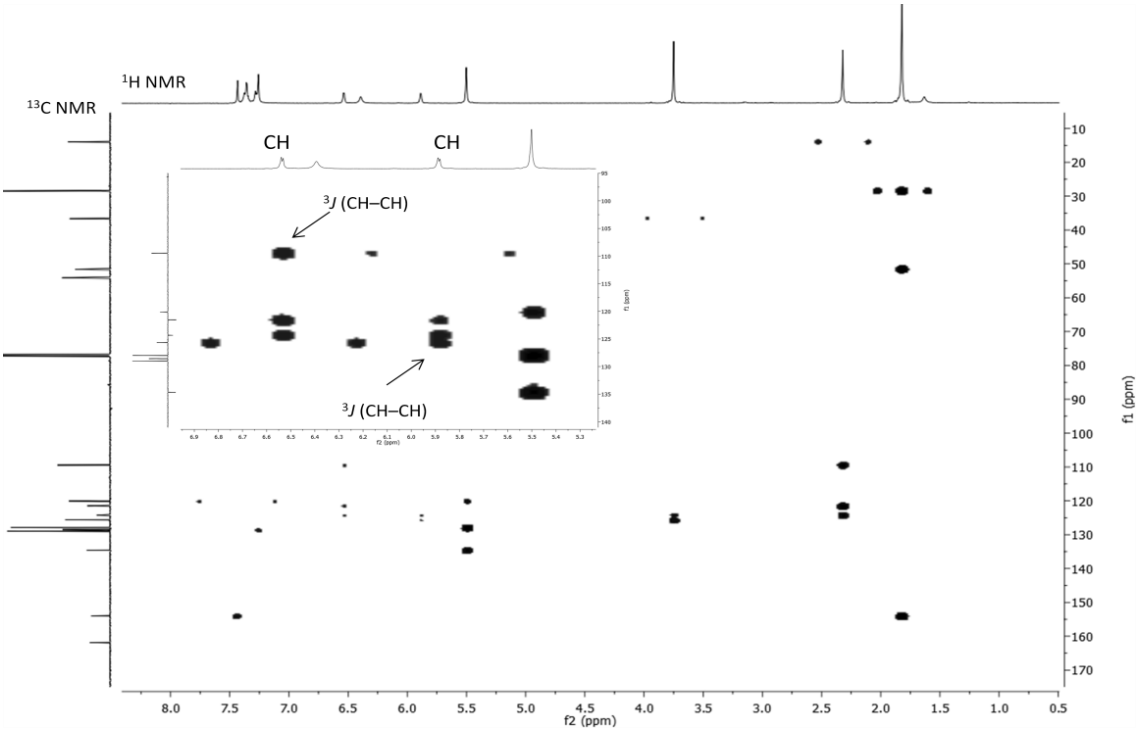
479 cm^{-1}. MS (EI) *m/z* (relative intensity): 384 (23) [M^+], 341 (20), 200 (27), 169 (50), 141 (45), 115 (25), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{24}H_{25}N_4O^+$ $[M+H]^+$ 385.2023, found 385.2026.

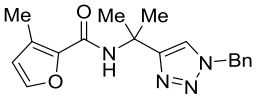


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-1,2-dimethyl-1*H*-pyrrole-3-carboxamide (113p):** The representative procedure **E** was followed using amide **112p** (65.6 mg, 0.20 mmol) $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and m MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113p** (35.5 mg, 57%) as a colorless solid. M. p. = 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1H), 7.38–7.32 (m, 3H), 7.26 (dt, *J* = 4.3, 2.4 Hz, 2H), 6.53 (d, *J* = 2.6 Hz, 1H), 6.40 (s, 1H), 5.88 (d, *J* = 2.6 Hz, 1H), 5.49 (s, 2H), 3.75 (s, 3H), 2.32 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (C_q), 154.1 (C_q), 134.7 (C_q), 129.0 (CH), 128.6 (CH), 128.0 (CH), 125.7 (CH), 124.3 (C_q), 121.6 (C_q), 120.1 (CH), 109.5 (CH), 54.1 (CH_2), 51.6 (C_q), 36.6 (CH_3), 28.4 (CH_3), 13.9 (CH_3). IR (neat): 3285, 1621, 1539, 1208, 1049, 726, 716, 680 cm^{-1}. MS (EI) *m/z* (relative intensity): 337 (27) $[M]^+$, 294 (15), 20 (20), 139 (25), 122 (70), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{19}H_{24}N_5O^+$ $[M+H]^+$ 338.1975, found 338.1977.

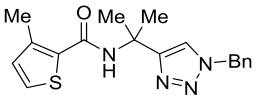


HMBC 113p



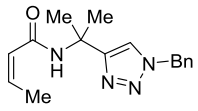


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-methylfuran-2-carboxamide (113ia):** The representative procedure **G** was followed using amide **110i** (62.8 mg, 0.20 mmol), $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113ia** (32.3 mg, 50%) as a colorless solid. M. p. = 133–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1H), 7.37–7.32 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 1.7 Hz, 1H), 6.92 (s, 1H), 6.26 (d, *J* = 1.7 Hz, 1H), 5.48 (s, 2H), 2.31 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0 (C_q), 153.8 (C_q), 142.4 (C_q), 141.8 (CH), 134.7 (C_q), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.1 (C_q), 120.3 (CH), 115.4 (CH), 54.1 (CH_2), 51.3 (C_q), 28.2 (CH_3), 11.1 (CH_3). IR (neat): 3278, 1644, 1529, 1298, 1219, 1051, 729, 596 cm^{-1}. MS (EI) *m/z* (relative intensity): 324 (1) [M$^+$], 281 (35), 200 (28), 109 (62), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{18}H_{19}N_4O_2^-$ [M-H]$^-$ 323.1513, found 323.1505.



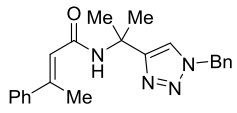
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-methylthiophene-2-carboxamide (113q):** The representative procedure **G** was followed using amide **112q** (66.8 mg, 0.21 mmol), $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113q** (41.8 mg, 60%) as a colorless solid. M. p. = 116–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.39–7.33 (m, 3H), 7.30–7.25 (m, 2H), 7.22 (d, *J* = 5.0 Hz, 1H), 6.84 (d, *J* = 5.0 Hz, 1H), 6.70 (s, 1H), 5.50 (s, 2H), 2.48 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.4 (C_q), 153.8 (C_q), 139.9 (C_q), 134.6 (C_q), 132.5 (C_q), 131.8 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 126.4 (CH), 120.2 (CH), 54.1 (CH_2), 52.1 (C_q), 28.1 (CH_3), 15.7 (CH_3). IR (neat): 3270, 1623, 1534, 1305, 1214, 717, 612, 539 cm^{-1}. MS (EI) *m/z* (relative intensity): 340 (10) [M]$^+$, 297 (40), 200 (10), 125 (88), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{18}H_{21}N_4OS^+$ [M+H]$^+$ 341.1431, found 341.1436.

(*Z*)-*N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]but-2-enamide (113r):

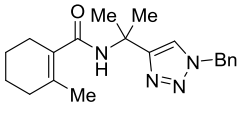


The representative **G** procedure was followed using acrylamide **112r** (56.1 mg, 0.21 mmol), $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113r** (33.9 mg, 57%) as a colorless solid. M. p. = 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1H), 7.36–7.31 (m, 3H), 7.25–7.22 (m, 2H), 6.21 (s, 1H), 5.99 (dq, *J* = 11.5, 7.2 Hz, 1H), 5.65 (dd, *J* = 11.5, 1.8 Hz, 1H), 5.46 (s, 2H), 2.02 (dd, *J* = 7.2, 1.8 Hz, 3H), 1.73 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1 (C_q), 153.8 (C_q), 139.4 (CH), 134.7 (C_q), 129.0 (CH), 128.6 (CH), 128.0 (CH), 124.0 (CH), 120.3 (CH), 54.1 (CH_2), 51.3 (C_q), 28.0 (CH_3), 14.8 (CH_3). IR (neat): 3255, 1668, 1546, 1526, 1220, 1053, 716, 696 cm^{-1}. MS (EI) *m/z* (relative intensity): 284 (2) [M^+], 256 (12), 241 (38), 201 (20), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{16}H_{21}N_4O^+$ $[M+H]^+$ 285.1710, found 285.1714.

(*E*)-*N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-phenylbut-2-enamide (113s):

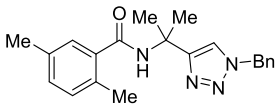


The representative procedure **G** was followed using cinnamamide **112s** (72.0 mg, 0.21 mmol), $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113s** (32.5 mg, 43%) as a colorless solid. M. p. = 156–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.40–7.14 (m, 10H), 6.29 (s, 1H), 5.98 (s, 1H), 5.49 (s, 2H), 2.46 (s, 3H), 1.77 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3 (C_q), 153.9 (C_q), 150.2 (C_q), 142.7 (C_q), 134.7 (C_q), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.1 (CH), 120.8 (CH), 120.3 (CH), 54.1 (CH_2), 51.4 (C_q), 28.0 (CH_3), 17.5 (CH_3). IR (neat): 3116, 1664, 1528, 1213, 1057, 724, 693, 484 cm^{-1}. MS (EI) *m/z* (relative intensity): 360 (12) [$M]^+$, 317 (33), 200 (15), 145 (38), 115 (33), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{25}N_4O^+$ $[M+H]^+$ 361.2023, found 361.2026.



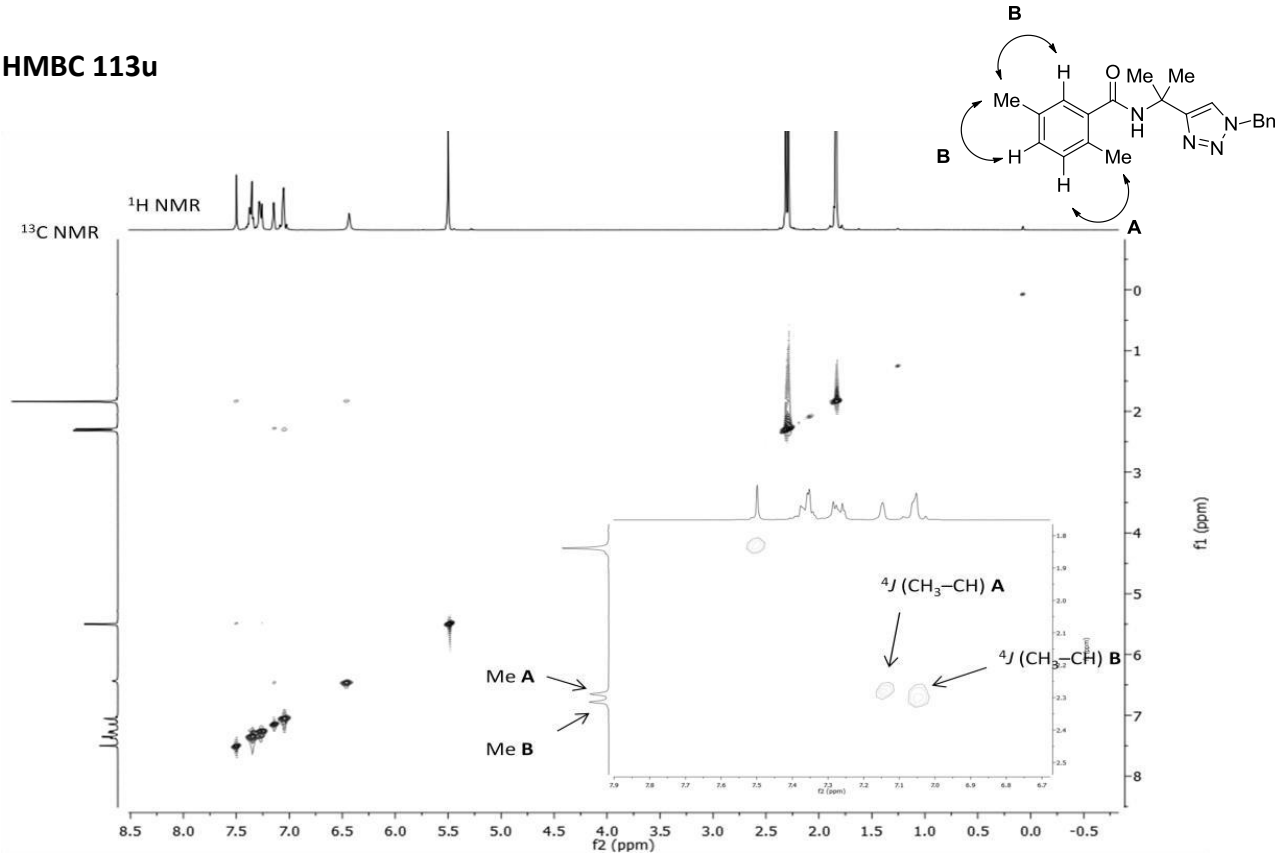
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methylcyclohex-1-ene-1-carboxamide (113t):** The representative procedure **E** was followed using amide **112t** (67.4 mg, 0.21 mmol), $ZnCl_2$·TMEDA (157 mg, 0.62 mmol) and MeMgBr (0.50 mL, 3 M, 1.50 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113t** (63.5 mg, 90%) as a colorless solid. M. p. = 134–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41 (s, 1H), 7.37–7.30 (m, 3H), 7.26–7.22 (m, 2H), 6.14 (s, 1H), 5.47 (s, 2H), 2.17–2.10 (m, 1H), 1.59–1.52 (m, 2H), 1.75 (s, 6H), 1.71 (s, 3H), 1.59–1.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4 (C_q), 153.9 (C_q), 134.7 (C_q), 134.0 (C_q), 130.0 (C_q), 129.1 (CH), 128.7 (CH), 128.0 (CH), 120.4 (CH), 54.1 (CH_2), 51.4 (C_q), 31.3 (CH_2), 28.0 (CH_3), 26.8 (CH_2), 22.4 (CH_2), 22.2 (CH_2), 20.8 (CH_3). IR (neat): 2934, 1638, 1527, 1054, 716, 695, 391, 381 cm^{-1}. MS (EI) *m/z* (relative intensity): 338 (15) $[M]^+$, 295 (20), 200 (33), 172 (15), 123 (18), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{20}H_{26}N_4O^+$ $[M]^+$ 338.2107, found 338.2107.

Intramolecular Competition Experiments



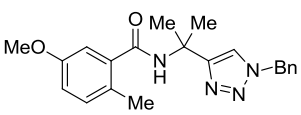
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,5-dimethylbenzamide (113u)**: The representative procedure **E** was followed using amide **112u** (67.6 mg, 0.20 mmol), $ZnCl_2$·TMEDA (151.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 25 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113u** (56.6 mg, 81%) as a colorless solid. M. p. = 109–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.40–7.33 (m, 3H), 7.30–7.23 (m, 2H), 7.15 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 5.50 (s, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 1.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 153.7 (C_q), 137.0 (C_q), 135.2 (C_q), 134.7 (C_q), 132.4 (C_q), 130.7 (CH), 130.3 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 127.2 (CH), 120.5 (CH), 54.0 (CH_2), 51.7 (C_q), 27.8 (CH_3), 20.6 (CH_3), 18.9 (CH_3). IR (neat): 3227, 3034, 1645, 1539, 1220, 1058, 810, 719, 693 cm^{-1}. MS (EI) *m/z* (relative intensity): 348 (20) $[M]^+$, 305 (32), 200 (17), 133 (53), 105 (25), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{25}N_4O^+$ $[M+H]^+$ 349.2023, found 349.2025.

HMBC 113u



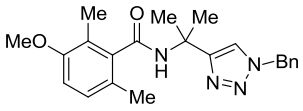
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-methoxy-2-methylbenzamide (113v) and *N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-3-methoxy-2,6-dimethylbenzamide (113v'):**

The representative procedure **G** was followed using amide **112v** (37.0 mg, 0.20 mmol), $ZnCl_2$·TMEDA (76.0 mg, 0.30 mmol) and MeMgBr (0.23 mL, 3 M, 0.7 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded products **113v** (13.2 mg, 20%) and **113v'** (48.3 mg, 65%) as colorless solids.



(**113v**): M. p. = 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.43–7.33 (m, 2H), 7.33–7.23 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.43 (s, 1H), 5.52 (s, 2H), 3.78 (s, 3H), 2.29 (s, 3H), 1.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 157.4 (C_q), 153.6 (C_q), 137.9 (C_q), 134.6 (C_q), 131.8 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 127.3 (C_q), 120.4 (CH), 115.3 (CH), 112.1 (CH), 55.4 (CH_3), 54.1 (CH_2), 51.9 (C_q), 27.9 (CH_3), 18.6 (CH_3). IR (neat):

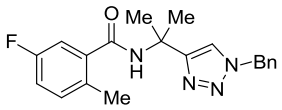
3240, 1655, 1242, 1226, 1050, 1032, 723, 694 cm^{-1}. MS (EI) *m/z* (relative intensity): 364 (18) $[M]^+$, 321 (15), 200 (25), 172 (12), 149 (37), 121 (22), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{24}N_4O_2^+$ $[M]^+$ 364.1899, found 364.1902.



(**113v'**): M. p. = 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 7.39–7.33 (m, 3H), 7.29–7.24 (m, 2H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.27 (s, 1H), 5.52 (s, 2H), 3.78 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 1.86 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3 (C_q), 155.7 (C_q), 153.5 (C_q), 139.0 (C_q), 134.7 (C_q), 129.1 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 125.7 (C_q), 122.9 (C_q), 120.6 (CH), 110.4 (CH), 55.6 (CH_3), 54.2 (CH_2), 51.8 (C_q), 27.8 (CH_3), 18.2 (CH_3), 12.5 (CH_3). IR (neat): 2917, 1641, 1518, 1083, 1050, 802, 720, 466 cm^{-1}. MS (EI) *m/z* (relative intensity): 378 (20) $[M]^+$, 335 (5), 200 (22), 162 (55), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O_2^+$ $[M+H]^+$ 379.2129, found 379.2132.

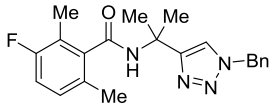
***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-fluoro-2-methylbenzamide (113w) and *N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-fluoro-2,6-dimethylbenzamide (113w'):**

The representative procedure **G** was followed using amide **112w** (68.1 mg, 0.20 mmol), $ZnCl_2$·TMEDA (152.5 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded products **113w** (10.6 mg, 15%) as a colorless oil and **113w'** (52.2 mg, 71%) as a colorless solid.

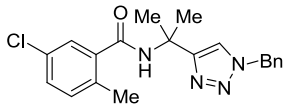


(**113w**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1H), 7.37–7.33 (m, 3H), 7.28–7.23 (m, 2H), 7.11 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.04 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.94 (td, *J* = 8.5, 2.8 Hz, 1H), 6.48 (s, 1H), 5.50 (s, 2H), 2.30 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2 (C_q), 160.5 (d, J_{C-F} = 245 Hz, C_q), 153.5 (C_q), 138.4 (d, J_{C-F} = 6 Hz, C_q), 134.5 (C_q), 132.3 (d, J_{C-F} = 8 Hz, CH), 131.2 (d, J_{C-F} = 3 Hz, CH), 129.1 (CH), 128.7 (CH), 128.1 (CH), 120.3 (CH), 116.4 (d, J_{C-F} = 21 Hz, CH), 113.7(d, J_{C-F} = 21 Hz, CH), 54.2 (CH_2), 52.0 (C_q), 27.9 (CH_3), 18.8 (CH_3). ^{19}F NMR (285 MHz, $CDCl_3$): δ = -117.15

(tdd, *J* = 8.5, 5.4, 1.2 Hz). IR (neat): 3268, 2977, 1650, 1491, 1224, 1049, 816, 720 cm^{-1}. MS (EI) *m/z* (relative intensity): 353 (100) $[M]^+$, 227 (25), 200 (35), 172 (45), 91 (15). HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}FN_4O^+$ $[M+H]^+$ 353.1772, found 353.1774.

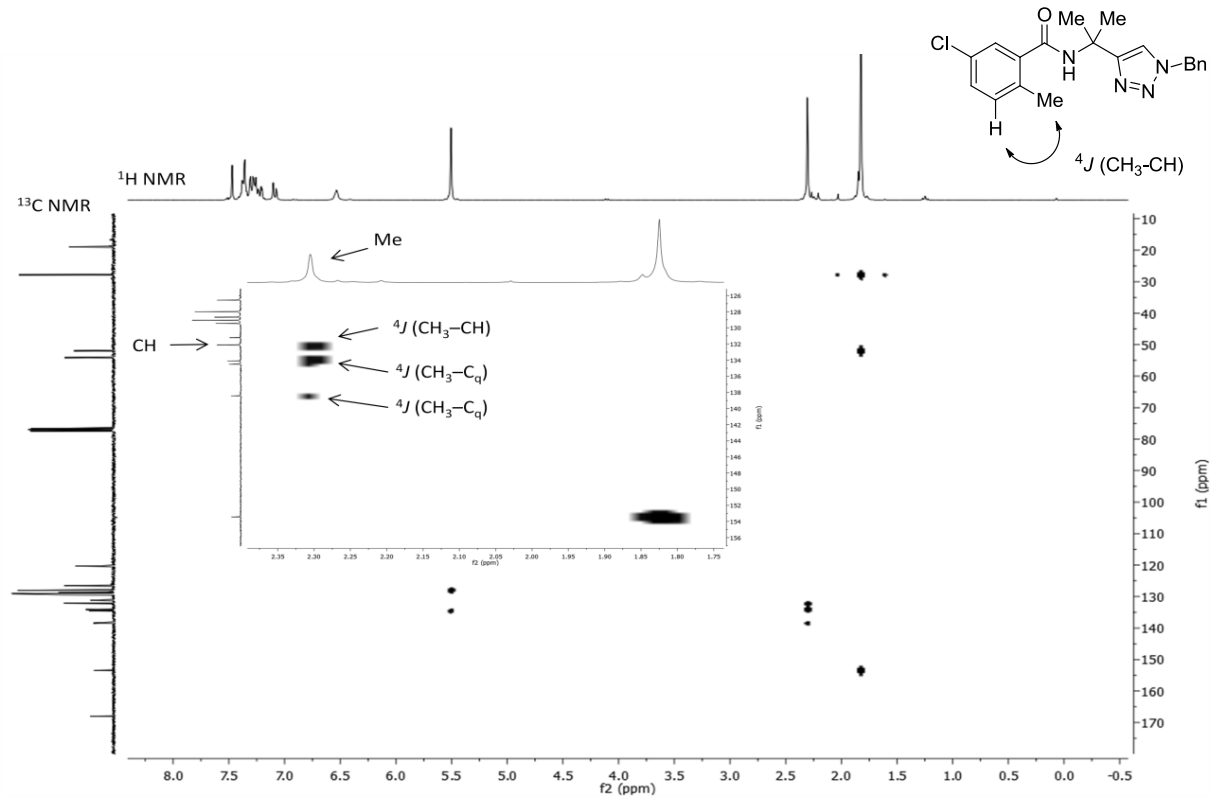


(**113w^{I}**): M. p. = 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.50 (s, 1H), 7.39–7.29 (m, 3H), 7.27–7.20 (m, 2H), 6.96–6.76 (m, 2H), 6.41 (s, 1H), 5.49 (s, 2H), 2.19 (s, 3H), 2.13 (d, *J* = 2.2 Hz, 3H), 1.83 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2 (d, $J_{C–F}$ = 3.2 Hz, C_q), 159.3 (d, $J_{C–F}$ = 243 Hz, C_q), 153.3 (C_q), 139.4 (d, $J_{C–F}$ = 4 Hz, C_q), 134.5 (C_q), 129.5 (d, $J_{C–F}$ = 4 Hz, C_q), 129.1 (CH), 128.7 (CH), 128.5 (d, *J* = 8 Hz, CH), 128.0 (CH), 121.3 (d, $J_{C–F}$ = 18 Hz, C_q), 120.4 (CH), 115.0 (d, $J_{C–F}$ = 23 Hz, CH), 54.1 (CH_2), 51.9 (C_q), 27.7 (CH_3), 18.4 (CH_3), 11.2 (d, $J_{C–F}$ = 4 Hz, CH_3). ^{19}F NMR (285 MHz, $CDCl_3$): δ = -120.39–120.48 (m). IR (neat): 3264, 1644, 1545, 1311, 1050, 817, 717, 688 cm^{-1}. MS (EI) *m/z* (relative intensity): 367 (100) $[M]^+$, 200 (35), 172 (37), 151 (5), 91 (10). HR-MS (EI) *m/z* calcd for $C_{21}H_{24}FN_4O^+$ $[M+H]^+$ 367.1929, found 367.1933.

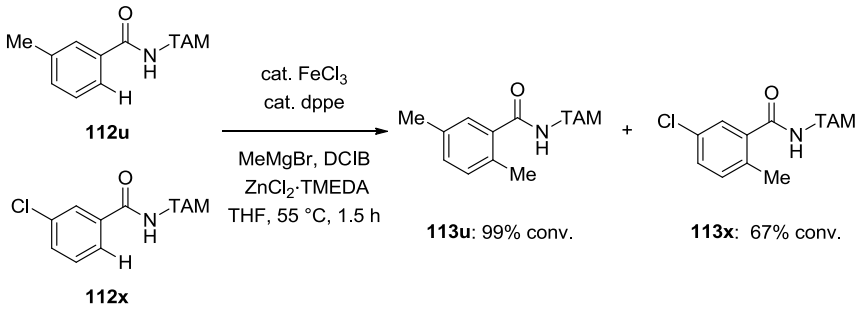


_N_-(2-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl)-3-chloro-2-methylbenzamide (113x): The representative procedure **G** was followed using amide **112x** (80.4 mg, 0.23 mmol) $ZnBr_2$·TMEDA (205 mg, 0.60 mmol) and MeMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **113x** (67.7 mg, 81%) as a colorless solid. M. p. = 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1H), 7.40–7.34 (m, 3H), 7.29 (dd, *J* = 8.4, 2.5 Hz, 2H), 7.26 (s, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.53 (s, 1H), 5.50 (s, 2H), 2.31 (s, 3H), 1.83 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0 (C_q), 153.4 (C_q), 138.4 (C_q), 134.5 (C_q), 134.1 (C_q), 132.1 (CH), 131.2 (C_q), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 126.6 (CH), 120.3 (CH), 54.1 (CH_2), 52.0 (C_q), 27.8 (CH_3), 19.0 (CH_3). IR (neat): 3238, 1656, 1555, 1542, 1308, 1055, 719, 518 cm^{-1}. MS (EI) *m/z* (relative intensity): 368 (8) $[M]^+$, 325 (22), 200 (8), 153 (37), 125 (20), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{20}H_{22}ClN_4O^+$ $[M+H^+]$ 369.1477, found 369.1474.

HMBC 113x



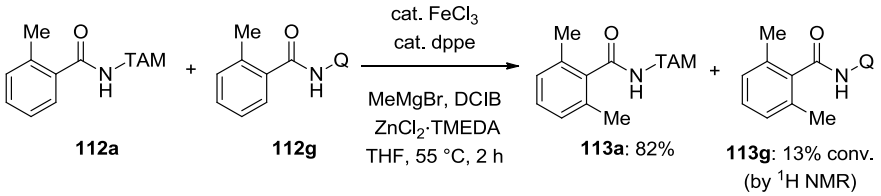
Intermolecular Competition Experiments with Differently Substituted Arenes



A solution of MeMgBr (0.47 mL, 3 M, 1.40 mmol) in dry THF (2.50 mL) was slowly added to a mixture of amides **112u** (66.9 mg, 0.20 mmol) and **112x** (71.0 mg, 0.20 mmol) with $ZnCl_2$·TMEDA (151 mg, 0.60 mmol) under N_2. The resulting mixture was stirred at ambient temperature for 5 min, then a solution of $FeCl_3$ (6.80 mg, 42 µmol, 21 mol %) and dppe (16.7 mg, 42 µmol, 21 mol %) in dry THF (2.50 mL) was added. Thereafter, DClB (50.1 mg, 0.40 mmol) was added. The mixture was stirred at 55 °C for 2 h. After cooling to ambient temperature, the mixture was diluted with H_2O (5 mL). The filtrate was extracted with EtOAc (2 × 20 mL), the combined organic extracts were dried over Na_2SO_4 and filtered. After

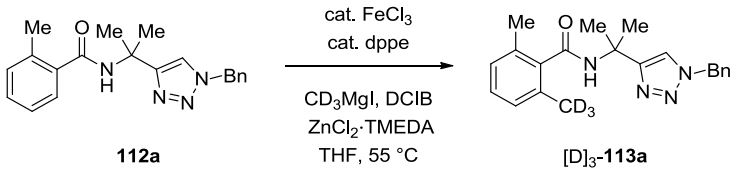
removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) to yield **113u** and **113x** as an inseparable mixture. The ratio of methylated products **113u** and **113x** was determined by ^{1}H NMR spectroscopy.

Intermolecular Competition Experiment with Compounds 112a and 112g

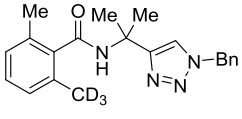


A solution of MeMgBr (0.47 mL, 3 M, 1.40 mmol) in dry THF (2.50 mL) was slowly added to a mixture of **112a** (67.1 mg, 0.20 mmol), **112g** (52.7 mg, 0.20 mmol) and $ZnCl_2$·TMEDA (150 mg, 0.60 mmol) under N_2. The resulting mixture was stirred at ambient temperature for 5 min, then a solution of $FeCl_3$ (5.80 mg, 18 mol %) and dppe (15.2 mg, 19 mol %) in dry THF (2.50 mL) was added. Subsequently, DClB (50.1 mg, 0.40 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h. After cooling to ambient temperature, the reaction was diluted with H_2O (5 mL). The filtrate was extracted with EtOAc (2 × 20 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) to yield **113a** (57.2 mg, 82%) and a mixture of **113g** and **112g** (20.5 mg, 37%) as a colorless solid. The ratio of substrate **112g** and methylated product **113g** was derived by ^{1}H NMR spectroscopy, verifying a conversion of **113g** to be 13%.

Experiments with Isotopically Labeled Substrates

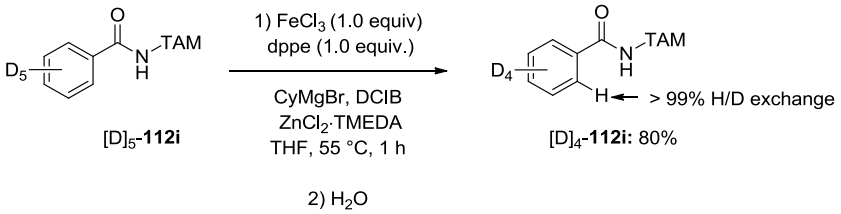


The representative procedure **G** was followed using amide **112a** (64.9 mg, 0.194 mmol), $ZnBr_2$·TMEDA (206 mg, 0.60 mmol) and [D_3]-methylmagnesium iodide (0.3 mL, 3 M, 0.9 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product [D]$_3$-**113a** (69.0 mg, 99%) as a colorless solid.

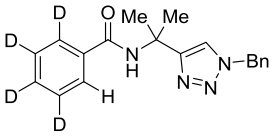


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-methyl-6-(methyl-*d*$_3$)benzamide (**[D]$_3$-**113a):** M. p. = 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.40–7.34 (m, 3H), 7.27–7.24 (m, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.29 (s, 1H), 5.52 (s, 2H), 2.26 (s, 3H), 1.86 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.7 (C_q), 153.6 (C_q), 138.0 (C_q), 134.7 (C_q), 134.2 (C_q), 134.1 (C_q), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.5 (CH), 120.6 (CH), 54.1 (CH_2), 51.8 (C_q), 27.7 (CH_3), 18.9 (CH_3), 18.1 (t, $J_{C–D}$ = 19 Hz, CD_3). IR (neat): 3261, 1643, 1542, 1215, 1193, 724, 964, 379 cm^{-1}. MS (ESI) *m/z* (relative intensity): 352 (11) [M]$^+$, 308 (53), 200 (23), 136 (86), 108 (43),91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{22}D_3N_4O^+$ [M+H]$^+$ 352.2211, found 352.2213.

Stoichiometric Experiment

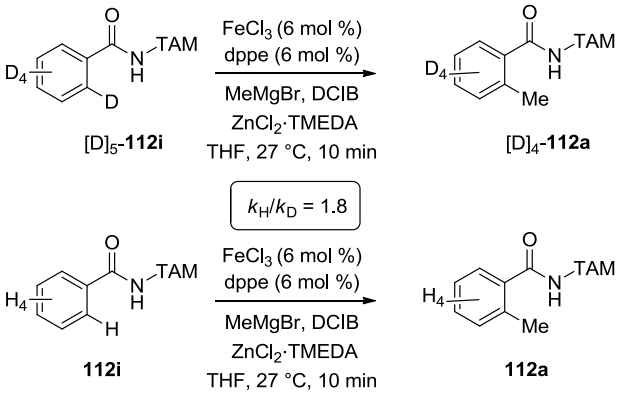


A solution of CyMgBr **135** (1.40 mL, 1M in *n*-hexane, 1.40 mmol) in dry THF (2.50 mL) was slowly added to a mixture of amide [D]$_5$-**112i** (66.6 mg, 0.204 mmol) and $ZnCl_2$·TMEDA (150 mg, 0.60 mmol) under N_2. The resulting mixture was stirred at ambient temperature for 5 min, then a solution of $FeCl_3$ (32.4 mg, 0.20 mmol) and dppe (79.7 mg, 0.20 mmol) in dry THF (2.50 mL) was added. The mixture was stirred at 55 °C for 1 h. After cooling to ambient temperature, the mixture was diluted with H_2O (5.0 mL). The filtrate was extracted with EtOAc (2 × 20 mL), the combined organic extracts were dried over Na_2SO_4 and filtered. After removal of the solvents under reduced pressure, the residue was purified by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) to yield [D]$_4$-**112i** (52.8 mg, 80%) as a colorless solid. The ratio of D/H exchange was determined by ^{1}H NMR, indicating an exchange of >99% H in the *ortho* position.



***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]benzamide-2,3,4,5-*d*$_4$ ([D]$_4$-112i):**. M. p. = 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.47 (d, J = 1.1 Hz, 1H), 7.42–7.33 (m, 3H), 7.32–7.24 (m, 2H), 7.02 (s, 1H), 5.51 (s, 2H), 1.85 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7 (C_q), 154.0 (C_q), 135.2 (t, $J_{C–D}$ = 10 Hz, CD), 134.6 (C_q), 130.9 (t, $J_{C–D}$ = 24 Hz, CD), 129.1 (CH), 128.7 (CH), 128.1 (CH), 127.8 (t, $J_{C–D}$ = 13 Hz, CD), 126.7 (CH), 126.4 (t, $J_{C–D}$ = 25 Hz, CD), 120.2 (CH), 54.2 (CH_2), 51.8 (C_q), 28.0 (CH_3). IR (neat): 3118, 1646, 1524, 1277, 1219, 1054, 727, 572, 558 cm^{-1}. MS (EI) *m/z* (relative intensity): 324 (2) [M]$^+$, 296 (12), 281 (32), 109 (40), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{19}H_{16}D_4N_4O^+$ [M]$^+$ 324.1888, found 324.1892.

Kinetic Isotope Effect Studies



A solution of MeMgBr (0.47 mL, 3 M in *n*-hexane, 1.4 mmol) in dry THF (2.50 mL) was slowly added to the two seperated reaction vessels containing amide [D]$_5$-**112i** (65.6 mg, 0.202 mmol) or amide **112i** (63.2 mg, 0.197 mmol), $ZnCl_2$·TMEDA (100 mg, 0.40 mmol) and *n*-dodecane (34.1 mg, 0.20 mmol) as internal standard in each case under N_2. The resulting mixtures were stirred at ambient temperature for 5 min, then the solutions of $FeCl_3$ (2.00 mg, 12 µmol, 6.0 mol %) and dppe (4.80 mg, 12 µmol, 6.0 mol %) in dry THF (2.50 mL) followed by DClB (51.0 mg, 0.40 mmol) were immediatelly added in each case. The reaction mixtures were stirred at 27 °C for 10 min. Every 1 min, 0.20 mL aliquots of the reaction mixtures were collected, filtered through a short pad of silica gel and Na_2SO_4 and directly injected into the GC instrument. The formation of the products was monitored by using *n*-dodecane as internal standard (Figure 11). This competition experiment with the isotopically labeled and unlabeled substrates [D]$_5$-**112i** and **112i**, respectively, indicated a kinetic isotope effect of $k_H/k_D \approx 1.8$.

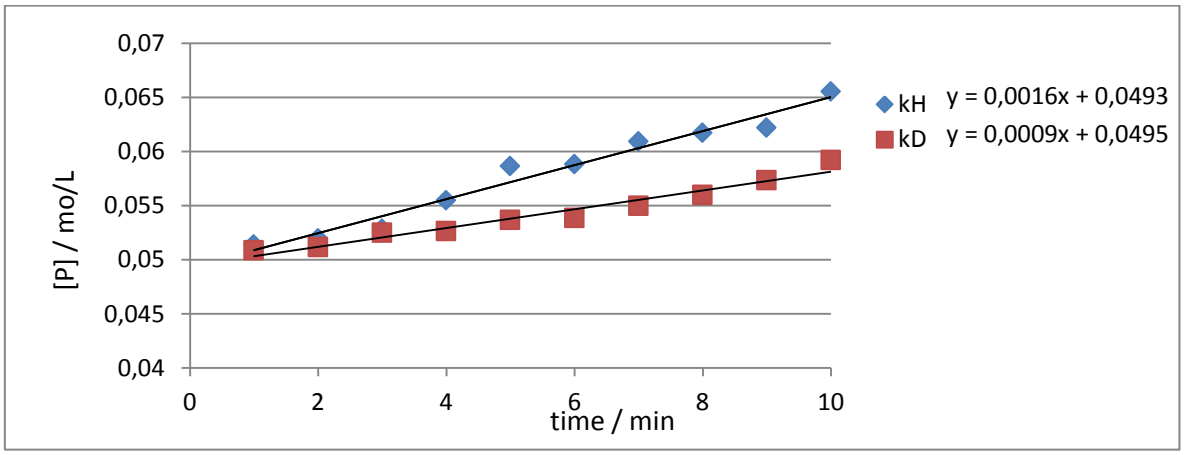
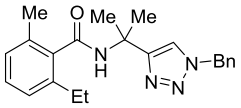
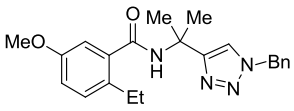


Figure 13: Linear regressions for the iron-catalyzed C–H methylations with substrates [D]$_5$-**112i** and **112i**.

6.4.4 Analytical Data for C(sp^2)–H Ethylation

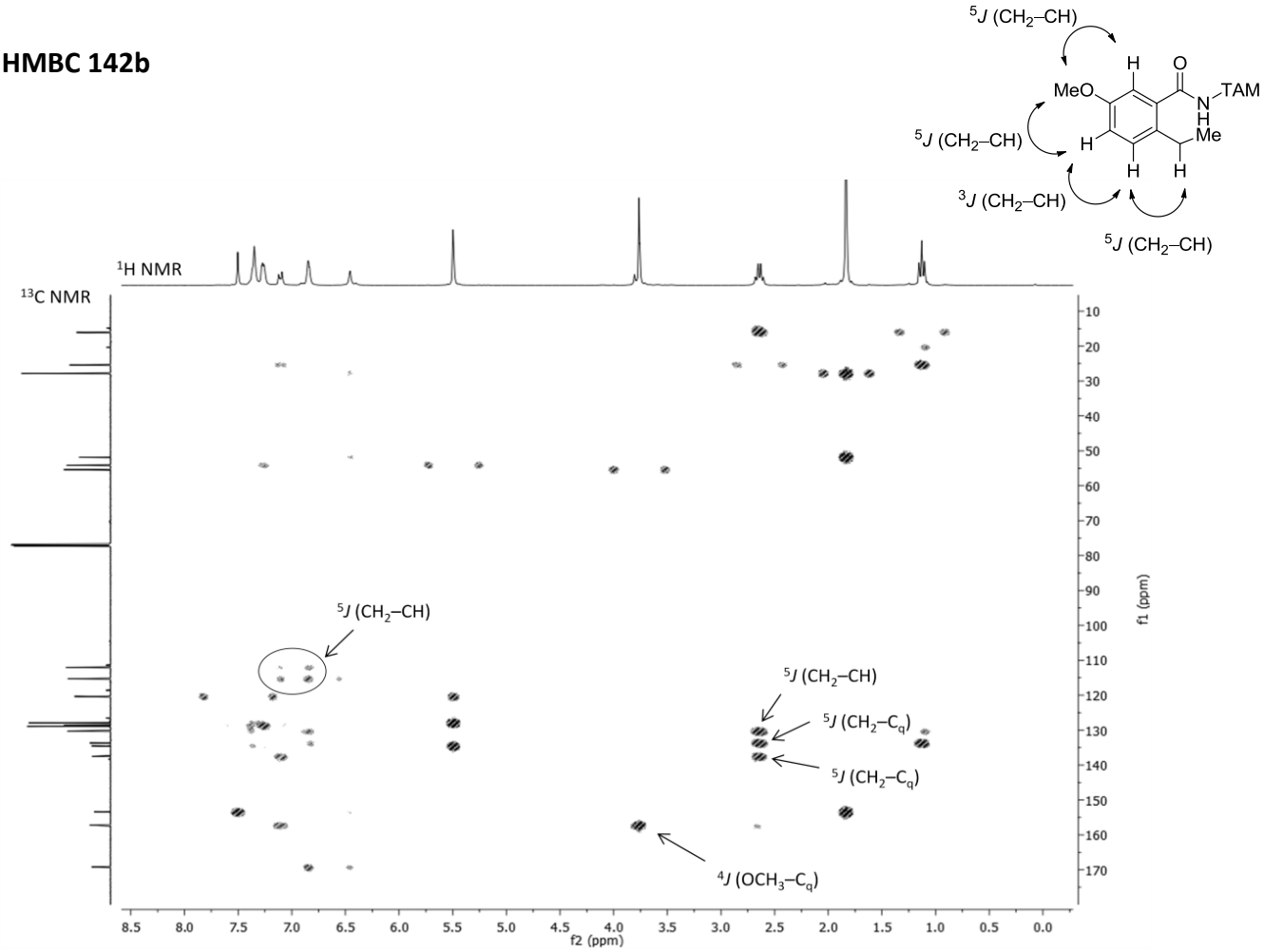


***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-ethyl-6-methylbenzamide (142a):** The representative procedure **G** was followed using amide **112a** (66.0 mg, 0.198 mmol), $ZnBr_2$·TMEDA (206 mg, 0.60 mmol) and EtMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **142a** (56.1 mg, 78%) as a colorless solid. M. p. = 108–109 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.37–7.31 (m, 3H), 7.26–7.23 (m, 2H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.29 (s, 1H), 5.49 (s, 2H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.23 (s, 3H), 1.84 (s, 6H), 1.14 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 153.5 (C_q), 140.5 (C_q), 137.5 (C_q), 134.7 (C_q), 134.1 (C_q), 129.1 (CH), 128.7 (CH), 128.7 (CH), 128.1 (CH), 127.5 (CH), 125.9 (CH), 120.6 (CH), 54.1 (CH_2), 51.8 (C_q), 27.7 (CH_3), 26.0 (CH_2), 18.9 (CH_3), 15.8 (CH_3). IR (neat): 3267, 1639, 1539, 1215, 1047, 716, 672 cm^{-1}. MS (EI) *m/z* (relative intensity): 362 (37) $[M]^+$, 319 (25), 200 (23), 146 (70), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{25}N_4O^+$ $[M–H]^+$ 361.2023, found 361.2034.

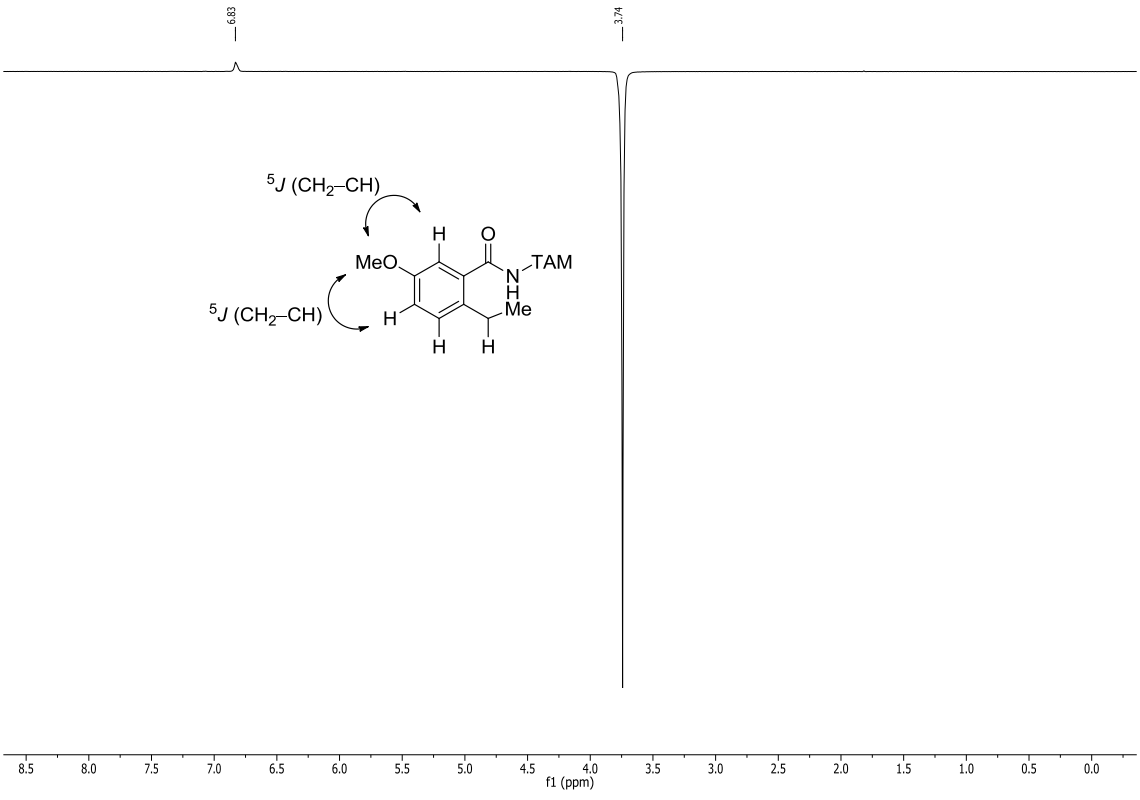


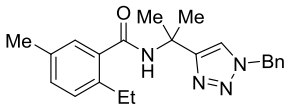
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-ethyl-3-methoxybenzamide (142b):** The representative procedure **G** was followed using **112v** (69.4 mg, 0.20 mmol), $ZnBr_2$·TMEDA (206 mg, 0.60 mmol) and EtMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded **142b** (55.4 mg, 74%) as a colorless solid. M. p. = 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.39–7.31 (m, 3H), 7.30–7.20 (m, 2H), 7.11 (d, *J* = 9.2 Hz, 1H), 6.89–6.80 (m, 2H), 6.46 (s, 1H), 5.50 (s, 2H), 3.76 (s, 3H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.84 (s, 6H), 1.13 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (C_q), 157.4 (C_q), 153.6 (C_q), 137.7 (C_q), 134.7 (C_q), 133.8 (C_q), 130.4 (CH), 129.1 (CH), 128.7 (CH), 128.1 (CH), 120.5 (CH), 115.4 (CH), 112.1 (CH), 55.4 (CH_3), 54.0 (CH_2), 51.8 (C_q), 27.7 (CH_3), 25.2 (CH_2), 15.9 (CH_3). IR (neat): 2967, 1662, 1533, 1239, 1215, 1035, 724, 381 cm^{-1}. MS (EI) *m/z* (relative intensity): 378 (17) $[M]^+$, 200 (27), 178 (42), 162 (33), 134 (27), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O_2^+$ $[M+H]^+$ 379.2129, found 379.2131.

HMBC 142b



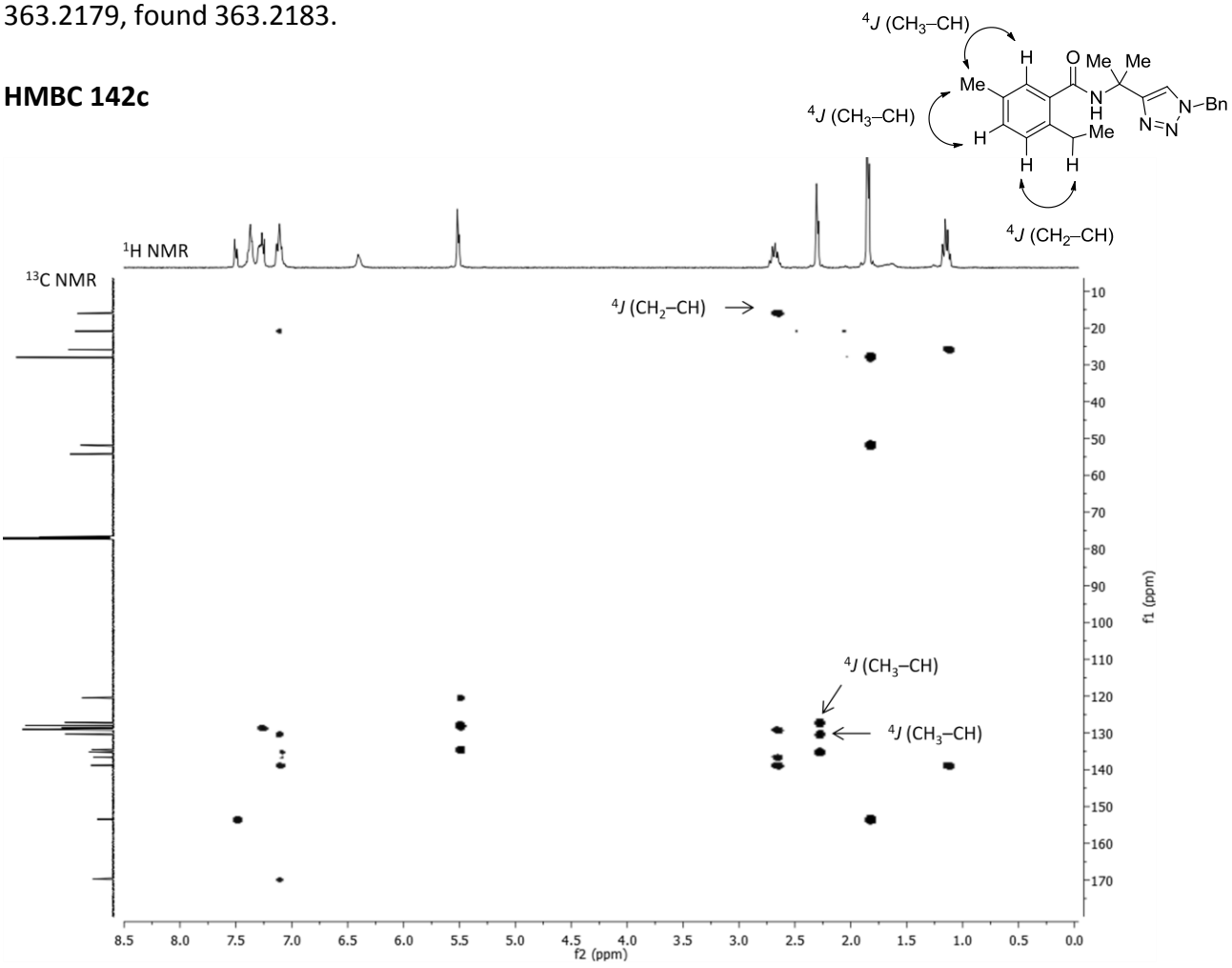
NOE 142b

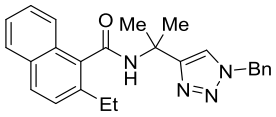




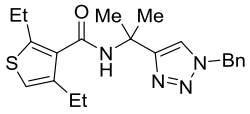
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-ethyl-5-methylbenzamide (142c):** The representative procedure **G** was followed using **112u** (67.6 mg, 0.20 mmol), $ZnBr_2$·TMEDA (208 mg, 0.60 mmol) and EtMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **142c** (50.1 mg, 69%) as a colorless solid. M. p. = 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.42–7.34 (m, 3H), 7.32–7.23 (m, 2H), 7.13 (s, 1H), 7.12–7.08 (m, 2H), 6.41 (s, 1H), 5.52 (s, 2H), 2.69 (q, *J* = 7.0 Hz, 2H), 2.31 (s, 3H), 1.85 (s, 6H), 1.16 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0 (C_q), 153.7 (C_q), 139.0 (C_q), 136.8 (C_q), 135.3 (C_q), 134.7 (C_q), 130.5 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.1 (CH), 127.3 (CH), 120.6 (CH), 54.2 (CH_2), 51.7 (C_q), 27.8 (CH_3), 25.7 (CH_2), 20.7 (CH_3), 15.8 (CH_3). IR (neat): 3131, 1650, 1530, 1215, 1054, 824, 716, 696 cm^{-1}. MS (EI) *m/z* (relative intensity): 362(15) $[M]^+$, 319 (13), 200 (30), 147 (35), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O^+$ $[M+H]^+$ 363.2179, found 363.2183.

HMBC 142c





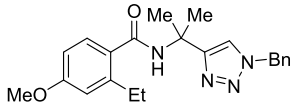
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-ethyl-1-naphthamide (142d):** The representative procedure **G** was followed using naphthamide **112y** (1.11 g, 3.00 mmol), $ZnBr_2$·TMEDA (3.07 g, 9.00 mmol) and EtMgBr (7.00 mL, 3 M, 21.0 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **142d** (1.10 g, 92%) as a colorless solid. M. p. = 146–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.8 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.59 (s, 1H), 7.43–7.38 (m, 2H), 7.38–7.33 (m, 3H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 5.49 (s, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.91 (s, 6H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1 (C_q), 153.4 (C_q), 138.1 (C_q), 134.7 (C_q), 133.6 (C_q), 131.7 (C_q), 130.1 (C_q), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 125.4 (CH), 124.7 (CH), 120.7 (CH), 54.0 (CH_2), 52.0 (C_q), 27.7 (CH_3), 26.5 (CH_2), 15.9 (CH_3). IR (neat): 3321, 1738, 1641, 1521, 1228, 821. 719, 392 cm^{-1}. MS (EI) *m/z* (relative intensity): 398 (20) $[M]^+$, 200 (23), 182 (100), 154 (18), 91 (73). HR-MS (ESI) *m/z* calcd for $C_{25}H_{27}N_4O^+$ $[M+H]^+$ 399.2179, found 399.2175.



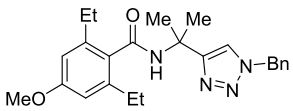
***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-diethyl-thiophene-3-carboxamide (142e):** The representative procedure **G** was followed using **112z** (35.6 mg, 0.11 mmol), $ZnCl_2$·TMEDA (76.5 mg, 0.30 mmol) and EtMgBr (0.30 mL, 3 M, 0.9 mmol). The reaction mixture was stirred at 55 °C for 48 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded **142e** (19.3 mg, 46%) as a colorless solid. M. p. = 67–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.43–7.32 (m, 3H), 7.32–7.21 (m, 2H), 6.67 (s, 1H), 6.38 (s, 1H), 5.50 (s, 2H), 2.87 (q, *J* = 6.3, Hz, 2H), 2.58 (q, *J* = 5.9 Hz, 2H), 1.83 (s, 6H), 1.24 (t, *J* = 5.9 Hz, 3H), 1.14 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9 (C_q), 153.6 (C_q), 146.9 (C_q), 142.8 (C_q), 134.6 (C_q), 134.5 (C_q), 129.1 (CH), 128.7 (CH), 128.0 (CH), 120.4 (CH), 117.0 (CH), 54.2 (CH_2), 51.8 (C_q), 27.9 (CH_3), 22.6 (CH_2), 22.3 (CH_2), 16.2 (CH_3), 14.1 (CH_3). IR (neat): 3297, 2965, 2030, 1633, 1532, 1456, 719, 395 cm^{-1}. MS (EI) *m/z* (relative intensity): 382 (13) $[M]^+$, 200 (28), 166 (67), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{21}H_{27}N_4OS^+$ $[M]^+$ 382.1827, found 382.1814.

***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-ethyl-4-methoxybenzamide (142f) and *N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,6-diethyl-4-methoxybenzamide (142f'):**

The representative procedure **G** was followed using amide **112aa** (69.4 mg, 0.20 mmol), $ZnBr_2$·TMEDA (206 mg, 0.60 mmol) and EtMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded products **142f** (22.6 mg, 30%) and **142f'** (43.1 mg, 44%) as colorless solids.



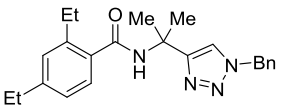
(**142f**): M. p. = 100–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.40–7.33 (m, 3H), 7.32 (s, 1H), 7.31–7.24 (m, 2H), 6.73 (d, *J* = 2.6 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.42 (s, 1H), 5.50 (s, 2H), 3.79 (s, 3H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.83 (s, 6H), 1.16 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 160.7 (C_q), 153.8 (C_q), 144.6 (C_q), 134.7 (C_q), 129.4 (C_q), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.1 (CH), 120.5 (CH), 115.1 (CH), 110.5 (CH), 55.2 (CH_3), 54.1 (CH_2), 51.7 (C_q), 27.8 (CH_3), 26.4 (CH_2), 15.6 (CH_3). IR (neat): 2965, 2148, 1637, 1528, 1191, 1050, 718, 392 cm^{-1}. MS (EI) *m/z* (relative intensity): 378 (17) $[M]^+$, 335 (17), 200 (33), 162 (73), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O_2^+$ $[M+H]^+$ 379.2129, found 379.2129.



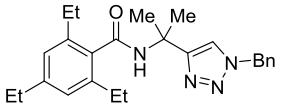
(**142f'**): M. p. = 146–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (s, 1H), 7.07–7.01 (m, 3H), 6.95 (d, *J* = 7.9 Hz, 2H), 6.25 (s, 2H), 5.98 (s, 1H), 5.19 (s, 2H), 3.46 (s, 3H), 2.25 (q, *J* = 7.6 Hz, 4H), 1.53 (s, 6H), 0.84 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6 (C_q), 159.8 (C_q), 153.5 (C_q), 142.3 (C_q), 134.7 (C_q), 130.2 (C_q), 129.1 (CH), 128.7 (CH), 128.0 (CH), 120.7 (CH), 111.2 (CH), 55.1 (CH_3), 54.0 (CH_2), 51.7 (C_q), 27.6 (CH_3), 26.2 (CH_2), 15.6 (CH_3). IR (neat): 3297, 1639, 1193, 1161, 1041, 718, 694, 390 cm^{-1}. MS (EI) *m/z* (relative intensity): 406 (10) $[M]^+$, 190 (100), 91 (45). HR-MS (ESI) *m/z* calcd for $C_{24}H_{31}N_4O_2^+$ $[M+H]^+$ 407.2442, found 407.2435.

***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-diethylbenzamide (142g) and *N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4,6-triethylbenzamide (142g'):**

The representative procedure **G** was followed using amide **112ab** (70.0 mg, 0.20 mmol), $ZnBr_2$·TMEDA (206 mg, 0.60 mmol) and EtMgBr (0.47 mL, 3 M, 1.40 mmol). The reaction mixture was stirred at 55 °C for 16 h. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 2:1→1:1) yielded product **142g** (19.0 mg, 25%) and **142g'** (44.1 mg, 54%) as colorless solids.



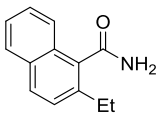
(**142g**): M. p. = 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.39–7.34 (m, 3H), 7.30–7.22 (m, 2H), 7.26 (d, *J* = 7.6, 1H) 7.03 (s, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.42 (s, 1H), 5.50 (s, 2H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.84 (s, 6H), 1.21 (t, *J* = 7.6 Hz, 3H), 1.16 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9 (C_q), 153.7 (C_q), 146.2 (C_q), 142.3 (C_q), 134.7 (C_q), 134.2 (C_q), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.1 (CH), 127.0 (CH), 125.1 (CH), 120.5 (CH), 54.1 (CH_2), 51.7 (C_q), 28.6 (CH_2), 27.8 (CH_3), 26.2 (CH_2), 15.8 (CH_3), 15.4 (CH_3). IR (neat): 2968, 2931, 1738, 1655, 1511, 1455, 1216, 721 cm^{-1}. MS (EI) *m/z* (relative intensity): 376 (15) $[M]^+$, 333 (22), 200 (38), 161 (52), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{23}H_{29}N_4O^+$ $[M+H]^+$ 377.2336, found 377.2330.



(**142g'**): M. p. = 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (s, 1H), 7.06–7.00 (m, 3H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.54 (s, 2H), 5.96 (s, 1H), 5.18 (s, 2H), 2.25 (q, *J* = 7.6 Hz, 2H), 2.23 (q, *J* = 7.6 Hz, 4H), 1.53 (s, 6H), 0.88 (t, *J* = 7.6 Hz, 3H), 0.83 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8 (C_q), 153.4 (C_q), 145.0 (C_q), 140.4 (C_q), 134.7 (C_q), 134.6 (C_q), 129.1 (CH), 128.7 (CH), 128.0 (CH), 125.4 (CH), 120.7 (CH), 54.0 (CH_2), 51.7 (C_q), 28.6 (CH_2), 27.6 (CH_3), 26.0 (CH_2), 15.8 (CH_3), 15.4 (CH_3). IR (neat): 2960, 1623, 1547, 1456, 1047, 826, 741, 389 cm^{-1}. MS (EI) *m/z* (relative intensity): 404 (18) $[M]^+$, 188 (100), 91 (45). HR-MS (ESI) *m/z* calcd for $C_{25}H_{33}N_4O^+$ $[M+H]^+$ 405.2649, found 405.2643.

Removal of the TAM Directing Group:

N-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2-ethyl-1-naphthamide (**142d**) (105 mg, 0.26 mmol) was added to aq. solution of HCl (37%, 3.0 mL) in a pressure tube. The reaction mixture was stirred at 140 °C for 24 h, allowed to cool to ambient temperature, carefully diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-pentane/EtOAc 1:1) yielded product **144** (45.9 mg, 89%) as a colorless solid.



2-Ethyl-1-naphthamide (144): M. p. = 74–78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.23 (s, 1H), 5.87 (s, 1H), 2.88 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.9 (C_q), 138.1 (C_q), 132.4 (C_q), 131.7 (C_q), 129.7 (C_q), 129.3 (CH), 127.9 (CH), 126.9 (CH), 126.8 (CH), 125.5 (CH), 124.7 (CH), 26.9 (CH_2), 16.1 (CH_3). IR (neat): 3366, 3169, 2968, 1637, 1618, 817, 747, 625 cm^{-1}. MS (EI) *m/z* (relative intensity): 199 (100) $[M]^+$, 182 (83), 153 (52), 78 (10). HR-MS (ESI) *m/z* calcd for $C_{13}H_{13}NO^+$ $[M]^+$ 199.0997, found 199.1001.

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Scientific Publications

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[4] L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *"Versatile Synthesis of Isocoumarins and α-Pyrones by Ruthenium-Catalyzed Oxidative C–H/O–H Bond Cleavages" Org. Lett.* **2012**, *14*, 930–933.

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