Carboxylate-Assisted Ruthenium-Catalyzed Direct C–H Bond Functionalizations

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1 Introduction

1.1 Metal-Catalyzed Direct C–H Bond Functionalizations

1.1.1 Metal-Catalyzed Direct C–H Bond Functionalizations: An Overview

The catalytic functionalization of unreactive C–H bonds represents one of the most powerful tools for sustainable syntheses and for opening new routes to pharmaceuticals and natural products.\(^1\)\(^2\) These methods are economically attractive alternatives to conventional cross-coupling reactions (Scheme 1).\(^3\)\(^4\) For instance, the prefunctionalized organometallics or main-group element arylation reagents 2 (M = MgX, ZnX, BR\(_2\), SnR\(_3\), SiR\(_3\), etc.) are often sensitive to air or are relatively expensive, and their preparation from the corresponding arenes 1 usually involves a number of synthetic operations (Scheme 1a).\(^3\) In contrast, direct C–H bond activations such as the direct arylation reactions represent an environmentally and economically more attractive strategy.

![Scheme 1](image)

**Scheme 1** Conventional cross-coupling (a) versus direct arylation (b)

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which are not only advantageous with respect to the overall minimization of byproduct formation, but also allow for a streamlining of organic syntheses (Scheme 1b).\textsuperscript{3a,4k,5} Early studies in the catalytic functionalization of unreactive C–H bonds were largely directed toward the challenging C–H bond activation of methane.\textsuperscript{6} However, during the past two decades, intensive research efforts have led to the development of C–H bond functionalizations\textsuperscript{5} with increasingly viable metal catalysts to improve the atom economy and more importantly the step-economy of organic syntheses.\textsuperscript{5} By far, a large variety of transition-metal catalysts have set the stage for efficient chemo-, site-, and enantioselective C–H bond functionalizations.\textsuperscript{1,4}

1.1.2 Mechanisms for Transition-Metal-Catalyzed C–H Bond Metalation

Key to the success to the direct C–H bond functionalizations was generally a detailed mechanistic understanding of the elementary C–H bond metalation step. Traditionally, three different modes of action were primarily considered for C–H bond metalations,\textsuperscript{7} namely, (i) oxidative addition with electron-rich late transition metals, (ii) σ-bond metathesis with early transition metals, and (iii) electrophilic activation with electron-deficient late transition metals (Scheme 2).

However, studies in the past years also indicated the existence of a continuum of electrophilic, ambiphilic, and nucleophilic interactions as well as base-assisted metalation reactions.\textsuperscript{8} As early as 1970s, the Shaw group\textsuperscript{9a} observed the beneficial effect exerted by NaOAc for stoichiometric


cyclometalation reactions (Scheme 3). Thus, detailed experimental and computational analysis by Davies and coworkers\(^\text{10}\) provided strong evidence for this novel C–H bond metatation mechanisms relying on the assistance of a bifunctional ligand bearing an additional Lewis-basic heteroatom or most prominently carboxylates (Scheme 2, iv).

This novel insight into metatations has thus served as stimulus for the development of C–H bond transformations based on cocatalytic amounts of carboxylates.\(^\text{8}\) To differentiate this type of base-assisted metatations mechanistically, new concepts have recently been introduced (Scheme 4). It has been proposed that a bidentate base is operating by the concerted-metatation-deprotonation pathway (CMD)\(^\text{11}\) or by the ambiphilic metal-ligand activation (AMLA) mechanism,\(^\text{12}\) both of which favor a six-membered transition state. Theoretical calculations\(^\text{13}\) disclose that the metal-acetate complexes have an ambiphilic character due to an intramolecular electrophilic activation of a C–H bond followed by deprotonation with an internal base. On the other hand, the mode of action of monodentate anionic ligands has been explored by the research groups of Oxgaard and Goddard as well as Gunnoe.\(^\text{14}\) DFT-studies favor an internal electrophilic substitution (IES) prior to traditional σ-bond metathesis.

\[ \begin{align*} 
\text{CMD} & \quad \begin{bmatrix} 
  \text{R}^+ \\
  \text{M}^+ \\
  \text{R}^+ \\
\end{bmatrix} \\
\text{AMLA} & \quad \begin{bmatrix} 
  \text{R}^+ \\
  \text{M}^+ \\
  \text{R}^+ \\
\end{bmatrix} \\
\text{IES} & \quad \begin{bmatrix} 
  \text{R}^+ \\
  \text{M}^+ \\
  \text{R}^+ \\
\end{bmatrix} 
\end{align*} \]

\[ \text{Scheme 4 Proposed transition states during C–H bond metatations} \]

1.1.3 Carboxylate-Assisted Ruthenium-Catalyzed Direct C–H Bond Functionalizations

The contributions for C–H bond functionalization brought by palladium catalysts\(^\text{14}\) have motivated the search for less expensive, active ruthenium catalysts.\(^\text{15}\) Notably, the pioneering


\(^{15}\) February 2014, http://taxfreegold.co.uk/preciousmetalpricesusdollars.html: prices of gold, platinum, rhodium, iridium, palladium and ruthenium: $1244, $1377, $1053, $400, $705, and $56 US per troy ounce, respectively.
studies on ruthenium-catalyzed direct hydroarylations of alkenes by Lewis\textsuperscript{16} as well as Murai\textsuperscript{17} highlighted the potential of efficient ruthenium catalysis for site-selective reactions of C–H bonds onto C–C and C–Het multiple bonds (see Chapter 1.4). The subsequent intensive search for easy-to-prepare and more stable ruthenium(II) catalysts during the following decades resulted in the discovery of efficient ruthenium catalysts, milder reaction conditions and new ruthenium-catalyzed reactions, as was demonstrated by Oi and Inoue in 2001 (Scheme 5).\textsuperscript{18} However, essential progress in ruthenium-catalyzed direct arylations of arenes with aryl halides was achieved employing ruthenium complexes \textit{in situ} derived from phosphine\textsuperscript{19} or N-heterocyclic carbene\textsuperscript{20} (NHC) ligands. Notably, all of these reactions required the use of highly polar N-methylpyrrolidinone (NMP) as solvent, which led to catalytic systems with lower robustness,\textsuperscript{21} particularly when being applied to more challenging substrate combinations.

![Scheme 5 Ruthenium-catalyzed direct arylation with aryl halides by Oi and Inoue](image)

Until 2008, carboxylates have not been used as efficient cocatalytic additives in ruthenium-catalyzed C–H bond functionalizations. Primary studies from the Ackermann group highlighted a significant reaction rate acceleration applying bifunctional secondary phosphine oxides (SPO) preligand\textsuperscript{22} in ruthenium-catalyzed direct arylations with organic electrophiles.\textsuperscript{23} Concerning the catalysis working mode,\textsuperscript{23} a base assistance with an intermediacy of the five-membered transition state 12 was proposed to be the decisive feature (Figure 1). Analogously, further studies from the same group showed that bifunctional ligands, especially carboxylates, were expected to give rise to six-membered transition state 13 (Figure 1).\textsuperscript{5}

Hence, the Ackermann group investigated the order of efficacy for various cocatalytic additives in direct arylations using toluene as inert solvent and N-aryl-substituted 1,2,3-triazoles 14 as substrates (Scheme 6).\textsuperscript{24} Herein, complexes of previously used ligands, such as NHC precursors or tertiary phosphines, demonstrated only poor activity. On the contrary, bifunctional sterically hindered SPO preligand (1-Ad)$_2$P(O)H enabled more efficient catalysis. Further screening showed that acids were superior, with optimal results being obtained with sterically congested MesCO$_2$H.

![Figure 1 Proposed transition states for base-assisted ruthenations](image)

Scheme 6 Cocatalytic additives in the ruthenium-catalyzed direct arylation

The subsequent intensive mechanistic studies\textsuperscript{24,25} disclosed the ruthenium(II)-catalyzed direct arylations to involve initial C–H bond activations \textit{via} carboxylate-assisted and thus deprotonative ruthenations \textit{via} the transition state 19 (Scheme 7).
Introduction

To address the mechanistic understanding, a ruthenium(II) biscarboxylate complex 23 was prepared (Scheme 8a). Notably, the well-defined complex 23 displayed a broad substrate scope in that various arenes were directly functionalized with (Het)ArCl in a highly regioselective fashion (Scheme 8b).

Scheme 7 Proposed mechanism for direct arylations and alkylations by carboxylate assistance

On the basis of experimental findings in ruthenium-catalyzed direct arylations (Scheme 9, 27) as well as alkylations (28 and 29), the Ackermann group intensively examined carboxylates as effective cocatalytic additives in ruthenium-catalyzed C–H bond functionalizations, such as

hydroarylations with alkenes (30),27 as well as oxidative C–C (32 and 33),28,29 C–O (34)30 and C–N (35)30 bond formations (Scheme 9). This thesis herein focuses on carboxylate-assisted ruthenium-catalyzed oxidative C–H bond functionalizations (32 and 33) and C(sp³)–H alkylations (31) with alkenes as well as direct ortho-C–Hal bond formations (36), which will be described in details in the following Chapters.

Scheme 9 Carboxylate-assisted ruthenium-catalyzed direct C–H bond functionalizations

1.2 Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations

Proceeding with the previously reported experimental results on direct arylations, the Ackermann group first tested carboxylates as cocatalytic additives for ruthenium-catalyzed oxidative C–H bond functionalizations,28,29 a research area that had thus far largely been dominated by the use of

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more expensive palladium \(^{31}\) or rhodium complexes.\(^{32}\)

Considering the importance for step-economical syntheses of bioactive heterocycles, Ackermann and coworkers hence set out to develop ruthenium-catalyzed oxidative annihilations of alkynes 38 through C–H and N–H bond cleavages for isoquinolones 39 synthesis (Scheme 10).\(^{33}\) Notably, preliminary studies\(^{33a}\) revealed [RuCl\(_2\)(p-cymene)]\(_2\) (15) to be optimal among a variety of ruthenium complexes, while Cu(OAc)\(_2\)·H\(_2\)O was found to be the terminal oxidant of choice.\(^{33a}\) The optimized ruthenium(II) catalyst 15 proved to be tolerant to valuable electrophilic functional groups, and was found to be applicable to benzamides 37 with different substituents on nitrogen atom. Furthermore, the annulation process proceeded with excellent regioselectivity with unsymmetrical internal alkynes.\(^{33}\)

\[
\begin{align*}
\text{R}^1 & | \text{N} & | \text{R}^2 \\
\text{O} & & \\
\text{37} & & \\
\text{R}^3 & & \\
\text{R}^4 & & \\
\text{38} & & \\
\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O} & & \text{100 °C, 22 h} \\
\end{align*}
\]

Scheme 10 Ruthenium-catalyzed oxidative annihilation via C–H/N–H bond cleavage

Based on mechanistic studies, the ruthenium(II)-catalyzed oxidative annihilation was proposed to proceed by an initial carboruthenation via acetate-assisted C–H bond cleavage,\(^{8,28}\) followed by migratory insertion, C–N bond-forming reductive elimination, and final reoxidation of the ruthenium(0) intermediate (Scheme 11).\(^{33a}\) Additional support for this proposed mechanism was recently provided through the independent synthesis and isolation of key intermediates by the groups of Li and Wang as well as Dixneuf.\(^{34}\)

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Introduction

Subsequently, acrylamides 45 turned out to be competent substrates through alkenylic C–H bond activation with the same ruthenium(II) catalytic system (Scheme 12). Likewise, Cu(OAc)$_2$·H$_2$O as the oxidant led to the most efficient transformation, again being indicative of acetate assistance.\(^{35}\)

Recently, Jeganmohan developed a route to isoquinolones 49 through ruthenium-catalyzed aerobic oxidative cyclization of (hetero)aromatic nitriles 47 with alkynes (Scheme 13).\(^{36}\) Mechanistic studies showed an acetamide intermediate 48 was generated with AcOH in the presence of Cu(OAc)$_2$·H$_2$O prior to oxidative annulation with alkynes.

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The C−H/N−H bond functionalization strategy was not restricted to arenes bearing electron-withdrawing directing groups. Indeed, the cationic ruthenium(II) complexes derived from KPF₆ facilitated oxidative C−H bond functionalizations with electron-rich anilines 50 through acetate assistance (Scheme 14).³⁷a A notable feature of this protocol was represented by the use of substrates bearing easily removable directing groups.³⁸ The C−H/N−H bond cleavages occurred most efficiently in water as a green reaction medium and provided general access to indole derivatives 51.

Furthermore, Ackermann and coworkers found the cationic ruthenium(II) complexes derived from AgSbF₆ additives allowed for highly efficient oxidative annihilations of aryl- and alkyl-substituted alkynes 38 by 5-aryl-1H-pyrazoles 52 under aerobic conditions (Scheme 15).³⁹

³⁸ Representative reviews on removable directing groups: (a) C. Wang, Y. Huang, Synlett 2013, 24, 145–149; (b) G. Rousseau, B. Breit, Angew. Chem. Int. Ed. 2011, 50, 2450–2494.
Very recently, the same group developed a ruthenium-catalyzed oxidative annulation of alkynes by ketimines 54 to furnish exo-methylene-1,2-dihydroisoquinolines 55. Particularly, carboxylate-assisted ruthenium(II) catalysis proved to be key to success for the synthesis of diversely decorated products in high yields (Scheme 16).

Besides this, oxidative annulations of alkynes 38 through C–H/O–H bond cleavages were independently achieved with ruthenium(II) complexes by the research groups of Ackermann and Jaganmohan (Scheme 17). Likewise, a cationic ruthenium(II) catalyst derived from KPF₆ or AgSbF₆ was employed for the synthesis of isocoumarins 57 through oxidative annulations of alkynes by (hetero)aromatic acids 56. Detailed optimization studies revealed acetates to be crucial additives and provided support for a kinetically relevant C–H bond ruthenation.

Moreover, acetate assistance was found to be key to success for ruthenium(II)-catalyzed oxidative alkyne annulations with hydroxyl groups. Thus, hydroxyl-assisted C–H bond functionalizations provided step-economical access to diversely decorated fluorescent coumarins 59 and quinolin-2-ones 61, respectively (Scheme 18).

Scheme 16 Oxidative annulation of alkynes 38 by ketimines 54

Scheme 17 Synthesis of isocoumarins 57 by Ackermann

Scheme 18 Hydroxyl-directed alkyne annulations
Along with the rapid development on C−H/N−H and C−H/O−H bond functionalizations, Lee developed the first ruthenium-catalyzed oxidative cyclization of phosphonic acid monoesters or phosphinic acids \( \text{62} \) with alkynes for the synthesis of phosphaisocoumarins \( \text{63} \) under aerobic conditions. A variety of arylphosphonic acid monoesters as well as arylphosphinic acids bearing electron-donating and -withdrawing groups were efficiently converted under aerobic reaction conditions (Scheme 19).\(^{44}\)

![Scheme 19 Ruthenium-catalyzed annulation of alkynes \( \text{38} \) with phosphonic acid derivatives \( \text{62} \)](image)

Furthermore, Jeganmohan developed a highly regioselective ruthenium-catalyzed cyclization of aromatic ketones \( \text{64} \) with alkynes. This methodology offers a simple and mild method for the synthesis of indenols \( \text{65} \) and benzofulvenes \( \text{66} \) in a highly regioselective manner. Herein, the amount of silver salt determined the nature of the product: In the presence of 8 mol % of \( \text{AgSbF}_6 \) favored the formation of indenols \( \text{65} \) (Scheme 20, left), whereas with 20 mol % of \( \text{AgSbF}_6 \) benzofulvenes \( \text{66} \) were obtained (Scheme 20, right).\(^{45}\)

![Scheme 20 Ketone-directed alkyne annulations](image)

Lam recently reported a catalytic alkyne oxidative annulation by 2-aryl-1,3-dicarbonyl compounds \( \text{67} \) involving the (formal) functionalization of C(sp\(^3\))−H bond and C(sp\(^2\))−H bond (Scheme 21a). Notably, this ruthenium-catalyzed process led to the synthesis of indenes \( \text{69} \) with the formation of an all-carbon quaternary center.\(^{46}\) In analogy, Luan’s intermolecular annulation reactions of 1-aryl-2-naphthols \( \text{70} \) with alkynes proceeded efficiently in the presence of the same ruthenium catalyst to generate spirocyclic compounds \( \text{71} \) by sequential cleavage of the C(sp\(^3\))−H bond, migratory insertion of the alkyne, and dearomatization of the naphthyl ring (Scheme 21b).\(^{47}\)

---


However, the success of the above-discussed ruthenium(II)-catalyzed annulations always relied on the use of an external oxidant in stoichiometric or cocatalytic amounts (vide supra). Thus, Cu(OAc)$_2$·H$_2$O proved to be essential for these transformations, since it not only acted as the (co)oxidant but also served as the source of acetate for the carboxylate-assisted C–H bond activation step. Conversely, an alternative strategy was viable through the use of substrates bearing N–O bonds as "internal" oxidants.

Herein, N-methoxybenzamides and free hydroxamic acid 72 were utilized by Ackermann and Fenner for highly selective syntheses of isoquinolones 49 in the absence of an external oxidant under notably mild reaction conditions (Scheme 22). Remarkably, cocatalytic amounts of carboxylates were found to be indispensable for achieving efficient C–H bond functionalizations, with optimal results being accomplished with KO$_2$CMes as the co-catalyst and H$_2$O as the reaction medium. Meanwhile, an alternative protocol by Li and Wang employed NaOAc as the additive in MeOH as the solvent, which was also rationalized in terms of acetate-assisted C–H bond ruthenation.

In analogy, this "internal" oxidant approach set the stage for an extension to the synthesis of isoquinolines 74 (Scheme 23). Thus, ketoximes 73 were selectively converted, with base

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assistance proving to be essential for the dehydrative alkyne annulation to occur in an efficient manner.\textsuperscript{51}

\[
\begin{align*}
\text{N} & \text{H} \\
\text{R}^1 & \text{R}^2 \\
\text{R}^3 & \text{R}^4
\end{align*}
\]

\[
\begin{align*}
\text{[RuCl}_2(\mu\text{-cymene})_2]_2 & \quad \text{KPF}_6 (30 \text{ mol %}) \\
\text{MeOH, 60 }\circ\text{C, 24 h}
\end{align*}
\]

Scheme 23 Synthesis of isoquinolines 74 by dehydrative alkyne annulations

1.3 Ruthenium-Catalyzed Direct Oxidative Alkenylation of Arenes

Styrene derivatives are useful intermediates in synthetic organic chemistry and represent key structural motifs in natural products as well as in medicinal chemistry.\textsuperscript{53} Conventional transition metal-catalyzed cross-coupling reactions,\textsuperscript{3} such as the Mizoroki–Heck reaction,\textsuperscript{54} have matured to being reliable tools for the preparation of styrene derivatives (Scheme 24a). Besides, alkenylation \textit{via} transmetallation employing stoichiometric amounts of palladium chloride and organomercury, -tin, or -lead arenes \textit{in lieu} of aryl halides were also reported (Scheme 24b).\textsuperscript{3,54} However, the Mizoroki–Heck reaction is accompanied by the formation of a stoichiometric amount of potentially hazardous halide salt and transmetallation reactions always require organometallic nucleophilic reagents, which are, however, often not commercially available or are relatively expensive. In contrast, the catalytic oxidative dehydrogenative alkenylation \textit{via} a twofold C–H bond activation approach, as initially demonstrated by Fujiwara and Moritani,\textsuperscript{55} presents a powerful tool for the synthesis of styrene derivatives (Scheme 24c).\textsuperscript{56} Importantly, this approach is not only advantageous with respect to the overall minimization of byproduct formation (atom-economy),\textsuperscript{5b,c} but also allows for significantly reducing the number of required reaction steps (step-economy).\textsuperscript{5a} Subsequently, a variety of synthetically useful protocols for palladium-catalyzed direct oxidative couplings between arenes and alkenes have been achieved by \textit{inter alia} Miura and Satoh, as well as Yu.\textsuperscript{56} Efficient and selective rhodium catalysts have also been developed in recent years.\textsuperscript{32}

\]

\[\text{The Mizoroki–Heck Reaction, M. Oestreich, ed.; Wiley, Chichester, 2009.}
\]

\]

\]
However, less expensive ruthenium complexes have only recently been exploited as catalysts for oxidative C–H bond alkenylations on arenes, starting from the work by Milstein and coworkers in 2001 (Scheme 25).\textsuperscript{57} According to this protocol, styrene derivatives \textsuperscript{77} were obtained from substituted arenes \textsuperscript{75}. Unfortunately, major limitations of this protocol were represented by the low reactivity of unactivated alkenes as well as the poor site-selectivities with substituted arenes.

\textbf{Scheme 25} Ruthenium-catalyzed direct alkenylations with simple arenes \textsuperscript{75}

The low selectivities observed in reactions of simple arenes were successfully addressed with the aid of Lewis-basic functional groups. Thus, a cationic ruthenium hydride complex \textsuperscript{80} enabled highly site-selective oxidative C–H bond alkenylations of benzamides \textsuperscript{78} (Scheme 26), as described by Yi and coworkers.\textsuperscript{58a} Since an external oxidant was not employed, an excess of the alkene \textsuperscript{79} as well as the newly formed alkenylated benzamide \textsuperscript{81} served as the hydrogen scavenger. Therefore, the products \textsuperscript{81} were unfortunately contaminated with hydrogenated benzamides \textsuperscript{82}.

\footnotesize
\begin{itemize}
\end{itemize}
The major breakthrough on the ruthenium-catalyzed oxidative alkenylation with directing groups was achieved by inter alia Ackermann as well as Miura and Satoh in recent years.\textsuperscript{29} In 2011, Ackermann and Pospech disclosed the ruthenium(II)-catalyzed oxidative C–H bond alkenylation of benzoic acids \textsuperscript{56} to smoothly proceed in water with Cu(OAc)\textsubscript{2}·H\textsubscript{2}O as the oxidant (Scheme 27).\textsuperscript{59} Yet, the expected alkenylated benzoic acids \textsuperscript{84} were not isolated, but the alkenylation products \textsuperscript{84} immediately underwent a subsequent intramolecular oxa-Michael reaction, affording isobenzofuran-1(3H)-ones \textsuperscript{85} in high yields. Experimental studies with isotopically labelled substrates suggested a kinetically relevant C–H bond ruthenation through acetate assistance in the transition state.\textsuperscript{59}

Satoh and Miura reported on the use of a cationic ruthenium catalyst, \textit{in situ} generated from \([\text{RuCl}_2(p\text{-cymene})]_2\) and AgSbF\textsubscript{6}, for oxidative alkenylations of benzamides \textsuperscript{78} (Scheme 28).\textsuperscript{60a} Notably, the reaction did not proceed in the absence of AgSbF\textsubscript{6}. Besides, Loh developed a ruthenium catalytic system with KPF\textsubscript{6} as the efficient additive for the direct cross-coupling of acrylamides with electron-deficient alkenes forming (Z,E)-dienamides.\textsuperscript{60b}

Alternatively, ruthenium-catalyzed C–H bond alkenylations can also be realized with

pre-functionalized starting materials bearing an “internal” oxidizing directing group. Notably, the reactions with acrylates resulted in C–H bond alkenylations of methoxybenzamides affording olefinated benzamides (Scheme 29).

Scheme 29 Ruthenium-catalyzed C–H bond alkenylation with an “internal” oxidizing directing group

With the success of chelation-assisted alkenylations on benzamides, analogous ruthenium-catalyzed oxidative functionalizations of weakly coordinating esters has until recently proven elusive. The research groups of Ackermann and Jeganmohan disclosed reaction conditions for the versatile oxidative direct functionalization of aromatic esters (Scheme 30). Thus, a catalytic system comprising [RuCl₂(p-cymene)]₂, AgSbF₆ and cocationic amounts of Cu(OAc)₂·H₂O utilizing air as the ideal terminal oxidant allowed for efficient aerobic C–H bond alkenylations in a highly site-selective fashion.

Scheme 30 Ruthenium-catalyzed oxidative alkenylations of weakly coordinating aromatic esters

This catalytic system was also found to be effective for alkenylations of aromatic ketones and benzaldehydes (Scheme 31). Thus, the ruthenium-catalyzed C–H bond functionalization provided alkenylated products in moderate to good yields with acrylates and styrenes.

Scheme 31 Ruthenium-catalyzed oxidative alkenylation of phenones and benzaldehydes

Moreover, the ruthenium catalytic system enabled oxidative alkenylations of electron-rich aryl carbamates with weakly coordinating and removable directing groups in a chemo- and

References:
site-selective fashion, affording diversely decorated phenol derivatives.\(^{93}\) (Scheme 32).

\[ \text{Scheme 32 Ruthenium-catalyzed oxidative alkenylation of aryl carbamates 92} \]

Recently, the ruthenium(II)-promoted oxidative alkenylations of phenols\(^{94}\) bearing easily cleavable directing groups\(^{38}\) was reported (Scheme 33).\(^{67}\) The double C−H functionalization process proceeded with excellent chemo-, site-, and diastereoselectivities in an aerobic fashion.

\[ \text{Scheme 33 Ruthenium(II)-catalyzed C−H alkenylations of arenes 94 with removable directing groups} \]

Besides, Dixneuf and Bruneau reported on ruthenium-catalyzed oxidative alkenylation of N-phenylpyrazole (96) with acrylates and acrylamides (Scheme 34).\(^{68}\) Unfortunately, in many cases the products\(^{97}\) were contaminated with by-products\(^{98}\) generated through dehydrogenative homocoupling of substrates 96.

\[ \text{Scheme 34 Ruthenium-catalyzed oxidative alkenylation of N-phenylpyrazole 96} \]

However, employing \([\text{RuCl}_2(p\text{-cymene})]_2\) complex instead of the above mentioned \([\text{Ru(OAc)}_2(p\text{-cymene})]\) analog, along with a higher loading of \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\), efficiently suppressed the competitive homocoupling reaction.\(^{69}\) Hence, alkenylations of 2-phenylazoles 100 with \([\text{RuCl}_2(p\text{-cymene})]_2\) in \(t\text{-AmOH}\) as the solvent was achieved, albeit with a significantly lower yields (Scheme 35).\(^{60a}\)

---


Furthermore, monoalkenylation of aromatic C–H bonds directed by an oxazoline group were found by the same group to take place efficiently using [RuCl₂(p-cymene)]₂ along with rac-BNPAN (104) as an efficient ligand (Scheme 36).

Essentially, ruthenium-catalyzed alkenylations of heteroarenes 105 with various directing groups were achieved with the catalytic systems described above, albeit with different catalytic efficacies. The experimental results are summarized in Scheme 37 and highlight various esters, benzamides, aldehydes and carbamates could be employed for chemo- and site-selective ruthenium-catalyzed twofold C–H bond functionalizations.

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Introduction

1.4 Ruthenium-Catalyzed Direct Hydroarylations

1.4.1 Ruthenium-Catalyzed Direct Hydroarylations

As discussed above, the oxidative direct functionalization with unreactive C–H bonds is a powerful tool for the construction of C–C bonds in a step-economical fashion. On the other hand, the prospects to develop metal-catalyzed hydroarylation reactions are alternatively attractive due to their perfect atom economy, with notable progress being accomplished with versatile ruthenium catalysts. As early as 1986, Lewis reported the first ortho-selective hydroarylation of phenol (107) with alkenes catalyzed by the ortho-metalated ruthenium complex 110 (Scheme 38).16

Scheme 38 Ruthenium-catalyzed direct C–H alkylation by Lewis

However, a major breakthrough in the ruthenium-catalyzed directed hydroarylations was achieved by Murai in 1993 (Scheme 39).17 According to this protocol, chelation-assistance resulted in
highly site-selective C–H bond cleavage, leading to addition of aromatic ketone 90 to alkenes 111 with a C–C bond formation.\textsuperscript{17}

![Chemical reaction diagram]

\textbf{Scheme 39} Ruthenium-catalyzed direct C–H alkylation by Murai

Intensive mechanistic studies\textsuperscript{73,74} on the Murai reaction showed that the initial formation of intermediate 117 \textit{via} transition state 116, subsequent coordination of alkene 111 and migratory insertion to the Ru–H bond are reversible (Scheme 40). Finally, reductive elimination of complex 119 delivers the target product 113 and regenerates the active ruthenium species 114. Besides, isotopically labelled experiment with substrates suggested that a branched species 119 is also probably formed, which, however, seems not to undergo reductive elimination, since no corresponding branched product was obtained.\textsuperscript{74} Further studies\textsuperscript{75} showed that the C–C bond formation is the rate determining step.

![Catalytic cycle diagram]

\textbf{Scheme 40} Catalytic cycle for the Murai reaction

Introduction

In the following years, Murai and coworkers extended the application of hydroarylations including replacement of the terminal alkenes 111 by acetylenes 77 and the use of esters, imines, oxazoline and aldehydes as efficient directing groups. Coinciding with Murai’s alkylations of cyclic and acyclic α,β-enones, Trost successfully applied the precatalyst [RuH₂(CO)(PPh₃)₂] (114) to the alkylation of acrylic acid esters. However, a major disadvantage of Murai’s protocol is the air sensitivity of catalyst [RuH₂(CO)(PPh₃)₂] (114). This promoted Darses and Genet to develop a new hydroarylation system through the elegant in situ formation of catalyst [RuH₂(PPh₃)₄] (121) from [RuCl₂(µ-cymene)]₂ (15) and sodium formate, in association with a phosphine ligand (Scheme 41). This novel system showed high activity in the ortho-hydroarylations of tetralone and acetophenone 122 with active alkenes, such as vinylsilane and styrene derivatives 111 (Scheme 41).

Besides, Ackermann and coworkers achieved the hydroarylation of highly strained methylenecyclopropanes 124 by the combination of [RuCl₂(cod)]₄ (125) and XPhos, which furnished anti-Markovnikov products 126 with complete conservation of all cyclopropane rings (Scheme 42).}

![Scheme 41: Ruthenium-catalyzed direct C–H alkylation by Genet and Darses](image)

![Scheme 42: Hydroarylation of methylenecyclopropanes](image)

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Despite notable advances in the oxidative C–H bond functionalizations, metal carboxylates were as of yet not exploited as cocatalytic additives for ruthenium-catalyzed hydroarylations. Very recently, Ackermann and co-workers reported on highly efficient carboxylate-assisted ruthenium-catalyzed hydroarylations of unactivated alkenes 111 and of methylenecyclopropanes 124 employing various (hetero)arenes 17 with ample scope (Scheme 43). 87

**Scheme 43** Carboxylate-assisted ruthenium-catalyzed hydroarylations

Ruthenium-catalyzed hydroarylations of aromatic amides 129 with various α,β-unsaturated ketones 130 using a removable 8-aminoquinoline bidentate directing group has been recently developed by Chatani (Scheme 44). 89 This methodology represented the first efficient utilization of active enones in the ortho-directed ruthenium-catalyzed addition of C–H bonds to C–C double bonds.

**Scheme 44** Ruthenium-catalyzed ortho-hydroarylation with α,β-unsaturated ketones

Along with the obvious progress in the ruthenium-catalyzed chelation-assisted hydroarylations, Nakamura and Yoshikai independently reported on the first examples of cobalt-catalyzed...
hydroarylation of terminal alkenes\textsuperscript{90,91} and internal alkynes\textsuperscript{92} using ketimines, N-methyl amide and pyridine as directing groups. However, the employment of this catalytic system was limited by low tolerance of many important functional groups. Besides, the first manganese-catalyzed hydroarylation of terminal alkynes was recently reported.\textsuperscript{93}

### 1.4.2 Ruthenium-Catalyzed Direct C(sp\textsuperscript{3})−H Alkylations

In contrast to the direct transformations of C(sp\textsuperscript{3})−H bonds, catalytic alkylations with alkenes involving the cleavage of the C(sp\textsuperscript{3})−H bonds\textsuperscript{94} have unfortunately thus far met with limited success. In 1998, Jun achieved the first chelation-assisted C(sp\textsuperscript{3})−H alkylation on benzylamines 133 employing Ru\textsubscript{3}(CO)\textsubscript{12} (132). However, only benzylic C−H bonds enabled addition to alkenes 134 under these conditions (Scheme 45).\textsuperscript{95}

![Scheme 45 Ruthenium-catalyzed hydroalkylation of benzylamines 133 with alkenes 134](image)

Promoted by the success of rhodium-catalyzed α-carbonylation of C(sp\textsuperscript{3})−H bonds to cyclic amino and amido groups,\textsuperscript{96} Murai, Kakiuchi and Chatani observed that Ru\textsubscript{3}(CO)\textsubscript{12} (132) enabled the addition of C(sp\textsuperscript{3})−H bond across the alkene bond to give the corresponding alkylated products 137 (Scheme 46).\textsuperscript{97} Intensive studies showed that the reactivity was improved using iso-propanol as the solvent. Various alkenes, including terminal, internal and cyclic alkenes, proved to be suitable applying this protocol, and the substrates were successfully extended to five-, six- and seven-membered rings.

The reaction mechanism proposed for Murai’s C(sp³)–H alkylation was similar to the mechanisms of C(sp²)–H bond functionalizations discussed above (Scheme 47). First, coordination of substrate 136 to ruthenium provides complex 140, in which the C–H bond undergoes cleavage to give a Ru–H complex 141. Subsequently, coordination of alkene 134 and its migratory insertion furnishes the Ru–alkyl complex 143, from which reductive elimination affords the final product 137, with the active ruthenium complex being regenerate.

Very recently, Maes reported a ruthenium(0)-catalyzed α-alkylation and -arylation of piperidines 144 with terminal alkenes 111a. Control experiments showed the carboxylic acid can efficiently increase the catalyst activation and longevity, along with that the alcohol reduces the side reactions (Scheme 48).

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Introduction

Besides, using the ruthenium-hydride complex 150, Yi showed that the alkylation of cyclic amines 149 without additional directing group can be achieved by invoking the dehydrogenation of amine and subsequent $\alpha$-C$-$H imine bond activation/alkene insertion sequence (Scheme 49).\(^{100}\)

Scheme 49 Ruthenium-catalyzed alkylation of unprotected cyclic amines with alkenes

1.5 Metal-Catalyzed ortho-C$-$H Halogenations

Aromatic halides are key intermediates in organic synthesis, and have been broadly utilized for natural products synthesis, material sciences and medicinal chemistry.\(^{101}\) As a consequence, the development of efficient and selective methods for their synthesis continues to be of prime importance. Conventionally, the most useful strategies for their synthesis rely on the electrophilic aromatic substitution ($S_{E}^{A}$), the Sandmeyer reaction or the directed ortho-lithiation approach (Scheme 50a–c).\(^{102}\) Unfortunately, these methods face considerable limitations, including tedious and/or hazardous reaction procedures, poor site selectivities, and harsh reaction conditions, resulting in low chemo-selectivities. In recent years, metal-catalyzed C$-$H activation has emerged as an increasingly viable tool for C$-$X bond formations (Scheme 50d).\(^{4}\) In this context, methods for the palladium-catalyzed chelation-assisted direct C$-$H bond functionalization with

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electrophilic halogenating reagents have been developed by several groups.\textsuperscript{103}

**Scheme 50** Conventional approaches for halogenation reactions

An early report on palladium catalysis involved the \textit{ortho}-halogenation of azobenzene 161 with $X_2$ (Scheme 51),\textsuperscript{104} which afforded a mixture of mono-, di-, tri-, and tetra-halogenated products. While this work elegantly demonstrated the viability of such transformations, the requirement for $X_2$ as the oxidant limited its widespread application in organic synthesis.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {161} ;
  \node (b) at (1,0) {162} ;
  \node (c) at (1,1) {163} ;
  \node (d) at (2,1) {164} ;
  \node (e) at (2,2) {165} ;
  \node (f) at (3,2) {166} ;
  \node (g) at (3,3) {167} ;
  \node (h) at (4,3) {168} ;
  \node (i) at (5,3) {169} ;
  \node (j) at (6,3) {170} ;
  \node (k) at (7,3) {171} ;
  \node (l) at (8,3) {172} ;
  \node (m) at (9,3) {173} ;
  \node (n) at (10,3) {174} ;
  \node (o) at (11,3) {175} ;
  \node (p) at (12,3) {176} ;
  \node (q) at (13,3) {177} ;
  \node (r) at (14,3) {178} ;
  \node (s) at (15,3) {179} ;
  \node (t) at (16,3) {180} ;
  \node (u) at (17,3) {181} ;
  \node (v) at (18,3) {182} ;
  \node (w) at (19,3) {183} ;
  \node (x) at (20,3) {184} ;
  \node (y) at (21,3) {185} ;
  \node (z) at (22,3) {186} ;

  \draw [->] (a) -- (b) node [midway, above] {$\text{PdCl}_2 (20 \text{ mol \%})$} node [midway, below] {$X_2$} node [midway, right] {1.4-dioxane/H$_2$O} node [midway, left] {85 $^\circ$C, 16 h} node [midway, above right] {+ Mixture of \textit{ortho-}halogenated products} ;
\end{tikzpicture}
\end{center}

**Scheme 51** Pd-catalyzed direct \textit{ortho}-halogenation of azobenzene 161

In 2005, Yu and coworkers reported an auxiliary approach for the chemo- and stereo- selective ambient-temperature iodination of methyl groups with oxazoline as directing group (Table 1, entry 1). This protocol has also been successfully applied to the activation of cyclopropanes (C−H bond $\beta$ to the carboxy group) and arenes (C−H bond $\gamma$ to the carboxy group).\textsuperscript{105a,b} Furthermore, they developed \textit{ortho}-iodination and bromination of arene carboxylic acids 56 with Suárez reagents.


(XOAc) as the halogen source as well as the terminal oxidant (entries 2–3). In this case, mechanistic study shows that employment of the large tetraalkylammonium cation can efficiently prevent the formation of dihalogenated product. In 2010, this group extended this protocol to phenylacetic acid as well as triflamide (NHTf) directing groups (entry 5). Very recently, palladium-catalyzed ortho-C–H iodination directed by a weakly coordinating amide auxiliary (using I2 as the sole oxidant was developed (entry 6). This reaction is compatible with a wide range of heterocycles including pyridines, imidazoles, oxazoles, thiazoles, isoxazoles, and pyrazoles. Furthermore, a similar protocol realized the enantioselective C–H iodination reaction using a mono-N-benzoyl-protected amino acid for the synthesis of chiral diarylmethylamines (entry 7).

### Table 1 Palladium-catalyzed direct C–H halogenations reported by the Yu group

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="NMe" /> <img src="image" alt="R1 R2" /> <img src="image" alt="t-Bu" /></td>
<td><img src="image" alt="I" /> <img src="image" alt="R1 R2" /> <img src="image" alt="t-Bu" /></td>
<td>I2 (1.0 equiv), Pd(OAc)2 (10 mol %), PhI(OAc)2 (1.0 equiv), CH2Cl2, 24 °C, 48–72 h.</td>
<td>105a</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="CO2H" /> <img src="image" alt="R3" /></td>
<td><img src="image" alt="CO2H" /> <img src="image" alt="R3" /></td>
<td>IOAc (2.0 equiv), Pd(OAc)2 (5.0 mol %), DCE, 76 °C, 2 h.</td>
<td>105c</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="CO2H" /> <img src="image" alt="R3" /></td>
<td><img src="image" alt="CO2H" /> <img src="image" alt="Br" /></td>
<td>IOAc (4.0 equiv), Pd(OAc)2 (5.0 mol %), Bu4NX (1.5 equiv), DCE, 100 °C, 24 h.</td>
<td>105c</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td>I2 (0.75 equiv), Pd(OAc)2 (10 mol %), PhI(OAc)2 (0.75 equiv), DMF, 60 °C, 24 h, no light.</td>
<td>105d</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td>I2 (2.0 equiv), Pd(OAc)2 (10 mol %), PhI(OAc)2 (2.0 equiv), NaHCO3 (2.0 equiv), DMF, 130 °C, 72 h.</td>
<td>105e</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td>I2 (2.5 equiv), Pd(OAc)2 (2.0 mol%), CsOAc (1.2 equiv), NaHCO3 (1.0 equiv), 4 Å molecular sieves, t-AmOH/DMF (1:1) 65 °C, 20 h.</td>
<td>105f</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td><img src="image" alt="CONHAr" /> <img src="image" alt="N" /> <img src="image" alt="n" /> <img src="image" alt="R4" /></td>
<td>I2 (2.5 equiv), Pd(OAc)2 (10 mol %), Bz-Leu-OH (40 mol %), CsOAc (3.0 equiv), Na2CO3 (3.0 equiv), DMSO (15 equiv), t-AmOH, 30 °C, air, 48 h.</td>
<td>105g</td>
</tr>
</tbody>
</table>

Meanwhile, distinct contributions arose also from the Sanford group. In 2004, Sanford and coworkers disclosed a highly regio- and chemo-selective palladium-catalyzed ortho-halogenation on benzo[h]quinoline (175), using NCS or NBS in place of PhI(OAc)2 as the stoichiometric
These transformations have been subsequently applied to a wide array of substrates and can provide products that are complementary to those obtained via conventional electrophilic aromatic substitution ($S^\mathrm{E}_{\mathrm{Ar}}$) reactions.

Further studies showed that the nature of the directing group and the substitution pattern on the arene ring of the substrate both led to different reactivity profiles, and often different and complementary products in the presence and absence of the catalyst (Scheme 52). In other words, arene C–H functionalization with an electrophilic oxidant can occurred by either a palladium-catalyzed pathway or an uncatalyzed electrophilic aromatic substitution ($S^\mathrm{E}_{\mathrm{Ar}}$). In certain cases, these two pathways afforded different and complementary site selectivity. For example, the halogenation of electron-rich oxime ether 176 (which selectively affords 178 in the absence of Pd and 177 under Pd catalysis), pyrazole 96 (forming 179 and 180, respectively), and quinolone 181 (generating 182 and 183) (Scheme 52).

![Scheme 52 Complementary site selectivity of halogenation in the presence and absence of palladium catalyst](image)

Along with Yu’s and Sanford’s independent work, Shi reported a highly regioselective C–H functionalization/halogenation of acetanilides 184 catalyzed by Pd(OAc)$_2$ and Cu(OAc)$_2$ with CuX$_2$ as the halogen source (Scheme 53).

![Scheme 53 Palladium-catalyzed C–H halogenation of acetanilides 184 with CuX$_2$ as the halogen source](image)

---


In 2011, Bedford achieved a facile palladium-catalyzed ortho-selective bromination and chlorination of anilides 186 under aerobic conditions at ambient temperature with N-halosuccinimides (NXS) as the halogen source (Scheme 54a). Mechanistic studies showed that p-toluenesulfonic acid (PTSA) plays a key role in the catalytic process. Following this report, analogous work was achieved with varieties of directing groups in the presence of PTSA as efficient additive. Likewise, Rao very recently reported a palladium-catalyzed regio- and chemoselective chlorination for the facile synthesis of aromatic chlorides 189. The reaction demonstrates excellent reactivity, good functional-group tolerance, and high yields. Control experiment showed that TfOH could accelerate the halogenation efficiently and that a co-oxidant was necessary (Scheme 54b).

\[ \text{Scheme 54 Palladium-catalyzed C–H halogenation in the presence of acid additives} \]

Meanwhile, Gevorgyan developed an efficient strategy for the synthesis of 1,2-ambiphilic aromatic and heteroannulated aromatic synthons (Scheme 55). This method featured installation of the removable/modifiable PyDipSi directing group on haloarenes and subsequent palladium-catalyzed directed ortho-halogenation reaction to give the ortho-halogenated PyDipSi-arene derivatives 191. The synthetic usefulness of these 1,2-ambiphilic building blocks was demonstrated in a variety of transformations, involving reactions on both nucleophilic aryl silane and electrophilic aryl iodide moieties.
Distinguished from the above protocols, Kakiuchi described a new strategy for catalytic halogenation of C–H bonds by means of electrochemical oxidation. Herein, combination of palladium-catalyzed aromatic C–H bond cleavage and halogenation with electrochemically generated halonium ions enables highly efficient, selective halogenations of aromatic compounds in a green-sustainable manner (Scheme 5).

\[ \begin{align*}
\text{Scheme 55 Palladium-catalyzed ortho-halogenation of aryl silanes} & \quad 190 \\
\text{Palladium-catalyzed regioselective halogenation via electrochemical oxidation} & \quad 195 \rightarrow 196
\end{align*} \]

In addition to palladium-catalyzed halogenation protocols, versatile copper-catalyzed/promoted ortho-halogenation strategies have also been applied to arenes. These reactions were usually directed by pyridyl or related heteroaryl directing groups along with employment of a proper halogen source (Table 2).

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### Table 2 Copper-catalyzed direct C–H halogenations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Py" /></td>
<td><img src="image" alt="Py" /> Cl or Cl</td>
<td>CuCl₂ (20 mol %), Cl₂, CHCHCl₂, O₂ (1 atm), 130 °C, 24 h</td>
<td>112a</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Py" /></td>
<td><img src="image" alt="Py" /> X</td>
<td>X = Br: Cu(OAc)₂ (1.0 equiv), air, Br₂, CHCHBr₂, 130 °C, 24 h. X = I: Cu(OAc)₂ (1.0 equiv), I₂ (1.0 equiv), air, DCE, 100 °C, 24 h.</td>
<td>112a</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Py" /></td>
<td><img src="image" alt="Py" /> Cl</td>
<td>Cu(OAc)₂ (20 mol %), benzyol chloride (3.0 equiv), Li₂CO₃ (2.0 equiv), PhMe, O₂, 145 °C, 48 h</td>
<td>112b</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Py" /> NH₂SO₃Py</td>
<td><img src="image" alt="Py" /> X</td>
<td>Cu(NO₃)₂·3H₂O (20 mol %), LiCl (3.0 equiv), HOAc, O₂ (1 atm), 150 °C.</td>
<td>112c</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Py" /></td>
<td><img src="image" alt="Py" /> X</td>
<td>CuX₂ (10 mol %), NXS (1.2 equiv), MeCN, O₂ (1 atm), 100 °C, 4–8 h</td>
<td>112d</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Py" /></td>
<td><img src="image" alt="Py" /> X</td>
<td>CuX (1.0 equiv, NXS (2.0 equiv), HOAc (0.5 equiv), MeCN, 100 °C, 24 h</td>
<td>112e</td>
</tr>
</tbody>
</table>

Furthermore, [RhCp*Cl₂]₂ (201) was very recently demonstrated to be a competent catalyst for the halogenation of aromatic C–H bonds in arenes 202, as reported by Glorius (Scheme 57). In addition, this protocol was realized for the iodination and bromination of vinylic C–H bonds which provides a variety of (Z)-haloacrylic acid derivatives.

![Scheme 57 Rh(III)-catalyzed ortho-halogenations](image)

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Recently, Jeganmohan reported an intramolecular halogenation of O-methylbenzohydroximoyl halides 204 in the presence of the widely used ruthenium complex [RuCl₂(p-cymene)]₂ (15) along with diphenylacetylene (38a) as the ligand, yielding substituted halo aromatic nitriles under base- and oxidant-free conditions (Scheme 58).  

![Diagram](image)

**Scheme 58** Ruthenium-catalyzed intramolecular halogenations

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Objectives

During the past decade, remarkable progress in organometallic chemistry has set the stage for the development of increasingly viable metal catalysts for C–H bond activation reactions. Among these methods, oxidative C–H bond functionalizations are particularly attractive because they avoid the use of prefunctionalized starting materials. Among such protocols, oxidative annulations that involve sequential C–H and heteroatom–H bond cleavages allow for the modular assembly of regioselectively decorated heterocycles. While other researchers have devised palladium or rhodium complexes for oxidative alkyne annulations, our group has focused on the application of significantly less expensive, yet highly selective ruthenium complexes in recent years.

Carboxylate-assisted oxidative annulations of alkynes by benzamides employing ruthenium catalysts were only disclosed in 2011. Unfortunately, these ruthenium-catalyzed transformations were as of yet restricted to the use of superstoichiometric amounts of copper(II) or silver(I) salts as the sacrificial oxidants, thereby leading to the formation of stoichiometric amounts of undesired heavy metal by-products. During our studies on ruthenium-catalyzed oxidative C–H bond functionalizations with substituted pyrroles, we focused on developing carboxylate-assisted ruthenium-catalyzed oxidative annulations with air as an ideal oxidant (Scheme 59). Thereby, we established a novel access to pyrrolo[2,1-a]isoquinolines, which are indispensable structural motifs of bioactive lamellarine alkaloids. An additional asset of our ruthenium-catalyzed process is represented by its complementary scope and chemoselectivity as compared to the previously reported rhodium-catalyzed transformation that was found by Miura and coworkers.

The recent years witnessed a rapid development of the ruthenium-catalyzed oxidative C–H/N–H bond functionalizations. However, these C–H/N–H bond functionalizations were hitherto restricted to electron-deficient Michael acceptors decorated with electron-withdrawing carbonyl groups. Herein, we wanted to devise a new protocol that could achieve the ruthenium-catalyzed oxidative alkyne annulations with challenging electron-rich alkenes for an expedient pyrrole synthesis, which was also accomplished in an aerobic manner with air as the ideal terminal oxidant (Scheme 60).

Scheme 59 Ruthenium-catalyzed aerobic oxidative annulation with substituted pyrroles

Notably, ruthenium-catalyzed oxidative alkyne annulations with air as ideal oxidant were also achieved during the preparation of this thesis, see ref. 36, 39, 40 and 44. T. Fukuda, F. Ishibashi, M. Iwao, Heterocycles 2011, 83, 491–529. K. Morimoto, K. Hirano, T. Satoh, M. Miura, Org. Lett. 2010, 12, 2068–2071.
Along with the rapidly developing oxidative annulation with alkynes, significant progress has been accomplished in direct alkenylations through twofold C–H bond functionalization of arenes and heteroarenes employing ruthenium catalysts. Herein, we were interested in the use of [RuCl$_2$(p-cymene)]$_2$ and KPF$_6$ for efficient oxidative alkenylations of electron-rich anilides in water as a green solvent (Scheme 61). Notably, this reaction also proved to be applicable to electron-deficient (hetero)aromatic amides. Mechanistic studies showed that the transformations of these two types of substrates displayed different rate-limiting steps, with an irreversible C–H bond metation in the case of oxidative alkenylations with benzamides.

Despite the progress in the ruthenium-catalyzed C(sp$^3$)–H alkylation with unactivated alkenes in the past years, all protocols were restricted to Ru$_3$(CO)$_{12}$ catalyst under relatively harsh reaction conditions and with high catalyst loadings. Thus, we became attached by developing a general procedure for ruthenium-catalyzed C(sp$^3$)–H alkylation of unactivated alkenes with pyrrolidines employing ruthenium(II) catalyst. Complementing to the above-discussed oxidative protocols, this procedure would be a new powerful tool to construct C–C bonds. Furthermore, the pyridyl directing group can easily be removed to furnish the corresponding (NH)-free cyclic amines (Scheme 62).
In addition to the C–C bond formations, ruthenium complexes have been identified as powerful catalysts for the oxidative transformation of otherwise unreactive C–H bonds into C–O and C–N bonds. In strict contrast, ruthenium-catalyzed intermolecular C–Hal bond forming processes were unfortunately thus far not available. As a consequence, we became intrigued by a catalytic system comprising of [Ru₃(CO)₁₂] and AgO₂CAd for first ruthenium-catalyzed intermolecular brominations and iodinations of electron-rich and electron-deficient benzamides 219 using N-halosuccinimides as halogen source (Scheme 63).

Scheme 63 Ruthenium-catalyzed direct ortho-halogenations
3 Ruthenium-Catalyzed Oxidative Annulation of Alkynes Through C–H/N–H Bond Functionalizations

3.1 Ruthenium-Catalyzed Aerobic Oxidative Annulation of Alkynes with 2-Aryl-Substituted Indoles and Pyrroles

As indicated in Chapter 1.2, transition metal-catalyzed oxidative annihilations that involve sequential C–H and heteroatom–H bond cleavages allow for the modular assembly of regioselectively decorated heterocycles. Publications on carboxylate-assisted oxidative annihilations of alkynes employing less expensive, yet highly selective ruthenium catalysts appeared only since the pioneering work in 2011. Unfortunately, these transformations were as of yet restricted to the use of superstoichiometric amounts of copper(II) or silver(I) salts as the sacrificial oxidants. We established a novel access to pyrrolo[2,1-a]isoquinolines through ruthenium-catalyzed oxidative C–H bond functionalizations with cocatalytic amounts of Cu(OAc)$_2$·H$_2$O under an atmosphere of ambient air.

3.1.1 Optimization Studies

At the outset of our studies, we explored representative oxidants and additives for the envisioned ruthenium-catalyzed annulation of tolane (38a) by indole (206a) (Table 3). Thus, the C–H/N–H bond functionalization was achieved with [RuCl$_2$(p-cymene)]$_2$ and stoichiometric amounts of Cu(OAc)$_2$·H$_2$O as the terminal oxidant (entries 1–3). Interestingly, catalytic amounts of Cu(OAc)$_2$·H$_2$O were found to be sufficient, provided that reactions were conducted under an atmosphere of air (entry 4). Furthermore, the use of cocatalytic additive KPF$_6$ that forms cationic ruthenium(II) catalyst did not improve the catalytic activity (entry 5). While reactions with CuBr$_2$ as the co-oxidant did not furnish the desired product (entry 6), cocatalytic amounts of metal acetates restored the catalytic efficacy (entries 7–10), thus providing strong evidence for carboxylate-assisted aerobic oxidations.

### Table 3 Optimization of oxidative annulation with indole 206a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-catalyst (mol %)</th>
<th>Additive (mol %)</th>
<th>207aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>&lt;5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;·H&lt;sub&gt;2&lt;/sub&gt;O (200)</td>
<td>—</td>
<td>84&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;·H&lt;sub&gt;2&lt;/sub&gt;O (10)</td>
<td>—</td>
<td>21&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;·H&lt;sub&gt;2&lt;/sub&gt;O (10)</td>
<td>—</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;·H&lt;sub&gt;2&lt;/sub&gt;O (10)</td>
<td>KPF&lt;sub&gt;6&lt;/sub&gt; (20)</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>CuBr&lt;sub&gt;2&lt;/sub&gt; (10)</td>
<td>—</td>
<td>&lt;5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>CuBr&lt;sub&gt;2&lt;/sub&gt; (10)</td>
<td>KPF&lt;sub&gt;6&lt;/sub&gt; (20)</td>
<td>&lt;5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>CuBr&lt;sub&gt;2&lt;/sub&gt; (10)</td>
<td>LiOAc·H&lt;sub&gt;2&lt;/sub&gt;O (20)</td>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>CuBr&lt;sub&gt;2&lt;/sub&gt; (10)</td>
<td>NaOAc (20)</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>CuBr&lt;sub&gt;2&lt;/sub&gt; (10)</td>
<td>CsOAc (20)</td>
<td>50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 206a (0.5 mmol), 38a (1.0 mmol), [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> (5.0 mol %), cocatalyst, t-AmOH (2.0 mL), 100 °C, 22 h, under air (1 atm); isolated yields. <sup>b</sup> GC-conversion. <sup>c</sup> Under N<sub>2</sub>.

### 3.1.2 Scope of the Annulation with 2-Aryl-Substituted Indoles

With an optimized catalytic system in hand, we explored the scope of this ruthenium-catalyzed aerobic oxidative annulation of alkynes 38 by indoles 206 (Table 4). Notably, the aerobic annulation proved to be broadly applicable, and occurred chemoselectively at the N–H functionality of indoles 206. Valuable functional groups, such as fluoro, bromo, nitro or ester substituents, were well tolerated by the catalytic system. Electron-deficient heteroarenes 206 were efficiently converted, generally furnishing moderate to high isolated yields (entries 1–3 and 5–8). Unfortunately, electron-rich heteroarenes 206<sup>e</sup> and 206<sup>k</sup> (entries 4 and 10) as well as substrates 206<sup>j</sup> and 206<sup>m</sup> (entries 9 and 12) gave low conversion. However, improved yields were obtained when switching to stoichiometric amounts of the terminal oxidant Cu(OAc)<sub>2</sub>·H<sub>2</sub>O. On the other hand, the aerobic annulation tolerated decorated tolane derivatives 38 as well (entries 13–14).<sup>118</sup> Likewise, dichlorotolane 38c delivered the desired annulated product 207 in good yield with stoichiometric amounts of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (entry 14).
Table 4 Aerobic oxidative annulation of alkynes 38 with indoles 206<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole 206</th>
<th>Alkyne 38</th>
<th>Product 207</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = F (206b)</td>
<td>-</td>
<td>207ba</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>R = Br (206c)</td>
<td>38a</td>
<td>207ca</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>R = NO₂ (206d)</td>
<td>-</td>
<td>207da</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>206e</td>
<td>38a</td>
<td>207ea</td>
<td>7, 65&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>R = F (206f)</td>
<td>-</td>
<td>207fa</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>R = CF₃ (206g)</td>
<td>38a</td>
<td>207ga</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>R = NO₂ (206h)</td>
<td>-</td>
<td>207ha</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>R = CO₂Me (206i)</td>
<td>-</td>
<td>207ia</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>206j</td>
<td>38a</td>
<td>207ja</td>
<td>13, 51&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>206k</td>
<td>38a</td>
<td>207ka</td>
<td>6, 55&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>206l</td>
<td>38a</td>
<td>207ia</td>
<td>46</td>
</tr>
<tr>
<td>12</td>
<td>206m</td>
<td>38a</td>
<td>207ma</td>
<td>6, 46&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Table continues...
Ruthenium-Catalyzed Oxidative Annulations with Alkynes

Table 4 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole 206</th>
<th>Alkyne 38</th>
<th>Product 207</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td><img src="image3" alt="" /></td>
<td>54</td>
</tr>
<tr>
<td>14</td>
<td><img src="image4" alt="" /></td>
<td><img src="image5" alt="" /></td>
<td><img src="image6" alt="" /></td>
<td>6, 82b</td>
</tr>
</tbody>
</table>

* Reaction conditions: 206 (0.5 mmol), 38 (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), Cu(OAc)₂·H₂O (10 mol %), t-AmOH (2.0 mL), 100 °C, 22 h, under air (1 atm); isolated yields. *b* Cu(OAc)₂·H₂O (1.0 mmol), under N₂.

3.1.3 Scope of the Annulation with 2-Aryl-Substituted Pyrroles

Importantly, the ruthenium catalysis was not restricted to the use of 2-aryl-substituted indoles 206, but also allowed for the first metal-catalyzed oxidative annulations with pyrroles 208 (Table 5). The remarkable chemoselectivity of the catalytic system enabled the preparation of substituted pyrrolo[2,1-α]isoquinolines 209 in a highly regioselective fashion (entries 1–4), a structural motif found among others in the biologically active lamellarine alkaloids. Likewise, the ruthenium system proved tolerant of various electrophilic functional groups, such as esters, cyano or enolizable ketones (entries 1–4), although 5-methylpyrrole derivative 208e failed to deliver the desired product (entry 5). Electron-rich as well as electron-deficient tolanes 38 were efficiently converted, with the latter furnishing higher isolated yields (entry 6).

Table 5 Aerobic oxidative annulation with pyrroles 208a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrole 208</th>
<th>Alkyne 38</th>
<th>Product 209</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image7" alt="" /></td>
<td><img src="image8" alt="" /></td>
<td><img src="image9" alt="" /></td>
<td>93</td>
</tr>
</tbody>
</table>

- 40 -
Table 5 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrole 208</th>
<th>Alkyne 38</th>
<th>Product 209</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="Image" alt="Pyrrole 208a" /></td>
<td><img src="Image" alt="Alkyne 38a" /></td>
<td><img src="Image" alt="Product 209aa" /></td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="Image" alt="Pyrrole 208b" /></td>
<td><img src="Image" alt="Alkyne 38a" /></td>
<td><img src="Image" alt="Product 209ba" /></td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td><img src="Image" alt="Pyrrole 208c" /></td>
<td><img src="Image" alt="Alkyne 38a" /></td>
<td><img src="Image" alt="Product 209ca" /></td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td><img src="Image" alt="Pyrrole 208d" /></td>
<td><img src="Image" alt="Alkyne 38a" /></td>
<td><img src="Image" alt="Product 209da" /></td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td><img src="Image" alt="Pyrrole 208e" /></td>
<td><img src="Image" alt="Alkyne 38a" /></td>
<td><img src="Image" alt="Product 209ea" /></td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td><img src="Image" alt="Pyrrole 208a" /></td>
<td><img src="Image" alt="Alkyne 38d" /></td>
<td><img src="Image" alt="Product 209ad" /></td>
<td>54</td>
</tr>
</tbody>
</table>

* Reaction conditions: 208 (0.5 mmol), 38 (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), Cu(OAc)₂·H₂O (10 mol %), t-AmOH (2.0 mL), 100 °C, 22 h, under air (1 atm); isolated yields.

Further, the aerobic ruthenium-catalyzed annulation displayed an improved chemoselectivity as compared to the reported rhodium-catalyzed process. For instance, alkyl-substituted alkynes 38 gave access to the desired products without the formation of structural isomers (Table 6). Hence, the annulated heteroarenes 209 were isolated in high yields with slightly increased loadings of Cu(OAc)₂·H₂O (entry 1 vs entry 2), while the related rhodium catalysis was shown to deliver a mixture of products. The selective transformation of n-alkyl-substituted alkynes 38 also enabled aerobic oxidative annihilations with unsymmetrically-substituted alkynes 38g and 38h, which proceeded with synthetically useful regiocontrol (entries 6–8).
Table 6 Aerobic oxidative annulation with pyrroles 208

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrole 208</th>
<th>Alkyne 38</th>
<th>Product 209</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>208f</td>
<td>38e</td>
<td>209fe</td>
<td>48(^b)</td>
</tr>
<tr>
<td>2</td>
<td>208d</td>
<td>38e</td>
<td>209de</td>
<td>77%</td>
</tr>
<tr>
<td>3</td>
<td>208f</td>
<td>38f</td>
<td>209ff</td>
<td>86%</td>
</tr>
<tr>
<td>4</td>
<td>208d</td>
<td>38f</td>
<td>209df</td>
<td>76%</td>
</tr>
<tr>
<td>5</td>
<td>208f</td>
<td>38g</td>
<td>209fg</td>
<td>74 (6:1)(^c)</td>
</tr>
<tr>
<td>6</td>
<td>208a</td>
<td>38g</td>
<td>209ag</td>
<td>76 (8:1)(^c)</td>
</tr>
</tbody>
</table>

(continued)
Table 6 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrole 208</th>
<th>Alkyne 38</th>
<th>Product 209</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>208a</td>
<td>38h</td>
<td>209ah</td>
<td>73 (6:1)</td>
</tr>
</tbody>
</table>

* Reaction conditions: 208 (0.5 mmol), 38 (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), Cu(OAc)₂·H₂O (30 mol %), t-AmOH (2.0 mL), 100 °C, 22 h, under air (1 atm); isolated yields. b Cu(OAc)₂·H₂O (10 mol %). c The ratio of isomers was determined by ¹H-NMR spectroscopy.

3.1.4 Mechanistic Studies

3.1.4.1 Inter- and Intramolecular Competition Experiments

Considering the unique selectivity and outstanding efficacy of our ruthenium catalyst, we became interested in understanding its mode of action. For this purpose, intermolecular competition experiments with indoles 206b and 206o were performed and selectively yielded fluoro-substituted indole 207ba as the sole product (Scheme 64a). Furthermore, electron-deficient alkyne 38b was preferentially reacted with indole 206a under the optimized reaction conditions (Scheme 64b).

(a)

(b)

Scheme 64 Intermolecular competition experiments
Additionally, an intramolecular competition experiment with *meta*-fluoro-substituted indole 206p predominantly gave isomer 207'pa (Scheme 65), which can be rationalized with a deprotonative ruthenation manifold.\textsuperscript{7c,8,120}

![Scheme 65](image)

**Scheme 65** Annulation with *meta*-fluorophenyl-substituted indole 206p

### 3.1.4.2 Reactions in Isotopically Labelled Solvents

Furthermore, no significant H/D scrambling was observed in the oxidative annulations with indole substrate 206d in [D]$_2$-MeOH under otherwise identical reaction conditions (Scheme 66). These results can be rationalized in terms of an irreversible carboxylate-assisted C–H bond metalation step with the ruthenium complex (Scheme 67).

![Scheme 66](image)

**Scheme 66** Aerobic oxidative annulation in [D]$_2$-MeOH

### 3.1.5 Proposed Catalytic Cycle

Based on our experimental mechanistic studies, the following catalytic cycle for the ruthenium(II)-catalyzed aerobic oxidative annulation is proposed (Scheme 67).\textsuperscript{28} Initially, the ruthenium-dimer is expected to form an acetate complex 222, similar to those observed in the ruthenium-catalyzed carboxylate-assisted direct arylation.\textsuperscript{8} Subsequently, N–H bond ruthenation of free N–H group followed by irreversible C–H bond metalation via a key transition state 223 with a loss of two molecules of acetic acid affords ruthenacycle 224. Coordination of alkyne 38 and regioselective migratory insertion delivers seven-membered ruthenacycle 225 as a key intermediate. Finally, the intermediate 225 releases the desired product 207 or 209 through

\textsuperscript{120} 2-Aryl-substituted indoles bearing electron-donating groups on the aryl moiety led to low conversion.
Ruthenium-Catalyzed Oxidative Annulations with Alkynes

reductive elimination, which is followed by reoxidation of the resulting ruthenium(0) species core 226 by the copper (II)-acetate.

Scheme 67 Proposed catalytic cycle for the aerobic oxidative alkyne annulations

3.2 Ruthenium-Catalyzed Oxidative Annulation of Alkynes with Enamines for Pyrrole Synthesis

Pyrroles are among the most abundant heterocycles and represent indispensable structural motifs in bioactive natural products or material sciences.\(^{121,12}\) Therefore, there is a continued strong demand for methods that give broad access to this important heteroaromatic scaffold after the pioneering Knorr-pyrrole synthesis.\(^{122,123}\) Among these methods, transition-metal-catalyzed C–H bond functionalization strategy for the pyrrole synthesis provides a more atom-economical approach and thus receives much recent attention.\(^2\) The seminal work by the research groups of Glorius\(^{122}\) as well as Stuart and Fagnou\(^{123}\) have revealed novel syntheses of polysubstituted pyrroles through rhodium(III)-catalyzed C–H activation of enamines followed by the cyclization with an internal alkyne. Unfortunately, the high costs of the required rhodium(III) catalyst were identified as a limitation of this approach.\(^15\) The past three years witness a rapid development of the ruthenium-catalyzed oxidative C–H/N–H bond functionalizations.\(^2\) However, these protocols were restricted to alkenes activated with electron-withdrawing carbonyl groups. To overcome these restrictions, we hence became intrigued

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by developing a new ruthenium(II)-catalyzed oxidative alkyne annulations with challenging electron-rich alkenes for the pyrrole synthesis.\textsuperscript{124,125}

### 3.2.1 Optimization Studies

We commenced our studies by probing oxidative annulations with differently N-substituted enamines 210 (Scheme 68). Among starting materials 210 bearing a variety of functional substituents, such as Boc, Ts, acetyl, solely the N-acetylated substrate delivered the product 211aa in a satisfactory yield of 70\%, while the corresponding trifluoroacetylated starting material led to the NH-free product 212aa, albeit in low yield (15\%).

![Scheme 68 Ruthenium(II)-catalyzed oxidative pyrrole synthesis](image)

Thereafter, we tested the influence of reaction conditions on the activity of the ruthenium(II) catalyst (Table 7). In the absence of either the ruthenium complex or the copper oxidant, the desired product 211aa was not formed (entries 1 and 2). Likewise, the use of cocatalytic additive KPF\textsubscript{6} that forms cationic ruthenium(II) catalyst did not improve the catalytic activity (entries 3–5),\textsuperscript{118} whereas the replacement with AgSbF\textsubscript{6} led to 211aa in 39\% yield, along with the formation of NH-free product 212aa in 19\% yield (entry 6). Further, a series of solvents, including DCE, H\textsubscript{2}O, DMF, NMP, PhMe, DMA and t-AmOH (entries 3–11), were tested and disclosed the latter to be the most efficient one. Moreover, the use of CuBr\textsubscript{2} instead of Cu(OAc)\textsubscript{2}·H\textsubscript{2}O\textsuperscript{8} as the sacrificial oxidant did not deliver the desired product 211aa (entries 12–14). Besides, the complex RuCl\textsubscript{3}·xH\textsubscript{2}O applied instead of [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} displayed no catalytic activity in the pyrrole synthesis (entry 15).


Table 7 Optimization study for the oxidative pyrrole synthesisa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>211aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>t-AmOH</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>t-AmOH</td>
<td>100</td>
<td>0b</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>t-AmOH</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>t-AmOH</td>
<td>120</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂·H₂O</td>
<td>KPF₆</td>
<td>t-AmOH</td>
<td>120</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)₂·H₂O</td>
<td>AgSbF₆</td>
<td>DCE</td>
<td>100</td>
<td>39c</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>H₂O</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>DMF</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>NMP</td>
<td>100</td>
<td>53</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>PhMe</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>DMA</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>CuBr₂</td>
<td>—</td>
<td>t-AmOH</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>CuBr₂</td>
<td>NaOAc</td>
<td>t-AmOH</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>CuBr₂</td>
<td>CsOAc</td>
<td>t-AmOH</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Cu(OAc)₂·H₂O</td>
<td>—</td>
<td>t-AmOH</td>
<td>100</td>
<td>0d</td>
</tr>
</tbody>
</table>

a Reaction conditions: 210a (0.5 mmol), 38a (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), oxidant (0.5 mmol), solvent (2.0 mL), 22 h; isolated yields. b In the absence of [RuCl₂(p-cymene)]₂. c 212aa (19%) was also isolated. d RuCl₃·H₂O (10 mol %) was used instead of [RuCl₂(p-cymene)]₂.

3.2.2 Scope of the Oxidative Pyrrole Synthesis

To evaluate the scope of the optimized ruthenium(II) catalyst, we tested its versatility in oxidative annihilations of tolane (38a) utilizing representative enamines 210 (Table 8). We were delighted to observe that numerous useful electrophilic functional groups were well tolerated, including ester, vinyl, bromo, cyano, and nitro substituents. Substrates 210d and 210e with a ketone moiety or without an additional substituent, respectively, provided only low conversion under the optimized reaction conditions (entries 3 and 4). Transformations of 1-aryl-substituted enamines (entries 6–15) proceeded very smoothly in most cases. However, electron-rich methyl and methoxy (entries 12, 13) as well as cyclopropyl groups only delivered the target product in low yields, while more sterically congested substrate 210p was efficiently converted to product 211pa (entry 15). Moreover, 1-heteroaryl-substituted substrates 210q and 210r furnished the desired pyrroles 211q and 211ra as well (entries 16 and 17), albeit in lower yields. In the latter case, the NH-free pyrrole 212ra was formed in a comparable yield, and the substrate 210s afforded analogous compound 212sa as a sole product in moderate yield (entry 18).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Enamine 210</th>
<th>Product 211</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = CO_2Et (210b)</td>
<td>211ba</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>R = CO_2i-Pr (210c)</td>
<td>211ca</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>R = COMe (210d)</td>
<td>211da</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>210b–e</td>
<td>R = H (210e)</td>
<td>211ba–211ea</td>
</tr>
<tr>
<td>5</td>
<td>210f</td>
<td>219fa</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>R = H (210g)</td>
<td>211ga</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>R = CF_3 (210h)</td>
<td>211ha</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>R = F (210i)</td>
<td>211ia</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>R = Br (210j)</td>
<td>211ja</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>R = CN (210k)</td>
<td>211ka</td>
<td>74</td>
</tr>
<tr>
<td>11</td>
<td>R = NO_2 (210l)</td>
<td>211la</td>
<td>71</td>
</tr>
<tr>
<td>12</td>
<td>R = Me (210m)</td>
<td>211ma</td>
<td>18</td>
</tr>
<tr>
<td>13</td>
<td>R = OMe (210n)</td>
<td>211na</td>
<td>28</td>
</tr>
<tr>
<td>14</td>
<td>210o</td>
<td>211oa</td>
<td>72</td>
</tr>
<tr>
<td>15</td>
<td>210p</td>
<td>211pa</td>
<td>68</td>
</tr>
<tr>
<td>16</td>
<td>210q</td>
<td>211qa</td>
<td>32</td>
</tr>
<tr>
<td>17</td>
<td>210r</td>
<td>X = Ac (211ra)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X = H (212ra)</td>
<td>30</td>
</tr>
</tbody>
</table>

(continued)
Table 8 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enamine 210</th>
<th>Product 211</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td><img src="210s" alt="Image" /></td>
<td><img src="212sa" alt="Image" /></td>
<td>48</td>
</tr>
</tbody>
</table>

*Reaction conditions: 210 (0.5 mmol), 38a (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), Cu(OAc)₂·H₂O (0.5 mmol), t-AmOH (2.0 mL), 22 h; isolated yields.

Thereafter, we probed different tolane derivatives 38 in the oxidative pyrrole synthesis (Table 9). The optimized ruthenium catalyst proved to be tolerant of functional groups in the para-, meta- and ortho-position of tolane (entries 1–8), but was not restricted to aryl alkynes 38. Dialkyl-substituted substrates 38e and 38f delivered the desired products 211ae and 211af, respectively, in high yields (entries 9 and 10). Notably, oxidative annulations of unsymmetrical alkynes 38h and 38o occurred with synthetically useful levels of regiocontrol, furnishing exclusively the products 211lh, 211ah and 211ao (entries 11–13). This selectivity pattern is in good agreement with the previously observed one for a related indole synthesis.37

Table 9 Oxidative annulation of alkynes 38 by enamines 210a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enamine 210</th>
<th>Alkyne 38</th>
<th>Product 211</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="210l" alt="Image" /></td>
<td>38i–l</td>
<td><img src="211ii%E2%80%93211ll" alt="Image" /></td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td><img src="210a" alt="Image" /></td>
<td><img src="38m" alt="Image" /></td>
<td><img src="211lm" alt="Image" /></td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td><img src="210l" alt="Image" /></td>
<td><img src="38n" alt="Image" /></td>
<td><img src="211an" alt="Image" /></td>
<td>57</td>
</tr>
</tbody>
</table>

(continued)
Table 9 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enamine 210</th>
<th>Alkyne 38</th>
<th>Product 211</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>R = n-Pr (38e)</td>
<td>211ae</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>R = Et (38f)</td>
<td>211af</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Ph=Me (38h)</td>
<td>211lh</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>R = Me (38h)</td>
<td>211ah</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>R = Et (38o)</td>
<td>211ao</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

*a* Reaction conditions: 210 (0.5 mmol), 38 (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), Cu(OAc)₂·H₂O (0.5 mmol), t-AmOH (2.0 mL), 22 h; isolated yields.

### 3.2.3 Ruthenium(II)-Catalyzed Aerobic Oxidative Pyrrole Synthesis

We were pleased that the C–H/N–H bond functionalization was also achieved in an aerobic fashion employing cocatalytic amounts of Cu(OAc)₂·H₂O under an ambient atmosphere of air as the ideal oxidant (Scheme 69).

![Scheme 69](image)

Scheme 69 Aerobic oxidative C–H/N–H bond functionalization under ambient air

### 3.2.4 Mechanistic Studies

#### 3.2.4.1 Intermolecular Competition Experiments

Given the remarkable catalytic activity of the ruthenium(II) catalyst, we became interested in elucidating the mechanistic aspects of this transformation. We conducted intermolecular competition experiments with alkynes 38, which revealed more electron-rich alkyne 38j to react preferentially (Scheme 70).
Additionally, competition experiments with differently 2-aryl-substituted enamines highlighted electron-donating substituents on the aryl moiety to be beneficial (Scheme 71).

**Scheme 70** Intermolecular competition between alkynes 38

**Scheme 71** Intermolecular competition between enamines 210
3.2.4.2 Reactions in Isotopically Labelled Solvents

Oxidative annihilations in isotopically labeled solvent [D₄]-MeOH unraveled the C–H bond activation on enamines 210 to be reversible in nature (Scheme 72a). Yet, the H/D scrambling was not observed in the presence of alkyne 38e under otherwise identical reaction conditions (Scheme 72b). These results can be rationalized in terms of an alkyne-coordinated ruthenium complex undergoing an irreversible C–H bond metalation step.

(a)

(b)

Scheme 72 Oxidative annihilations in [D₄]-MeOH

3.2.5 Proposed Catalytic Cycle

Based on the above discussed experiments and on the known mechanisms of transition-metal-catalyzed oxidative annulation reactions, a plausible catalytic cycle for the ruthenium(II)-catalyzed pyrrole synthesis is proposed (Scheme 73). Initially, the ruthenium-dimer reacts with Cu(OAc)₂·H₂O to form an acetate-ligated species 227, which is subsequently coordinated by 210 via the amide oxygen to generate complex 228. Then an alkyne-coordinate ruthenium complex undergoes an irreversible C–H bond metalation step to deliver a six-membered ruthenacycle 230 with concomitant formation of acetic acid via an acetate-assisted transition state 229. Regioselectively migratory insertion into the Ru–C bond and cleavage of N–H bond furnish a six-membered ruthenacycle intermediate 231. Subsequently, the oxidative coupling of the C–N bond takes place to form the pyrrole product 211 with the reduction of the ruthenium core from ruthenium(II) to ruthenium(0). Finally, the ruthenium(0) species 232 undergoes oxidation to regenerate the active ruthenium(II) complex with the aid of the copper oxidant.
Scheme 73 Proposed catalytic cycle for the pyrrole synthesis
4 Ruthenium-Catalyzed Oxidative C–H Alkenylations

4.1 Ruthenium-Catalyzed Oxidative C–H Alkenylations of Anilides

Along with the rapid developing oxidative annulations of alkynes, significant progress has been accomplished in direct oxidative alkenylations of (hetero)arenes via twofold C–H bond cleavages employing ruthenium catalysts. However, ruthenium-catalyzed direct oxidative alkenylations continue to be limited to (hetero)arenes bearing electron-withdrawing directing groups. Given the importance of anilines as key intermediates for the preparation of bioactive compounds and functional materials, we set out to develop the first ruthenium-catalyzed oxidative olefinations with electron-rich anilines.

4.1.1 Optimization Studies

At the outset of our studies, we optimized reaction conditions for the oxidative alkenylation of acetanilide with alkene in water (Table 10). In the absence of an additive, only trace amounts of the desired product were formed (entries 1 and 2). However, high catalytic efficiency was ensured by a complex generated in situ from [RuCl₂(p-cymene)]₂ and cocatalytic amounts of KPF₆ (entries 3–9), reaction conditions previously established for the generation of cationic ruthenium(II) complexes. An aerobic oxidative alkenylation with cocatalytic amounts of Cu(OAc)₂·H₂O was viable, albeit with reduced efficacy (entry 10). Further, the use of silver(I) salts as terminal oxidants provided less satisfactory results but indicated a strong dependence of the catalyst’s performance on the presence of acetates (entries 11 and 12).

Table 10 Optimization of alkenylation with acetanilide

<table>
<thead>
<tr>
<th>Entry</th>
<th>[RuCl₂(p-cymene)]₂ (mol %)</th>
<th>Oxidant (equiv)</th>
<th>Additive (mol %)</th>
<th>213aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>KPF₆ (10)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>—</td>
<td>2b</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>KPF₆ (5)</td>
<td>43b</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>AgSbF₆ (10)</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>KPF₆ (10)</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>KPF₆ (5)</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (2.0)</td>
<td>KPF₆ (10)</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>KPF₆ (20)</td>
<td>86</td>
</tr>
</tbody>
</table>

(continued)

126 For the recent reports on ruthenium-catalyzed oxidative olefinations with electron-rich arenes appeared during the preparation of this thesis, see ref. 66 and 67.
Table 10 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>[RuCl₂(p-cymene)]₂ (mol %)</th>
<th>Oxidant (equiv)</th>
<th>Additive (mol %)</th>
<th>213aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (1.0)</td>
<td>KPF₆ (10)</td>
<td>77c</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>Cu(OAc)₂·H₂O (0.05)</td>
<td>KPF₆ (10)</td>
<td>48b,c,d</td>
</tr>
<tr>
<td>11</td>
<td>2.5</td>
<td>Ag₂CO₃ (1.0)</td>
<td>KPF₆ (10)</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>2.5</td>
<td>AgOAc (1.0)</td>
<td>KPF₆ (10)</td>
<td>40b</td>
</tr>
</tbody>
</table>

* Reaction conditions: 212a (0.50 mmol), 76a (0.75 mmol), [RuCl₂(p-cymene)]₂ (2.5 mol %), additive (10 mol %), oxidant (0.5 mmol), H₂O (2.0 mL), 120 °C, 20 h, under N₂; isolated yields. b GC conversion. c 100 °C. d Under air (1 atm).

Notably, the replacement of water by organic solvents, such as t-AmOH and DMF, led to lower-yielding reactions (Table 11, entries 2–6). Hence, the reaction mixture was biphasic, which suggested that the reaction occurred "on" water, rather than "in water." However, addition of surfactants, such as Triton X-100, surprisingly delivered the alkenylated product in similar yield in H₂O (entry 7 vs entry 1).

Table 11 Influence of solvent on the alkenylation with acetonilide 212a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Surfactant</th>
<th>213aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>—</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>t-AmOH</td>
<td>—</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>—</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>H₂O/DMF (9:1)</td>
<td>—</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>H₂O/DMF (1:1)</td>
<td>—</td>
<td>10b</td>
</tr>
<tr>
<td>6</td>
<td>H₂O/DMF (1:9)</td>
<td>—</td>
<td>11b</td>
</tr>
<tr>
<td>7</td>
<td>H₂O</td>
<td>Triton X-100 (10 mol %)</td>
<td>81</td>
</tr>
</tbody>
</table>

* Reaction conditions: 212a (0.50 mmol), 76a (0.75 mmol), [RuCl₂(p-cymene)]₂ (2.5 mol %), KPF₆ (10 mol %), Cu(OAc)₂·H₂O (0.5 mmol), solvent (2.0 mL), 120 °C, 20 h, under N₂; isolated yields. b GC conversion.

4.1.2 Effect of Directing Groups

Furthermore, we probed the ruthenium-catalyzed oxidative alkenylation with differently N-substituted substrates 212 (Scheme 74). Among a variety of starting materials 212, N-phenylacetamide (212d) delivered the product 213da in best yield in H₂O (68%), while the corresponding N,N-disubstituted substrate 212f led to the target product 213fa with a low conversion (15%).

With the optimized catalytic system in hand, we explored the scope in the ruthenium-catalyzed oxidative alkenylation of anilides 212 (Table 12). Thus, the catalytic C–H bond functionalization in water allowed for the efficient conversion of para-substituted substrates 212g–i via chemoselective monoalkenylation (entries 1–5). Intramolecular competition experiments with meta-substituted anilides 212 site selectively delivered the products 213 through alkenylation in position C-6, likely due to steric interactions (entries 6–10). Notably, this reactivity pattern was not observed when using meta-fluoro-substituted anilide 212m (entry 11), as was previously noted for ruthenium-catalyzed C–H bond functionalization with organic electrophiles.14 Unfortunately, ortho-substituted substrate 212n delivered the alkenylated product 213na in only 41% conversion (entry 13). However, hydroarylation of alkenes surprisingly occurred with methy vinyl ketone (76c), yielding the corresponding alkylated product 213ac in 31% yield (entry 12).130

Table 12 Oxidative alkenylations with anilides 212

<table>
<thead>
<tr>
<th>Entry</th>
<th>Anilide 212</th>
<th>Alkene 76</th>
<th>Product 213</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>212g</td>
<td>76a</td>
<td>213ga</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>212g</td>
<td>76b</td>
<td>213ga–213gb</td>
<td></td>
</tr>
</tbody>
</table>

(continued)

130 For a similar subsequent example, see: L. Huang, Q. Wang, J. Qi, X. Wu, K. Huang, H. Jiang, Chem. Sci. 2013, 4, 2665–2669.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Anilide 212</th>
<th>Alkene 76</th>
<th>Product 213</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td>76a</td>
<td>R = Et (213ha)</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>76b</td>
<td>R = Bu (213hb)</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>76a</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>76b</td>
<td></td>
<td>56 (1:0)³</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>76a</td>
<td>R = Et (213ja)</td>
<td>58 (10:1)³</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>76b</td>
<td>R = Bu (213jb)</td>
<td>52 (6:1)³</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>76a</td>
<td></td>
<td>66 (17:1)³</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>76a</td>
<td></td>
<td>53 (1:0)³</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>76a</td>
<td></td>
<td>70 (4:1)³</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>76c</td>
<td></td>
<td>31 (1:0)³</td>
</tr>
</tbody>
</table>
Furthermore, we were pleased to observe that this ruthenium-catalyzed oxidative C–H alkenylation proceeded smoothly even on a large scale (0.5g–5.0 g).\textsuperscript{131} Herein, 5 mmol scale anilide loadings delivered the target product 213aa in 73% yield (Scheme 75).

Scheme 75 Ruthenium(II)-catalyzed oxidative alkenylations of anilide 212a in 5 mmol scale

The cationic ruthenium(II) system unfortunately led to low conversions with acrylonitrile (76d), styrene (76e), tert-butyl acrylate (76f), acrolein (76g) and α- or β-substituted alkenes (76h–k) (Table 13), even when switching H$_2$O to the organic solvent t-AmOH (entry 3).

Table 13 Oxidative alkenylations with alkene derivatives 76

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene 76</th>
<th>213 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\equiv$CN (76d)</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>$\equiv$Ph (76e)</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>$\equiv$CO$_2$Bu (76f)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>CHO (76g)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>$\equiv$MeCN (76h)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>$\equiv$CO$_2$Et (76i)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>$\equiv$Me (76j)</td>
<td>0</td>
</tr>
</tbody>
</table>

(continued)

\begin{table}[h]
\centering
\begin{tabular}{cccc}
\hline
Entry & Anilide 212 & Alkene 76 & Product 213 & Yield (%) \\
\hline
13 & 212n & 76a & 213na & 41$^c$ \\
\hline
\end{tabular}
\caption{Contd.}
\end{table}

\textsuperscript{a} Reaction conditions: 212 (0.50 mmol), 76 (0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (5.0 mol%), KPF$_6$ (10 mol%), Cu(OAc)$_2$·H$_2$O (0.5 mmol), H$_2$O (2.0 mL), 120 °C, 20 h, under N$_2$; isolated yields (of the major isomers). \textsuperscript{b} Ratio of the regioisomers determined by GC. \textsuperscript{c} GC conversion.


- 58 -
Table 13 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene 76</th>
<th>213 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>EtO₂C=OC₂Et (76j)</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>EtO₂C=OC₂Et (76k)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reaction conditions: 212a (0.50 mmol), 76 (0.75 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), KPF₆ (20 mol %), Cu(OAc)₂·H₂O (0.5 mmol), H₂O (2.0 mL), 120 °C, 20 h, under N₂; GC conversion. b t-AmOH as solvent.

4.1.4 Mechanistic Studies

4.1.4.1 Intermolecular Competition Experiments

Considering the unique features of our ruthenium catalyst, we became interested in understanding its mode of action. Thus, intermolecular competition experiments revealed electron-rich anilides 212 to be preferentially functionalized (Scheme 76), which is in good agreement with an electrophilic activation manifold.

![Scheme 76 Intermolecular Competition Experiments](image_url)

4.1.4.2 Reactions in Isotopically Labelled Solvents
Oxidative alkenylation in D$_2$O unraveled the C–H bond activation in anilide 212d to be reversible in nature (Scheme 77a). Consistence with this result, an obvious H/D scrambling on both the recycled starting material [D]$_n$-212a and target product [D]$_n$-213aa were observed in the presence of alkene 76a under identical reaction conditions in D$_2$O (Scheme 77b). These findings can be rationalized in that the ruthenium-catalyzed alkenylation proceeds by a reversible C–H bond metatation step.

4.1.5 Proposed Catalytic Cycle

Based on our mechanistic studies, we propose the catalytic cycle to involve an initial reversible acetate-assisted cycloruthenation of the cationic species 233 with anilide 212 to form complex 235 through a transition state 234 (Scheme 78), which subsequently undergoes a migratory insertion with alkene 76 to furnish the six-membered intermediate 236. Finally, β-hydride elimination yields the desired product 213, and oxidation of [RuH] species with Cu(OAc)$_2$ regenerates the catalytically active cationic catalyst 233.
4.2 Ruthenium-Catalyzed Oxidative C–H Alkenylations of Benzamides

Notably, the efficient catalysis achieved with the cationic ruthenium(II) complex in water allowed for efficient oxidative alkenylations of benzamides. Thus, direct C–H bond functionalization of heteroaromatic amides occurred with high catalytic efficacy and excellent site selectivity (Table 14). However, the alkenylation of NH-free indole did not proceed under the identical reaction conditions (entry 3).

**Table 14 Oxidative alkenylation of heteroaromatic amides**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Alkene</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214a</td>
<td>76a</td>
<td>215aa</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>214b</td>
<td>76a</td>
<td>215ba</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>214c</td>
<td>76a</td>
<td>215ca</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>214d</td>
<td>76a</td>
<td>215da</td>
<td>36, 64b</td>
</tr>
<tr>
<td>5</td>
<td>214e</td>
<td>76a</td>
<td>215ea R = Et (215ea)</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>214e</td>
<td>76b</td>
<td>215eb R = Bu (215eb)</td>
<td>72</td>
</tr>
</tbody>
</table>

a Reaction conditions: 214 (0.50 mmol), 76 (0.75 mmol), [RuCl₂(μ-cymene)]₂ (5.0 mol %), KPF₆ (20 mol %), Cu(OAc)₂·H₂O (0.5 mmol), H₂O (2.0 mL), 120 °C, 20 h, under N₂; isolated yield. b t-AmOH as solvent.

Furthermore, the site selectivity within intramolecular competition experiments with heteroaromatic amides was largely governed by electrophilic effects. Hence, substrate 214f was...
preferentially functionalized at its C-2 position (Scheme 79).

Scheme 79 Intramolecular competition experiments with amide 214f
5 Ruthenium(II)-Catalyzed C(sp³)–H α-Alkylation of Pyrrolidines with Alkenes

In spite of the progress on ruthenium-catalyzed C(sp³)–H alkylations with alkenes in the past years, these protocols were largely restricted to Ru₃(CO)₁₂ catalysis under harsh conditions, i.e. relatively high pressure and reaction temperature. Taking into consideration our group’s recent report on ruthenium-catalyzed hydroarylations with unactivated alkenes through carboxylate-assistance, we hence set out to develop a novel directed C(sp³)–H alkylation of alkenes on pyrrolidines by ruthenium(II) catalyst.

5.1 Optimization Studies

Based on recently obtained results from our group, we were interested in exploring representative cocatalytic additives for the envisioned hydroalkylation of unactivated alkenes. Not surprisingly, test reactions clearly illustrated the importance of [RuCl₂(PPh₃)₃] as well as of rac-BINAP. Indeed, simple [RuCl₂(PPh₃)₃] did not affect the desired C–H bond functionalization in the absence of ligands and additives (entry 1). Likewise, in the absence of rac-BINAP satisfactory results were not obtained (entries 2–4). Notably, more promising results were achieved utilizing metal triflate as additives, and AgOTf was identified as being optimal (entries 5–7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>217aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>4b</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>0c</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf</td>
<td>&lt;1b</td>
</tr>
<tr>
<td>5</td>
<td>AgOTf</td>
<td>73d</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>NaOTf</td>
<td>70d</td>
</tr>
</tbody>
</table>

* Reaction conditions: 216a (1.5 mmol), 111a (0.5 mmol), [RuCl₂(PPh₃)₃] (5.0 mol %), rac-BINAP (6.0 mol %), additive (12 mol %), 120 °C, 18 h; GC analysis with n-tridecane as an internal standard. Without rac-BINAP. Without [RuCl₂(PPh₃)₃]. Isolated yield.

5.2 Scope and Limitations

With a highly selective catalytic system in hand (Table 15, entry 5), we next examined the influence exerted by substituents at the heteroaromatic moiety (Table 16). Thus, the optimized

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Ruthenium(II)-catalyzed C(sp\(^3\))–H \(\alpha\)-Alkylation with Alkenes

... catalyst proved applicable to high-yielding transformations of pyrrolidines with 3-, 4- or 5-substituents on the pyridyl group, thereby selectively delivering the monoalkylated products 217ba–217ea (entries 1–4). Notably, the optimized catalyst system was not restricted to pyridine moieties, but also enabled the C–H activation using an isoquinoline (entry 6). Contrarily, methyl groups either on the pyridine (216f) or on the pyrrolidine (216h) had a detrimental effect (entries 5 and 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrolidine 216</th>
<th>Product 217</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>216b–c</td>
<td>217ba–217ca</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>216d</td>
<td>217da</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>216e</td>
<td>217ea</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>216f</td>
<td>217fa</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>216g</td>
<td>217ga</td>
<td>67</td>
</tr>
</tbody>
</table>

(continued)
Table 16 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyrrolidine 216</th>
<th>Product 217</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>7b</td>
</tr>
<tr>
<td></td>
<td>216h</td>
<td>217ha</td>
<td></td>
</tr>
</tbody>
</table>

\[ \text{Reaction conditions: 216 (1.5 mmol), 111a (0.5 mmol), [RuCl}_2\text{(PPh}_3\text{)}_3] (5.0 mol %), rac-BINAP (6.0 mol %), AgOTf (12 mol %), 120 \degree \text{C, 18 h; isolated yield.} \]

Thereafter, we explored the versatility of this method by testing a representative set of unactivated alkenes 111 (Table 17). Different alkenes 111b–h furnished the corresponding products 217bb–bh in high yields even at a significantly reduced temperature of 80 \degree \text{C (entries 1–7). Notably, the catalytic system tolerated functional groups, such as silanes (111i and 111j) or ethers (111k) (entries 8–10). Intriguingly, competition experiments with haloalkenes 111l and 111m highlighted the excellent chemoselectivity of the C(sp\(^3\))–H alkylations with substrates 111l–n (entries 11–12), in that products stemming from direct C–H bond alkylations with the alkyl halide moieties were not observed.\(^{26,133}\) Likewise, styrene derivatives 111o–s proved to be suitable substrates, delivering the corresponding alkylated products 217bo–217bs in good yields (entries 13–18).

Table 17 Ruthenium(II)-catalyzed C(sp\(^3\))–H alkylation with alkene 111

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene 111</th>
<th>Product 217</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>73b</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>78a</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>90</td>
</tr>
</tbody>
</table>

Table 17 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene 111</th>
<th>Product 217</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>111e</td>
<td>217be</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>111f</td>
<td>217bf</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>111g</td>
<td>217bg</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>111h</td>
<td>217bh</td>
<td>50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>111i</td>
<td>217bi</td>
<td>59&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>111j</td>
<td>217bj</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>111k</td>
<td>217bk</td>
<td>65&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>111l</td>
<td>217bl</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>111m</td>
<td>217bm</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>111n</td>
<td>217bn</td>
<td>82</td>
</tr>
<tr>
<td>14</td>
<td>111o–r</td>
<td>217bo–217br</td>
<td>R = H (217bo) 73</td>
</tr>
<tr>
<td>15</td>
<td>111o–r</td>
<td>217bo–217br</td>
<td>R = OMe (217bp) 70</td>
</tr>
<tr>
<td>16</td>
<td>111o–r</td>
<td>217bo–217br</td>
<td>R = Br (217bq) 65</td>
</tr>
<tr>
<td>17</td>
<td>111o–r</td>
<td>217bo–217br</td>
<td>R = F (217br) 64</td>
</tr>
</tbody>
</table>

(continued)
Table 17 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene 111</th>
<th>Product 217</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>111s</td>
<td>2-py 117bs</td>
<td>57</td>
</tr>
</tbody>
</table>

* Reaction conditions: 216b (1.5 mmol), 111 (0.5 mmol), [RuCl₂(PPh₃)₃] (5.0 mol %), rac-BINAP (6.0 mol %), AgOTf (12 mol %), 120 °C, 18 h; Isolated yield. ** 216b (0.5 mmol), 111h (1.5 mmol). ** DCE as solvent.

However, nucleophilic substitution occurred upon alkylation of the substrate 111t in the protic solvent i-BuOH, affording product 219bt (Scheme 80a). Fortunately, simply switching the solvent to aprotic DCE delivered the target product 219bt in good yield applying the optimized ruthenium catalyst. Besides, alkene 111u with a ketone moiety was well tolerated, while alkylation along with unexpected hydrogen transfer generated the reduced product 217bv in a moderate yield (Scheme 80b).

Scheme 80 Ruthenium(II)-catalyzed C(sp³)-H alkylation with alkenes 111t–v

Unfortunately, substrates with six- or seven-membered rings fused to a pyrrolidine moiety, and among others compounds 237a–b gave unsatisfactory results under the identical conditions (Scheme 81). ** Furthermore, substrates 237c–g bearing oxazole, pyrrole, imine, acetyl or cyano directing groups proved inefficient. On the other hand, products of reduction were obtained in low yield from activated alkenes 76a, 76c and 238a–c. Terminal, internal and cyclic alkenes 238d–g and diene 238h as well as alkynes 238i–j and 38a were inactive under the standard reaction conditions.

** For details, see also: B.Sc. Thesis, K. Bielefeld, University of Göttingen, Göttingen, Germany, 2012.
5.3 Mechanistic Studies

5.3.1 Reactions in the Presence of Radical Scavengers

Given the unique reactivity profile of the novel ruthenium(II) catalyst, we subsequently performed mechanistic studies to rationalize its mode of action. Thus, SET-type processes could be ruled out by successfully performing the C(sp\(^3\))–H alkylation in the presence of stoichiometric amounts of the radical scavenger TEMPO (Scheme 82).

5.3.2 Reactions in Isotopically Labelled Reagents

Next, the H/D exchange reaction was undertaken to obtain information concerning the reaction mechanism. In the present case, ruthenium(II)-catalyzed C(sp\(^3\))–H alkylation in [D]\(_4\)-MeOH (Schemes 83a–b) or with isotopically enriched substrate [D]\(_n\)-216b (Scheme 84) indicated the C–H bond metalation step to be reversible. Surprisingly, the treatment of 216b under catalytic reaction conditions (either in the absence or presence of 111a) in [D]\(_4\)-MeOH showed significant deuterium incorporation at the β-positions of the pyrrolidine (Scheme 83a–b). However, this result is in line with the observation reported by Murai and coworkers for ruthenium(0) catalyst (Scheme 83c).\(^9\)
5.4 Proposed Catalytic Cycle

Based on our experimental mechanistic studies, the following catalytic cycle for the ruthenium(II)-catalyzed C(sp\(^3\))–H alkylation of pyrrolidines 216 is postulated (Scheme 85). Initially, the active species 239 is in situ formed from ruthenium precursor. Subsequently, reversible C–H bond metalation via transition state 240 forms ruthenacycle 241, which is similar to those observed in the carboxylate-assisted ruthenium-catalyzed oxidative direct C–H activations. Coordination of alkene 111 followed by its regioselective migratory insertion deliver a key intermediate 243. Finally, reductive elimination of 243 affords complex 244, which subsequently releases the desired product 217 and regenerates the active species 239. However, it should be noted that a precise investigation of the exact intermediate structures in terms of the
ligand sphere is required. Due to the important role of rac-BINAP in the process (Table 15, entry 1), it remains questionable as to whether exchange of rac-BINAP with PPh₃ as a ligand occurs.⁸⁴

![Scheme 85 Proposed reaction mechanism](image)

5.5 Removal of the Directing Groups

The pyridyl directing group was efficiently removed according to Maes’ recent "one-pot" protocols, namely, hydrogenation/hydride reduction and quaternization/hydride reduction strategies (Scheme 86).¹³⁵ Thus, the hydrogenation/hydride reduction protocol was successfully applied to substrate 217ba and 217bj, delivering the desired (NH)-free pyrrolidines under comparably mild conditions (Scheme 86a). Although the pyridine directing group in substrate 217bo was removed under the hydrogenation/hydride reduction strategy as well, the arene ring of the phenethyl moiety was simultaneously reduced. Further switching to the quaternization/hydride reduction strategy led to unsatisfactory result (Scheme 86b).

(a) "Hydrogenation Hydride Reduction" Strategy

1) Pt/C (10 mol %), H₂ (1 atm) 
HCl (1.2 equiv), EtOH 
23 °C, 24 h 
2) NaBH₄ (4.0 equiv) 
MeOH, 0 °C, 15 min
R = n-C₉H₁₇ (218ba): 70% 
R = SiEt₃ (218bb): 61%

(b) "Quaternization Hydride Reduction" Strategy

1) Pt/C (10 mol %), H₂ (1 atm) 
HCl (1.2 equiv), EtOH 
23 °C, 24 h 
2) NaBH₄ (4.0 equiv) 
MeOH, 0 °C, 15 min

1) MeOTf (3.6 equiv) 
MeCN, 23 °C, 5 min 
2) NaBH₄ (10.0 equiv) 
MeOH, 0 °C, 15 min

S.M. was recovered, no target product

Scheme 86 Removal of the directing groups
6 Ruthenium-Catalyzed ortho-C–H Halogenations

In addition to the C–C bond formations, ruthenium complexes have been identified as powerful catalysts for the oxidative transformation of otherwise unreactive C–H bonds into C–O and C–N bonds. In strict contrast, ruthenium-catalyzed intermolecular C–Hal bond forming processes are unfortunately not available. Herein, we established a ruthenium catalytic system which enabled the first ruthenium-catalyzed intermolecular brominations and iodinations of benzamides using N-halosuccinimides as halogen sources.

6.1 Preliminary Studies with Ruthenium(II)-Catalysis

6.1.1 ortho-Halogenations of Electron-Rich Arenes

At the outset of our studies, we explored the widely used [RuCl$_2$(p-cymene)]$_2$ complex for the halogenation of electron-rich anilide 184a with CuBr$_2$ or NBS as a halogen source (Table 18). To our disappointment, only classical electrophilic aromatic substitution ($S_{E_1}^A$) occurred delivering the corresponding para-brominated product 245a both in the absence and presence of the catalyst. Further efforts to probe parameters, including oxidant, additive and solvent, unfortunately did not offer the target ortho-brominated product even at the lower reaction temperature (entries 2, 10 and 11). In addition, no conversion was observed with CuCl$_2$ as a halogenating reagent (entries 7 and 8).

Table 18 Screenings of the ruthenium(II)-catalyzed C–H halogenations of acetanilide 184a

<table>
<thead>
<tr>
<th>Entry</th>
<th>[X] (equiv)</th>
<th>Oxidant (equiv)</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>$T$ (°C)</th>
<th>245a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr$_2$ (2.0)</td>
<td>—</td>
<td>PivOH (1.1)</td>
<td>MeCN</td>
<td>100</td>
<td>76$^c$</td>
</tr>
<tr>
<td>2</td>
<td>CuBr$_2$ (2.0)</td>
<td>—</td>
<td>—</td>
<td>DCE</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>CuBr$_2$ (2.0)</td>
<td>Cu(OAc)$_2$ (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>100</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>CuBr$_2$ (2.0)</td>
<td>—</td>
<td>PTSA-H$_2$O (1.1)</td>
<td>DCE</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>CuBr$_2$ (2.0)</td>
<td>Cu(OAc)$_2$ (2.0)</td>
<td>PivOH (1.1)</td>
<td>AcOH</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>CuBr$_2$ (2.0)</td>
<td>Cu(OAc)$_2$ (2.0)</td>
<td>PivOH (1.1)</td>
<td>MeCN</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>CuCl$_2$ (2.0)</td>
<td>—</td>
<td>—</td>
<td>DCE</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>CuCl$_2$ (2.0)</td>
<td>Cu(OAc)$_2$ (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>NBS (1.1)</td>
<td>Cu(OAc)$_2$ (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>120</td>
<td>100$^b$</td>
</tr>
<tr>
<td>10</td>
<td>NBS (1.1)</td>
<td>—</td>
<td>—</td>
<td>DCE</td>
<td>60</td>
<td>71</td>
</tr>
<tr>
<td>11</td>
<td>NBS (1.1)</td>
<td>—</td>
<td>PTSA-H$_2$O (0.5)</td>
<td>DCE</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 187a (0.5 mmol), halogen source [X], [RuCl$_2$(p-cymene)]$_2$ (5.0 mol %), Ag$_2$SbF$_6$ (20 mol %), additive, solvent (2.0 mL), 60–120 °C, 16 h; GC conversion. $^b$ Without [RuCl$_2$(p-cymene)]$_2$.

Further screenings of directing groups (DG) with \([\text{RuCl}_2(p\text{-cymene})]_2\) as the catalyst gave unsatisfactory results as well (Scheme 87). For instance, the use of 184b and 184c delivered para-brominated products in low yields, whereas no conversion was observed for electron-rich substrates 184d–g.

\[
\begin{align*}
\text{Scheme 87 } & \text{Ruthenium(II)-catalyzed } C-H \text{ brominations of electron-rich arenes 184}
\end{align*}
\]

6.1.2 ortho-Halogenations of Electron-Deficient Arenes

As the bromination of electron-rich substrates always led to significant formation of para electrophilic substitution products, we subsequently turned to more challenging electron-deficient arenes (Table 19). Herein, ortho-bromination on benzamide 219a was observed employing CuBr$_2$ as the halogen source, yet with low conversion (6%). However, further screenings proved N-bromosuccinimide (NBS) to be more efficient for ruthenium(II)-catalyzed ortho-C–H halogenations under otherwise identical reaction conditions (entry 2). In spite of acids are known to serve as critical additives in the palladium-\textsuperscript{107,108} and rhodium-catalyzed\textsuperscript{113} ortho-C–H halogenations, to our disappointment, no better results were obtained with acidic additives in our ruthenium(II) system. The reason for this is obviously a competitive ortho-C–O bond formation (246a) (entries 3–14), and addition of an external oxidant did not improve the situation (entries 8 and 12). However, we were pleased to observe that switching to a catalytic amount of the corresponding silver(I) carboxylate salt significantly improved the efficacy (entries 15–20), and the target product 220a was obtained in 43% isolated yield with AgO$_2$CCF$_3$ (entry 16). In addition, base additives did shut down the reaction almost completely (entries 21–22).

\[
\begin{align*}
\text{Table 19 } & \text{Screenings of the ruthenium(II)-catalyzed } C-H \text{ brominations of benzamide 219a}^a
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>Yield of 220a (%)</th>
<th>246a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>—</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>—</td>
<td>DCE</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PTSA·H$_2$O (1.1)</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TIOH (1.1)</td>
<td>DCE</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 19 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>Yield of 220a (%)</th>
<th>246a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>MesCO₂H (1.1)</td>
<td>DCE</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>(1-Ad)CO₂H (1.1)</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PivOH (1.1)</td>
<td>DCE</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PivOH (1.1)</td>
<td>DCE</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>TFA (1.1)</td>
<td>DCE</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>TFA (1.1)</td>
<td>MeCN</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>TFA (1.1)</td>
<td>AcOH</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>12&lt;sup&gt;d&lt;/sup&gt;</td>
<td>TFA (1.1)</td>
<td>DCE</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>TFAAA (1.1)</td>
<td>DCE</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
<td>TFA (1.1)</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AgO₂CCF₃ (0.2)</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>AgO₂CCF₃ (0.2)</td>
<td>DCE</td>
<td>51 (43&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>18</td>
</tr>
<tr>
<td>17</td>
<td>AgO₂CCF₃ (0.5)</td>
<td>DCE</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>AgO₂CCF₃ (0.2)</td>
<td>DCE</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>19</td>
<td>Ag₂O (0.2)</td>
<td>DCE</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>AgOTf (0.2)</td>
<td>DCE</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>21</td>
<td>KO₂CCF₃ (0.2)</td>
<td>DCE</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>CsOPiv (1.1)</td>
<td>DCE</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 219a (0.5 mmol), NBS (1.0 mmol), [RuCl₂(p-cymene)]₂ (5.0 mol %), AgSbF₆ (20 mol %), additive, solvent (2.0 mL), 100–120 °C, 16 h; GC-yield. <sup>b</sup> Without [RuCl₂(p-cymene)]₂. <sup>c</sup> Cu(OAc)₂ (1.0 mmol). <sup>d</sup> CuBr₂ (0.1 mmol). <sup>e</sup> KPF₆ was used instead of AgSbF₆. <sup>f</sup> Isolated yield. <sup>g</sup> 100 °C.

Functional directing groups, such as amide, ester, ketone and pyridine (Scheme 88), were also examined under the optimal reaction conditions (Table 19, entry 16). Unfortunately, only low conversions to the ortho-brominated products were observed. Moreover, significant side reactions such as bromination of the methyl group and ortho-oxygenation occurred in acetophenone (247e) and 2-phenylpyridine (247f), respectively.

![Scheme 88](image)

Scheme 88 Ruthenium(II)-catalyzed ortho-C–H halogenations of electron-deficient arenes 247

6.2 Ruthenium(0)-Catalyzed ortho-C–H Halogenations of Benzamides
6.2.1 Optimization Studies

To our delight, simply switching the catalyst to Ru$_3$(CO)$_{12}$ for the ortho-C–H halogenations of benzamide 219a successfully delivered the desired product 220a in 27% yield (Table 20, entry 1). Notably, control experiment showed that no conversion of the starting material 219a was detected in the absence of Ru$_3$(CO)$_{12}$, highlighting the efficiency of the ruthenium(0)-catalyzed pathway (entries 2 and 14). Further investigations indicated that stoichiometric quantities of carboxylate acid not only promoted the ortho-halogenation, but also provoked ortho-oxygenation affording small amounts of the by-product 246a (entries 3–13). Maes has recently reported that alcohol additives were efficient in ruthenium(0)-catalyzed C(sp$^3$)–H α-alkylation reactions. However, alcohol additives herein completely inhibited the halogenation process (entry 16). It is noteworthy that the use of additional oxidants, such as copper(II) salts, did not improve the yield (entries 5 and 15). Furthermore, switching the solvent to AcOH, MeCN, or even neat reaction did not improve the reaction efficacy (entries 17–19).

Table 20 Screens of the ruthenium(0)-catalyzed ortho-C–H halogenations with acids as additives$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive A (equiv)</th>
<th>Additive B (equiv)</th>
<th>Solvent</th>
<th>Yield of 220a (%)</th>
<th>246a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>DCE</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>2$^b$</td>
<td>—</td>
<td>—</td>
<td>DCE</td>
<td>&lt;2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PTSA·H$_2$O (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TFA (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>TFA (2.0)</td>
<td>Cu(OAc)$_2$ (2.0)</td>
<td>DCE</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>AcOH (1.0)</td>
<td>—</td>
<td>DCE</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Ac$_2$O (1.0)</td>
<td>—</td>
<td>DCE</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>AcOH (1.0) + Ac$_2$O (1.0)</td>
<td>—</td>
<td>DCE</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>MesCO$_2$H (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>PhCO$_2$H (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>(1-Ad)CO$_2$H (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>57</td>
<td>&lt;3</td>
</tr>
<tr>
<td>12</td>
<td>PivOH (2.0)</td>
<td>—</td>
<td>DCE</td>
<td>57</td>
<td>11</td>
</tr>
<tr>
<td>13</td>
<td>PivOH (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>14$^a$</td>
<td>PivOH (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>&lt;2</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>PivOH (2.0)</td>
<td>CuBr$_2$ (2.0)</td>
<td>DCE</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>PivOH (2.0)</td>
<td>i-PrCHOH (5.0)</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>PivOH (0.2)</td>
<td>—</td>
<td>AcOH</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>PivOH (0.2)</td>
<td>—</td>
<td>MeCN</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>PivOH (0.2)</td>
<td>—</td>
<td>neat</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>20$^c$</td>
<td>—</td>
<td>—</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 219a (0.5 mmol), NBS (1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), additives, solvent (2.0 mL), 120 °C, 16 h; $^b$ without [Ru$_3$(CO)$_{12}$]. $^c$ RuCl$_3$ (10 mol %) was used instead of [Ru$_3$(CO)$_{12}$].
Further investigations revealed that, as in the case of the above-discussed catalytic system from [RuCl₂(ρ-cymene)]₂ (Table 19), base additives did not accelerate the halogenation process catalyzed with Ru₃(CO)₁₂ (Table 21, entry 1). On the other hand, replacing carboxylic acid with a catalytic amount of silver(I) carboxylate salt significantly improved the desired formation of target product 220a (entries 3–20). To our delight, AgO₂CCF₃(1-Ad) delivered the best isolated yield, and meanwhile no C–O bond formation was detected due to the steric effect of the adamantyl moiety (entry 19). It is noteworthy to mention that 0.05 equivalent amount of phosphine ligand slightly accelerated the transformation, while increasing the loadings to 0.2 equivalent completely inhibited the process (entry 11 vs entry 12). Further screenings proved 1,2-dichloroethane (DCE) to be superior to other solvents with this ruthenium(0) catalyst (entries 14–17).

**Table 21** Screenings of the ruthenium(0)-catalyzed ortho-C–H halogenations with metal salts as additives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive A (equiv)</th>
<th>Additive B (equiv)</th>
<th>Solvent</th>
<th>Yield of 220a (%)</th>
<th>246a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsOAc (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>KPF₆(0.2)</td>
<td>—</td>
<td>DCE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>AgSbF₆(0.2)</td>
<td>—</td>
<td>DCE</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>AgCl (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ag₂CO₃(0.2)</td>
<td>—</td>
<td>DCE</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>AgO₂CCF₃(0.2)</td>
<td>—</td>
<td>DCE</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>AgOAc (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>AgOAc (0.05)</td>
<td>—</td>
<td>DCE</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>AgOAc (0.5)</td>
<td>—</td>
<td>DCE</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>—</td>
<td>PPh₃ (0.05)</td>
<td>DCE</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>AgOAc (0.2)</td>
<td>PPh₃ (0.05)</td>
<td>DCE</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>AgOAc (0.2)</td>
<td>PPh₃ (0.2)</td>
<td>DCE</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>AgOAc (0.2)</td>
<td>PivOH (1.1)</td>
<td>DCE</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>AgOAc (0.2)</td>
<td>—</td>
<td>t-BuOH</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>AgOAc (0.2)</td>
<td>—</td>
<td>PhMe</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>AgOAc (0.2)</td>
<td>—</td>
<td>Pinacolone</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>AgOAc (0.2)</td>
<td>—</td>
<td>NMP</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>AgOPiv (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>AgO₂C(1-Ad) (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>64 (60b)</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>AgO₂C(1-Ad) (0.2)</td>
<td>—</td>
<td>DCE</td>
<td>&lt;2</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction conditions: **219a** (0.5 mmol), NBS (1.0 mmol), [Ru₃(CO)₁₂] (3.3 mol %), additives, solvent (2.0 mL), 120 °C, 16 h; ¹H-NMR yield with 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard. b Isolated yield. c without [Ru₃(CO)₁₂].
6.2.2 Scope of the Ruthenium(0)-Catalyzed ortho-C–H halogenations

With the optimized conditions in hand (Table 21, entry 19), we initially examined the influence of different amide N-substituents on the efficacy of the corresponding brominations as well as iodinations (Table 22). Thus, a variety of benzamides 219 provided the desired halogenated products 220 and 221 in good yields. Herein, electron-donating amide group gave a slightly better performance and bulky substituent such as N,N-diisopropylamide efficiently directed the bromination as well. In contrast to brominations, successive addition of N-iodosuccinimide (NIS) in two equal portions was required to deliver the iodinated products 221 in best yield. Besides, control experiments demonstrated that omission of the ruthenium(0) catalyst proved to be detrimental.

Table 22 Effect of N-substituents on C–H halogenations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene 219</th>
<th>Product 220 / 219</th>
<th>Yield (%) Cond. (A)</th>
<th>Yield (%) Cond. (B)</th>
<th>Yield (%) Cond. (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>X = Br (220b)</td>
<td>68</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>219b</td>
<td>X = I (221b)</td>
<td>74</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>X = Br (220c)</td>
<td>56</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>219c</td>
<td>X = I (221c)</td>
<td>54</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>5‡</td>
<td></td>
<td>X = Br (220d)</td>
<td>89</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>219d</td>
<td>X = I (221d)</td>
<td>70</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>X = Br (220e)</td>
<td>36</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>219e</td>
<td>X = I (221e)</td>
<td>72</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>X = Br (220f)</td>
<td>62</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>219f</td>
<td>X = I (221f)</td>
<td>62</td>
<td>76</td>
<td>0</td>
</tr>
</tbody>
</table>

(continued)

‡ Primary and secondary benzamides provided thus far only unsatisfactory results (<15% conversion).
Table 22 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arene 219</th>
<th>Product 220 / 219</th>
<th>Yield (%) Cond. (A)</th>
<th>Yield (%) Cond. (B)</th>
<th>Yield (%) Cond. (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>[Image of benzene ring with N and nitrogen atoms]</td>
<td>X = Br (220g)</td>
<td>52</td>
<td>—$^b$</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>[Image of benzene ring with N and nitrogen atoms]</td>
<td>X = I (221g)</td>
<td>54</td>
<td>72</td>
<td>1</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions A: 219 (1.0 mmol), NXS (2.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (3.0 mL), 120 °C, 16 h; B: 219 (1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (3.0 mL), 120 °C, NXS (1.0 equiv) was added and stirred for 8 h, then the second equiv of NXS was added and the stirring was continued for 14 h; C: 219 (0.5 mmol), NXS (1.0 mmol), DCE (2.0 mL), 120 °C, 16 h; GC analysis. $^b$ Not tested. $^c$ 80 °C.

Thereafter, we probed the scope of the C–H bromination with differently decorated benzamides 219 (Table 23). Intramolecular competition experiments with meta-methyl arene 219h bearing two chemically inequivalent ortho C–H bonds showed the less hindered C–H bond to be predominantly brominated (entry 1). In contrast, the electron-deficient benzamide 219i afforded mainly isomer 220i, most probably because of the secondary directing group effect (entry 2).$^7$a The C–H functionalizations of substrates bearing additional (hetero)aromatic moieties proceeded with excellent site-selectivities in the ortho-position to the amide (entries 3−10). Thereby, synthetically useful heterocycles (220q) and functional groups, such as acetyl (220n and 220o) or ester (220p), were well tolerated by the catalyst.$^{138}$

Table 23 Ruthenium(0)-catalyzed ortho-C–H bromination on benzamides 219

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzamide 219</th>
<th>Product 220</th>
<th>A/B</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>219h</td>
<td>220h</td>
<td>A</td>
<td>64 (3:1)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>219i</td>
<td>220i</td>
<td>B</td>
<td>55 (3:1)$^b$</td>
</tr>
</tbody>
</table>

$^{138}$ Under the optimized reaction conditions, the mass balance accounted for the unreacted starting materials as well as the second regioisomers in case of meta-substituted substrates 219.
Ruthenium-Catalyzed ortho-C–H Halogenations

Table 23 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzamide 219</th>
<th>Product 220</th>
<th>A/B</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image" alt="219j" /></td>
<td><img src="image" alt="220j" /></td>
<td>B</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="219k–o" /></td>
<td><img src="image" alt="220k–o" /></td>
<td>B</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="219l" /></td>
<td><img src="image" alt="220l" /></td>
<td>B</td>
<td>47%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="219m" /></td>
<td><img src="image" alt="220m" /></td>
<td>B</td>
<td>54%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="219n" /></td>
<td><img src="image" alt="220n" /></td>
<td>B</td>
<td>57%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="219o" /></td>
<td><img src="image" alt="220o" /></td>
<td>B</td>
<td>34%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="219p" /></td>
<td><img src="image" alt="220p" /></td>
<td>B</td>
<td>46%</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="219q" /></td>
<td><img src="image" alt="220q" /></td>
<td>B</td>
<td>37%</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions A: 219 (0.5–1.0 mmol), NBS (1.0–2.0 mmol), [Ru\(_3\)(CO)\(_{12}\)] (3.3 mol %), AgO\(_2\)C(1-Ad) (20 mol %), DCE (3.0 mL), 120 °C, 16 h; B: 219 (0.5–1.0 mmol), [Ru\(_3\)(CO)\(_{12}\)] (3.3 mol %), AgO\(_2\)C(1-Ad) (20 mol %), DCE (2.0 mL), 120 °C, NBS (1.0 equiv) was added and stirred for 8 h, then the second equiv of NBS was added and the stirring was continued for 14 h; Isolated yield. \(^b\) Isolated yields of the major isomer; ratio of regioisomers (major: minor) in the crude reaction mixture, as determined by GC analysis in parenthesis. \(^c\) Only one isomer was observed by GC analysis.

However, ortho-substitution turned out to be detrimental for this transformation, due to the sterically demanding tertiary benzamide directing group: The brominated product 220r was detected in 13% conversion by GC analysis of the crude reaction mixture (Scheme 89).\(^{139}\) Besides, electron-withdrawing groups at the para-position, such as F (219s) and CF\(_3\) (219t), only led to low conversions. para-Methoxyl benzamide 219u proceeded in high reactivity, however, poor regioselectivities were obtained.

\(^{139}\) Similar result was obtained applying rhodium(I) catalyst, see ref. 113.
Furthermore, the versatile ruthenium(0) catalyst displayed a broad substrate scope and allowed for C–H iodinations of differently substituted arenes 219 (Table 24). Thus, benzamide 219a provided the mono-halogenated products 221a in moderate yield (entry 1). Importantly, meta-substituted arenes 219 gave the desired products 221 with useful site-selectivities (entries 2–8). As was observed for the bromination (vide supra), the C–H iodination herein was neither viable in the absence of the ruthenium(0) catalyst nor of the additive AgO2C(1-Ad) for all benzamides 219.

Table 24 Ruthenium(0)-catalyzed ortho-C–H iodination on benzamides 219\(^{*}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzamide 219</th>
<th>Product 221</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>219a</td>
<td>221a</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>219h</td>
<td>221h</td>
<td>64 (3:1)(^{6})</td>
</tr>
<tr>
<td>3</td>
<td>219v</td>
<td>221v</td>
<td>52 (5:1)(^{6})</td>
</tr>
<tr>
<td>4</td>
<td>219i</td>
<td>221i</td>
<td>36 (4:1)(^{6})</td>
</tr>
</tbody>
</table>

(continued)
Table 24 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzamide 219</th>
<th>Product 221</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td>73 (5:1)$^a$</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td>R = H (221k) 64$^c$</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td>R = Me (221l) 68$^c$</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td>59$^c$</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 219 (0.5–1.0 mmol), [Ru$_3$(CO)$_{12}$] (3.3 mol %), AgO$_2$C(1-Ad) (20 mol %), DCE (2.0 mL), 120 °C, NIS (1.0 equiv) was added and stirred for 8 h, then the second equiv of NIS was added and the stirring was continued for 14 h; Isolated yield. $^b$ Isolated yields of the major isomer; ratio of regioisomers (major: minor) in the crude reaction mixture, as determined by GC analysis in parenthesis. $^c$ Only one isomer was observed by GC analysis.

6.2.3 Mechanistic Studies

6.2.3.1 Reactions in the Presence of Radical Scavengers

In consideration of the unique reactivity profile of the novel ruthenium(0) catalyst, we performed mechanistic studies to delineate its mode of action. To this end, (co)catalysis with a Brønsted acid could be ruled out by successfully performing the C–H bromination in the presence of stoichiometric amounts of 2,6-di-tert-butylpyridine (249a)\(^{140}\) (Table 25, entry 1). Furthermore, a radical inhibition test was next carried out in order to get insight into whether the reaction proceeds via radical intermediates. When such known effective radical scavengers as 2,2,6,6-tetramethylpiperidin-1-ylloxy (TEMPO, 249b), 2,2-diphenyl-1-picrylhydrazyl (DPPH, 249c), 2,6-di-tert-butyl-4-methylphenol (BHT, 249d), trans-stilbene (249e) or 1,1-diphenylethylene (249f) were added to the reaction mixture under otherwise identical conditions, the reaction process was significantly suppressed (Table 25, entries 2–7). The latter could be rationalized in terms of SET-type processes\(^{141}\) being operative.


Table 25 Effect of additives on the ortho-C–H bromination of benzamide 219a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive 249 (equiv)</th>
<th>220a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.6-di-tert-Butylpyridine (249a) (1.0)</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>TEMPO (249b) (0.2)</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>TEMPO (249b) (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DPPH (249c) (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>BHT (249d) (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>trans-Stilbene (249e) (2.0)</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>1,1-Diphenylethene (249f) (2.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Reaction conditions: 219a (0.5 mmol), NBS (1.0 mmol), [Ru3(CO)12] (3.3 mol %), AgO2C(1-Ad) (20 mol %), additive 249 (0.5–1.0 mmol), DCE (2.0 mL), 120 °C, 16 h; 1H-NMR yield with 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard.

6.2.3.2 Reactions in Isotopically Labelled Reagents

Furthermore, the catalytic C–H functionalization in the presence of isotopically labelled additive [D]1-250 highlighted a reversible C–H ruthenation event (Scheme 90).

In good agreement with these observations were the results of kinetic isotope effect (KIE) measurements. The independent experiments with substrates 219a and [D]1-219a disclosed a KIE of k_H/k_D ≈ 1.0, hence indicating the C–H cleavage step not to be kinetically relevant (Scheme 91).

---

6.2.4 Proposed Catalytic Cycle

Based on our experimental mechanistic studies and independent kinetic isotope effect measurements, the following catalytic cycle for the ruthenium(0)-catalyzed C–H halogenation is proposed (Scheme 92). Analogously to the general mechanism of the carboxylate-assisted ruthenium-catalyzed oxidative direct C–H activations, after chelation with amide substituent, the ruthenium species is expected to form initially a ruthenacycle 254 through reversible C–H bond metalation via transition state 253. Subsequently, migratory insertion of N-halosuccinimide (NXS) through a SET sequence delivers intermediate 255. Finally, reductive elimination of intermediate 255 releases the desired product 220 or 221 and regenerates ruthenium (0) species 251.

Scheme 91 Kinetic isotope effect studies

Scheme 92 Proposed catalytic cycle for the ruthenium(0)-catalyzed ortho-C–H halogenations
7 Summary and Outlook

Ruthenium-catalyzed direct C–H bond functionalizations was shown to be an attractive approach for the development of sustainable chemical processes. The significant rate acceleration of cycloruthenations by carboxylates has provided the bases for various catalyzed C–H bond functionalizations.

In a first project, ruthenium(II)-catalyzed oxidative annulations were realized in an aerobic fashion with cocatalytic amounts of Cu(OAc)$_2$·H$_2$O under an atmosphere of ambient air. Pleasingly, the C–H/N–H bond functionalization occurred with unparalleled selectivities and ample scope to deliver indole 207 and pyrrole derivatives 209 (Scheme 93). While reactions with CuBr$_2$ as the co-oxidant did not furnish the desired products, cocatalytic amounts of metal acetates restored the catalytic efficacy, thus providing strong evidence for carboxylate-assisted aerobic oxidations. Furthermore, the highly selective conversion of unsymmetrical alkynes 38 constituted a strong testament to the unique features of chemoselective ruthenium catalysts.

![Scheme 93 Ruthenium(II)-catalyzed aerobic oxidative annulation](image)

This efficient ruthenium(II) catalyst also enabled broadly applicable oxidative alkyne annulations with electron-rich enamines 210 to provide diversely decorated pyroles 211, even with air as the ideal oxidant (Scheme 94). We were delighted to observe that numerous useful electrophilic functional groups were well tolerated, including ester, vinyl, bromo, cyano, and nitro substituents. Notably, oxidative annulations of unsymmetrical alkynes 38 occurred with synthetically useful levels of regiocontrol.
Along with the rapid development of the oxidative annulations, challenging oxidative olefinations with electron-rich anilides 212 as well as electron-deficient benzamides 214 were elaborated with \([\text{RuCl}_2(\mu\text{-cymene})]_2\), KPF$_6$ and Cu(OAc)$_2$·H$_2$O as the catalytic system (Scheme 95). Remarkably, this protocol proved to be most effective with water as the reaction medium and provided an expedient access to differently decorated arenes 213 and 215. Furthermore, we were pleased to observe that this ruthenium-catalyzed oxidative C–H alkenylations proceeded smoothly even on a large scale.

A catalytic system comprising of \([\text{RuCl}_3(\text{PPh}_3)_3]\), AgOTf and \textit{rac}-BINAP enabled step-economical additions of C(sp$^3$)–H bonds (216) onto unactivated alkenes 111 with ample scope under comparably mild reaction conditions (Scheme 96). Furthermore, the pyridyl directing group was efficiently removed to furnish (NH)-free pyrrolidines 218.
Summary and Outlook

Finally, \([\text{Ru}_3(\text{CO})_{12}]\) and AgO_2C(1-Ad) enabled the first ruthenium-catalyzed intermolecular ortho-selective halogenations of benzamides 219 via C–H activation (Scheme 97). Thereby, brominations and iodinations of electron-rich and electron-deficient benzamides were achieved in a highly selective fashion as well as with excellent functional group tolerance. Preliminary mechanistic studies provided evidence for a reversible C–H metalaion event in this process.

In summary, recent years have witnessed significant progress in transition-metal-catalyzed C–H bond functionalizations. Importantly, direct C–H arylation, alkylations and hydroarylations with alkenes, as well as challenging oxidative C–C, C–O, C–N and C–Hal bond formations have proven viable with ruthenium complexes with considerable progress being accomplished in the past several years. Notable features of the most user-friendly ruthenium catalysts include the remarkably broad substrate scope and the extraordinarily high chemo- and site-selectivity. Particularly, the significant rate acceleration of stoichiometric cyclometalations by carboxylates along with recent detailed experimental and computational studies has provided strong evidence for various C–H bond ruthenations to proceed by base-assisted deprotonations. Considering the highly sustainable nature of ruthenium-catalyzed direct C–H bond functionalizations, along with
the improved mechanistic understanding of base-assisted metalations, further exciting developments are expected in this rapidly evolving research area.
8 Experimental Section

8.1 General Remarks

Unless otherwise noticed, all reactions were performed under a N₂ atmosphere using pre-dried glassware and standard Schlenk techniques.

Solvents

All solvents for reactions involving moisture-sensitive reagents were dried, distilled and stored under inert atmosphere (argon or nitrogen) according to the following standard procedures. tert-Amylalcohol (t-AmOH) was used as supplied by Merck or stirred over sodium chips for 5 h at 120 °C and distilled under ambient pressure; water (H₂O) was degassed before its use applying repeated Freeze-Pump-Thaw degassing procedure; 1,2-dichloroethane (DCE), i-BuOH, N,N-dimethylformamide (DMF), acetonitrile (MeCN) and dimethylacetamide (DMA) were dried over CaH₂ for 8 h, degassed and distilled under reduced pressure; dichloromethane (DCM) and tetrahydrofuran (THF) were purified using a solvent purification system (SPS) from MBRAUN; N-methyl-2-pyrrolidone (NMP) was stirred over CaH₂ for 4 h at 150 °C and subsequently distilled under reduced pressure; methanol (MeOH) was distilled from magnesium methanolate; toluene (PhMe) was either pre-dried over KH followed by distillation from sodium benzophenone ketyl; 1,4-dioxane was dried by distillation from sodium benzophenone ketyl.

Vacuum

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

Melting Points (M. p.)

Melting points were measured using a 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 visualized under UV-light or developed by treatment with a KMnO₄ solution followed by careful applying a heat gun. Chromatographic purification of products was accomplished by flash column chromatography on MERCK silica gel, grade 60 (0.040–0.063 mm and 0.063–0.200 mm).

Gas Chromatography (GC)

The conversion of the reactions was monitored applying coupled gas chromatography/mass spectrometry using G1760C GC/6plus 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 equipped with HP-5MS columns (30 m × 0.25 mm × 0.25 m) were used.

High Performance Liquid Chromatography (HPLC)

Preparative and analytical separations were performed on an HPLC-System from KNAUER (Smartline Pump 100, Dynamic Mixing Chamber, Injection- and Control-Valve, Smartline UV
Detector 2500). Separation normal phase column (250 × 10 mm) from MACHEREY-NAGEL (MN) was used. Organic solvents of HPLC grade were employed. All samples were filtered through Polytetrafluorethylene Filter from ROTH (Ø 25 mm, 0.2 μm) or VWR (Ø 13 mm, 0.2 μm) prior to separation.

Nuclear Magnetic Resonance Spectroscopy (NMR)
Nuclear magnetic resonance (NMR) spectroscopy was performed at 300 or 600 MHz (1H-NMR), 75 or 125 MHz (13C-NMR, APT) and 283 MHz (19F-NMR) on BRUKER AM 250, VARIAN Unity-300 and Inova 500 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual proton peak of the deuterated solvent or its carbon atom, respectively, or the standard trimethylsilyl (TMS) peak. For characterization of the observed resonance multiplicities the following abbrevations were applied: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), or analogue representations. The coupling constants \( J \) are reported in Hertz (Hz).

Infrared Spectroscopy (IR)
Infrared spectra were recorded on a BRUKER Alpha-P ATR-spectrometer. Liquid probes have been measured as film and solid probes neat. Analysis of the spectral data has been done by using the OPUS 3.1 software from BRUKER, respectively OPUS 6. Absorption (\( \nu \)) is given in wave numbers (cm\(^{-1}\)). Spectra were recorded in the range of 4000 to 400 cm\(^{-1}\).

Mass Spectrometry (MS)
MS (EI) and HR-MS (EI) 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-HR-MS spectra were recorded on a BRUKER APEX IV or a BRUKER DALTONIC (7T, Fourier Transform Ion Cyclotron Resonance (FTICR)) mass spectrometer. The ratios of mass to charge (m/z) are indicated, intensities relative to the base peak (I = 100) are written in parentheses.

Reagents
Chemicals obtained from commercial sources with purity above 95% were used without further purification.

8.2 Synthesis of Starting Materials
The following starting materials were synthesized according to previously described methods: Alkynes 38b–f, 143 38j, 144 381–o, 143 38q; 144 1,1-dimethyl-3-phenylurea (184d), 145 N-phenylpiperidine-1-carboxamide (184e), 146 2-{dimethyl(phenyl)silyl}pyridine (184f), 147

dimethyl(phenyl)silanol (184g), \(^{148}\) 2-aryl-substituted indoles 206b–c, \(^{149}\) 206d, \(^{150}\) 206e–h, \(^{149}\) 206i, \(^{151}, 152\) 206j–n, \(^{149}\) 2-aryl-substituted pyroles 208a–d, \(^{153}\) 208e, \(^{154}\) 208f, \(^{155}\) enamines 210a–b, \(^{156}\) 210c, \(^{157}\) 210d, \(^{158}\) 210f, \(^{121}\) 210g, \(^{159}\) anilides 212a, \(^{160}\) 212b, \(^{161}\) 212c, \(^{162}\) 212d–e, \(^{161}\) 212f, \(^{163}\) 212g–o, \(^{161}\) (hetero)amides 214a, \(^{164}, 165\) 214b, \(^{166}, 167\) 214c, \(^{164}, 168\) 214d, \(^{166}, 168\) 214e, \(^{164}, 167\) 214f, \(^{164}, 166\) pyrrolidines 216a–I, \(^{169}\) benzamides 219a–j, \(^{113a}\) 219r–u, \(^{113a}\) 219k–q, \(^{113a}\) 2-(pyridin-2-yl)isoindoline (237a), \(^{172}\) 1-(pyridin-2-yl)indoline (237b), \(^{169}\) 2-(pyrrolidin-1-yl)-benzof[d]oxazole (237c), \(^{173}\) 5-(pyrrolidin-1-yl)-3,4-dihydro-2H-pyrrole (237d), \(^{174}\) (E)-2-methyl-N-(pyrrolidin-1-ylmethylene)propan-2-amine (237e), \(^{175}\) 1-(pyrrolidin-1-yl)ethanone (237f), \(^{160}\) propa-1,2-dien-1-ylbenzene (238h), \(^{176}\) [D]_1-succinimide ([D]_1-250). \(^{177}\)

The following compounds were obtained by the generous courtesy of the persons named below:

Dr. Marvin Schinkel: alkenes 111k–n, \(^{132}\) 111t–v, \(^{132}\) Karsten Rauch: [RuCl\(_2\)(p-cymene)]\(_2\).

### 8.3 General Procedures

**General procedure A for ruthenium-catalyzed aerobic coupling of substituted indoles 206 and pyroles 208 with alkynes 38:**


A mixture of 2-aryl indole 206 or pyrrole 208 (0.50 mmol), alkyne 38 (1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)₂·H₂O (200 mg, 1.00 mmol) in t-AmOH (2.0 mL) was stirred at 100 °C under air (1 atm) for 22 h. At ambient temperature, the reaction mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc or n-hexane/CH₂Cl₂) to yield compound 207 and 209.

General procedure B for ruthenium-catalyzed oxidative coupling of substituted indoles 206 and pyrroles 208 with alkynes 38:
A mixture of 2-aryl indole 206 or pyrrole 208 (0.50 mmol), alkyne 38 (1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)₂·H₂O (200 mg, 1.00 mmol) in t-AmOH (2.0 mL) was stirred at 100 °C under N₂ for 22 h. At ambient temperature, the reaction mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc or n-hexane/CH₂Cl₂) to yield compound 207 and 209.

General procedure C for ruthenium-catalyzed oxidative annulation of alkynes 38 with enamines 210:
A mixture of enamine 210 (0.50 mmol), alkyne 38 (1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)₂·H₂O (200 mg, 1.00 mmol) in t-AmOH (2.0 mL) was stirred at 120 °C under N₂ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH₄Cl/NH₃ (1.5 mmol), KPF₆ (18.4 mg, 20 mol %) and Cu(OAc)₂·H₂O (99.5 mg, 1.00 mmol) in H₂O (2.0 mL) (sealed tube) was stirred at 120 °C under N₂ for 20 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc) to yield compound 211.

General procedure D for ruthenium-catalyzed oxidative alkenylation of anilides 212 and heteroamides 214:
A mixture of anilide 212 or heteroaryl amide 214 (0.50 mmol), acrylate 76 (0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %), KPF₆ (18.4 mg, 20 mol %) and Cu(OAc)₂·H₂O (99.5 mg, 1.00 mmol) in H₂O (2.0 mL) (sealed tube) was stirred at 120 °C under N₂ for 20 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc) to yield compound 213 and 215.

General procedure E for ruthenium-catalyzed C(sp³)–H α-alkylation of pyrrolidine 216 with alkene 111:
A suspension of [RuCl₂(PPh₃)₃] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), pyrrolidine 216 (1.5 mmol) and alkene 111 (0.5 mmol) in i-BuOH (1.0 mL)
was stirred at 120 °C under N₂ for 18 h. At ambient temperature, CuCl (50 mg), tridecane (25 µL) and EtOAc (5 mL) were added to the reaction mixture. After GC analysis, the solvents were evaporated in reduced pressure. Purification by column chromatography on silica gel (n-hexane/EtOAc) yielded compound 217.

**General procedure F for the removal of 2-pyridyl directing groups (217):**

**Step 1:** A 25 mL Schlenk flask was charged with compound 217 (0.5 mmol) and Pt/C (5% Pt, 195 mg, 10 mol %). Under N₂, EtOH (4.5 mL) was added. To the resulting black suspension was added 1.25 M HCl in EtOH (0.5 mL, 0.6 mmol), and the reaction mixture was subsequently flushed twice with H₂. The reaction mixture was then stirred under H₂ (1 atm) at 23 °C for 24 h. The solids were removed by filtration through a short pad of celite, the pad was washed with CH₂Cl₂ (3 × 10 mL), and the combined filtrate was evaporated to dryness.

**Step 2:** The residue was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 °C using an ice/water bath. NaBH₄ (76 mg, 2.0 mmol) was added portionwise to the cooled solution under magnetic stirring at 0 °C. After complete addition of NaBH₄, the reaction mixture was stirred further at 0 °C for 15 min. The volatiles were removed in reduced pressure. Purification by column chromatography on silica gel (CH₂Cl₂/MeOH) yielded compound 218.

**General procedure G for ruthenium-catalyzed ortho-C–H halogenation of benzamide 219:**

To a seal tube equipped with a magnetic stir bar were added Ru₃(CO)₁₂ (10.5 mg, 3.3 mol %), AgO₂C(1-Ad) (28.7 mg, 20 mol %) and DCE (2.0 mL) under N₂. Benzamide substrate 219 (0.5 mmol) and N-halosuccinimide (1.0 mmol) were added. After being stirred at ambient temperature for 10 min, the tube was placed in a pre-heated oil-bath and stirred at 120 °C for 16 h. The reaction mixture was then allowed to cool to ambient temperature, diluted with EtOAc (5 mL) and filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, purification by column chromatography on silica gel (n-hexane/EtOAc) yielded the corresponding compound 220.

**General procedure H for ruthenium-catalyzed ortho-C–H halogenation of benzamides 219:**

To a seal tube equipped with a magnetic stir bar were added Ru₃(CO)₁₂ (10.5 mg, 3.3 mol %), AgO₂C(1-Ad) (28.7 mg, 20 mol %) and DCE (2.0 mL) under N₂. Benzamide substrate 219 (0.5 mmol) and the first portion of N-halosuccinimide (0.5 mmol) were added. After being stirred at ambient temperature for 10 min, the tube was placed in a pre-heated oil-bath and stirred at 120 °C for 8 h. The mixture was then allowed to cool to ambient temperature, the second portion of N-halosuccinimide (0.5 mmol) was added under N₂ and the stirring was continued for further 14 h at 120 °C. The mixture was then allowed to cool to ambient temperature, diluted with EtOAc (5 mL) and filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, purification by column chromatography on silica gel (n-hexane/EtOAc) yielded the corresponding compound 220 and 221.

### 8.4 Analytical Data

**8.4.1 Analytical Data for the Products of Ruthenium-Catalyzed Aerobic Coupling of Substituted Indoles 206 or Pyrroles 208 with Alkynes 38**

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**Experimental Section**

**Synthesis of 5,6-diphenylindolo[2,1-α]isoquinoline (207a)**

The general procedure A was followed using 2-phenylindole (206a) (96.5 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)$_2$-H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 207aa (151 mg, 82%) as a white solid.

M. p. = 205−206 °C.

1H-NMR (300 MHz, CDCl$_3$): δ = 8.31 (d, J = 6.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.51 (ddd, J = 7.7, 7.2, 1.3 Hz, 1H), 7.38 (s, 1H), 7.38−7.14 (m, 13H), 6.82 (ddd, J = 7.8, 7.0, 1.3 Hz, 1H), 6.01 (d, J = 8.7 Hz, 1H).

13C-NMR (75 MHz, CDCl$_3$): δ = 136.7 (C$_q$), 136.0 (C$_q$), 135.9 (C$_q$), 135.3 (C$_q$), 132.7 (C$_q$), 131.8 (CH), 130.8 (CH), 130.2 (C$_q$), 129.7 (C$_q$), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.3 (CH), 127.0 (CH), 126.7 (CH), 126.2 (CH), 125.4 (C$_q$), 123.3 (CH), 121.6 (CH), 121.4 (C$_q$), 120.2 (CH), 120.1 (CH), 114.6 (CH), 94.2 (CH).

IR (ATR): ν = 1543, 1484, 1443, 1377, 1338, 1245, 1030, 756, 736, 696 cm$^{-1}$.

MS (EI) m/z (relative intensity): 369 (100) [M$^+$]+, 291 (13).

HR-MS (El) m/z calcld for C$_{28}$H$_{19}$NO$^+$ 369.1517, found 369.1518.

The spectral data were in accordance with those reported in the literature.$^{117}$

**Synthesis of 10-fluoro-5,6-diphenylindolo[2,1-α]isoquinoline (207b)**

The general procedure A was followed using 5-fluoro-2-phenyl-1H-indole (206b) (106 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)$_2$-H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 50/1) yielded 207ba (102 mg, 54%) as a yellow solid.

M. p. = 227−228 °C.

1H-NMR (300 MHz, CDCl$_3$): δ = 8.26 (d, J = 7.8 Hz, 1H), 7.49 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.39−7.11 (m, 14H), 6.52 (ddd, J = 9.2, 9.1, 2.6 Hz, 1H), 5.86 (dd, J = 9.4, 4.6 Hz, 1H).

13C-NMR (75 MHz, CDCl$_3$): δ = 158.6 (d, $^1$J$_{C-F}$ = 238 Hz, C$_q$), 137.4 (C$_q$), 136.5 (C$_q$), 135.7 (C$_q$), 135.0 (C$_q$), 131.7 (CH), 130.8 (CH), 130.3 (d, $^3$J$_{C-F}$ = 10 Hz, C$_q$), 130.2 (C$_q$), 129.4 (C$_q$), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 126.2 (CH), 124.9 (C$_q$), 123.4 (CH), 121.6 (C$_q$), 111.6 (d, $^3$J$_{C-F}$ = 9 Hz, CH), 108.5 (d, $^2$J$_{C-F}$ = 26 Hz, CH), 104.3 (d, $^2$J$_{C-F}$ = 23 Hz, CH), 94.0 (d, $^3$J$_{C-F}$ = 4 Hz, CH).

19F-NMR (283 MHz, CDCl$_3$): δ = (−121.7−121.8) (m).

IR (ATR): ν = 3054, 1610, 1539, 1485, 1441, 1117, 855, 787, 753, 696 cm$^{-1}$.

MS (EI) m/z (relative intensity): 387 (100) [M$^+$]+, 309 (30).

HR-MS (El) m/z calcld for C$_{28}$H$_{19}$FN$^+$ 387.1383, found 387.1382.

**Synthesis of 10-bromo-5,6-diphenylindolo[2,1-α]isoquinoline (207c)**

The general procedure A was followed using 5-bromo-2-phenyl-1H-indole (206c) (136 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)$_2$-H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH$_2$Cl$_2$: 5/1) yielded 207ca (72 mg, 32%) as a yellow solid.

M. p. = 213−214 °C.
Experimental Section

The general procedure A was followed using 5-nitro-2-phenyl-1H-indole (206d) (119 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol%). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 25/1) yielded 207da (141 mg, 71%) as a yellow solid.

M. p. = 281–282 °C.

The general procedure A was followed using 5-methyl-2-phenyl-1H-indole (206e) (103 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol%). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 4/1) yielded 207ea (14 mg, 7%) as a yellow solid.

M. p. = 236–237 °C.

The general procedure B was followed using 5-methyl-2-phenyl-1H-indole (206e) (103 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 4/1) yielded 207ea (126 mg, 65%) as a yellow solid.

1H-NMR (300 MHz, CDCl₃): δ = 8.29 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 7.6, 7.2 Hz, 1H), 7.38–7.12 (m, 13H), 6.87 (dd, J = 9.0, 2.0 Hz, 1H), 5.81 (d, J = 9.0 Hz, 1H).

13C-NMR (75 MHz, CDCl₃): δ = 138.5 (Cq), 138.8 (CH), 135.9 (Cq), 135.3 (Cq), 134.9 (Cq), 134.5 (CH), 131.4 (CH), 130.7 (Cq), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 126.6 (Cq), 124.7 (Cq), 123.6 (CH), 123.6 (Cq), 116.7 (Cq), 114.8 (Cq), 114.6 (CH), 95.9 (CH).

IR (ATR): ν = 3056, 1620, 1487, 1377, 1030, 725, 696 cm⁻¹.

MS (EI) m/z (relative intensity): 449 (100) [M⁺], 447 (97) [M⁺], 367 (44), 291 (37).

HR-MS (ESI) m/z calcd for C₈₂H₁₈BrN⁺ 447.0623, found 447.0634.

Synthesis of 10-methyl-5,6-diphenylindolo[2,1-a]isoquinoline (207ea)

Synthesis of 10-nitro-5,6-diphenylindolo[2,1-a]isoquinoline (207da)

Synthesis of 10-nitro-5,6-diphenylindolo[2,1-a]isoquinoline (207da)
IR (ATR): \( \tilde{\nu} = 3047, 1614, 1574, 1443, 1376, 745, 697, 650 \text{ cm}^{-1} \).
MS (EI) \( m/z \) (relative intensity): 383 (100) \([M^+]\), 367 (25), 306 (10).
HR-MS (EI) \( m/z \) calcd for C\(_{29}\)H\(_22\)F\(_7\)N\(_2\) 383.1674, found 399.1676.

**Synthesis of 3-fluoro-5,6-diphenylindolo[2,1-\(\alpha\)]isoquinoline (207fa)**

The general procedure A was followed using 2-(4-fluorophenyl)-1\(H\)-indole (206f) (106 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)\(_2\)-H\(_2\)O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 207fa (164 mg, 84%) as a yellow solid.

M. p. = 225–226 °C.

**Synthesis of 5,6-diphenyl-3-(trifluoromethyl)indolo[2,1-\(\alpha\)]isoquinoline (207ga)**

The general procedure A was followed using 2-(4-(trifluoromethyl)phenyl)-1\(H\)-indole (207g) (131 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)\(_2\)-H\(_2\)O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH\(_2\)Cl\(_2\): 5/1) yielded 207ga (158 mg, 72%) as a yellow solid.

M. p. = 225–226 °C.
Synthesis of 3-nitro-5,6-diphenylindolo[2,1-α]isoquinoline (207ha)

The general procedure A was followed using 2-(4-nitrophenyl)-1H-indole (206h) (119 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)_2·H_2O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH_2Cl_2: 7/1) yielded 207ha (92 mg, 44%) as a yellow solid.

M. p. = 224–225 °C.

1H-NMR (300 MHz, CDCl_3): δ = 8.38 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.51 (s, 1H), 7.45–7.08 (m, 12H), 6.87 (dd, J = 8.2, 7.4 Hz, 1H), 6.01 (d, J = 8.8 Hz, 1H).

13C-NMR (75 MHz, CDCl_3): δ = 137.3 (C_q), 135.7 (C_q), 134.9 (C_q), 134.7 (C_q), 132.9 (C_q), 131.7 (CH), 130.6 (C_q), 130.2 (C_q), 129.5 (C_q), 128.9 (CH), 128.7 (CH), 128.1 (CH), 127.9 (C_q), 127.2 (CH), 125.9 (C_q), 123.8 (CH), 123.2 (CH), 121.1 (CH), 121.0 (CH), 120.9 (C_q), 120.6 (CH), 114.7 (CH), 96.0 (CH).

IR (ATR): ν = 3061, 3032, 1618, 1597, 1544, 1485, 1444, 1169, 825, 658 cm⁻¹.

MS (EI) m/z (relative intensity): 414 (100) [M⁺], 384 (27), 368 (30).

HR-MS (EI) m/z calcd for C_26H_18N_2O_4⁺ 414.1368, found 414.1368.

Synthesis of methyl 5,6-diphenylindolo[2,1-α]isoquinoline-3-carboxylate (207ia)

The general procedure A was followed using methyl 4-(1H-indol-2-yl)benzoate (206i) (126 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)_2·H_2O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH_2Cl_2: 2/1) yielded 207ia (122 mg, 57%) as a yellow solid.

M. p. = 256–257 °C.

1H-NMR (300 MHz, CDCl_3): δ = 8.33 (d, J = 8.3 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.86 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.39–7.28 (m, 5H), 7.27–7.15 (m, 6H), 6.86 (dd, J = 7.8, 7.7 Hz, 1H), 6.00 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H).

13C-NMR (75 MHz, CDCl_3): δ = 166.8 (C_q), 136.7 (C_q), 135.9 (C_q), 135.0 (C_q), 134.9 (C_q), 133.0 (C_q), 131.7 (CH), 130.7 (CH), 129.9 (C_q), 129.5 (C_q), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5 (C_q), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.0 (CH), 123.2 (CH), 121.9 (CH), 121.3 (C_q), 120.9 (CH), 120.6 (CH), 114.7 (CH), 96.3 (CH), 52.1 (CH_3).

IR (ATR): ν = 3025, 1708, 1604, 1544, 1484, 1441, 1382, 762, 738, 701 cm⁻¹.

MS (EI) m/z (relative intensity): 387 (100) [M⁺], 367 (9), 291 (10).

HR-MS (EI) m/z calcd for C_{26}H_{19}N_2O_{4}⁺ 387.1572, found 387.1578.

The spectral data were in accordance with those reported in the literature.¹¹⁷

Synthesis of 3-chloro-5,6-diphenylindolo[2,1-α]isoquinoline (207ja)

The general procedure A was followed using 2-2-(4-chlorophenyl)-1H-indole (206j) (113 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)_2·H_2O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH_2Cl_2: 10/1) yielded 207ja (26mg, 13%) as a yellow solid.

The general procedure B was followed using 2-2-(4-chlorophenyl)-1H-indole (206j) (113 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/CH_2Cl_2: 10/1) yielded 207ja (26mg, 13%) as a yellow solid.
chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 207ja (104 mg, 51%) as a yellow solid.

M. p. = 241–238 °C.

$^1$H-NMR (300 MHz, CDCl₃): $\delta$ = 8.17 (d, $J = 8.7$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.48–7.10 (m, 1H), 6.92 (dd, $J = 8.2$, 7.1 Hz, 1H), 6.03 (d, $J = 8.2$ Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl₃): $\delta$ = 137.1 (C₆), 135.9 (C₆), 135.0 (C₆), 134.9 (C₆), 133.1 (C₆), 132.7 (C₆), 131.6 (CH), 131.6 (C₆), 130.6 (C₆), 129.6 (C₆), 128.6 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 127.0 (CH), 125.4 (CH), 124.7 (CH), 123.7 (C₆), 121.8 (CH), 120.4 (CH), 120.4 (C₆), 120.3 (CH), 114.6 (CH), 94.6 (CH).

IR (ATR): $\tilde{\nu}$ = 3048, 1594, 1546, 1479, 1441, 1417, 1071, 759, 700 cm⁻¹.

MS (EI) m/z (relative intensity): 403 (100) [M⁺], 367 (10), 291 (10).

HR-MS (ESI) $m/z$ calc for C₂₈H₁₈ClN⁺ 403.1128, found 403.1118.

The spectral data were in accordance with those reported in the literature.¹¹⁷

**Synthesis of 3-methyl-5,6-diphenylindolo[2,1-a]isoquinoline (207ka)**

The general procedure A was followed using 2-2-(p-tolyl)-1H-indole (206ka) (104 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 207ka (11 mg, 6%) as a yellow solid.

The general procedure B was followed using 2-2-(p-tolyl)-1H-indole (206ka) (104 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 207ka (106 mg, 55%) as a yellow solid.

M. p. = 249–250 °C.

$^1$H-NMR (300 MHz, CDCl₃): $\delta$ = 8.21 (d, $J = 8.2$ Hz, 1H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.43–7.14 (m, 12H), 6.95 (s, 1H), 6.81 (dd, $J = 7.8$, 7.8 Hz, 1H), 5.99 (d, $J = 8.7$ Hz, 1H), 2.36 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl₃): $\delta$ = 137.3 (C₆), 136.1 (C₆), 136.0 (C₆), 135.4 (C₆), 132.6 (C₆), 131.8 (CH), 130.8 (CH), 130.2 (C₆), 129.8 (C₆), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 126.7 (CH), 126.0 (CH), 123.3 (CH), 123.0 (C₆), 121.5 (CH), 121.3 (C₆), 120.0 (CH), 119.8 (CH), 114.5 (CH), 93.4 (CH), 21.7 (CH₃).

IR (ATR): $\tilde{\nu}$ = 3024, 1595, 1541, 1483, 1417, 1071, 759, 692 cm⁻¹.

MS (EI) m/z (relative intensity): 383 (100) [M⁺], 367 (7), 207 (10).

HR-MS (EI) $m/z$ calc for C₂₉H₂₁N⁺ 383.1674, found 383.1664.

The spectral data were in accordance with those reported in the literature.¹¹⁷

**Synthesis of 7, 8-diphenylbenzo[h]indolo[2,1-a]isoquinoline (207la)**

The general procedure A was followed using 2-(naphthalen-1-yl)-1H-indole (206l) (122 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 5/1) yielded 207la (97 mg, 46%) as a yellow solid.

M. p. = 213–215 °C.

$^1$H-NMR (300 MHz, CDCl₃): $\delta$ = 9.40 (d, $J = 8.6$ Hz, 1H), 8.06 (s, 1H), 7.96 (dd, $J = 9.0$, 8.6 Hz, 2H), 7.84 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 1H), 7.76 (d, $J = 8.6$ Hz, 1H), 7.66 (dd, $J = 7.3$, 7.3 Hz, 1H).
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7.46–7.18 (m, 12H), 6.92 (ddd, 8.0, 7.8, 1.2 Hz, 1H), 6.17 (d, J = 8.7 Hz, 1H).

13C-NMR (75 MHz, CDCl3): δ = 137.2 (Cq), 136.6 (Cq), 135.6 (Cq), 134.9 (Cq), 132.8 (Cq), 132.0 (CH), 131.7 (Cq), 130.7 (CH), 130.2 (Cq), 129.5 (Cq), 129.5 (Cq), 128.9 (CH), 128.6 (CH), 128.6 (CH), 127.9 (CH), 127.9 (CH), 127.2 (CH), 126.8 (CH), 125.9 (CH), 125.7 (CH), 124.2 (CH), 122.1 (Cq), 122.0 (CH), 121.2 (Cq), 120.3 (CH), 120.2 (CH), 114.9 (CH), 99.3 (CH).

IR (ATR): ν = 3057, 1588, 1543, 1467, 1360, 1208, 1017, 818, 730, 695 cm⁻¹.

MS (EI) m/z (relative intensity): 419 (100) [M⁺], 341 (20).

HR-MS (EI) m/z calcld for C_{13}H_{21}N^{7} 419.1674, found 419.1678.

The spectral data were in accordance with those reported in the literature.¹¹⁷

Synthesis of 6,7-Diphenylbenz[g]indolo[2,1-a]isoquinoline (207ma)

The general procedure A was followed using 2-(naphthalen-2-yl)-1H-indole (206m) (121 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)$_2$·H$_2$O (10 mg, 0.10 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH$_2$Cl$_2$: 5/1) yielded 207ma (13 mg, 6%) as a yellow solid.

The general procedure B was followed using 2-(naphthalen-2-yl)-1H-indole (206m) (121 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/CH$_2$Cl$_2$: 5/1) yielded 207ma (97 mg, 46%) as a yellow solid.

M. p. = 262–263 °C.

1H-NMR (300 MHz, CDCl$_3$): δ = 8.73 (s, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 2.8 Hz, 2H), 7.54–7.16 (m, 13H), 6.89 (dd, J = 7.8, 7.8 Hz, 1H), 5.99 (d, J = 8.2 Hz, 1H).

13C-NMR (75 MHz, CDCl$_3$): δ = 136.8 (Cq), 135.8 (Cq), 135.6 (Cq), 135.3 (Cq), 133.6 (Cq), 132.6 (Cq), 132.2 (Cq), 131.9 (CH), 130.9 (CH), 129.5 (Cq), 129.2 (Cq), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 126.8 (CH), 126.0 (CH), 125.8 (CH), 124.8 (CH), 124.2 (Cq), 121.9 (CH), 121.7 (CH), 121.4 (Cq), 120.8 (CH), 120.3 (CH), 114.4 (CH), 96.7 (CH).

IR (ATR): ν = 3051, 3021, 1625, 1487, 1375, 1022, 736, 722, 694 cm⁻¹.

MS (EI) m/z (relative intensity): 419 (100) [M⁺], 341 (18).

HR-MS (EI) m/z calcld for C$_{13}$H$_{21}$N$_{7}$ 419.1674, found 419.1678.

Synthesis of 5,6-bis[4-(trifluoromethyl)phenyl]indolo[2,1-a]isoquinoline (207ab)

The general procedure A was followed using 2-phenyl-1H-indole (206a) (97.0 mg, 0.50 mmol), 1,2-bis[4-(trifluoromethyl)phenyl]ethyne (38b) (314 mg, 1.00 mmol) and Cu(OAc)$_2$·H$_2$O (10 mg, 0.10 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH$_2$Cl$_2$: 10/1) yielded 207ab (137 mg, 54%) as a yellow solid.

M. p. = 287–288 °C.

1H-NMR (300 MHz, CDCl$_3$): δ = 8.32 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.59–7.48 (m, 3H), 7.48–7.33 (m, 4H), 7.33–7.18 (m, 3H), 7.05 (d, J = 7.8 Hz, 1H), 6.88 (dd, J = 7.8, 7.8 Hz, 1H), 5.95 (d, J = 8.6 Hz, 1H).

13C-NMR (75 MHz, CDCl$_3$): δ = 140.2 (Cq), 138.5 (Cq), 135.7 (Cq), 134.5 (Cq), 132.5 (Cq), 132.1 (CH), 131.2 (q, $^3$J$_{C-F}$ = 33 Hz, Cq), 131.2 (CH), 129.8 (Cq), 129.7 (q, $^3$J$_{C-F}$ = 33 Hz, Cq), 129.2 (Cq), 127.8 (q, $^3$J$_{C-F}$ = 11 Hz, CH), 125.9 (CH), 125.8 (q, $^4$J$_{C-F}$ = 4 Hz, CH), 125.6 (Cq), 125.1 (q,
Experimental Section

After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded yellow solid. The spectral data were in accordance with those reported in the literature.¹¹⁷

Synthesis of 5,6-di-p-tolyl]indolo[2,1-a]isoquinoline (207ac)

The general procedure A was followed using 2-phenyl-1H-indole (206a) (97 mg, 0.43 mmol), 1,2-bis(4-chlorophenylethyne (38c) (247 mg, 0.97 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 207ac (14 mg, 6%) as a yellow solid.

M. p. = 251–252 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.29 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.50 (ddd, J = 7.8, 7.5, 1.2 Hz, 1H), 7.38 (s, 1H), 7.39–7.35 (m, 3H), 7.29–7.21 (m, 5H), 7.13–7.06 (m, 3H), 6.90 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 6.09 (d, J = 8.6 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ = 155.7 (C₉), 135.0 (C₈), 134.9 (C₇), 134.9 (C₆), 133.5 (C₅), 133.0 (C₄), 133.0 (CH), 132.5 (C₃), 132.1 (CH), 129.7 (C₂), 129.6 (C₁), 129.2 (CH), 128.3 (CH), 127.5 (CH), 127.4 (CH), 125.9 (CH), 125.4 (C₄), 123.4 (CH), 121.9 (CH), 120.6 (C₃), 120.5 (CH), 120.4 (CH), 114.2 (CH), 94.6 (CH).

IR (ATR): ν = 3064, 1619, 1591, 1538, 1484, 1443, 1393, 1087, 1014, 737 cm⁻¹.

MS (EI) m/z (relative intensity): 505 (100) [M⁺], 435 (10), 359 (15), 291 (10).

HR-MS (EI) m/z calcd for C₃₀H₂₁F₆N⁺ 505.1265, found 505.1269.

The spectral data were in accordance with those reported in the literature.¹¹⁷

Synthesis of ethyl 5,6-diphenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209aa)

The general procedure A was followed using ethyl 5-phenyl-1H-pyrrole-3-carboxylate (208a) (108 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 5/1) yielded 209aa (182 mg, 93%) as a yellow solid.

M. p. = 200–201°C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.15 (d, J = 8.0 Hz, 1H), 7.54–7.37 (m, 2H), 7.38 (d, J = 1.6 Hz, 1H), 7.36–7.19 (m, 10H), 7.19–7.11 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 165.1 (C₉), 136.2 (C₈), 133.8 (C₇), 133.8 (C₆), 133.3 (C₅), 131.3 (CH), 130.8 (C₄), 130.5 (CH), 128.7 (CH), 128.7 (CH), 128.4 (C₃), 127.9 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 126.2 (CH), 125.7 (C₉), 124.6 (C₈), 122.1 (CH), 118.7 (CH), 118.3 (C₇), 101.3 (CH), 60.1 (CH₂), 14.5 (CH₃).

IR (ATR): ν = 2979, 1702, 1513, 1454, 1418, 1235, 1207, 1144, 749, 700 cm⁻¹.
Experimental Section

MS (El) m/z (relative intensity): 391 (100) [M⁺], 318 (90).
HR-MS (El) m/z calcld for C₇H₂₃NO₃⁺ 391.1572, found 391.1576.

Synthesis of 5,6-diphenylpyrrolo[2,1-a]isoquinoline-2-carbonitrile (209ba)

The general procedure A was followed using 5-phenyl-1H-pyrrole-3-carbonitrile (208b) (84.0 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 209ba (70 mg, 40%) as a white solid.
M. p. = 228−229 °C.

1H-NMR (300 MHz, CDCl₃): δ = 8.11 (d, J = 8.0 Hz, 1H), 7.55 (ddd, J = 7.6, 7.4, 1.3 Hz, 1H), 7.40−7.30 (m, 4H), 7.30−7.21 (m, 8H), 7.21−7.10 (m, 2H).

Synthesis of 1-(5,6-diphenylpyrrolo[2,1-a]isoquinolin-2-yl)ethanone (209ca)

The general procedure A was followed using 1-(5-phenyl-1H-pyrrol-3-yl)ethanone (208c) (93.0 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 209ca (137 mg, 76%) as a white solid.
M. p. = 206 °C (dec.).

1H-NMR (300 MHz, CDCl₃): δ = 8.15 (d, J = 8.2 Hz, 1H), 7.56−7.38 (m, 2H), 7.39−7.10 (m, 13H), 2.49 (s, 3H).

Synthesis of ethyl 1,5,6-triphenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209da)

The general procedure A was followed using ethyl 4,5-diphenyl-1H-pyrrole-3-carboxylate (208d) (146 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) yielded 209da (176 mg, 75%) as a white solid.
M. p. = 243−244 °C.
1H-NMR (300 MHz, CDCl₃): δ = 7.57−7.38 (m, 7H), 7.41−7.29 (m, 5H), 7.29−7.06 (m, 8H), 4.08 (q, J = 7.0 Hz, 2H), 1.04 (t, J = 7.0 Hz, 3H).
Experimental Section

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 164.8 (C$_q$), 136.8 (C$_q$), 136.4 (C$_q$), 133.6 (C$_q$), 133.3 (C$_q$), 131.3 (CH), 130.6 (CH), 130.5 (CH), 129.1 (C$_q$), 128.8 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 126.7 (C$_q$), 126.6 (CH), 126.4 (C$_q$), 125.7 (CH), 124.7 (C$_q$), 122.7 (CH), 119.9 (C$_q$), 118.9 (CH), 117.6 (C$_q$), 59.6 (CH$_2$), 13.9 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3049, 1713, 1601, 1514, 1456, 1206, 1137, 776, 761, 699 cm$^{-1}$.

MS (EI) m/z (relative intensity): 467 (100) [M$^+$], 394 (30).

HR-MS (EI) m/z calcld for C$_{33}$H$_{26}$NO$_2$ $^+$ 467.1885, found 467.1872.

Synthesis of ethyl 5,6-di(4-fluorophenyl)pyrrolo[2,1-$a$]isoquinoline-2-carboxylate (209ad)

The general procedure A was followed using ethyl 5-phenyl-1H-pyrrole-3-carboxylate (208a) (108 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)ethyne (38d) (206 mg, 1.00 mmol) and Cu(OAc)$_2$·H$_2$O (10 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/CH$_2$Cl$_2$: 10/1) yielded 209ad (116 mg, 54%) as a yellow solid.

M. p. = 240–241°C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 8.14 (d, $J$ = 8.0 Hz, 1H), 7.56–7.41 (m, 2H), 7.41–6.84 (m, 11H); 4.34 (q, $J$ = 7.1 Hz, 2H), 1.37 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 164.9 (C$_q$), 162.6 (d, $^1$J$_{C-F}$ = 250 Hz, C$_q$), 161.9 (d, $^1$J$_{C-F}$ = 247 Hz, C$_q$), 133.0 (C$_q$), 132.9 (d, $^3$J$_{C-F}$ = 8 Hz, CH), 132.4 (d, $^3$J$_{C-F}$ = 8 Hz, CH), 132.0 (d, $^4$J$_{C-F}$ = 4 Hz, C$_q$), 130.8 (C$_q$), 129.2 (d, $^4$J$_{C-F}$ = 4 Hz, C$_q$), 128.1 (C$_q$), 128.0 (CH), 126.4 (CH), 126.4 (CH), 125.8 (C$_q$), 124.0 (C$_q$), 122.2 (CH), 118.6 (C$_q$), 118.4 (CH), 116.2 (d, $^2$J$_{C-F}$ = 22 Hz, CH), 111.2 (d, $^2$J$_{C-F}$ = 22 Hz, CH), 101.6 (CH), 60.2 (CH$_2$), 14.4 (CH$_3$).

$^{19}$F-NMR (283 MHz, CDCl$_3$): $\delta$ = -(111.2–111.4) (m), -(114.3–114.5) (m).

IR (ATR): $\tilde{\nu}$ = 3144, 2989, 1697, 1598, 1545, 1501, 1216, 816, 789, 756 cm$^{-1}$.

MS (EI) m/z (relative intensity): 387 (100) [M$^+$], 354 (60).

HR-MS (EI) m/z calcld for C$_{27}$H$_{16}$F$_2$NO$_2$ $^+$ 387.1384, found 387.1379.

Synthesis of dimethyl 3-methyl-5,6-di(n-propyl)pyrrolo[2,1-$a$]isoquinoline-1,2-dicarboxylate (209fe)

The general procedure A was followed using dimethyl 2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (208f) (137 mg, 0.50 mmol), 4-octyne (38e) (110 mg, 1.00 mmol) and Cu(OAc)$_2$·H$_2$O (10.0 mg, 10.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/ EtOAc: 10/1) yielded 209fe (99 mg, 48%) as a yellow oil.

The general procedure A was followed using dimethyl 2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (208f) (137 mg, 0.50 mmol), 4-octyne (38e) (110 mg, 1.00 mmol) and Cu(OAc)$_2$·H$_2$O (30.0 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/ EtOAc: 10/1) yielded 209fe (141 mg, 74%) as a yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 8.17 (d, $J$ = 7.2 Hz, 1H), 7.67 (d, $J$ = 7.0 Hz, 1H), 7.46–7.36 (m, 2H), 3.99 (s, 3H), 3.87 (s, 3H), 3.12 (t, $J$ = 8.2 Hz, 2H), 2.97 (s, 3H), 2.79 (t, $J$ = 8.2 Hz, 2H), 1.70–1.52 (m, 4H), 1.09 (t, $J$ = 7.3 Hz, 3H), 1.02 (t, $J$ = 7.3 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 169.0 (C$_q$), 165.7 (C$_q$), 154.7 (C$_q$), 128.8 (C$_q$), 128.4 (C$_q$), 127.9 (C$_q$), 126.9 (CH), 126.8 (CH), 124.7 (C$_q$), 123.6 (CH), 123.1 (CH), 122.2 (C$_q$), 116.4 (C$_q$), 109.2
(C₆H₅), 52.5 (CH₃), 51.7 (CH₃), 50.5 (CH₂), 50.2 (CH₂), 25.4 (CH₂), 25.0 (CH₂), 14.8 (CH₃), 14.4 (CH₃), 13.4 (CH₃).

IR (ATR): ν = 2954, 1708, 1526, 1455, 1438, 1199, 1118, 1091, 755, 730 cm⁻¹.

MS (El) m/z (relative intensity): 381 (100) [M⁺], 350 (30), 334 (38), 263 (28).

HR-MS (El) m/z calcd for C₃₂H₅₆NO₂⁺ 381.1940, found 381.1933.

Synthesis of ethyl 5,6-dimethyl-1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209de)

The general procedure A was followed using ethyl 4,5-diphenyl-1H-pyrrole-3-carboxylate (208d) (72.8 mg, 0.25 mmol), 4-octyne (38e) (55.0 mg, 0.50 mmol) and Cu(OAc)₂·H₂O (15.0 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 209de (77 mg, 77%) as a yellow oil.

¹H-NMR (300 MHz, CDCl₃): δ = 7.97 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.65–7.57 (m, 6H), 7.32 (ddd, J = 7.7, 7.7, 1.2 Hz, 1H), 7.09 (ddd, J = 7.7, 7.7, 1.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 2.87 (t, J = 8.0 Hz, 2H), 1.92–1.77 (m, 2H), 1.75–1.61 (m, 2H), 1.22–1.01 (m, 9H).

¹³C-NMR (75 MHz, CDCl₃): δ = 166.0 (C₆H₅), 157.2 (C₆H₅), 152.5 (C₆H₅), 150.6 (CH), 128.5 (CH), 127.7 (C₆H₅), 127.0 (CH), 126.5 (C₆H₅), 126.1 (CH), 125.7 (CH), 123.6 (CH), 123.1 (CH), 119.8 (C₆H₅), 119.4 (C₆H₅), 117.4 (C₆H₅), 116.5 (CH), 59.6 (CH₂), 30.7 (CH₂), 30.0 (CH₂), 23.4 (CH₂), 20.3 (CH₃), 14.5 (CH₃), 14.3 (CH₃), 13.9 (CH₃).

IR (ATR): ν = 2958, 1698, 1604, 1540, 1456, 1202, 1111, 758, 731, 698 cm⁻¹.

MS (El) m/z (relative intensity): 399 (100) [M⁺], 370 (45), 282 (35).

HR-MS (El) m/z calcd for C₂₃H₂₉NO₂⁺ 399.2178, found 399.2178.

Synthesis of dimethyl 5,6-diethyl-3-methylpyrrolo[2,1-a]isoquinoline-1,2-dicarboxylate (209ff)

The general procedure A was followed using dimethyl 2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (208f) (137 mg, 0.50 mmol), 3-hexyne (38f) (82.0 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (30.0 mg, 30.0 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 209ff (152 mg, 86%) as a yellow oil.

¹H-NMR (300 MHz, CDCl₃): δ = 8.17 (d, J = 6.8 Hz, 1H), 7.71 (d, J = 6.7 Hz, 1H), 7.46–7.34 (m, 2H), 3.99 (s, 3H), 3.88 (s, 3H), 3.21 (q, J = 7.4 Hz, 2H), 3.01 (s, 3H), 2.89 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H), 1.24 (t, J = 7.4 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 168.8 (C₆H₅), 165.7 (C₆H₅), 155.7 (C₆H₅), 128.6 (C₆H₅), 128.5 (C₆H₅), 127.6 (C₆H₅), 126.9 (CH), 126.8 (CH), 125.0 (C₆H₅), 125.4 (CH), 125.4 (CH), 125.2 (C₆H₅), 116.6 (C₆H₅), 109.6 (C₆H₅), 52.4 (CH₂), 51.6 (CH₂), 21.6 (CH₂), 20.9 (CH₃), 14.9 (CH₃), 14.4 (CH₃), 14.4 (CH₃). IR (ATR): ν = 2948, 1706, 1525, 1482, 1439, 1200, 1131, 1083, 784, 755 cm⁻¹.

MS (El) m/z (relative intensity): 353 (76) [M⁺⁺], 322 (38), 306 (100), 235 (74).

HR-MS (El) m/z calcd for C₂₁H₂₃NO₄⁺ 353.1627, found 353.1636.

Synthesis of ethyl 5,6-diethyl-1-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209df)

The general procedure A was followed using ethyl 2-methyl-4,5-diphenyl-1H-pyrrole-3-carboxylate (208d) (72.8 mg, 0.25 mmol), 3-hexyne (38f) (55.0 mg, 0.50 mmol) and Cu(OAc)₂·H₂O (15.0 mg, 30.0 mol %). After 22 h,
purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 209df (74 mg, 76%) as a white solid. M. p. = 141–143 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.01 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.64–7.38 (m, 6H), 7.32 (dd, J = 7.7, 7.6, 1.3 Hz, 1H), 7.09 (dd, J = 7.7, 7.6, 1.2 Hz, 1H), 4.16 (q, J = 7.4 Hz, 2H), 3.09 (q, J = 7.6 Hz, 2H), 2.96 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H), 1.31 (t, J = 7.6 Hz, 3H), 1.11 (t, J = 7.4 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 166.0 (Cq), 157.3 (Cq), 155.4 (Cq), 150.7 (CH), 128.5 (CH), 127.6 (Cq), 127.0 (CH), 126.5 (Cq), 126.5 (Cq), 126.2 (CH), 125.8 (CH), 123.6 (CH), 123.3 (CH), 120.8 (Cq), 119.6 (Cq), 117.7 (Cq), 116.4 (CH), 59.6 (CH2), 21.8 (CH2), 20.8 (CH2), 14.7 (CH3), 14.0 (CH3), 11.7 (CH3).

IR (ATR): ν = 2966, 1695, 1602, 1444, 1268, 1034, 757, 703 cm⁻¹.

MS (El) m/z (relative intensity): 371 (100) [M⁺], 298 (23), 282 (20).

HR-MS (El) m/z calcd for C38H36NO2⁺ 571.1885, found 571.1887.

Synthesis of dimethyl 6-(n-buty1)-5-(4-methoxyphenyl)-3-methylpyrrolo[2,1-a]isoquinoline-1,2-di-carboxylate (209fg)

The general procedure A was followed using dimethyl 2-methyl-5-phenyl-1H-pyrrole-3,4-dicarboxylate (208f) (137 mg, 0.50 mmol), 1-(hex-1-yn-1-yl)-4-methoxybenzene (38g) (188 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (30 mg, 0.30 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 209fg (169 mg, 74%), 6:1 mixture of regioisomers according to 1H-NMR as a yellow oil. Purification by a second column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded the major regioisomer (146 mg, 64%) as a yellow solid.

M. p. = 138–143 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.31–8.24 (d, J = 7.1 Hz, 1H), 7.76–7.71 (d, J = 7.0 Hz, 1H), 7.50–7.45 (m, 2H), 7.27 (d, J = 10.8 Hz, 2H), 6.99 (d, J = 10.8 Hz, 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 2.49 (t, J = 8.2 Hz, 2H), 1.92 (s, 3H), 1.52–1.39 (m, 2H), 1.31–1.18 (m, 2H), 0.76 (t, J = 7.3 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 168.9 (Cq), 165.6 (Cq), 160.0 (Cq), 133.2 (Cq), 132.0 (CH), 130.1 (Cq), 127.6 (Cq), 127.5 (Cq), 127.4 (CH), 126.9 (CH), 125.3 (Cq), 124.1 (CH), 124.0 (Cq), 123.4 (CH), 111.9 (Cq), 113.6 (CH), 112.2 (Cq), 109.0 (Cq), 55.3 (CH3), 52.5 (CH3), 51.6 (CH3), 32.3 (CH2), 28.2 (CH2), 22.9 (CH2), 14.1 (CH3), 13.6 (CH3).

IR (ATR): ν = 2954, 1705, 1604, 1525, 1509, 1438, 1240, 1171, 1021, 798 cm⁻¹.

MS (El) m/z (relative intensity): 459 (100) [M⁺], 386 (70), 341 (60).

HR-MS (El) m/z calcd for C38H36NO2⁻ 571.1885, found 549.2046, 459.2041.

Synthesis of ethyl 6-buty1-5-(4-methoxyphenyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate (209ag)

The general procedure A was followed using ethyl 5-phenyl-1H-pyrrole-3-carboxylate (208a) (108 mg, 0.50 mmol), 1-(hex-1-yn-1-yl)-4-methoxybenzene (38g) (188 mg, 1.00 mmol) and Cu(OAc)₂·H₂O (30.0 mg, 0.30 mol %). After 22 h, purification by column chromatography on silica gel (n-hexane/ EtOAc: 30/1) yielded 209ag (160 mg, 76%), 8:1 mixture of regioisomers according to 1H-NMR as a

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yellow oil. Purification by a second column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded the major regioisomer (95 mg, 47%) as a yellow oil.

**1H-NMR** (300 MHz, CDCl$_3$): $\delta = 8.10$ (d, $J = 7.6$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.55–7.45 (m, 2H), 7.40 (s, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.20 (s, 1H), 7.10 (d, $J = 8.4$ Hz, 2H), 4.52 (q, $J = 7.4$ Hz, 2H), 3.92 (s, 3H), 2.60 (t, $J = 8.0$ Hz, 2H), 1.61–1.49 (m, 2H), 1.36 (t, $J = 7.0$ Hz, 3H), 1.29 (m, 2H), 0.85 (t, $J = 7.4$ Hz, 3H).

**13C-NMR** (75 MHz, CDCl$_3$): $\delta = 165.1$ (C$_q$), 160.0 (C$_q$), 152.8 (C$_q$), 131.2 (CH), 130.4 (C$_q$), 127.2 (CH), 127.1 (C$_q$), 126.2 (C$_q$), 125.9 (C$_q$), 124.5 (CH), 122.6 (CH), 121.7 (C$_q$), 118.4 (CH), 117.6 (C$_q$), 114.8 (CH), 100.9 (CH), 60.0 (CH$_2$), 55.3 (CH$_3$), 32.5 (CH$_2$), 22.9 (CH$_2$), 14.4 (CH$_3$), 13.7 (CH$_3$).

**IR (ATR)**: $\bar{\nu} = 2955, 1705, 1607, 1508, 1454, 1289, 1241, 1173, 1025, 751$ cm$^{-1}$.

**MS (EI)** $m$/z (relative intensity): 401 (100) [M$^+$], 358 (20), 285 (35).

**HR-MS (EI)** $m$/z calcd for C$_{26}$H$_{27}$NO$_3^+$ 401.1991, found 401.1989.

**Synthesis of ethyl 6-methyl-5-phenylpyrrolo[2,1-a]isoquinoline-2-carboxylate (209a)**

The general procedure A was followed using ethyl 5-phenyl-1H-pyrrole-3-carboxylate (108 mg, 0.50 mmol) (208a), 1-phenyl-1-propyne (38h) (116 mg, 1.00 mmol) and Cu(OAc)$_2$·H$_2$O (30.0 mg, 30.0 mol%). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 209a (120 mg, 73%, 5:1 mixture of regioisomers according to 1H-NMR) as a yellow solid. Purification by a second column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded the major regioisomer (41 mg, 25%) as a yellow solid.

M. p. = 114–111 °C.

**1H-NMR** (300 MHz, CDCl$_3$): $\delta = 8.10$ (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.60–7.38 (m, 8H), 7.25 (d, $J = 1.6$ Hz, 1H), 4.51 (q, $J = 7.1$ Hz, 2H), 2.21 (s, 3H), 1.55 (t, $J = 7.1$ Hz, 3H).

**13C-NMR** (75 MHz, CDCl$_3$): $\delta = 165.2$ (C$_q$), 153.9 (C$_q$), 153.0 (C$_q$), 150.6 (C$_q$), 150.1 (CH), 129.6 (CH), 129.5 (CH), 128.1 (C$_q$), 127.6 (CH), 126.5 (CH), 125.9 (C$_q$), 124.2 (CH), 122.5 (CH), 118.5 (CH), 117.7 (C$_q$), 116.6 (C$_q$), 101.1 (CH), 60.0 (CH$_2$), 15.0 (CH$_3$), 14.4 (CH$_3$).

**IR (ATR)**: $\bar{\nu} = 2974, 1695, 1544, 1516, 1454, 1240, 1178, 1019, 747, 703$ cm$^{-1}$.

**MS (EI)** $m$/z (relative intensity): 329 (100) [M$^+$], 256 (55).

**HR-MS (EI)** $m$/z calcd for C$_{22}$H$_{19}$NO$_2^+$ 329.1416, found 329.1417.

**Intermolecular competition experiment with indoles 206b and 206o (Scheme 64a)**

A mixture of 2-(4-fluorophenyl)-1H-indole (206b) (219 mg, 1.00 mmol), 2-(4-methoxyphenyl)-1H-indole (206o) (209 mg, 1.00 mmol), diphenylacetylene (38a) (89.0 mg, 0.50 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$·H$_2$O (10.0 mg, 10.0 mol %)
in t-AmOH (2.0 mL) was stirred at 100 °C under air for 22 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 50/1) to yield 207ba as a yellow solid (66 mg, 34%).

**Intermolecular competition experiment with alkynes 38b and 38i (Scheme 64b)**

A mixture of 2-phenylindole (206a) (48.0 mg, 0.25 mmol), 1,2-di-(p-tolyl)ethyne (38i) (103 mg, 0.50 mmol), 1,2-bis{4-(trifluoromethyl)phenyl}ethyne (38b) (157 mg, 0.50 mmol), [RuCl₂(p-cymene)]₂ (7.7 mg, 5.0 mol %) and Cu(OAc)₂·H₂O (5.0 mg, 10.0 mol %) in t-AmOH (2.0 mL) was stirred at 100 °C under air for 22 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 50/1) to yield 207ab as a yellow solid (43 mg, 34%).

**Annulation with meta-fluorophenyl-substituted indole 206p (Scheme 65)**

A mixture of 2-(3-fluorophenyl)-1H-indole (206p) (106 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol%) and Cu(OAc)₂·H₂O (10.0 mg, 10.0 mol %) in t-AmOH (2.0 mL) was stirred at 100 °C under air for 22 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/CH₂Cl₂: 10/1) to yield 207pa (78 mg, 40%) as yellow solid and 207"pa (17 mg, 9%) as yellow solid.
4-Fluoro-5,6-diphenylindolo[2,1-a]isoquinoline (207′pa)

M. p. = 209–210 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 8.12 (d, $J$ = 7.8 Hz, 1H), 7.83 (d, $J$ = 7.8 Hz, 1H), 7.52–7.10 (m, 13H), 7.05 (dd, $J$ = 12.4, 7.8 Hz, 1H), 6.88 (dd, $J$ = 7.8, 7.8 Hz, 1H), 5.96 (d, $J$ = 8.8 Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 159.1 (d, $^1J_{C-F}$ = 254 Hz, C$_q$), 138.7 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 137.5 (C$_q$), 134.9 (d, $^4J_{C-F}$ = 3 Hz, C$_q$), 134.8 (C$_q$), 132.8 (C$_q$), 131.0 (CH), 130.9 (CH), 129.6 (C$_q$), 128.7 (CH), 128.5 (CH), 128.0 (d, $^3J_{C-F}$ = 9 Hz, CH), 127.7 (d, $^3J_{C-F}$ = 4 Hz, C$_q$), 127.1 (CH), 126.3 (CH), 121.9 (CH), 120.6 (CH), 119.4 (d, $^4J_{C-F}$ = 4 Hz, CH), 118.6 (d, $^2J_{C-F}$ = 9 Hz, C$_q$), 117.0 (d, $^1J_{C-F}$ = 3 Hz, C$_q$), 114.7 (CH), 114.4 (d, $^2J_{C-F}$ = 22 Hz, CH), 96.1 (CH).

$^{19}$F-NMR (283 MHz, CDCl$_3$): $\delta$ = $-(107.8–108.9)$ (m).

IR (ATR): $\tilde{\nu}$ = 3056, 1608, 1539, 1487, 1461, 1440, 1230, 773, 739, 693 cm$^{-1}$.

MS (EI) m/z (relative intensity): 387 (100) [M$^+$], 309 (13).

HR-MS (EI) m/z calc'd for C$_{29}$H$_{18}$FN$^+$ 387.1383, found 387.1411.

2-Fluoro-5,6-diphenylindolo[2,1-a]isoquinoline (207''pa)

M. p. = 226–227 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.93 (dd, $J$ = 9.7, 2.6 Hz, 1H), 7.81 (d, $J$ = 8.0 Hz, 1H), 7.43–7.27 (m, 6H), 7.27–7.09 (m, 7H), 7.05 (dd, $J$ = 8.8, 8.6, 2.6 Hz, 1H), 6.84 (ddd, $J$ = 8.0, 7.7, 1.3 Hz, 1H), 6.01 (d, $J$ = 8.8 Hz, 1H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 161.8 (d, $^1J_{C-F}$ = 247 Hz, C$_q$), 136.7 (C$_q$), 136.7 (C$_q$), 135.3 (C$_q$), 135.3 (C$_q$), 133.0 (C$_q$), 131.8 (CH), 131.0 (CH), 129.6 (C$_q$), 129 (CH), 128.6 (CH), 128.5 (d, $^3J_{C-F}$ = 9 Hz, CH), 127.9 (CH), 127.2 (d, $^3J_{C-F}$ = 9 Hz, C$_q$), 126.9 (CH), 126.8 (d, $^4J_{C-F}$ = 2 Hz, C$_q$), 121.9 (CH), 121.0 (C$_q$), 120.6 (CH), 120.5 (CH), 111.3 (CH), $^2J_{C-F}$ = 23 Hz, 114.7 (CH), 108.7 (d, $^2J_{C-F}$ = 23 Hz, CH), 96.1 (CH).

$^{19}$F-NMR (283 MHz, CDCl$_3$): $\delta$ = $-(113.7–113.8)$ (m).

IR (ATR): $\tilde{\nu}$ = 3061, 1608, 1538, 1487, 1340, 1167, 956, 732, 694, 651 cm$^{-1}$.

MS (EI) m/z (relative intensity): 387 (100) [M$^+$], 309 (9).

HR-MS (EI) m/z calc'd for C$_{29}$H$_{18}$FN$^+$ 387.1383, found 387.1419.

Aerobic oxidative annulation in [D]$_{4}$-MeOH (Scheme 66a)

A mixture of 5-nitro-2-phenyl-1H-indole (206d) (119 mg, 0.50 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ (9.1 mg, 10.0 mol %) in [D]$_{4}$-MeOH (2.0 mL) was stirred at 76 °C under air for 22 h. At ambient temperature, the crude mixture was evaporated under reduced pressure and purified by column chromatography on silica gel (n-hexane/EtOAc: 10/1) to yield 206d (116 mg, 97%) as a yellow solid. No deuterium incorporation was detected by $^1$H-NMR spectroscopy.
Aerobic oxidative annulation in [D]$_4$-MeOH (Scheme 6b)

A mixture of 5-nitro-2-phenyl-1H-indole (206d) (119 mg, 0.50 mmol), 4-octyne (38e) (110 mg, 1.00 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$ (27.1 mg, 30.0 mol %) in [D]$_4$-MeOH (2.0 mL) was stirred at 76 °C under air for 22 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 40/1 → 10/1) to yield 207de (76 mg, 46%) as a yellow solid and 206d (49 mg, 41%) as a yellow solid. No deuterium incorporation was detected by $^1$H-NMR spectroscopy.

### 8.4.2 Analytical Data for the Products of Ruthenium-Catalyzed Oxidative Annulation of Alkynes 38 with Enamines 210

**Synthesis of methyl 1-acetyl-4,5-diphenyl-1H-pyrrole-2-carboxylate (211aa)**

The general procedure C was followed using 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 211aa (111 mg, 70%) as a yellow oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.48$–7.28 (m, 5H), 7.28–7.07 (m, 6H), 3.89 (s, 3H), 2.33 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 173.8$ (C$_q$), 161.0 (C$_q$), 134.5 (C$_q$), 133.9 (C$_q$), 130.6 (C$_q$), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 124.8 (C$_q$), 118.3 (CH), 51.8 (CH$_3$), 28.8 (CH$_3$).

IR (ATR): $\tilde{\nu} = 3060, 2953, 1759, 1702, 1440, 1381, 1253, 1207, 756, 694$ cm$^{-1}$.

MS (El) $m/z$ (relative intensity): 319 (18) [M$^+$], 277 (100), 245 (33), 215 (34), 43 (27).

HR-MS (El) $m/z$ calcd for C$_{20}$H$_{17}$NO$_3$ $^+$ 319.1206, found 319.1197.

The spectral data were in accordance with those reported in the literature.$^{123a}$

**Synthesis of methyl 4,5-diphenyl-1H-pyrrole-2-carboxylate (212aa)**

The general procedure C was followed using 2-(2,2,2-trifluoroacetamido)acrylate (98.5 mg, 0.50 mmol), and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 212aa as a white solid (21 mg, 15%).

M.p. = 174–175 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 9.56$ (sbr, 1H), 7.55–7.18 (m, 10H), 7.07 (d, $J = 2.8$ Hz, 1H),
3.85 (s, 3H).
\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 161.7\) (C\(_q\)), 136.3 (C\(_q\)), 133.4 (C\(_q\)), 131.8 (C\(_q\)), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 126.3 (CH), 124.1 (C\(_q\)), 122.0 (C\(_q\)), 116.8 (CH), 51.6 (CH\(_3\)).
IR (ATR): \(\tilde{\nu} = 3257, 1768, 1697, 1499, 1460, 1258, 1203, 1009, 762\) cm\(^{-1}\).
MS (EI) \(m/z\) (relative intensity): 277 (100) [M\(^+\)], 245 (72), 215 (70), 189 (28), 43 (20).
HR-MS (EI) \(m/z\) calcd for C\(_{18}\)H\(_{12}\)NO\(_2\) 277.1103, found 277.1094.

**Synthesis of ethyl 1-acetyl-4,5-diphenyl-1H-pyrrole-2-carboxylate (211ba)**

The general procedure C was followed using ethyl 2-acetamidoacrylate (210b) (78.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ba (113 mg, 68%) as a white solid.

M.p. = 94–95 °C.
\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.49–7.26\) (m, 5H), 7.25–7.03 (m, 6H), 4.36 (q, \(J = 7.2\) Hz, 2H), 3.00 (s, 3H), 1.39 (t, \(J = 7.2\) Hz, 3H).
\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 173.9\) (C\(_q\)), 160.6 (C\(_q\)), 134.4 (C\(_q\)), 134.0 (C\(_q\)), 130.7 (C\(_q\)), 130.7 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.4 (CH), 124.7 (C\(_q\)), 123.3 (C\(_q\)), 118.2 (CH), 60.8 (CH\(_3\)), 28.9 (CH\(_3\)), 14.3 (CH\(_3\)).
IR (ATR): \(\tilde{\nu} = 2998, 1753, 1697, 1499, 1460, 1258, 1219, 1190, 770\) cm\(^{-1}\).
MS (EI) \(m/z\) (relative intensity): 333 (5) [M\(^+\)], 291 (100), 245 (62), 215 (38), 189 (20).
HR-MS (EI) \(m/z\) calcd for C\(_{21}\)H\(_{16}\)NO\(_2\)\(^+\) 333.1365, found 333.1356.

**Synthesis of isopropyl 1-acetyl-4,5-diphenyl-1H-pyrrole-2-carboxylate (211ca)**

The general procedure C was followed using isopropyl 2-acetamidoacrylate (210c) (85.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 210ca (111 mg, 66%) as a colorless oil.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.38–7.27\) (m, 5H), 7.21–7.11 (m, 6H), 5.21 (sept., \(J = 6.2\) Hz, 1H), 2.30 (s, 3H), 1.36 (d, \(J = 6.2\) Hz, 6H).
\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 173.9\) (C\(_q\)), 160.2 (C\(_q\)), 134.2 (C\(_q\)), 134.0 (C\(_q\)), 130.7 (C\(_q\)), 130.7 (CH), 128.8 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 126.3 (CH), 124.7 (C\(_q\)), 123.7 (C\(_q\)), 118.0 (CH), 68.5 (CH\(_3\)), 28.9 (CH\(_3\)), 21.9 (CH\(_3\)).
IR (ATR): \(\tilde{\nu} = 3030, 1760, 1695, 1460, 1385, 1254, 1104, 757, 695\) cm\(^{-1}\).
MS (EI) \(m/z\) (relative intensity): 347 (9) [M\(^+\)], 305 (100), 263 (70), 245 (77), 214 (47), 191 (22).
HR-MS (EI) \(m/z\) calcd for C\(_{22}\)H\(_{16}\)NO\(_2\)\(^+\) 347.1521, found 347.1516.

**Synthesis of 1-acetyl-2-methyl-4,5-diphenyl-1H-pyrrole-3-carbonitrile (211fa)**

The general procedure C was followed using N-(1-cyanoprop-1-en-2-yl)acetamide (210f) (62.0 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 211fa (65 mg, 43%) as a white solid.

M.p. = 243–244 °C.
\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.39–7.31\) (m, 3H), 7.28–7.14 (m, 7H), 2.64 (s, 3H), 1.95 (s, 3H).
Synthesis of 1-(2,3,5-triphenyl-1H-pyrrol-1-yl)ethanone (211ga)

The general procedure C was followed using N-(1-phenylvinyl)acetamide (210g) (76.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ga (88 mg, 52%) as a yellow solid.

M.p. = 131−132 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.46−7.40 (m, 4H), 7.38−7.33 (m, 6H), 7.21−7.14 (m, 5H), 6.54 (s, 1H), 2.02 (s, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 172.8 (Cq), 134.8 (Cq), 134.7 (Cq), 133.4 (Cq), 132.8 (Cq), 131.0 (CH), 130.9 (Cq), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 126.2 (CH), 125.5 (Cq), 113.6 (CH), 28.6 (CH₃).

IR (ATR): ν = 3061, 3029, 1721, 1620, 1485, 1288, 1268, 1026, 789, 762 cm⁻¹.

MS (EI) m/z (relative intensity): 337 (M⁺, 23), 295 (100), 189 (23), 43 (33).

HR-MS (EI) m/z calcd for C₂₃H₃₅NO⁺ 337.1467, found 337.1461.

Synthesis of 1-[5-[4-(trifluoromethyl)phenyl]-2,3-diphenyl-1H-pyrrol-1-yl]ethanone (211ha)

The general procedure C was followed using N-[1-[4-(trifluoromethyl)phenyl]vinyl]-acetamide (210h) (111 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 211ha (138 mg, 68%) as a white solid.

M.p. = 133−134 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.67 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.43−7.33 (m, 5H), 7.24−7.13 (m, 5H), 6.59 (s, 1H), 2.03 (s, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 172.5 (Cq), 137.0 (Cq), 134.4 (Cq), 133.6 (Cq), 132.5 (Cq), 131.5 (Cq), 130.9 (CH), 129.7 (q, 3J_C_F = 32 Hz, Cq), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.7 (q, 3J_C_F = 273 Hz, Cq), 126.4 (CH), 125.9 (Cq), 125.3 (q, 3J_C_F = 4 Hz, CH), 114.8 (CH), 28.5 (CH₃).

19F-NMR (283 MHz, CDCl₃): δ = −62.5 (s).

IR (ATR): ν = 3063, 3032, 1723, 1615, 1268, 1111, 1064, 847, 766, 694 cm⁻¹.

MS (EI) m/z (relative intensity): 405 (18) [M⁺], 363 (100), 293 (4), 189 (10), 43 (15).

HR-MS (EI) m/z calcd for C₂₅H₁₉F₃NO⁺ 405.1340, found 405.1346.

Synthesis of 1-[5-(4-fluorophenyl)-2,3-diphenyl-1H-pyrrol-1-yl]ethanone (211ia)

The general procedure C was followed using N-[1-(4-fluorophenyl)vinyl]acetamide (210i) (89.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by...
column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ia (94 mg, 53%) as a white solid.

M.p. = 144–145 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.46–7.30 (m, 7H), 7.24–7.07 (m, 7H), 6.51 (s, 1H), 2.01 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 172.7 (Cₜₜ), 162.3 (d, ¹JC-F = 248 Hz, Cₜ), 134.7 (Cₜ), 133.9 (Cₜ), 132.8 (Cₜ), 130.8 (CH), 130.7 (Cₜ), 130.4 (d, ³JC-F = 8 Hz, CH), 129.5 (d, ⁴JC-F = 3 Hz, Cₜ), 128.5 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 126.3 (CH), 125.5 (Cₜ), 111.4 (d, ²JC-F = 21 Hz, CH), 113.7 (CH), 28.6 (CH₃).

¹⁹F-NMR (283 MHz, CDCl₃): δ = –(114.1–114.2) (m).

IR (ATR): ν = 3024, 1722, 1585, 1493, 1267, 1

MS (EI) m/z (relative intensity): 355 (15) [M⁺], 313 (100), 207 (7), 189 (7), 43 (13).

HR-MS (EI) m/z calcd for C₃₄H₄₁BrNO⁺ 555.1372, found 555.1384.

Synthesis of 1-[5-(4-bromophenyl)-2,3-diphenyl-1H-pyrrol-1-yl]ethanone (211ja)

The general procedure C was followed using N-[1-(4-bromophenyl)vinyl]acetamide (210ja) (119 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ja (120 mg, 58%) as a white solid.

M.p. = 120–121 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.54 (d, J = 8.6 Hz, 2H), 7.40–7.34 (m, 5H), 7.31 (d, J = 8.6 Hz, 2H), 7.23–7.14 (m, 5H), 6.53 (s, 1H), 2.02 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 172.5 (Cₜₜ), 134.5 (Cₜ), 133.7 (Cₜ), 132.6 (Cₜ), 132.3 (Cₜ), 131.5 (CH), 131.0 (Cₜ), 130.8 (CH), 130.0 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 126.3 (CH), 125.7 (Cₜ), 121.6 (Cₜ), 114.0 (CH), 28.5 (CH₃).

IR (ATR): ν = 3060, 3026, 1722, 1585, 1482, 1365, 1279, 958, 840, 767, 694 cm⁻¹.

MS (EI) m/z (relative intensity): 417 (17) [M⁺] (¹⁸Br), 415 (17) [M⁺] (⁷⁹Br), 373 (100), 293 (20), 189 (27), 43 (52).

HR-MS (EI) m/z calcd for C₃₄H₃₂BrNO⁺ 515.1372, found 515.1389.

Synthesis of 4-(1-acetyl-4,5-diphenyl-1H-pyrrol-2-yl)benzonitrile (211ka)

The general procedure C was followed using N-[1-(4-cyanophenyl)vinyl]acetamide (210ka) (93.0 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ka (134 mg, 74%) as a yellow solid.

M.p. = 145–146 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.66 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.41–7.31 (m, 5H), 7.21–7.10 (m, 5H), 6.59 (s, 1H), 2.00 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 172.4 (Cₜₜ), 138.0 (Cₜ), 134.2 (Cₜ), 133.3 (Cₜ), 132.3 (Cₜ), 132.0 (CH), 132.0 (Cₜ), 130.9 (CH), 128.7 (CH), 128.7 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 126.2 (Cₜ), 118.8 (Cₜ), 111.4 (CH), 110.7 (Cₜ), 28.4 (CH₃).

IR (ATR): ν = 3061, 2103, 1731, 1603, 1490, 1267, 1208, 824, 696, 552 cm⁻¹.

MS (EI) m/z (relative intensity): 362 (10) [M⁺], 320 (100), 214 (6), 189 (8), 43 (15).
Experimental Section

HR-MS (El) m/z calcd for C_{25}H_{18}N_{2}O^+ 362.1419, found 362.1416.

Synthesis of 1-(5-(4-nitrophenyl)-2,3-diphenyl-1H-pyrrol-1-yl)ethanone (211la)

The general procedure C was followed using N-{1-(4-nitrophenyl)vinyl}acetamide (211I) (103 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 211la (136 mg, 71%) as a yellow solid.

M.p. = 184–185 °C.

1H-NMR (300 MHz, CDCl_3): δ = 8.27 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.44–7.32 (m, 5H), 7.24–7.11 (m, 5H), 6.66 (s, 1H), 2.03 (s, 3H).

13C-NMR (75 MHz, CDCl_3): δ = 172.3 (C_q), 146.6 (C_q), 139.6 (C_q), 134.1 (C_q), 133.0 (C_q), 132.3 (C_q), 132.2 (C_q), 130.9 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 126.6 (CH), 126.4 (C_q), 123.6 (CH), 111.9 (CH), 28.4 (CH_3).

IR (ATR): ν = 3104, 1733, 1595, 1508, 1338, 1264, 1206, 784, 692, 491 cm\(^{-1}\).

MS (El) m/z (relative intensity): 382 (10) [M\(^+\)], 340 (100), 310 (17), 294 (30), 189 (20), 43 (50).

HR-MS (El) m/z calcd for C_{33}H_{26}NO_{2}^+ 382.1317, found 382.1330.

Synthesis of 1-[2,3-diphenyl-5-(p-tolyl)-1H-pyrrol-1-yl]ethanone (211ma)

The general procedure C was followed using N-{1-(p-tolyl)vinyl}acetamide (210m) (87.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 211ma (32 mg, 18%) as a white solid.

M.p. = 104–105 °C.

1H-NMR (300 MHz, CDCl_3): δ = 7.44–7.30 (m, 7H), 7.26–7.13 (m, 7H), 6.53 (s, 1H), 2.38 (s, 3H), 2.05 (s, 3H).

13C-NMR (75 MHz, CDCl_3): δ = 172.9 (C_q), 137.5 (C_q), 134.9 (C_q), 134.8 (C_q), 132.9 (C_q), 130.9 (CH), 130.6 (C_q), 130.5 (C_q), 129.2 (CH), 128.3 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 128.0 (CH), 126.1 (CH), 125.4 (C_q), 113.2 (CH), 28.6 (CH_3), 21.2 (CH_3).

IR (ATR): ν = 3050, 1723, 1601, 1495, 1276, 1206, 957, 764, 694, 546 cm\(^{-1}\).

MS (El) m/z (relative intensity): 351 (13) [M\(^+\)], 309 (100), 189 (7), 43 (10).

HR-MS (El) m/z calcd for C_{25}H_{21}NO_{2}^+ 351.1623, found 351.1627.

Synthesis of 1-[5-(4-methoxyphenyl)-2,3-diphenyl-1H-pyrrol-1-yl]ethanone (211na)

The general procedure C was followed using N-{1-(4-methoxyphenyl)vinyl}acetamide (210n) (95.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 211na (52 mg, 28%) as a white solid.

M.p. = 105–106 °C.

1H-NMR (300 MHz, CDCl_3): δ = 7.38–7.32 (m, 7H), 7.23–7.11 (m, 5H), 6.97 (d, J = 8.4 Hz, 2H), 6.48 (s, 1H), 3.86 (s, 3H), 2.03 (s, 3H).

13C-NMR (75 MHz, CDCl_3): δ = 172.9 (C_q), 159.2 (C_q), 134.9 (C_q), 134.6 (C_q), 132.9 (C_q), 130.9 (CH), 130.4 (C_q), 129.8 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 126.1 (CH), 125.8 (C_q), 125.4 (C_q), 113.9 (CH), 113.0 (CH), 55.3 (CH_3), 28.6 (CH_3).
IR (ATR): $\tilde{\nu} = 3058, 3028, 1730, 1599, 1281, 1246, 1174, 1023, 764, 694 \text{ cm}^{-1}$.
MS (El) $m/z$ (relative intensity): 367 (30) [M$^+$], 325 (100), 310 (27), 276 (13), 178 (14), 43 (52).
HR-MS (El) $m/z$ calcd for C$_{25}$H$_{24}$NO$_2^+$ 367.1572, found 367.1562.

Synthesis of 1-[5-[3-(trifluoromethyl)phenyl]-2,3-diphenyl-1H-pyrrol-1-yl]ethanone (211oa)

The general procedure C was followed using N-{1-[3-(trifluoromethyl)phenyl]vinyl}-acetamide (210o) (111 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211oa (146 mg, 72%) as a white solid.
M.p. = 111–112 °C.

1H-NMR (300 MHz, CDCl$_3$): $\delta = 7.70$ (s, 1H), 7.59 (d, $J = 7.3$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.50 (dd, $J = 7.8$, 7.3 Hz, 1H), 7.38–7.31 (m, 5H), 7.22–7.12 (m, 5H), 6.56 (s, 1H), 1.99 (s, 3H).

13C-NMR (75 MHz, CDCl$_3$): $\delta = 172.4$ (C$_q$), 134.4 (C$_q$), 134.3 (C$_q$), 133.6 (C$_q$), 132.6 (C$_q$), 131.8 (q, $J_{C-F} = 1$ Hz, CH), 131.2 (C$_q$), 130.9 (CH), 130.7 (q, $J_{C-F} = 32$ Hz, C$_q$), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 127.7 (q, $J_{C-F} = 272$ Hz, C$_q$), 126.4 (CH), 125.9 (C$_q$), 125.3 (q, $J_{C-F} = 4$ Hz, CH), 124.1 (q, $J_{C-F} = 4$ Hz, CH), 114.7 (CH), 28.5 (CH$_3$).

19F-NMR (283 MHz, CDCl$_3$): $\delta = -62.7$ (s).
IR (ATR): $\tilde{\nu} = 3072, 1733, 1585, 1446, 1365, 1119, 1111, 1072, 763, 693 \text{ cm}^{-1}$.

MS (El) $m/z$ (relative intensity): 405 (10) [M$^+$], 363 (100), 189 (9), 43 (12).

HR-MS (El) $m/z$ calcd for C$_{25}$H$_{19}$F$_3$NO$^+$ 405.1327, found 405.1327.

Synthesis of 1-{2,3-diphenyl-5-(o-tolyl)-1H-pyrrol-1-yl}ethanone (211pa)

The general procedure C was followed using N-{1-(o-tolyl)vinyl}acetamide (210p) (87.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211pa (120 mg, 68%) as a yellow solid.
M.p. = 145–146 °C.

1H-NMR (300 MHz, CDCl$_3$): $\delta = 7.46–7.15$ (m, 14H), 6.45 (s, 1H), 2.37 (s, 3H), 1.94 (s, 3H).

13C-NMR (75 MHz, CDCl$_3$): $\delta = 171.6$ (C$_q$), 137.6 (C$_q$), 137.6 (C$_q$), 134.8 (C$_q$), 133.8 (C$_q$), 133.7 (C$_q$), 133.3 (C$_q$), 130.7 (CH), 130.3 (CH), 129.9 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 126.1 (CH), 125.6 (CH), 125.5 (C$_q$), 113.7 (CH), 27.6 (CH$_3$), 20.2 (CH$_3$).
IR (ATR): $\tilde{\nu} = 3053, 1733, 1615, 1445, 1318, 1267, 1111, 1071, 762, 692 \text{ cm}^{-1}$.

MS (El) $m/z$ (relative intensity): 351 (25) [M$^+$], 309 (100), 230 (11), 202 (12), 191 (10), 43 (65).

HR-MS (El) $m/z$ calcd for C$_{22}$H$_{21}$NO$^+$ 351.1623, found 351.1634.

Synthesis of 1-{2,3-diphenyl-5-(pyridin-3-yl)-1H-pyrrol-1-yl}ethanone (211qa)

The general procedure C was followed using N-{1-(pyridin-3-yl)vinyl}acetamide (211q) (81.0 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211qa (54 mg, 32%) as a yellow solid.
M.p. = 100–101 °C.

1H-NMR (300 MHz, CDCl$_3$): $\delta = 8.71$ (s, 1H), 7.57 (dt, 1H), 7.75 (dt, 1H), 7.48–7.30 (m, 6H), 7.26–7.13 (m, 5H), 6.56 (s, 1H), 1.99 (s, 3H).
13C-NMR (75 MHz, CDCl3): δ = 172.2 (Cq), 149.2 (CH), 148.4 (CH), 136.1 (CH), 134.3 (Cq), 132.6 (Cq), 131.7 (Cq), 131.2 (Cq), 130.7 (CH), 129.5 (Cq), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.4 (CH), 126.0 (Cq), 122.8 (CH), 114.8 (CH), 28.3 (CH3).

IR (ATR): ν = 3060, 3030, 1720, 1672, 1599, 1571, 1267, 1208, 764, 693 cm⁻¹.

MS (EI) m/z (relative intensity): 338 (20) [M⁺], 296 (100), 191 (11), 43 (12).

HR-MS (EI) m/z calcd for C23H19N2O⁺ 338.1419, found 338.1410.

Synthesis of 1-[2,3-diphenyl-5-(thiophen-2-yl)-1H-pyrrol-1-yl]ethanone (211ra) and 2,3-diphenyl-5-(thiophen-2-yl)-1H-pyrrole (212ra)
The general procedure C was followed using N-[1-(thiophen-2-yl)vinyl]acetamide (210r) (83.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ra (57 mg, 33%) as a yellow solid and 212ra (46 mg, 30%) as a yellow solid.

1-[2,3-diphenyl-5-(thiophen-2-yl)-1H-pyrrol-1-yl]ethanone (211ra):

M.p. = 171–172 °C.

1H-NMR (300 MHz, CDCl3): δ = 7.38–7.29 (m, 6H), 7.21–7.12 (m, 6H), 7.06 (dd, J = 5.1, 5.1 Hz, 1H), 6.59 (s, 1H), 2.02 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ = 172.8 (Cq), 134.6 (Cq), 134.0 (Cq), 132.6 (Cq), 131.0 (Cq), 130.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 127.1 (Cq), 126.3 (CH), 126.1 (CH), 125.6 (Cq), 114.8 (CH), 28.3 (CH3).

IR (ATR): ν = 3097, 1722, 1600, 1496, 1363, 1277, 1197, 1028, 767, 695 cm⁻¹.

MS (EI) m/z (relative intensity): 343 (13) [M⁺], 301 (100), 267 (10), 197 (10), 43 (17).

HR-MS (EI) m/z calcd for C22H17NOS⁺ 343.1031, found 343.1043.

2,3-Diphenyl-5-(thiophen-2-yl)-1H-pyrrole (212ra):

M.p. = 92–94 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.27 (sbr, 1H), 7.44–7.16 (m, 11H), 7.11 (d, J = 3.5 Hz, 1H), 7.05 (dd, J = 5.1, 5.1 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H).

13C-NMR (75 MHz, CDCl3): δ = 136.0 (Cq), 135.6 (Cq), 132.8 (Cq), 128.9 (Cq), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.4 (CH), 127.0 (CH), 126.9 (Cq), 126.0 (CH), 123.6 (Cq), 123.0 (CH), 121.1 (CH), 109.2 (CH).

IR (ATR): ν = 3411, 3055, 3024, 1600, 1492, 1439, 1199, 1070, 759, 689 cm⁻¹.

MS (EI) m/z (relative intensity): 301 (100) [M⁺], 267 (7), 197 (10).

HR-MS (EI) m/z calcd for C20H15NOS⁺ 301.0925, found 301.0939.

Synthesis of (E)-2,3-diphenyl-5-styryl-1H-pyrrole (212sa)
The general procedure C was followed using (E)-N-(4-phenylbuta-1,3-dien-2-yl)acetamide (210s) (87.5 mg, 0.50 mmol) and diphenylacetylene (38a) (178 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 211sa (78 mg, 48%) as a yellow solid.

M.p. = 87–88 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.35 (sbr, 1H), 7.54–7.44 (m, 2H), 7.38–7.23 (m, 13 H), 7.01 (d, J = 16.6 Hz, 1H), 6.77 (d, J = 16.6 Hz, 1H), 6.55 (d, J = 2.7 Hz, 1H).

13C-NMR (75 MHz, CDCl3): δ = 137.3 (Cq), 136.2 (Cq), 132.8 (Cq), 130.9 (Cq), 129.5 (Cq), 128.7 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 125.9 (CH), 28.3 (CH3).
125.9 (CH), 123.9 (CH), 123.8 (C₆), 118.3 (CH), 111.7 (CH).
IR (ATR): ν = 3058, 3026, 2951, 2925, 1684, 1598, 1504, 1447, 1261, 760, 693 cm⁻¹.
MS (EI) m/z (relative intensity): 321 (100) [M⁺], 243 (9), 213 (8).
HR-MS (EI) m/z calcld for C₂₃H₁₈N⁺ 321.1517, found 321.1519.

**Synthesis of 1-[5-(4-nitrophenyl)-2,3-di-p-tolyl-1H-pyrrol-1-yl]ethanone (211li)**

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210i) (103 mg, 0.50 mmol) and 1,2-di-p-tolylacetylene (38ii) (206 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211li (130 mg, 63%) as a yellow solid.
M.p. = 143–144 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.23 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 6.61 (s, 1H), 2.39 (CH₃), 2.28 (CH₃), 2.01 (CH₃).

¹³C-NMR (75 MHz, CDCl₃): δ = 172.5 (C₆), 146.4 (C₆), 140.1 (C₆), 138.7 (C₆), 136.2 (C₆), 132.8 (C₆), 132.2 (C₆), 131.2 (C₆), 130.7 (CH), 129.5 (CH), 129.3 (C₆), 129.0 (CH), 128.6 (CH), 127.9 (CH), 126.1 (C₆), 123.6 (CH), 116.0 (CH), 28.4 (CH₃), 21.4 (CH₃), 21.1 (CH₃).
IR (ATR): ν = 3025, 2905, 1723, 1593, 1502, 1334, 1262, 1108, 817, 752 cm⁻¹.
MS (EI) m/z (relative intensity): 410 (20) [M⁺], 368 (100), 322 (23), 43 (17).
HR-MS (EI) m/z calcld for C₂₆H₂₅N₂O₃⁺ 410.1630, found 410.1633.

**Synthesis of 1-[2,3-bis(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrrol-1-yl]ethanone (211lj)**

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210i) (103 mg, 0.50 mmol) and 1,2-bis(4-methoxyphenyl)ethyne (38jii) (238 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 211lj (111 mg, 52%) as a yellow solid.
M.p. = 117–118 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.22 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 6.59 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.01 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 172.4 (C₆), 159.8 (C₆), 158.3 (C₆), 146.4 (C₆), 140.1 (C₆), 132.7 (C₆), 132.2 (CH), 131.8 (C₆), 129.1 (CH), 128.5 (CH), 126.6 (C₆), 125.9 (C₆), 124.4 (C₆), 123.6 (CH), 111.9 (CH), 114.2 (CH), 113.7 (CH), 55.2 (CH₃), 55.1 (CH₃), 28.4 (CH₃).
IR (ATR): ν = 2952, 2836, 1726, 1595, 1515, 1493, 1339, 1245, 1029, 752 cm⁻¹.
MS (EI) m/z (relative intensity): 438 (26) [M⁺], 400 (100), 385 (23), 354 (17), 339 (15), 43 (26).
HR-MS (EI) m/z calcld for C₂₆H₂₃N₂O₃⁺ 438.1529, found 438.1511.
Synthesis of 1-[2,3-bis[4-(trifluoromethyl)phenyl]-5-(4-nitrophenyl)-1H-pyrrol-1-yl]ethanone (211lb)

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210) (103 mg, 0.50 mmol) and 1,2-bis[4-(trifluoromethyl)phenyl]acetylene (38b) (314 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 211lb (174 mg, 67%) as a yellow solid.

M.p. = 161–162 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.30 (d, J = 8.9 Hz, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.54–7.43 (m, 4H), 7.22 (d, J = 8.4 Hz, 2H), 6.68 (s, 1H), 2.07 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ = 171.7 (Cq), 147.0 (Cq), 139.0 (Cq), 137.3 (J = 4 Hz, Cq), 135.2 (J = 1 Hz, Cq), 133.5 (Cq), 131.3 (Cq), 131.2 (CH), 130.8 (J = 32 Hz, Cq), 128.9 (J = 8 Hz, Cq), 128.7 (CH), 128.3 (CH), 125.8 (Cq), 125.7 (q, J = 4 Hz, CH), 125.4 (q, J = 4 Hz, CH), 124.1 (d, J = 272 Hz, Cq), 123.9 (CH), 123.7 (q, J = 272 Hz, Cq), 111.5 (CH), 28.8 (CH3).

19F-NMR (283 MHz, CDCl3): δ = −62.6 (s), −62.7 (s).

IR (ATR): v = 1727, 1613, 1593, 1514, 1338, 1321, 1265, 1117, 854, 832 cm⁻¹.

MS (EI) m/z (relative intensity): 518 (4) [M⁺], 476 (100), 446 (28), 430 (30), 43 (52).

HR-MS (EI) m/z calcd for C20H16F6N2O3⁺ 518.1065, found 518.1081.

Synthesis of 1-[2,3-bis(4-fluorophenyl)-5-(4-nitrophenyl)-1H-pyrrol-1-yl]ethanone (211lk)

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210) (103 mg, 0.50 mmol) and 1,2-bis(4-fluorophenyl)acetylene (38k) (212 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 211lk (140 mg, 67%) as a yellow solid.

M.p. = 172–173 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.25 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.31 (dd, J = 8.8, 8.4 Hz, 2H), 7.14–7.03 (m, 4H), 6.90 (dd, J = 8.8, 8.7 Hz, 2H), 6.59 (s, 1H), 2.04 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ = 172.0 (Cq), 162.7 (d, J = 251 Hz, Cq), 161.9 (d, J = 245 Hz, Cq), 146.7 (Cq), 139.6 (Cq), 132.9 (Cq), 132.9 (d, J = 8 Hz, CH), 131.2 (Cq), 130.0 (d, J = 3 Hz, Cq), 129.7 (d, J = 8 Hz, CH), 128.5 (CH), 127.9 (d, J = 3 Hz, Cq), 125.8 (Cq), 123.8 (CH), 116.0 (d, J = 22 Hz, CH), 111.7 (CH), 111.3 (d, J = 22 Hz, CH), 28.5 (CH3).

19F-NMR (283 MHz, CDCl3): δ = −(114.4–114.7) (m), −(111.2–111.5) (m).

IR (ATR): v = 1721, 1595, 1492, 1333, 1217, 1118, 1104, 847, 816, 523 cm⁻¹.

MS (EI) m/z (relative intensity): 418 (10) [M⁺], 376 (100), 346 (20), 330 (30), 207 (12), 43 (20).

HR-MS (EI) m/z calcd for C24H16F2N2O3⁺ 418.1129, found 418.1125.
Synthesis of 1-[2,3-bis(4-chlorophenyl)-5-(4-nitrophenyl)-1H-pyrrolyl-1-yl]ethanone (211lc)

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210l) (103 mg, 0.50 mmol) and 1,2-bis(4-chlorophenyl)acetylene (38c) (247 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211lc (154 mg, 68%) as a yellow solid.

M.p. = 117–118 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.25$ (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.37 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 7.04 (d, $J = 8.6$ Hz, 2H), 6.59 (s, 1H), 2.04 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 171.8$ (C$_q$), 146.7 (C$_q$), 139.3 (C$_q$), 135.0 (C$_q$), 133.1 (C$_q$), 132.6 (C$_q$), 132.3 (C$_q$), 132.1 (CH), 131.2 (C$_q$), 130.2 (C$_q$), 129.3 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 125.6 (C$_q$), 123.7 (CH), 111.5 (CH), 28.7 (CH$_3$).

IR (ATR): $\tilde{\nu} = 3104$, 1729, 1514, 1486, 1341, 1257, 1091, 1012, 832 cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 450 (9) [M$^+$], 408 (100), 378 (20), 362 (28), 327 (13), 291 (15), 189 (12), 43 (43).

HR-MS (El) $m/z$ calcld for C$_{24}$H$_{16}$Cl$_2$N$_2$O$_7$ $^+$ 450.0538, found 450.0539.

Synthesis of diethyl 4,4’-(1-acetyl-5-(4-nitrophenyl)-1H-pyrrol-2,3-diyl)dibenzoate (211ll)

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210l) (103 mg, 0.50 mmol) and diethyl 4,4’-(ethyne-1,2-diyl)dibenzoate (38l) (322 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1) yielded 211ll (168 mg, 64%) as a yellow solid.

M.p. = 188–189 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.26$ (d, $J = 9.0$ Hz, 2H), 8.06 (d, $J = 8.2$ Hz, 2H), 7.87 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 2H), 7.16 (d, $J = 8.7$ Hz, 2H), 6.66 (s, 1H), 4.39 (q, $J = 7.2$ Hz, 2H), 4.32 (q, $J = 7.2$ Hz, 2H), 2.04 (s, 3H), 1.40 (t, $J = 7.2$ Hz, 3H), 1.37 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 171.8$ (C$_q$), 166.1 (C$_q$), 165.8 (C$_q$), 146.9 (C$_q$), 139.2 (C$_q$), 138.4 (C$_q$), 136.2 (C$_q$), 133.5 (C$_q$), 131.8 (C$_q$), 130.7 (CH), 129.8 (CH), 129.6 (CH), 128.8 (CH), 128.7 (C$_q$), 128.7 (C$_q$), 127.9 (CH), 126.1 (C$_q$), 123.7 (CH), 111.5 (CH), 61.3 (CH$_2$), 61.0 (CH$_2$), 28.7 (CH$_3$), 14.4 (CH$_3$), 14.4 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2995$, 1723, 1707, 1594, 1514, 1341, 1269, 1104, 1024, 752 cm$^{-1}$.

MS (El) $m/z$ (relative intensity): 526 (7) [M$^+$], 484 (100), 454 (38), 438 (17), 291 (11), 43 (77).

HR-MS (El) $m/z$ calcld for C$_{30}$H$_{26}$N$_2$O$_7$ $^+$ 526.1740, found 526.1735.

Synthesis of 1-[2,3-bis(3-chlorophenyl)-5-(4-nitrophenyl)-1H-pyrrolyl-1-yl]ethanone (211lm)

The general procedure C was followed using N-[1-(4-nitrophenyl)vinyl]acetamide (210l) (103 mg, 0.50 mmol) and 1,2-bis(3-chlorophenyl)acetylene (38m) (247 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 211lm (152 mg, 67%) as a yellow solid.
M.p. = 120–121 °C.

\(^{1}H\)-NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.25\) (d, \(J = 9.0\) Hz, 2H), 7.54 (d, \(J = 9.0\) Hz, 2H), 7.38–7.30 (m, 3H), 7.24 (dt, \(J = 7.2, 1.4\) Hz, 1H), 7.18 (s, 1H), 7.08–7.04 (m, 2H), 6.94 (dt, \(J = 7.2, 1.7\) Hz, 1H), 6.61 (s, 1H), 2.06 (s, 3H).

\(^{13}C\)-NMR (75 MHz, CDCl\(_3\)): \(\delta = 171.8\) (C\(_q\)), 146.9 (C\(_q\)), 139.4 (C\(_q\)), 135.6 (C\(_q\)), 134.7 (C\(_q\)), 134.3 (C\(_q\)), 133.5 (C\(_q\)), 133.3 (C\(_q\)), 130.0 (C\(_q\)), 130.0 (C\(_q\)), 129.6 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 126.9 (CH), 126.2 (CH), 125.6 (C\(_q\)), 123.8 (CH), 111.5 (CH), 28.6 (CH)。

IR (ATR): \(\bar{\nu} = 3062\), 1749, 1593, 1565, 1308, 762 cm\(^{-1}\).

MS (EI) \(m/z\) (relative intensity): 450 (10) [M\(^+\)], 408 (100), 362 (22), 327 (15), 291 (15), 43 (39).

HR-MS (EI) \(m/z\) calcld for C\(_{26}\)H\(_{16}\)Cl\(_2\)N\(_3\)O\(_7\): found 450.0534, 450.0538.

Synthesis of methyl 1-acetyl-4,5-di(naphthalen-1-yl)-1H-pyrrole-2-carboxylate (211an)

The general procedure C was followed using methyl 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol), and 1,2-di(naphthalen-1-yl)acetylene (38n) (278 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EntOAc: 10:1) yielded 211an (120 mg, 57%) as a white solid.

M.p. = 176–181 °C.

\(^{1}H\)-NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.11\) (d, \(J = 7.2\) Hz, 1H), 7.84–7.71 (m, 3H), 7.70–7.55 (m, 2H), 7.52–7.27 (m 7H), 7.16–7.03 (m, 2H), 3.93 (s, 3H), 2.16 (s, 3H).

\(^{13}C\)-NMR (75 MHz, CDCl\(_3\)): \(\delta = 172.2\) (C\(_q\)), 161.4 (C\(_q\)), 134.6 (C\(_q\)), 133.5 (C\(_q\)), 133.2 (C\(_q\)), 133.1 (C\(_q\)), 132.3 (C\(_q\)), 131.5 (C\(_q\)), 129.8 (CH), 129.5 (CH), 128.3 (CH), 128.2 (C\(_q\)), 128.2 (CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 126.1 (CH), 125.9 (CH), 125.7 (CH), 125.6 (CH), 125.3 (CH), 125.1 (C\(_q\)), 125.0 (CH), 124.9 (CH), 123.8 (C\(_q\)), 121.4 (CH), 52.0 (CH), 27.7 (CH).

IR (ATR): \(\bar{\nu} = 3056\), 1744, 1708, 1486, 1382, 1249, 1230, 760, 775 cm\(^{-1}\).

MS (EI) \(m/z\) (relative intensity): 419 (16) [M\(^+\)], 377 (100), 317 (70), 289 (25), 163 (7).

HR-MS (EI) \(m/z\) calcld for C\(_{29}\)H\(_{22}\)NO\(_{4}\): found 419.1521, 419.1519.

Synthesis of methyl 1-acetyl-4,5-dipropyl-1H-pyrrole-2-carboxylate (211ae)

The general procedure C was followed using methyl 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol), and 4-octyne (38e) (110 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EntOAc: 10:1) yielded 211ae (72 mg, 57%) as a colorless oil.

\(^{1}H\)-NMR (300 MHz, CDCl\(_3\)): \(\delta = 6.82\) (s, 1H), 3.76 (s, 3H), 2.57 (t, \(J = 7.6\) Hz, 2H), 2.50 (s, 3H), 2.32 (t, \(J = 7.4\) Hz, 2H), 1.63–1.43 (m, 4H), 0.93 (t, \(J = 7.2\) Hz, 3H), 0.91 (t, \(J = 7.2\) Hz, 3H).

\(^{13}C\)-NMR (75 MHz, CDCl\(_3\)): \(\delta = 174.0\) (C\(_q\)), 161.1 (C\(_q\)), 138.4 (C\(_q\)), 123.3 (C\(_q\)), 121.5 (C\(_q\)), 121.4 (CH), 51.5 (CH\(_3\)), 28.5 (CH\(_3\)), 27.4 (CH\(_2\)), 27.0 (CH\(_2\)), 23.6 (CH\(_2\)), 23.6 (CH\(_2\)), 13.9 (CH\(_3\)), 13.9 (CH\(_3\)).

IR (ATR): \(\bar{\nu} = 2960\), 1738, 1702, 1478, 1437, 1374, 1227, 1186, 1054, 762 cm\(^{-1}\).

MS (EI) \(m/z\) (relative intensity): 251 (5) [M\(^+\)], 207 (36), 176 (100), 148 (25), 43 (34).

HR-MS (EI) \(m/z\) calcld for C\(_{16}\)H\(_{22}\)NO\(_{4}\): found 251.1521, 251.1525.

The spectral data were in accordance with those reported in the literature.\(^{123a}\)
Synthesis of methyl 1-acetyl-4,5-diethyl-1H-pyrrole-2-carboxylate (211af)

The general procedure C was followed using methyl 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol), and 3-hexyne (38f) (82 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1) yielded 211af (76 mg, 71%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): δ = 6.84 (s, 1H), 3.79 (s, 3H), 2.62 (q, $J = 7.2$ Hz, 2H), 2.50 (s, 3H), 2.37 (q, $J = 7.2$ Hz, 2H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.11 (t, $J = 7.2$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 173.9 (C$q$), 161.0 (C$q$), 139.4 (C$q$), 124.3 (C$q$), 121.4 (C$q$), 120.9 (C$q$), 51.5 (CH$_3$), 28.4 (CH$_3$), 18.4 (CH$_2$), 14.9 (CH$_3$), 14.7 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2966, 1738, 1698, 1481, 1437, 1378, 1239, 1186, 940, 762 cm$^{-1}$.

MS (EI) m/z (relative intensity): 219 (5) [M$^+$], 181 (52), 166 (100), 134 (43).

HR-MS (EI) m/z calc'd for C$_{12}$H$_{17}$NO$_3$: 219.1206, found 219.1208.

Synthesis of 1-[3-methyl-5-(4-nitrophenyl)-2-phenyl-1H-pyrrol-1-yl]ethanone (211lh)

The general procedure C was followed using N-{-[4-(4-nitrophenyl)viny]acetamide (210l) (103 mg, 0.50 mmol) and propyn-1-benzene (38h) (116 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211lh (72 mg, 45%) as a yellow solid.

M.p. = 149–150 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): δ = 8.19 (d, $J = 8.9$ Hz, 2H), 7.50–7.38 (m, 5H), 7.36–7.28 (m, 2H), 6.32 (s, 1H), 1.99 (s, 3H), 1.99 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 171.8 (C$q$), 146.3 (C$q$), 140.4 (C$q$), 133.1 (C$q$), 132.7 (C$q$), 132.7 (C$q$), 130.0 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 123.4 (CH), 121.9 (C$q$), 117.7 (CH), 28.1 (CH$_3$), 11.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2924, 1720, 1592, 1506, 1344, 1264, 1107, 853, 752, 701 cm$^{-1}$.

MS (EI) m/z (relative intensity): 320 (15) [M$^+$], 278 (100), 248 (12), 232 (30), 43 (27).

HR-MS (EI) m/z calc'd for C$_{19}$H$_{16}$N$_2$O$_3$: 320.1161, found 320.1114.

Synthesis of methyl 1-acetyl-5-phenyl-1H-pyrrole-2-carboxylate (211ah)

The general procedure C was followed using methyl 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol), and prop-1-yn-1-ylbenzene (38h) (116 mg, 1.00 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ah (85 mg, 66%) as a white solid.

M.p. = 109–110 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): δ = 7.46–7.37 (m, 3H), 7.32–7.26 (m, 2H), 6.85 (s, 1H), 3.84 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): δ = 173.5 (C$q$), 161.2 (C$q$), 135.6 (C$q$), 131.0 (C$q$), 129.8 (CH), 128.4 (CH), 128.4 (CH), 122.6 (C$q$), 120.5 (CH), 119.6 (C$q$), 51.7 (CH$_3$), 28.5 (CH$_3$), 11.1 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 2952, 1747, 1696, 1556, 1464, 1443, 1375, 1230, 772, 584 cm$^{-1}$. MS (EI) m/z (relative intensity): 257 (7) [M$^+$], 213 (100), 183 (63), 155 (39), 43 (25).

HR-MS (EI) m/z calc'd for C$_{15}$H$_{16}$NO$_3$: 257.1052, found 257.1056.

The spectral data were in accordance with those reported in the literature.\textsuperscript{123a}
Synthesis of methyl 1-acetyl-4-ethyl-5-phenyl-1H-pyrrole-2-carboxylate (211ao)

The general procedure C was followed using methyl 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol), and but-1-yn-1-ylbenzene (38o) (130 mg, 1.00 mmol).

After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 211ao (74 mg, 54%) as a yellow oil.

1H-NMR (300 MHz, CDCl3): δ = 7.45−7.37 (m 3H), 7.32−7.26 (m, 2H), 6.92 (s, 1H), 3.85 (s, 3H), 2.34 (q, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 173.3 (Cq), 161.0 (Cq), 135.0 (Cq), 131.0 (Cq), 129.9 (CH), 128.4 (CH), 128.3 (CH), 126.3 (Cq), 122.7 (Cq), 118.8 (CH), 51.8 (CH3), 28.5 (CH3), 18.8 (CH2), 15.2 (CH3).

IR (ATR): ʋ = 2961, 2927, 1726, 1599, 1448, 1261, 1070, 759, 699 cm⁻¹.

MS (EI) m/z (relative intensity): 271 (4) [M⁺], 229 (100), 212 (73), 197 (20), 182 (40), 169 (15), 154 (32), 43 (57).

HR-MS (EI) m/z calcd for C16H17NO3⁺ 271.1206, found 271.1211.

Ruthenium-catalyzed aerobic oxidative coupling with enamine 210a (Scheme 69)

A mixture of methyl 2-acetamidoacrylate (210a) (71.5 mg, 0.50 mmol), diphenylacetylene (38a) (178 mg, 1.00 mmol), [RuCl₂(η-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)₂·H₂O (30.0 mg, 30 mol %) in t-AmOH (2.0 mL) was stirred at 100 °C under ambient air for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH₄Cl/NH₃ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH₄Cl/NH₃ (1:1, 50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 10/1) to yield 211aa (128 mg, 76%) as a yellow oil.

Intermolecular competition experiment with alkynes 38m and 38b (Scheme 70)

A mixture of N-{1-(4-nitrophenyl)vinyl}acetamide (210l) (103 mg, 0.50 mmol),
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1,2-bis(4-methoxyphenyl)acetylene (38j) (238 mg, 1.00 mmol), 1,2-bis{4-((trifluoromethyl)phenyl)acetylene (38b) (314 mg, 1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$·H$_2$O (200 mg, 1.00 mmol) in t-AmOH (2.0 mL) was stirred at 120 °C under N₂ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH₄Cl/NH₃ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH₄Cl/NH₃ (1:1, 50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 20/1) to yield a mixture of 211lj and 211lb as a yellow solid. The ratio of products 211lj/211lb was found to be 1.5/1.0 by $^1$H-NMR spectroscopy.

Intermolecular competition experiment with enamines 210n and 210l (Scheme 71a)

A mixture of N-{1-(4-methoxyphenyl)vinyl}acetamide (210n) (191 mg, 1.00 mmol), N-{1-(4-nitrophenyl)vinyl}acetamide (210l) (206 mg, 1.00 mmol), diphenylacetylene (38a) (89.0 mg, 0.50 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and Cu(OAc)$_2$·H₂O (200 mg, 1.00 mmol) in t-AmOH (2.0 mL) was stirred at 120 °C under N₂ for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. NH₄Cl/NH₃ (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. NH₄Cl/NH₃ (1:1, 50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 20/1) to yield a mixture of 211na and 211la as a yellow oil. The ratio of products 211na/211la was found to be 2.0/1.0 by $^1$H-NMR spectroscopy.

Intermolecular competition experiment with enamines 210n and 210g (Scheme 71b)
A mixture of \(N\)-\{1-(4-methoxyphenyl)vinyl\}acetamide \(210\text{n}\) (191 mg, 1.00 mmol), \(N\)-\{1-phenylvinyl\}acetamide \(210\text{g}\) (161 mg, 1.00 mmol), diphenylacetylene \(38\text{a}\) (89.0 mg, 0.50 mmol), \([\text{RuCl}_2(\text{p-cymene})]_2\) (15.3 mg, 5.0 mol %) and \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (200 mg, 1.00 mmol) in \(t\)-AmOH (2.0 mL) was stirred at 120 °C under \(\text{N}_2\) for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. \(\text{NH}_4\text{Cl}/\text{NH}_3\) (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. \(\text{NH}_4\text{Cl}/\text{NH}_3\) (1:1, 50 mL) and dried over anhydrous \(\text{Na}_2\text{SO}_4\). After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (\(n\)-hexane/EtOAc: 20/1) to yield a mixture of \(211\text{na}\) and \(211\text{ga}\) as a yellow oil. The ratio of products \(211\text{na}/211\text{ga}\) was found to be 1.2/1.0 by \(^1\text{H}-\text{NMR}\) spectroscopy.

**Intermolecular competition experiment with enamines 210\text{g} and 210\text{l} (Scheme 71c)**

A mixture of \(N\)-\{1-phenylvinyl\}acetamide \(210\text{g}\) (161 mg, 1.00 mmol), \(N\)-\{1-(4-nitrophenyl)vinyl\}acetamide \(210\text{l}\) (206 mg, 1.00 mmol), diphenylacetylene \(38\text{a}\) (89.0 mg, 0.50 mmol), \([\text{RuCl}_2(\text{p-cymene})]_2\) (15.3 mg, 5.0 mol %) and \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (200 mg, 1.00 mmol) in \(t\)-AmOH (2.0 mL) was stirred at 120 °C under \(\text{N}_2\) for 22 h. At ambient temperature, the reaction mixture was diluted with sat. aq. \(\text{NH}_4\text{Cl}/\text{NH}_3\) (1:1, 75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with sat. aq. \(\text{NH}_4\text{Cl}/\text{NH}_3\) (1:1, 50 mL) and dried over anhydrous \(\text{Na}_2\text{SO}_4\). After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (\(n\)-hexane/EtOAc: 20/1) to yield a mixture of \(211\text{ga}\) and \(211\text{la}\) as a yellow oil. The ratio of products \(211\text{ga}/211\text{la}\) was found to be 3.0/1.0 by \(^1\text{H}-\text{NMR}\) spectroscopy.

**Ruthenium-catalyzed H/D exchange with 210\text{l} (Scheme 72a)**

A mixture of \(N\)-\{1-(4-nitrophenyl)vinyl\}acetamide \(210\) (103 mg, 0.50 mmol), \([\text{RuCl}_2(\text{p-cymene})]_2\) (15.3 mg, 5.0 mol %), and \(\text{Cu(OAc)}_2\) (182 mg, 1.00 mmol) in \([\text{D}]_2\text{MeOH}\) (2.0 mL) was stirred at 80 °C for 18 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. \(\text{NH}_4\text{Cl}/\text{NH}_3\) (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with brine (30 mL) and dried over \(\text{Na}_2\text{SO}_4\). After filtration
and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 1/1) to give the mixture of [D]_4-210l and 210l as a white solid (63 mg, 60%). The deuterium incorporation was estimated to be 85% by ¹H-NMR spectroscopy.

**Ruthenium-catalyzed oxidative annulation of alkyne with enamine 210l in [D]_4-MeOH**

(Scheme 72b)

A mixture of N-{1-(4-nitrophenyl)vinyl}acetamide (210l) (103 mg, 0.50 mmol), diphenylacetylene (38e) (178 mg, 1.00 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %), and Cu(OAc)₂ (182 mg, 1.00 mmol) in [D]_4-MeOH (2.0 mL) was stirred at 80 °C under N₂ for 18 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. NH₄Cl/NH₃ (50 mL) and extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with brine (30 mL) and dried over Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the mixture was separated by column chromatography on silica gel (n-hexane/EtOAc: 10/1 to 1/1) to give 211l as a red solid (33 mg, 17%) and 210l as a white solid (35 mg, 34%). No deuterium incorporation was detected by ¹H-NMR spectroscopy.

### 8.4.3 Analytical Data for the Products of Ruthenium-Catalyzed Oxidative Alkenylation of Anilides 212 and Heteroamides 214

**Synthesis of (E)-ethyl 3-(2-acetamido-4-methylphenyl)acrylate (213aa)**

The general procedure D was followed using acetalanlide 212a (74.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (7.7 mg, 5.0 mol %) and KPF₆ (9.2 mg, 10 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1) yielded 213aa (108 mg, 87%) as a white solid.

- **M.p.** = 155–156 °C.
- **¹H-NMR** (300 MHz, CDCl₃): δ = 7.76 (d, J = 15.6 Hz, 1H), 7.54 (q, 1H), 7.50 (s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.33 (d, J = 15.6 Hz, 1H), 6.22 (q, J = 7.1 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).
- **¹³C-NMR** (75 MHz, CDCl₃): δ = 168.9 (Cq), 166.9 (Cq), 141.4 (Cq), 139.2 (CH), 135.7 (Cq), 126.9 (CH), 126.9 (CH), 125.9 (Cq), 124.9 (Cq), 119.3 (CH), 60.6 (CH₂), 24.1 (CH₃), 21.4 (CH₃), 14.2 (CH₃).
- IR (ATR): ν = 3226, 1711, 1660, 1635, 1609, 1537, 1493, 1163, 984, 814 cm⁻¹.
- **MS (EI) m/z** (relative intensity): 247 (28) [M⁺], 204 (25), 160 (97), 138 (20) 132 (92), 117 (22).
- **HR-MS (EI) m/z** calcd for C₁₄H₁₇NO₃⁺ 247.1206, found 247.1209.
Synthesis of (E)-ethyl 3-(2-pivalimidophenyl)acrylate (213ea)

The representative procedure D was followed using acetanilide 213e (88.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1) yielded 213ea (86 mg, 62%) as a white solid.

M.p. = 81–82 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.75 (d, J = 16.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.37 (dd, J = 8.4, 7.8 Hz, 1H), 7.20 (dd, J = 8.0, 7.8 Hz, 1H), 6.38 (d, J = 16.4 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.36 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 176.9 (Cq), 166.5 (Cq), 139.2 (CH), 136.1 (Cq), 130.6 (CH), 128.1 (Cq), 127.1 (CH), 125.8 (CH), 125.1 (CH), 120.8 (CH), 60.3 (CH₂), 39.6 (Cq), 27.6 (CH₃), 14.2 (CH₃).

IR (ATR): v = 3266, 2979, 1711, 1638, 1477, 1365, 1173, 1036, 984, 760 cm⁻¹.

MS (EI) m/z (relative intensity): 275 (20) [M⁺], 190 (22), 174 (12), 146 (38), 117 (36), 90 (15), 57 (100).

HR-MS (EI) m/z calcd for C₁₆H₂₁NO₃⁺ 275.1521, found 275.1522.

Synthesis of (E)-ethyl 3-(2-acetamido-5-methylphenyl)acrylate (213ga)

The general procedure D was followed using acetanilide 212g (74.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 213ga (83 mg, 67%) as a white solid.

M.p. = 134–135 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.76 (d, J = 15.8 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 7.35 (sH, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.37 (d, J = 15.8 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 169.0 (Cq), 166.8 (Cq), 139.4 (CH), 135.7 (Cq), 133.4 (Cq), 131.5 (CH), 127.8 (Cq), 127.3 (CH), 125.5 (CH), 120.2 (CH), 60.6 (CH₂), 24.0 (CH₃), 20.9 (CH₃), 14.2 (CH₃).

IR (ATR): v = 3269, 1712, 1658, 1636, 1525, 1363, 1299, 1174, 970, 815 cm⁻¹.

MS (EI) m/z (relative intensity): 247 (40) [M⁺], 205 (37), 160 (100), 132 (76), 117 (12).

HR-MS (EI) m/z calcd for C₁₄H₁₇NO₅⁺ 247.1206, found 247.1204.

Synthesis of (E)-(n)-butyl 3-(2-acetamido-5-methylphenyl)acrylate (213gb)

The general procedure D was followed using acetanilide 212g (74.5 mg, 0.50 mmol), n-butyl acrylate (76b) (96.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 1/1) yielded 213gb (75 mg, 55%) as a white solid.

M.p. = 112–113 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.76 (d, J = 16.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.34 (sH, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 4.16 (t, J = 6.7 Hz, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 1.70–1.59 (m, 2H), 1.47–1.32 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H).
The spectral data were in accordance with those reported in the literature.\textsuperscript{178}

**Experimental Section**

\textbf{Synthesis of (E)-ethyl 3-(2-acetamido-5-fluorophenyl)acrylate (213ha)}

\[\text{The general procedure D was followed using acetonilide 212h (76.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl}(p\text{-cymene})]_2 (15.3 mg, 5.0 mol %) and KPF}_6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 213ha (93 mg, 74\%)} as a white solid.

M.p. = 143–144 °C.

\(\text{1H-NMR (300 MHz, CDCl}_3\): } \delta = 7.72 (d, J = 15.6 Hz, 1H), 7.59 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.05 (dd, J = 8.2, 8.0 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

\(\text{13C-NMR (75 MHz, CDCl}_3\): } \delta = 169.3 (C_q), 166.4 (C_q), 160.2 (d, \text{ } J_{C-F} = 247 \text{ Hz, C_q}), 138.3 (d, \text{ } J_{C-F} = 2 \text{ Hz, CH}), 131.9 (d, \text{ } J_{C-F} = 3 \text{ Hz, CH}), 130.2 (d, \text{ } J_{C-F} = 8 \text{ Hz, C_q}), 127.9 (d, \text{ } J_{C-F} = 8 \text{ Hz, CH}), 121.4 (CH), 117.7 (d, \text{ } J_{C-F} = 23 \text{ Hz, CH}), 113.1 (d, \text{ } J_{C-F} = 23 \text{ Hz, CH}), 60.8 (CH_2), 23.8 (CH_2), 14.2 (CH_3).

\(\text{19F-NMR (CDCl}_3, 283 \text{ MHz): } \delta = -(111.3–111.5) \text{ (m).}\)

IR (ATR): \(\tilde{\nu} = 3249, 1717, 1656, 1636, 1527, 1486, 1419, 1264, 1177, 971, 852 \text{ cm}^{-1} \).

MS (EI) \(m/z\) (relative intensity): 251 (20) [M\textsuperscript{+}], 207 (32), 164 (100), 146 (22), 136 (70), 108 (16).

HR-MS (EI) \(m/z\) calcd for C\textsubscript{13}H\textsubscript{14}FNO\textsubscript{3}\textsuperscript{+} 251.0958, found 251.0956.

**Synthesis of (E)-(n)-butyl 3-(2-acetamido-5-fluorophenyl)acrylate (213hb)**

\[\text{The general procedure D was followed using acetonilide 212h (76.5 mg, 0.50 mmol), n-butyl acrylate (76b) (96.0 mg, 0.75 mmol), [RuCl}(p\text{-cymene})]_2 (15.3 mg, 5.0 mol %) and KPF}_6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 1/1) yielded 213hb (74 mg, 53\%) as a white solid.\]

M.p. = 138–139 °C.

\(\text{1H-NMR (300 MHz, CDCl}_3\): } \delta = 7.71 (s, 1H), 7.68 (d, J = 15.8 Hz, 1H), 7.51 (dd, J = 8.8, 5.4 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.01 (dd, J = 8.2, 2.9 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 4.14 (t, J = 6.5 Hz, 2H), 2.15 (s, 3H), 1.70–1.56 (m, 2H), 1.46–1.31 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

\(\text{13C-NMR (75 MHz, CDCl}_3\): } \delta = 169.3 (C_q), 166.5 (C_q), 160.3 (d, \text{ } J_{C-F} = 246 \text{ Hz, C_q}), 138.3 (CH), 131.8 (d, \text{ } J_{C-F} = 2 \text{ Hz, C_q}), 130.3 (d, \text{ } J_{C-F} = 8 \text{ Hz, C_q}), 128.0 (d, \text{ } J_{C-F} = 8 \text{ Hz, CH}), 121.2 (CH), 117.6 (d, \text{ } J_{C-F} = 22 \text{ Hz, CH}), 113.0 (d, \text{ } J_{C-F} = 22 \text{ Hz, CH}), 64.7 (CH_2), 30.6 (CH_2), 23.7 (CH_3), 19.1 (CH_2), 13.6 (CH_3).

\(\text{19F-NMR (CDCl}_3, 283 \text{ MHz): } \delta = -111.4 \text{ (m).}\)

IR (ATR): \(\tilde{\nu} = 3255, 2955, 1717, 1656, 1636, 1527, 1486, 1174, 1015, 852 \text{ cm}^{-1} \).

MS (El) m/z (relative intensity): 279 (11) [M⁺], 237 (16), 164 (100), 136 (55), 108 (10).
HR-MS (El) m/z calcd for C₁₃H₁₉FNO₃⁺ 279.1271, found 279.1268.
The spectral data were in accordance with those reported in the literature.¹⁷⁸

**Synthesis of (E)-ethyl 3-(2-acetamido-5-(trifluoromethyl)phenyl)acrylate (213ia)**

The general procedure D was followed using acetonilide 212i (101.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1) yielded 213ia (69 mg, 46%) as a white solid.

M.p. = 168–169 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.01 (s, 1H), 7.78 (d, J = 16.3 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 16.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.23 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 169.0 (Cₗ), 166.3 (Cₗ), 138.8 (Cₗ), 137.8 (CH), 127.2 (q, Jₖ₋ₐ = 10 Hz, CH), 127.0 (q, Jₖ₋ₐ = 33 Hz, Cₗ), 124.4 (q, Jₖ₋ₐ = 4 Hz, CH), 124.2 (q, Jₖ₋ₐ = 11 Hz, CH), 123.6 (q, Jₖ₋ₐ = 273 Hz, Cₗ), 122.4 (CH), 121.8 (Cₗ), 61.0 (CH₂), 24.2 (CH₃), 14.2 (CH₃).

¹⁹F-NMR (CDCl₃, 283 MHz): δ = −62.6 (s).

IR (ATR): υ = 3269, 1719, 1661, 1585, 1527, 1369, 1278, 1108, 1039, 834 cm⁻¹.

MS (El) m/z (relative intensity): 301 (12) [M⁺], 259 (20), 212 (100), 196 (20), 186 (55), 166 (21), 43 (38).

HR-MS (El) m/z calcd for C₁₄H₁₅F₃NO⁺ 301.0926, found 301.0920.

**Synthesis of (E)-(n)-butyl 3-(2-acetamido-4-methylphenyl)acrylate (213ab)**

The general procedure D was followed using acetonilide 212a (74.5 mg, 0.50 mmol), n-butyl acrylate (76b) (96.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1) yielded 213ab (77 mg, 56%) as a white solid.

M.p. = 138–139 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 7.77 (d, J = 16.0 Hz, 1H), 7.51 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 16.0 Hz, 1H), 4.17 (t, J = 6.7 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 1.72–1.59 (m, 2H), 1.48–1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 168.9 (Cₗ), 167.0 (Cₗ), 141.4 (Cₗ), 139.2 (CH), 135.7 (Cₗ), 126.9 (CH), 126.8 (CH), 125.9 (Cₗ), 124.9 (CH), 119.3 (CH), 64.5 (CH₂), 30.7 (CH₂), 24.1 (CH₃), 21.4 (CH₄), 19.1 (CH₃), 13.7 (CH₃).

IR (ATR): υ = 3267, 2958, 1708, 1656, 1569, 1532, 1251, 1067, 973, 813 cm⁻¹.

MS (El) m/z (relative intensity): 275 (17) [M⁺], 233 (10), 160 (92), 138 (20), 132 (100), 117 (13).

HR-MS (El) m/z calcd for C₁₄H₁₂FNO⁺ 275.1521, found 275.1525.

The spectral data were in accordance with those reported in the literature.¹⁷⁸

**Synthesis of (E)-ethyl 3-(2-acetamido-4-methoxyphenyl)acrylate (213ja)**

The general procedure D was followed using acetonilide 212j (82.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h,
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purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 213ja (77 mg, 58%) as a white solid.

M.p. = 132–133 °C.

1H-NMR (300 MHz, CDCl3): δ = 7.75 (d, J = 15.7 Hz, 1H), 7.58 (sbr, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 2.22 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 168.8 (Cq), 167.1 (Cq), 161.6 (Cq), 138.7 (CH), 137.4 (Cq), 128.2 (CH), 119.3 (Cq), 117.8 (CH), 112.5 (CH), 109.2 (CH), 60.5 (CH2), 55.4 (CH3), 14.3 (CH3).

IR (ATR): ν = 3258, 2976, 1697, 1660, 1610, 1573, 1435, 132−133 °C.

MS (EI) m/z (relative intensity): 267 (18) [M+], 218 (20), 176 (65), 148 (70), 132 (38), 104 (22).

HR-MS (EI) m/z calcd for C14H17NO4+ 263.1118, found 263.1114.

Synthesis of (E)-(n)-butyl 3-(2-acetamido-4-methoxyphenyl)acrylate (213jb)

The general procedure D was followed using acetanilide 212j (82.5 mg, 0.50 mmol), n-butyl acrylate (76b) (96.0 mg, 0.75 mmol), [RuCl3(p-cymene)]2 (15.3 mg, 5.0 mol %) and KPF6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1) yielded 213jb (76 mg, 52%) as a white solid.

M.p. = 138–139 °C.

1H-NMR (300 MHz, CDCl3): δ = 7.75 (d, J = 16.4 Hz, 1H), 7.61 (sbr, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.40 (s, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.27 (d, J = 16.4 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.76 (s, 3H), 2.22 (s, 3H) 1.78–1.59 (m, 2H), 1.51–1.33 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 167.1 (Cq), 161.8 (Cq), 138.7 (CH), 137.6 (Cq), 137.6 (Cq), 128.4 (CH), 118.2 (CH), 112.6 (CH), 112.6 (Cq), 109.3 (CH), 64.4 (CH2), 55.5 (CH3), 30.8 (CH2), 24.2 (CH3), 19.2 (CH2), 13.6 (CH3).

IR (ATR): ν = 3266, 2952, 1697, 1660, 1609, 1573, 1444, 1110, 972, 767 cm−1.

MS (EI) m/z (relative intensity): 291 (25) [M+], 249 (20), 176 (65), 148 (100), 132 (26), 104 (13).

HR-MS (EI) m/z calcd for C14H17NO4+ 291.1471, found 291.1472.

The spectral data were in accordance with those reported in the literature.178

Synthesis of (E)-ethyl 3-(2-acetamido-4-chlorophenyl)acrylate (213ka)

The general procedure D was followed using acetanilide 212k (84.5 mg, 0.50 mmol), ethyl acrylate (76a) (150 mg, 1.50 mmol), [RuCl3(p-cymene)]2 (15.3 mg, 5.0 mol %) and KPF6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 1/1) yielded 213ka (88 mg, 66%) as a white solid.

M.p. = 167–168 °C.

1H-NMR (300 MHz, CDCl3): δ = 7.87 (s, 1H), 7.75 (sbr, 1H), 7.69 (d, J = 15.8 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 4.22 (q, J = 7.3 Hz, 2H), 2.19 (s, 3H), 1.30 (t, J = 7.3 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 169.1 (Cq), 166.6 (Cq), 138.2 (CH), 136.8 (Cq), 136.3 (Cq), 127.8 (CH), 125.8 (CH), 125.6 (Cq), 124.9 (CH), 120.6 (CH), 60.8 (CH2), 24.0 (CH3), 14.2 (CH3).

IR (ATR): ν = 3249, 1712, 1665, 1568, 1521, 1474, 1266, 1244, 975, 810 cm−1.

MS (EI) m/z (relative intensity): 267 (18) [M+], 225 (25), 176 (100), 152 (90), 117 (30), 89 (32).
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HR-MS (EI) m/z calcld for C_{13}H_{14}ClNO_{3}^+ 267.0662, found 267.0622.

**Synthesis of (E)-ethyl 3-[2-acetamido-4-(trifluoromethyl)phenyl]acrylate (213la)**

The general procedure D was followed using acetanilide 2131 (102 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl_2(p-cymene)]_2 (15.3 mg, 5.0 mol %) and KPF_6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 4/1) yielded 213la (76 mg, 53%) as a white solid.

M. p. = 138–139 °C.

1H-NMR (300 MHz, CDCl_3): δ = 7.98 (s, 1H), 7.96 (s, 1H), 7.73 (d, J = 15.8 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.20 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl_3): δ = 169.3 (C_q), 166.2 (C_q), 138.0 (CH), 136.2 (C_q), 132.1 (q, 2J_{C-F} = 33 Hz, C_q), 130.6 (C_q), 127.4 (CH), 123.4 (q, J_{C-F} = 273 Hz, C_q), 122.5 (CH), 121.1 (q, 3J_{C-F} = 14 Hz, CH), 121.7 (q, 3J_{C-F} = 12 Hz, CH), 60.9 (CH_2), 23.9 (CH_3), 14.1 (CH_3).

19F-NMR (CDCl_3, 283 MHz): δ = −63.0 (s).

IR (ATR): ν = 3255, 2984, 1712, 1661, 1531, 1387, 1328, 1110, 822, 553 cm\(^{-1}\).

MS (EI) m/z (relative intensity): 301 (10) [M^+] , 259 (20), 212 (100), 196 (20), 186 (65), 166 (25).

HR-MS (EI) m/z calcld for C_{14}H_{13}F_3NO_{3}^+ 301.0926, found 301.0918.

**Synthesis of (E)-ethyl 3-(2-acetamido-6-fluorophenyl)acrylate (213ma)**

The general procedure D was followed using acetanilide 212m (76.5 mg, 0.50 mmol), ethyl acrylate (76a) (75.0 mg, 0.75 mmol), [RuCl_2(p-cymene)]_2 (15.3 mg, 5.0 mol %) and KPF_6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 213ma (88 mg, 70%) as a white solid.

M. p. = 138–143 °C.

1H-NMR (300 MHz, CDCl_3): δ = 7.65–7.52 (m, 2H), 7.60 (d, J = 16.9 Hz, 1H), 7.30 (dd, J = 9.6, 9.6 Hz, 1H), 6.93 (dd, J = 9.6, 8.7 Hz, 1H), 6.57 (d, J = 16.9 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.21 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl_3): δ = 168.8 (C_q), 166.9 (C_q), 161.3 (d, J_{C-F} = 252 Hz, C_q), 137.3 (d, J_{C-F} = 4 Hz, C_q), 133.3 (CH), 130.8 (d, J_{C-F} = 10 Hz, CH), 124.8 (d, J_{C-F} = 11 Hz, CH), 120.5 (CH), 116.1 (d, J_{C-F} = 10 Hz, C_q), 112.8 (d, J_{C-F} = 24 Hz, CH), 60.8 (CH_2), 24.2 (CH_3), 14.2 (CH_3).

19F-NMR (CDCl_3, 283 MHz): δ = −110.4 (s).

IR (ATR): ν = 3264, 1719, 1664, 1636, 1572, 1364, 1184, 1029, 751, 530 cm\(^{-1}\).

MS (EI) m/z (relative intensity): 251 (10) [M^+] , 207 (8), 164 (58), 146 (15), 136 (38), 108 (10).

HR-MS (EI) m/z calcld for C_{14}H_{13}FNO_{3}^+ 251.0958, found 251.0959.

**Synthesis of N-(5-methyl-2-(3-oxobutyl)phenyl)acetamide (213ac)**

The general procedure D was followed using N-(m-tolyl)acetamide 212a (74.5 mg, 0.50 mmol), 3-buten-2-one (76c) (52.5 mg, 0.75 mmol), [RuCl_2(p-cymene)]_2 (15.3 mg, 5.0 mol %) and KPF_6 (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1→2/1) yielded 213ac (34 mg, 31%) as a white solid.
M.p. = 132–133 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 9.00$ (s, 1H), 7.62 (s, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 2.88 (t, $J = 6.7$ Hz, 2H), 2.76 (t, $J = 6.7$ Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 208.7$ (C$_q$), 169.1 (C$_q$), 137.0 (C$_q$), 135.6 (C$_q$), 129.8 (CH), 129.7 (C$_q$), 126.2 (CH), 125.0 (CH), 45.7 (CH$_2$), 30.2 (CH$_3$), 24.5 (CH$_3$), 23.7 (CH$_2$), 21.3 (CH$_3$).

IR (ATR): $\tilde{\nu} = 3276, 2949, 1708, 1650, 1576, 1531, 1370, 1284, 1161, 814, 553$ cm$^{-1}$.

MS (EI) m/z (relative intensity): 217 (28) [M$^+$], 176 (67), 158 (25), 134 (100), 120 (90), 107 (20).

HR-MS (EI) m/z calcd for C$_{13}$H$_{17}$NO$_2$ $^{+}$ 217.1259, found 217.1257.

### Ruthenium-catalyzed oxidative alkenylations of anilide 212a in 5 mmol scale (Scheme 75)

A mixture of acetanilide 212a (715 mg, 5.0 mmol), ethyl acrylate (76a) (750 mg, 7.5 mmol), [RuCl$_2$(p-cymene)]$_2$ (76.5 mg, 2.5 mol %), KPF$_6$ (92.0 mg, 10 mol %) and Cu(OAc)$_2$·H$_2$O (1.0 g, 5.0 mmol) in H$_2$O (2.0 mL) was stirred at 105 °C under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phase was dried over anhydrous Na$_2$SO$_4$ (50 g). After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc/CH$_2$Cl$_2$: 9/5/1 → 6/4/1) to yield 213aa (901 mg, 73%) as a white solid.

### Intermolecular competition experiment with anilides 212h and 212d (Scheme 76a)

A mixture of N-(4-fluorophenyl)acetamide (212h) (153 mg, 1.00 mmol), N-phenylacetamide (212d) (135 mg, 1.00 mmol), ethyl acrylate (76a) (50.0 mg, 0.50 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %), KPF$_6$ (18.4 mg, 20 mol %) and Cu(OAc)$_2$·H$_2$O (99.5 mg, 1.00 mmol) in H$_2$O (2.0 mL) was stirred at 120 °C under N$_2$ for 20 h. At ambient temperature, the mixture was diluted with H$_2$O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the conversion of the crude mixture was determined by GC (38%, 213ha:213da = 1.0:2.5).
Intermolecular competition experiment with anilides 212o and 212d (Scheme 76b)

A mixture of N-(4-methoxyphenyl)acetamide (212o) (165 mg, 1.00 mmol), N-phenylacetamide (212d) (135 mg, 1.00 mmol), ethyl acrylate (76a) (50.0 mg, 0.50 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %), KPF₆ (18.4 mg, 20 mol %) and Cu(OAc)₂·H₂O (99.5 mg, 1.00 mmol) in H₂O (2.0 mL) was stirred at 120 °C under N₂ for 20 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 2/1) to yield a mixture of 213oa and 213da as a white solid. The ratio of products 213oa:213da was found to be 1.3:1.0 by ¹H-NMR spectroscopy.

Intermolecular competition experiment with anilides 212h and 212o (Scheme 76c)

A mixture of N-(4-fluorophenyl)acetamide (212h) (153 mg, 1.00 mmol), N-(4-methoxyphenyl)acetamide (212o) (165 mg, 1.00 mmol), ethyl acrylate (76a) (50.0 mg, 0.50 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %), KPF₆ (18.4 mg, 20 mol %) and Cu(OAc)₂·H₂O (99.5 mg, 1.00 mmol) in H₂O (2.0 mL) was stirred at 120 °C under N₂ for 20 h. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 2/1) to yield a mixture of 213ha and 213oa as a white solid. The ratio of products 213ha:213oa was found to be 1.0:1.1 by ¹H-NMR spectroscopy.

Ruthenium-catalyzed H/D exchange in D₂O (Scheme 77b)

A mixture of acetanilide (212a) (149 mg, 1.00 mmol), ethyl acrylate (76a) (150 mg, 1.50 mmol), [RuCl₂(p-cymene)]₂ (30.6 mg, 5.0 mol %), KPF₆ (36.8 mg, 20 mol %) and Cu(OAc)₂ (181 mg, 1.00 mmol) in D₂O (2.0 mL) was stirred at 120 °C for 45 min. The mixture was then washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 2/1) to yield a mixture of 213oa as a white solid. The ratio of products 213oa was found to be 67% by ¹H-NMR spectroscopy.
1.00 mmol) in D$_2$O (3.0 mL) was stirred at 120 °C under N$_2$ for 45 min. At ambient temperature, the mixture was diluted with sat. aq. NH$_4$Cl/NH$_3$ (1:1, 50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 2/1→1/1) to yield [D]$_{212a}$ (100 mg, 67%) as a white solid and [D]$_{213aa}$ (67 mg, 27%) as a white solid. The deuterium incorporation was estimated by $^1$H-NMR spectroscopy.

**Synthesis of (E)-ethyl 3-[1-methyl-3-(methylcarbamoyl)-1H-indol-2-yl]acrylate (215aa)**

The general procedure D was followed using indole 214a (94 mg, 0.50 mmol), ethyl acrylate (76a) (75 mg, 0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 1/1) yielded 215aa (75 mg, 52%) as a white solid.

M.p. = 193–194 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 8.08 (d, $J$ = 16.3 Hz, 1H), 7.79 (d, $J$ = 8.0 Hz, 1H), 7.36–7.30 (m, 2H), 7.21 (dd, $J$ = 8.0, 5.1 Hz, 1H), 6.53 (d, $J$ = 16.3 Hz, 1H), 6.00 (s$_{\text{sr}}$, 1H), 4.28 (q, $J$ = 7.1 Hz, 2H), 3.78 (CH$_3$), 3.05 (d, $J$ = 5.0 Hz, 3H), 1.35 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 164.4 (C$_q$), 165.7 (C$_q$), 138.1 (C$_q$), 135.1 (C$_q$), 132.1 (CH), 125.2 (C$_q$), 124.2 (CH), 123.4 (CH), 121.7 (CH), 120.2 (CH), 113.8 (C$_q$), 110.1 (CH), 60.8 (CH$_2$), 31.4 (CH$_3$), 26.6 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3264, 1698, 1628, 1543, 1467, 1400, 1377, 1027, 731 cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 286 (30) [M$^+$], 219 (100), 199 (40), 184 (25), 128 (10).

HR-MS (EI) $m/z$ calcld for C$_{16}$H$_{13}$N$_2$O$_3$+ 286.1317, found 286.1321.

**Synthesis of (E)-ethyl 3-[1-methyl-2-(methylcarbamoyl)-1H-indol-3-yl]acrylate (215ba)**

The general procedure D was followed using indole 214b (94 mg, 0.50 mmol), ethyl acrylate (76a) (75 mg, 0.75 mmol), [RuCl$_2$(p-cymene)]$_2$ (15.3 mg, 5.0 mol %) and KPF$_6$ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 1/1) yielded 215ba (102 mg, 71%) as a white solid.

M.p. = 173–174 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 7.97 (d, $J$ = 16.0 Hz, 1H), 7.91 (d, $J$ = 8.2 Hz, 1H), 7.46–7.32 (m, 2H), 7.26 (dd, $J$ = 8.8, 4.0 Hz, 1H), 6.48 (d, $J$ = 16.0 Hz, 1H), 6.30 (s$_{\text{sr}}$, 1H), 4.19 (q, $J$ = 7.1 Hz, 2H), 3.85 (s, 3H), 3.10 (d, $J$ = 5.1 Hz, 3H), 1.29 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 167.9 (C$_q$), 162.2 (C$_q$), 138.1 (C$_q$), 136.4 (C$_q$), 136.3 (CH), 124.6 (C$_q$), 124.5 (CH), 122.0 (CH), 121.4 (CH), 116.1 (CH), 111.3 (CH), 110.4 (C$_q$), 60.3 (CH$_2$), 31.3 (CH$_3$), 26.9 (CH$_3$), 14.3 (CH$_3$).

IR (ATR): $\tilde{\nu}$ = 3271, 2981, 1709, 1623, 1547, 1469, 1368, 1131, 977, 730 cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 286 (40) [M$^+$], 228 (26), 219 (100), 200 (32), 184 (25), 111 (15).

HR-MS (EI) $m/z$ calcld for C$_{16}$H$_{14}$N$_2$O$_3$+ 286.1317, found 286.1321.
Synthesis of (E)-ethyl 3-[2-(methylcarbamoyl)benzofuran-3-yl]acrylate (215da)

The general procedure D was followed using benzofurane 214d (87.5 mg, 0.50 mmol), ethyl acrylate (76a) (75 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %) in H₂O (2.0 mL). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 215da as a white solid (49 mg, 36%).

The general procedure D was followed using benzofurane 214d (87.5 mg, 0.50 mmol), ethyl acrylate (76a) (75 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %) in t-AmOH (2.0 mL). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 215da as a white solid (87 mg, 64%).

M.p. = 141−138 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.66 (d, J = 16.0 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.52−7.30 (m, 3H), 6.86 (sbr, 1H), 6.69 (d, J = 16.0 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.04 (d, J = 5.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 166.5 (Cₘ), 159.6 (C₂₂), 153.5 (Cₗ), 145.5 (Cₗ), 124.8 (CH), 127.4 (CH), 125.7 (Cₘ), 124.4 (CH), 122.7 (CH), 122.3 (CH), 120.1 (Cₗ), 111.9 (CH), 60.6 (CH₂), 26.0 (CH₃), 14.3 (CH₃).

IR (ATR): ν = 3308, 1714, 1649, 1539, 1247, 1170, 1146, 743, 692 cm⁻¹.

MS (El) m/z (relative intensity): 239 (25 [M⁺]), 200 (100), 187 (9), 111 (10).

HR-MS (El) m/z calcd for C₁₃H₁₂NO₃ 273.1001, found 273.0997.

Synthesis of (E)-ethyl 3-[2-(methylcarbamoyl)thiophen-3-yl]acrylate (215ea)

The general procedure D was followed using thiophene 214e (70.5 mg, 0.50 mmol), ethyl acrylate (76a) (75 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 1/1) yielded 215ea (92 mg, 76%) as a white solid.

M.p. = 92−93 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.25 (d, J = 16.0 Hz, 1H), 7.31 (dd, J = 6.1, 5.4 Hz, 1H), 7.29 (dd, J = 6.1, 5.4 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 5.94 (sbr, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.00 (d, J = 4.9 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 166.7 (Cₘ), 162.2 (C₂₂), 138.4 (Cₗ), 136.4 (CH), 136.0 (Cₗ), 127.0 (CH), 126.7 (CH), 121.4 (CH), 60.6 (CH₂), 27.0 (CH₃), 14.3 (CH₃).

IR (ATR): ν = 3266, 2976, 1707, 1624, 1539, 1247, 1119, 1036, 981, 613 cm⁻¹.

MS (El) m/z (relative intensity): 239 (25 [M⁺]), 166 (76), 152 (100), 137 (23), 125 (22), 97 (25).

HR-MS (El) m/z calcd for C₁₃H₁₂NO₃S⁺ 239.0616, found 239.0615.

Synthesis of (E)-(n)-butyl 3-[2-(methylcarbamoyl)thiophen-3-yl]acrylate (215eb)

The general procedure D was followed using thiophene 214e (70.5 mg, 0.50 mmol), n-butyl acrylate (76b) (96 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %) and KPF₆ (18.4 mg, 20 mol %). After 20 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1) yielded 215eb (96 mg, 72%) as a white solid.

M.p. = 93−94 °C.

¹H-NMR (300 MHz, CDCl₃): δ = 8.18 (d, J = 16.1 Hz, 1H), 7.26 (d, J = 5.2 Hz, 1H), 7.22 (d, J =
5.2 Hz, 1H), 6.25 (d, J = 16.1 Hz, 1H), 6.20 (s, 1H), 4.14 (q, J = 6.4 Hz, 2H), 2.93 (d, J = 5.0 Hz, 1H), 1.69–1.57 (m, 2H), 1.44–1.29 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 166.8 (Cq), 162.6 (Cq), 138.2 (Cq), 136.4 (CH), 126.9 (CH), 126.5 (CH), 121.0 (CH), 109.1 (Cq), 64.3 (CH3), 30.7 (CH3), 26.9 (CH3), 18.8 (CH3), 13.7 (CH3).

IR (ATR): ν = 3272, 2952, 1706, 1625, 1541, 1270, 1227, 1066, 987, 737 cm⁻¹.

MS (EI) m/z (relative intensity): 267 (25) [M⁺], 208 (10), 166 (100), 152 (16).

HR-MS (EI) m/z calcd for C₁₁H₁₂NO₃S² 267.0929, found 267.0922.

Intramolecular competition experiments with amide 214f (Scheme 81)

A mixture of thiophene 214f (70.5 mg, 0.50 mmol), ethyl acrylate (76a) (75 mg, 0.75 mmol), [RuCl₂(p-cymene)]₂ (15.3 mg, 5.0 mol %), KPF₆ (18.4 mg, 20 mol %) and Cu(OAc)₂·H₂O (99.5 mg, 1.00 mmol) in H₂O (2.0 mL) was stirred under N₂ for 20 h at 120 °C. At ambient temperature, the mixture was diluted with H₂O (75 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 1/1) to yield a mixture of 215fa and 215fa (59 mg, 49%, 12:1 mixture of regioisomers according to 1H-NMR) as a white solid. Recrystallization (n-hexane/CH₂Cl₂: 2/1) gave the major regioisomer 215fa (44 mg, 37%) as a white solid.

(E)-Ethyl 3-[3-(methylcarbamoyl)thiophen-2-yl]acrylate (215fa)

M.p. = 128–129 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.32 (d, J = 15.9 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 5.1 Hz, 1H), 6.26 (d, J = 15.9 Hz, 1H), 6.03 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.96 (d, J = 4.5 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 166.2 (Cq), 164.3 (Cq), 141.0 (Cq), 137.3 (Cq), 135.4 (CH), 127.6 (CH), 126.9 (CH), 120.0 (CH), 60.6 (CH₃), 26.7 (CH₃), 14.3 (CH₃).

IR (ATR): ν = 3381, 3103, 1712, 1626, 1549, 1436, 1296, 1252, 982, 719 cm⁻¹.

MS (EI) m/z (relative intensity): 239 (13) [M⁺], 166 (100), 152 (20), 137 (20) 109 (10).

HR-MS (EI) m/z calcd for C₁₁H₁₂NO₃S² 239.0616, found 239.0611.

8.4.4 Analytical Data for the Products of Ruthenium-Catalyzed C(sp³)–H α-Alkylation of Pyrrolidine 209 with Alkene 111

Synthesis of 2-(2-α-decylpyrrolidin-1-yl)-3-methylpyridine (217ba)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 1-decene (111a) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded 217ba (138 mg, 94%) as a colorless oil.

1H-NMR (300 MHz, CDCl3): δ = 8.06 (dd, J = 5.0, 2.0 Hz, 1H), 7.30–7.27 (m, 1H), 6.65 (dd, J = 7.1, 5.0 Hz, 1H), 4.28–4.20 (m, 1H), 3.70–3.62 (m, 1H), 3.23–3.11 (m, 1H), 2.23 (s, 3H), 2.19–2.09 (m, 1H), 1.95–1.54 (m, 4H), 1.29–1.17 (m, 17H), 0.89–0.85 (m, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 159.6 (Cq), 144.6 (CH), 139.1 (CH), 121.9 (Cq), 114.6 (CH), 58.2 (CH), 51.7 (CH₂), 34.2 (CH₂), 31.9 (CH₂), 31.2 (CH₂), 29.9 (CH₂), 29.6 (CH₂), 29.6 (CH₂),
29.6 (CH3), 29.3 (CH2), 25.9 (CH2), 24.9 (CH2), 22.7 (CH2), 20.1 (CH3), 14.1 (CH3).
IR (ATR): \(\tilde{\nu} = 2922, 2853, 1588, 1564, 1384, 1346, 1186, 993, 775 \text{ cm}^{-1}\).
MS (EI) \(m/z\) (relative intensity): 302 (5) [M+], 287 (3), 208 (5), 161 (100), 133 (10), 107 (9), 92 (14), 43 (10).
HR-MS (EI) \(m/z\) calcld for C20H33N2+ 302.2722, found 302.2724.

**Synthesis of 2-(2-n-decylpyrrolidin-1-yl)-3-(trifluoromethyl)pyridine (217ca)**

The general procedure E was followed using 2-(pyrrolidin-1-yl)-3-(trifluoromethyl)pyridine (216c) (324 mg, 1.5 mmol) and 1-decene (2a) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 100/1) yielded 217ca (128 mg, 72%) as a colorless oil.

\(^1\)H-NMR (300 MHz, CDCl₃): \(\delta = 8.25\) (dd, \(J = 4.9, 1.8\) Hz, 1H), 7.75 (d, \(J = 7.4\) Hz, 1H), 6.61 (dd, \(J = 7.4, 4.9\) Hz, 1H), 4.47–4.36 (m, 1H), 3.65–3.53 (m, 1H), 3.41–3.31 (m, 1H), 2.14–2.04 (m, 1H), 1.97–1.87 (m, 1H), 1.82–1.56 (m, 3H), 1.35–1.16 (m, 17H), 0.85 (t, \(J = 6.6\) Hz, 3H).

\(^1^3\)C-NMR (75 MHz, CDCl₃): \(\delta = 155.7\) (Cq), 150.4 (CH), 137.0 (q, \(J_{C,F} = 6\) Hz, CH), 124.6 (q, \(J_{C,F} = 272\) Hz, Cq), 111.8 (CH), 110.7 (q, \(J_{C,F} = 32\) Hz, Cq), 58.9 (CH), 51.6 (q, \(J_{C,F} = 5\) Hz, CH₂), 33.6 (CH₂), 31.9 (CH₂), 30.5 (CH₂), 29.8 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 25.6 (CH₂), 25.5 (CH₂), 22.7 (CH₂), 14.1 (CH₃).

\(^1^9\)F-NMR (283 MHz, CDCl₃): \(\delta = -56.6\) (s).

IR (ATR): \(\tilde{\nu} = 2923, 2854, 1596, 1556, 1449, 1369, 1302, 1097, 767 \text{ cm}^{-1}\).

MS (EI) \(m/z\) (relative intensity): 356 (4) [M⁺], 213 (100), 175 (4), 146 (5).

HR-MS (EI) \(m/z\) calcld for C₂₀H₃₁F₃N₂⁺ 356.2439, found 356.2432.

**Synthesis of 3-methyl-2-(2-n-nonylpyrrolidin-1-yl)pyridine (217da)**

The general procedure E was followed using 4-methyl-2-(pyrrolidin-1-yl)pyridine (216d) (243 mg, 1.5 mmol) and 1-decene (111a) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 217da (97 mg, 64%) as a colorless oil.

\(^1\)H-NMR (300 MHz, CDCl₃): \(\delta = 7.99\) (d, \(J = 5.2\) Hz, 1H), 6.32 (dd, \(J = 5.2, 1.2\) Hz, 1H), 6.12 (s, 1H), 3.93–3.82 (m, 1H), 3.56–3.46 (m, 1H), 3.41–3.29 (m, 1H), 2.22 (s, 3H), 2.04–1.65 (m, 5H), 1.38–1.12 (m, 17H), 0.86 (t, \(J = 6.6\) Hz, 3H).

\(^1^3\)C-NMR (75 MHz, CDCl₃): \(\delta = 157.4\) (Cq), 147.9 (CH), 147.4 (Cq), 112.5 (CH), 106.8 (CH), 57.6 (CH), 47.4 (CH₂), 33.0 (CH₂), 31.9 (CH₂), 30.1 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 26.4 (CH₂), 23.4 (CH₂), 22.7 (CH₂), 21.3 (CH₃), 14.1 (CH₃).

IR (ATR): \(\tilde{\nu} = 2921, 2852, 1708, 1604, 1553, 1453, 1297, 1176, 792, 447 \text{ cm}^{-1}\).

MS (EI) \(m/z\) (relative intensity): 302 (5) [M⁺], 161 (100), 133 (7), 92 (9), 41 (7).

HR-MS (EI) \(m/z\) calcld for C₂₀H₃₁N₂⁺ 302.2722, found 302.2722.

**Synthesis of 2-(2-n-decylpyrrolidin-1-yl)-5-fluoropyridine (217ea)**

The general procedure E was followed using 5-fluoro-2-(pyrrolidin-1-yl)pyridine (216e) (249 mg, 1.5 mmol) and 1-decene (111a) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217ea (116 mg,
76%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.99$ (d, $J = 3.0$ Hz, 1H), 7.17 (ddd, $J = 8.8, 3.0, 1.1$ Hz, 1H), 6.24 (dd, $J = 8.8, 3.0$ Hz, 1H), 3.87–3.78 (m, 1H), 3.52–3.43 (m, 1H), 3.35–3.25 (m, 1H), 2.04–1.65 (m, 5H), 1.34–1.16 (m, 17H), 0.86 (t, $J = 6.6$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 154.1$ (C$_q$), 152.4 (d, $^1J_{C-F} = 240$ Hz, C$_q$), 134.6 (d, $^2J_{C-F} = 24$ Hz, CH), 124.6 (d, $^2J_{C-F} = 20$ Hz, CH), 106.4 (d, $^3J_{C-F} = 4$ Hz, CH), 58.2 (CH), 47.4 (CH$_2$), 33.1 (CH$_2$), 31.9 (CH$_3$), 30.2 (CH$_3$), 29.8 (CH$_3$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 26.5 (CH$_2$), 23.5 (CH$_2$), 22.7 (CH$_3$), 14.1 (CH$_3$).

$^{19}$F-NMR (283 MHz, CDCl$_3$): $\delta = -(146.91–146.95)$ (m).

IR (ATR): $\tilde{\nu} = 2922, 2852, 1613, 1492, 1407, 1224, 762$ cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 306 (22) [M$^+$], 305 (100) [M–H$^+$], 165 (18).

HR-MS (EI) $m/z$ calcld for C$_{19}$H$_{31}$F$_2$N$_2^+$ 306.2471, found 306.2387.

**Synthesis of 1-(2-n-decylpyrroolidin-1-yl)isoquinoline (217ga)**

The general procedure E was followed using 1-(pyrroolidin-1-yl)isoquinoline (216g) (297 mg, 1.5 mmol) and 1-decene (111a) (70.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217ga (113 mg, 67%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.10$ (d, $J = 8.6$ Hz, 1H), 8.03 (d, $J = 5.7$ Hz, 1H), 7.65 (d, $J = 8.2$ Hz, 1H), 7.52 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.38 (ddd, $J = 8.6, 8.2, 1.2$ Hz, 1H), 7.01 (d, $J = 5.7$ Hz, 1H), 4.61–4.50 (m, 1H), 4.02–3.92 (m, 1H), 3.65–3.56 (m, 1H), 2.26–2.13 (m, 1H), 1.99–1.81 (m, 1H), 1.81–1.61 (m, 2H), 1.43–1.16 (m, 17H), 0.87 (t, $J = 6.7$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 158.8$ (C$_q$), 140.9 (CH), 138.6 (C$_q$), 129.0 (CH), 126.5 (CH), 126.3 (CH), 124.4 (CH), 121.4 (C$_q$), 112.4 (CH), 58.9 (CH), 54.8 (CH$_2$), 34.0 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_3$), 29.9 (CH$_3$), 29.6 (CH$_3$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 25.9 (CH$_2$), 25.9 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2921, 2852, 1585, 1551, 1503, 1408, 1346, 761, 743, 681$ cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 338 (14) [M$^+$], 255 (7), 225 (6), 197 (100), 183 (15), 169 (22), 143 (33), 128 (27).

HR-MS (EI) $m/z$ calcld for C$_{23}$H$_{31}$N$_2^+$ 338.2722, found 338.2730.

**Synthesis of 2-(2-n-hexylpyrroolidin-1-yl)-3-methylpyridine (217bb)**

The general procedure E was followed using 3-methyl-2-(pyrroolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 1-hexene (111b) (38.0 mg, 0.5 mmol) at 80 °C. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217bb (90 mg, 73%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.04$ (dd, $J = 5.0, 1.8$ Hz, 1H), 7.26 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.62 (dd, $J = 7.4, 5.0$ Hz, 1H), 4.29–4.16 (m, 1H), 3.70–3.58 (m, 1H), 3.21–3.09 (m, 1H), 2.20 (s, 3H), 2.17–2.05 (m, 1H), 1.93–1.52 (m, 4H), 1.29–1.14 (m, 9H), 0.83 (t, $J = 6.3$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 159.7$ (C$_q$), 144.7 (CH), 138.9 (CH), 121.9 (C$_q$), 114.7 (CH), 58.1 (CH), 51.7 (CH$_2$), 34.3 (CH$_2$), 31.9 (CH$_2$), 31.2 (CH$_2$), 29.6 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 22.6 (CH$_2$), 20.0 (CH$_3$), 14.1 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2922, 2856, 1588, 1563, 1383, 1345, 975, 774$ cm$^{-1}$. MS (EI) $m/z$ (relative
Experimental Section

Synthesis of 2-(2-<i>n</i>-heptylpyrrolidin-1-<i>yl</i>)-3-methylpyridine (217bc)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-<i>yl</i>)pyridine (216b) (243 mg, 1.5 mmol) and 1-heptene (111c) (49.0 mg, 0.5 mmol) at 80 °C. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217bc (103 mg, 78%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, <i>J</i> = 4.9, 1.8 Hz, 1H), 7.26 (dd, <i>J</i> = 7.4, 1.8 Hz, 1H), 6.62 (dd, <i>J</i> = 7.4, 4.9 Hz, 1H), 4.28–4.15 (m, 1H), 3.70–3.57 (m, 1H), 3.21–3.09 (m, 1H), 2.21 (s, 3H), 2.17–2.05 (m, 1H), 1.95–1.52 (m, 5H), 1.35–1.11 (m, 10H), 0.84 (t, <i>J</i> = 6.1 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (Cq), 144.7 (CH), 138.9 (CH), 121.8 (Cq), 114.7 (CH), 58.1 (CH), 51.7 (CH₂), 34.2 (CH₂), 31.8 (CH₃), 31.2 (CH₂), 29.8 (CH₂), 29.3 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 22.6 (CH₂), 20.0 (CH₃), 14.1 (CH₃).

IR (ATR): ν = 2922, 2854, 1588, 1383, 1346, 774 cm⁻¹.

MS (EI) m/z (relative intensity): 260 (5) [M⁺], 168 (5), 161 (100), 133 (10), 92 (16).

HR-MS (EI) m/z calcd for C₁₅H₂₆N₂⁺ 260.2252, found 260.2244.

Synthesis of 3-methyl-2-(2-<i>n</i>-octylpyrrolidin-1-<i>yl</i>)pyridine (217bd)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-<i>yl</i>)pyridine (216b) (243 mg, 1.5 mmol) and 1-octene (111d) (56.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded 217bd (123 mg, 90%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, <i>J</i> = 4.9, 1.8 Hz, 1H), 7.26 (dd, <i>J</i> = 7.4, 1.8 Hz, 1H), 6.62 (dd, <i>J</i> = 7.4, 4.9 Hz, 1H), 4.28–4.15 (m, 1H), 3.69–3.58 (m, 1H), 3.20–3.10 (m, 1H), 2.20 (s, 3H), 2.17–2.06 (m, 1H), 1.95–1.50 (m, 5H), 1.34–1.11 (m, 12H), 0.84 (t, <i>J</i> = 6.1 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (Cq), 144.7 (CH), 138.9 (CH), 121.8 (Cq), 114.7 (CH), 58.1 (CH), 51.7 (CH₂), 34.2 (CH₂), 31.9 (CH₃), 31.2 (CH₂), 29.9 (CH₂), 29.6 (CH₂), 29.2 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 22.6 (CH₂), 20.0 (CH₃), 14.1 (CH₃).

IR (ATR): ν = 2921, 2853, 1588, 1383, 1346, 775 cm⁻¹.

MS (EI) m/z (relative intensity): 274 (5) [M⁺], 182 (6), 161 (100), 133 (7), 84 (17).

HR-MS (EI) m/z calcd for C₁₈H₃₈N₂⁺ 274.2409, found 274.2405.

Synthesis of 3-methyl-2-(2-<i>n</i>-nonylpyrrolidin-1-<i>yl</i>)pyridine (217be)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-<i>yl</i>)pyridine (216b) (243 mg, 1.5 mmol) and 1-nonene (111e) (63.0 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded 217be (129 mg, 89%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, <i>J</i> = 4.9, 1.8 Hz, 1H), 7.26 (dd, <i>J</i> = 7.4, 1.8 Hz, 1H), 6.62 (dd, <i>J</i> = 7.4, 4.9 Hz, 1H), 4.28–4.15 (m, 1H), 3.69–3.58 (m, 1H), 3.20–3.10 (m, 1H), 2.21 (s, 3H), 2.17–2.06 (m, 1H), 1.95–1.51 (m, 5H), 1.32–1.12 (m, 14H), 0.85 (t, <i>J</i> = 6.1 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (Cq), 144.7 (CH), 139.0 (CH), 121.9 (Cq), 114.7 (CH),
58.2 (CH), 51.7 (CH₂), 34.2 (CH₂), 31.9 (CH₂), 31.2 (CH₂), 29.9 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 22.7 (CH₂), 20.0 (CH₃), 14.1 (CH₃).

IR (ATR): ν = 2921, 2853, 1584, 1383, 1345, 775 cm⁻¹.

MS (EI) m/z (relative intensity): 288 (5) [M⁺], 196 (5), 161 (100), 133 (7), 92 (7).

HR-MS (EI) m/z calcd for C₁₉H₂₅N₂⁺: 288.2565, found 288.2562.

Synthesis of 3-methyl-2-(2-n-pentadecylpyrrolidin-1-yl)pyridine (217bf)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 1-pentadecene (111f) (105 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 217bf (159 mg, 85%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, J = 4.9, 2.0 Hz, 1H), 7.26 (dd, J = 7.4, 2.0 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.27–4.16 (m, 1H), 3.69–3.59 (m, 1H), 3.20–3.11 (m, 1H), 2.21 (s, 3H), 2.17–2.06 (m, 1H), 1.95–1.51 (m, 5H), 1.35–1.10 (m, 26H), 0.86 (t, J = 6.6 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 159.6 (Cq), 144.6 (CH), 138.9 (CH), 121.8 (Cq), 114.6 (CH), 58.2 (CH), 51.7 (CH₂), 34.3 (CH₂), 32.0 (CH₂), 31.3 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.4 (CH₂), 26.0 (CH₂), 25.0 (CH₂), 22.8 (CH₂), 20.1 (CH₃), 14.2 (CH₃).

IR (ATR): ν = 2920, 2851, 1588, 1346, 1186, 992, 775 cm⁻¹.

MS (EI) m/z (relative intensity): 372 (4) [M⁺], 276 (6), 161 (100), 133 (7), 107 (9), 92 (8).

HR-MS (EI) m/z calcd for C₂₅H₄₆N₂⁺: 372.3504, found 372.3510.

Synthesis of 2-(2-n-hexadecylpyrrolidin-1-yl)-3-methylpyridine (217bg)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 1-hexadecene (111g) (112 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217bg (168 mg, 87%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, J = 4.9, 1.9 Hz, 1H), 7.26 (dd, J = 7.4, 1.9 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.27–4.16 (m, 1H), 3.68–3.58 (m, 1H), 3.20–3.11 (m, 1H), 2.21 (s, 3H), 2.17–2.06 (m, 1H), 1.98–1.50 (m, 5H), 1.30–1.15 (m, 28H), 0.86 (t, J = 6.6 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (Cq), 144.7 (CH), 139.0 (CH), 121.9 (Cq), 114.7 (CH), 58.2 (CH), 51.7 (CH₂), 34.3 (CH₂), 31.9 (CH₂), 31.2 (CH₂), 29.9 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.4 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 22.7 (CH₂), 20.0 (CH₃), 14.1 (CH₃).

IR (ATR): ν = 2920, 2851, 1588, 1346, 992, 775 cm⁻¹.

MS (EI) m/z (relative intensity): 386 (5) [M⁺], 371 (4), 294 (7), 161 (100), 133 (7), 107 (8), 92 (7).

HR-MS (EI) m/z calcd for C₂₅H₄₄N₂⁺: 386.3661, found 386.3662.

Synthesis of 2-[2-(3,3-dimethylbutyl)pyrrolidin-1-yl]-3-methylpyridine (217bh)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (81.0 mg, 0.5 mmol) and 3,3-dimethyl-1-buten (111h) (63.1 mg, 1.5 mmol) at 80 °C. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1)
yielded 217bh (62 mg, 50%) as a colorless oil.

\[ ^1H-NMR \ (300 \ MHz, \ CDCl_3): \ \delta = 8.04 \ (dd, \ J = 5.0, \ 1.9 \ Hz, \ 1H), \ 7.26 \ (dd, \ J = 7.2, \ 1.9 \ Hz, \ 1H), \ 6.62 \ (dd, \ J = 7.2, \ 5.0 \ Hz, \ 1H), \ 4.22-4.12 \ (m, \ 1H), \ 3.69-3.59 \ (m, \ 1H), \ 3.22-3.13 \ (m, \ 1H), \ 2.21 \ (s, \ 3H), \ 2.16-2.06 \ (m, \ 1H), \ 1.91-1.53 \ (m, \ 4H), \ 1.20-1.07 \ (m, \ 3H), \ 0.78 \ (s, \ 9H). \]

\[ ^13C-NMR \ (75 \ MHz, \ CDCl_3): \ \delta = 159.5 \ (C_\beta), \ 144.7 \ (CH), \ 139.0 \ (CH), \ 121.7 \ (C_\beta), \ 114.6 \ (CH), \ 58.6 \ (CH), \ 51.7 \ (CH_2), \ 39.8 \ (CH_2), \ 31.2 \ (CH_2), \ 30.1 \ (C_\beta), \ 29.3 \ (CH_3), \ 29.0 \ (CH_2), \ 24.9 \ (CH_2), \ 20.0 \ (CH_3). \]

IR (ATR): \ \tilde{\nu} = 2951, \ 2864, \ 1588, \ 1383, \ 1343, \ 992, \ 775 \ cm^{-1}.

MS (EI) m/z (relative intensity): 246 \ (7) \ [{M^+}], \ 161 \ (100), \ 143 \ (5), \ 92 \ (5).

HR-MS (EI) m/z calcd for C_{16}H_{26}N_2Si^+ 246.2076, found 246.2078.

**Synthesis of 3-methyl-2-[2-(trimethylsilyl)ethyl]pyrrolidin-1-yl]pyridine (217bi)**

The general procedure E was followed using 3-methyl-2-[pyrrolidin-1-yl]pyridine (216b) (243 mg, 1.5 mmol) and trimethyl(vinyl)silane (111i) (50.1 mg, 0.5 mmol) at 80 °C. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217bi (78 mg, 59%) as a colorless oil.

\[ ^1H-NMR \ (300 \ MHz, \ CDCl_3): \ \delta = 8.03 \ (dd, \ J = 5.0, \ 1.9 \ Hz, \ 1H), \ 7.25 \ (dd, \ J = 7.2, \ 1.9 \ Hz, \ 1H), \ 6.62 \ (dd, \ J = 7.2, \ 5.0 \ Hz, \ 1H), \ 4.25-4.13 \ (m, \ 1H), \ 3.71-3.60 \ (m, \ 1H), \ 3.24-3.15 \ (m, \ 1H), \ 2.21 \ (s, \ 3H), \ 2.17-2.07 \ (m, \ 1H), \ 1.94-1.55 \ (m, \ 4H), \ 1.25-1.11 \ (m, \ 1H), \ 0.54-0.31 \ (m, \ 2H), \ -0.11 \ (s, \ 9H). \]

\[ ^13C-NMR \ (75 \ MHz, \ CDCl_3): \ \delta = 159.5 \ (C_\beta), \ 144.7 \ (CH), \ 139.0 \ (CH), \ 121.5 \ (C_\beta), \ 114.5 \ (CH), \ 60.4 \ (CH), \ 52.0 \ (CH_2), \ 30.7 \ (CH_2), \ 27.9 \ (CH_2), \ 24.8 \ (CH_2), \ 20.1 \ (CH_3), \ 12.1 \ (CH_2), \ -1.8 \ (CH_3). \]

IR (ATR): \ \tilde{\nu} = 2952, \ 2870, \ 1588, \ 1384, \ 1348, \ 1245, \ 1186, \ 832, \ 774, \ 691 \ cm^{-1}.

MS (EI) m/z (relative intensity): 262 \ (6) \ [{M^+}], \ 261 \ (10) \ [(M-H)^+], \ 161 \ (100), \ 92 \ (18), \ 73 \ (20).

HR-MS (ESI) m/z calcd for [C_{15}H_{28}N_2Si]H^+ 263.1938, found 263.1940.

**Synthesis of 3-methyl-2-[2-(triethylsilyl)ethyl]pyrrolidin-1-yl]pyridine (217bj)**

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and triethyl(vinyl)silane (111j) (71.2 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1) yielded 217bj (131 mg, 86%) as a colorless oil.

\[ ^1H-NMR \ (300 \ MHz, \ CDCl_3): \ \delta = 8.03 \ (dd, \ J = 4.9, \ 1.9 \ Hz, \ 1H), \ 7.24 \ (dd, \ J = 7.2, \ 1.9 \ Hz, \ 1H), \ 6.60 \ (dd, \ J = 7.2, \ 4.9 \ Hz, \ 1H), \ 4.25-4.13 \ (m, \ 1H), \ 3.71-3.60 \ (m, \ 1H), \ 3.25-3.15 \ (m, \ 1H), \ 2.20 \ (s, \ 3H), \ 2.18-2.08 \ (m, \ 1H), \ 1.94-1.53 \ (m, \ 4H), \ 1.27-1.14 \ (m, \ 1H), \ 0.84 \ (t, \ J = 7.4 \ Hz, \ 9H), \ 0.49-0.35 \ (m, \ 8H). \]

\[ ^13C-NMR \ (75 \ MHz, \ CDCl_3): \ \delta = 159.4 \ (C_\beta), \ 144.7 \ (CH), \ 138.9 \ (CH), \ 121.5 \ (C_\beta), \ 114.5 \ (CH), \ 60.6 \ (CH), \ 51.9 \ (CH_2), \ 30.6 \ (CH_2), \ 27.6 \ (CH_2), \ 24.8 \ (CH_2), \ 20.1 \ (CH_3), \ 7.3 \ (CH_2), \ 6.4 \ (CH_2), \ 3.2 \ (CH_3). \]

IR (ATR): \ \tilde{\nu} = 2950, \ 2872, \ 1588, \ 1385, \ 1347, \ 1186, \ 1014, \ 772, \ 725 \ cm^{-1}.

MS (EI) m/z (relative intensity): 304 \ (3) \ [{M^+}], \ 275 \ (4), \ 161 \ (100), \ 92 \ (5).

HR-MS (EI) m/z calcd for C_{18}H_{28}N_2Si^+ 304.2335, found 304.2299.
Experimental Section

Synthesis of 2-{2-(10-methoxy-n-decyl)pyrrolidin-1-yl)-3-methylpyridine (217bk)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 10-methoxy-1-decene (111k) (79.1 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1→20/1) yielded 217bk (104 mg, 65%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.03 (dd, J = 4.9, 2.0 Hz, 1H), 7.25 (dd, J = 7.4, 2.0 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.27–4.16 (m, 1H), 3.68–3.58 (m, 1H), 3.33 (t, J = 6.76 Hz, 2H), 3.30 (s, 3H), 3.19–3.10 (m, 1H), 2.20 (s, 3H), 2.17–2.06 (m, 1H), 1.94–1.46 (m, 6H), 1.32–1.15 (m, 15H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (C₆), 144.6 (CH), 138.9 (CH), 121.8 (C₆), 114.7 (CH), 72.9 (CH₂), 58.5 (CH₂), 58.1 (CH₃), 51.7 (CH₂), 34.2 (CH₂), 31.2 (CH₂), 29.9 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 26.1 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 20.0 (CH₃).

IR (ATR): ν = 2922, 2853, 1588, 1116, 992, 775 cm⁻¹.

MS (ESI) m/z (relative intensity): 332 (5) [M⁺], 292 (4), 217 (11).

HR-MS (ESI) m/z calcd for C₂₇H₂₈N₂O⁺ 332.2828, found 332.2826.

Synthesis of 2-{2-(10-chloro-n-decyl)pyrrolidin-1-yl)-3-methylpyridine (217bl)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 10-chloro-1-decene (111b) (87.3 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 217bl (138 mg, 82%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, J = 4.9, 1.9 Hz, 1H), 7.26 (dd, J = 7.4, 1.9 Hz, 1H), 6.62 (dd, J = 7.4, 4.9 Hz, 1H), 4.27–4.16 (m, 1H), 3.68–3.59 (m, 1H), 3.50 (t, J = 7.4 Hz, 2H), 3.19–3.10 (m, 1H), 2.21 (s, 3H), 2.17–2.06 (m, 1H), 1.93–1.54 (m, 6H), 1.44–1.14 (m, 15H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (C₆), 144.7 (CH), 138.9 (CH), 121.8 (C₆), 114.7 (CH), 58.1 (CH), 51.7 (CH₂), 45.2 (CH₂), 34.2 (CH₂), 32.6 (CH₂), 31.2 (CH₂), 29.8 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.4 (CH₂), 28.8 (CH₂), 26.8 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 20.0 (CH₃).

IR (ATR): ν = 2923, 2853, 1588, 1383, 1346, 992, 776, 650 cm⁻¹.

MS (EI) m/z (relative intensity): 336 (4) [M⁺], 292 (4), 217 (11).

HR-MS (EI) m/z calcd for C₂₀H₂₁ClN₂⁺ 336.2332, found 336.2336.

Synthesis of 2-{2-(10-bromo-n-decyl)pyrrolidin-1-yl)-3-methylpyridine (217bm)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 10-bromo-1-decene (111m) (110 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 217bm (114 mg, 60%) as a colorless oil.

1H-NMR (300 MHz, CDCl₃): δ = 8.04 (dd, J = 4.9, 1.9 Hz, 1H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 6.62 (dd, J = 7.2, 4.9 Hz, 1H), 4.28–4.17 (m, 1H), 3.69–3.58 (m, 1H), 3.50 (t, J = 7.2 Hz, 2H), 3.19–3.10 (m, 1H), 2.20 (s, 3H), 2.16–2.05 (m, 1H), 1.94–1.52 (m, 6H), 1.43–1.12 (m, 15H).

13C-NMR (75 MHz, CDCl₃): δ = 159.7 (C₆), 144.7 (CH), 138.9 (CH), 121.8 (C₆), 114.7 (CH), 58.1 (CH), 51.7 (CH₂), 45.1 (CH₂), 34.2 (CH₂), 32.6 (CH₂), 31.2 (CH₂), 29.8 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.4 (CH₂), 28.8 (CH₂), 26.8 (CH₂), 25.9 (CH₂), 24.9 (CH₂), 20.0 (CH₃).

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IR (ATR): $\tilde{\nu} = 2923, 2853, 1707, 1588, 1384, 1346, 992, 775, 650$ cm$^{-1}$.

MS (ESI) m/z (relative intensity): 383 (100) [(M+H)$^+$] ($^{79}$Br), 381 (100) [(M+H)$^+$] ($^{81}$Br).

HR-MS (ESI) m/z calcd for [(C$_{20}$H$_{33}$BrN$_2$)$_2$H]$^+$ 381.1900, found 381.1897.

**Synthesis of 2-{2-[4-(2-bromophenyl)butyl]pyrrolidin-1-yl}-3-methylpyridine (217bn)**

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 1-bromo-2-(but-3-en-1-yl)benzene (111n) (105 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 217bn (152 mg, 82%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.05$ (dd, $J = 4.9, 1.9$ Hz, 1H), 7.48 (dd, $J = 8.1, 1.1$ Hz, 1H), 7.26 (dd, $J = 7.4, 1.9$ Hz, 1H), 7.21–7.11 (m, 2H), 7.00 (ddd, $J = 7.4, 7.4, 2.6$ Hz, 1H), 6.62 (dd, $J = 7.4, 4.9$ Hz, 1H), 4.34–4.23 (m, 1H), 3.70–3.60 (m, 1H), 3.19–3.10 (m, 1H), 3.50 (td, $J = 7.4, 7.2$ Hz, 2H), 2.21 (s, 3H), 2.18–2.07 (m, 1H), 1.96–1.83 (m, 1H), 1.82–1.67 (m, 2H), 1.65–1.49 (m, 3H), 1.46–1.21 (m, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 159.7$ (C$_4$), 144.6 (CH), 138.0 (C$_3$), 139.0 (CH), 132.6 (CH), 130.2 (CH), 127.2 (CH), 127.2 (CH), 124.4 (C$_4$), 121.9 (C$_6$), 114.8 (CH), 58.0 (CH), 51.9 (CH$_2$), 36.0 (CH$_2$), 33.9 (CH$_2$), 31.1 (CH$_2$), 30.0 (CH$_2$), 25.6 (CH$_2$), 25.0 (CH$_2$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2930, 2858, 1587, 1382, 1346, 1020, 776, 746$ cm$^{-1}$.

MS (EI) m/z (relative intensity): 373 (100) [M$^+$] ($^{79}$Br), 371 (100) [M$^+$] ($^{81}$Br), 317 (6), 265 (13), 171 (35), 161 (40), 33 (22), 92 (17).

HR-MS (ESI) m/z calcd for [(C$_{20}$H$_{33}$BrN$_2$)$_2$H]$^+$ 373.1274, found 373.1274.

**Synthesis of 3-methyl-2-(2-phenethylpyrrolidin-1-yl)pyridine (217bo)**

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and styrene (111o) (52.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 25/1) yielded 217bo (98 mg, 73%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.06$ (dd, $J = 4.9, 1.9$ Hz, 1H), 7.30–7.18 (m, 3H), 7.17–7.09 (m, 3H), 6.65 (dd, $J = 7.2, 4.9$ Hz, 1H), 4.41–4.31 (m, 1H), 3.73–3.64 (m, 1H), 3.22–3.14 (m, 1H), 2.68–2.56 (m, 2H), 2.25–2.14 (m, 1H), 2.19 (s, 3H), 2.06–1.90 (m, 2H), 1.84–1.54 (m, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 159.7$ (C$_4$), 144.8 (CH), 138.8 (C$_3$), 139.1 (CH), 128.3 (CH), 128.2 (CH), 125.5 (CH), 122.1 (C$_6$), 111.0 (CH), 57.8 (CH), 51.7 (CH$_2$), 35.9 (CH$_2$), 32.2 (CH$_2$), 31.1 (CH$_2$), 24.9 (CH$_2$), 19.8 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2956, 2862, 1587, 1382, 1346, 1186, 1099, 776, 696$ cm$^{-1}$.

MS (EI) m/z (relative intensity): 266 (5) [M$^+$], 175 (26), 161 (100), 133 (7), 92 (17).

HR-MS (EI) m/z calcd for C$_{18}$H$_{22}$N$_2$: 266.1783, found 266.1792.

**Synthesis of 2-{2-[4-methoxystyrenyl]pyrrolidin-1-yl}-3-methylpyridine (217bp)**

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 4-methoxystyrene (111p) (67.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1→20/1) yielded 217bp (104 mg, 70%) as a colorless oil.
Synthesis of 2-β-(4-bromophenethyl)pyrrolidin-1-yl)-3-methylpyridine (217bq)

The general procedure was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 4-bromostyrene (111q) (91.5 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1) yielded 217bq (112 mg, 65%) as a colorless oil.

Synthesis of 2-β-(4-fluorophenethyl)pyrrolidin-1-yl)-3-methylpyridine (217br)

The general procedure was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 4-fluorostyrene (111r) (61.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 30/1→20/1) yielded 217br (91 mg, 64%) as a colorless oil.
IR (ATR): $\tilde{\nu} = 2955, 2864, 1587, 1508, 1382, 1348, 1216, 822, 776$ cm$^{-1}$.
MS (EI) $m/z$ (relative intensity): 284 (5) [M$^+$], 175 (32), 161 (100), 133 (12), 109 (17), 92 (27).
HR-MS (EI) $m/z$ calcd for $C_{18}H_{22}FN_2^+$ 284.1689, found 284.1692.

Synthesis of 3-methyl-2-[2-[2-(naphthalen-2-yl)ethyl]pyrrolidin-1-yl]pyridine (217bs)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 2-vinylnaphthalene (111s) (77.1 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel ($n$-hexane/EtOAc: 25/1) yielded 217bs (91 mg, 57%) as a white solid.

M.p. = 93–94 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.09$ (dd, $J = 4.9, 2.0$ Hz, 1H), 7.79–7.69 (m, 3H), 7.58 (s, 1H), 7.45–7.35 (m, 2H), 7.31–7.25 (m, 2H), 6.67 (dd, $J = 7.4, 4.9$ Hz, 1H), 4.48–4.36 (m, 2H), 3.75–3.65 (m, 1H), 3.23–3.14 (m, 1H), 2.87–2.72 (m, 2H), 2.27–2.07 (m, 2H), 2.20 (s, 3H), 2.00–1.64 (m, 4H).

$^1$C-NMR (75 MHz, CDCl$_3$): $\delta = 159.7$ (C$_\beta$), 144.7 (CH), 140.2 (C$_\alpha$), 139.0 (CH), 133.6 (C$_\gamma$), 131.8 (C$_\delta$), 127.5 (CH), 127.4 (CH), 127.3 (CH), 126.0 (CH), 125.7 (CH), 124.9 (CH), 122.0 (C$_\alpha$), 111.0 (CH), 57.9 (CH), 51.9 (CH$_2$), 35.7 (CH$_2$), 32.4 (CH$_2$), 31.2 (CH$_2$), 25.0 (CH$_2$), 19.9 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2963, 2919, 2858, 1588, 1563, 1382, 1320, 862, 815, 786, 475$ cm$^{-1}$.
MS (EI) $m/z$ (relative intensity): 316 (10) [M$^+$], 175 (50), 161 (100), 141 (20), 111 (15), 92 (30).
HR-MS (EI) $m/z$ calcd for $C_{22}H_{35}N_2^+$ 316.1939, found 316.1927.

Synthesis of 2-[2-(10-isobutoxy-n-decyl)pyrrolidin-1-yl]-3-methylpyridine (217'bt)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 9-decen-1-yl 4-methylbenzenesulfonate (111) (155 mg, 0.5 mmol).

After 18 h, purification by column chromatography on silica gel ($n$-hexane/EtOAc: 40/1→30/1) yielded 217'bt (144 mg, 77%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 8.04$ (dd, $J = 4.9, 2.0$ Hz, 1H), 7.25 (dd, $J = 7.4, 2.0$ Hz, 1H), 6.61 (dd, $J = 7.4, 4.9$ Hz, 1H), 4.97–4.16 (m, 1H), 3.68–3.58 (m, 1H), 3.35 (t, $J = 6.7$ Hz, 2H), 3.31 (d, $J = 6.7$ Hz, 2H), 2.67 (s, 3H), 2.17–2.06 (m, 1H), 1.95–1.87 (m, 8H), 1.33–1.13 (m, 15H), 0.87 (d, $J = 7.0$ Hz, 6H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 159.7$ (C$_\beta$), 144.7 (CH), 138.9 (CH), 121.8 (C$_\alpha$), 114.7 (CH), 77.8 (CH$_2$), 71.0 (CH$_2$), 58.1 (CH), 51.7 (CH$_2$), 34.2 (CH$_2$), 31.2 (CH$_2$), 29.9 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.5 (CH$_2$), 28.4 (CH), 26.2 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_2$), 20.0 (CH$_3$), 19.4 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2923, 2852, 1588, 1565, 1384, 1346, 1110, 992, 775$ cm$^{-1}$.
MS (EI) $m/z$ (relative intensity): 217'bt (5) [M$^+$], 331 (6), 282 (5), 161 (100), 133 (7), 107 (96), 92 (6).
HR-MS (EI) $m/z$ calcd for $C_{24}H_{36}N_2O$ 374.3297, found 374.3285.
Synthesis of 10-\{(3-methylpyridin-2-yl)pyrrolidin-2-yl\}-n-decyl 4-methylbenzenesulfonate (217bt)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 9-decen-1-y1 4-methylbenzenesulfonate (111t) (155 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 15/1→5/1) yielded 217bt (148 mg, 63%) as a colorless oil.

1H-NMR (300 MHz, CDCl3): δ = 8.03 (dd, J = 4.9, 1.9 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.25 (dd, J = 7.2, 1.9 Hz, 1H), 6.61 (dd, J = 7.2, 4.9 Hz, 1H), 4.28–4.15 (m, 1H), 3.98 (t, J = 6.6 Hz, 2H), 3.69–3.58 (m, 1H), 3.21–3.08 (m, 1H), 2.41 (s, 3H), 2.20 (s, 3H), 2.16–2.05 (m, 1H), 1.94–1.52 (m, 6H), 1.30–1.09 (m, 15H).

13C-NMR (75 MHz, CDCl3): δ = 159.6 (Cq), 144.5 (CH), 144.5 (Cq), 139.0 (CH), 133.2 (Cq), 129.7 (CH), 127.8 (CH), 121.9 (Cq), 114.6 (CH), 70.6 (CH2), 58.1 (CH), 51.7 (CH2), 34.2 (CH2), 31.2 (CH3), 29.8 (CH2), 29.5 (CH2), 29.3 (CH2), 29.3 (CH2), 28.8 (CH2), 28.7 (CH2), 25.8 (CH2), 25.2 (CH2), 24.9 (CH2), 21.6 (CH3), 20.0 (CH3).

IR (ATR): ν = 2923, 2851, 1588, 1356, 1174, 1097, 956, 775, 553 cm⁻¹.

MS (EI) m/z (relative intensity): 472 (3) [M⁺], 376 (3), 161 (100), 133 (10), 107 (14), 92 (13).

HR-MS (ESI) m/z calc'd for C22H26N2O3S⁺ 472.2760, found 472.2767.

Synthesis of 12-\{(3-methylpyridin-2-yl)pyrrolidin-2-yl\}dodecan-2-one (217bu)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 11-dodecen-1-y1 (111u) (99.1 mg, 0.5 mmol) in DCE. After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 217bu (69 mg, 38%) as a white solid.

M.p. = 62–63 °C.

1H-NMR (300 MHz, CDCl3): δ = 8.01 (dd, J = 4.9, 1.9 Hz, 1H), 7.23 (dd, J = 7.2, 1.9 Hz, 1H), 6.60 (dd, J = 7.2, 4.9 Hz, 1H), 4.27–4.15 (m, 1H), 3.68–3.56 (m, 1H), 3.17–3.06 (m, 1H), 2.36 (t, J = 6.9 Hz, 2H), 2.18 (s, 3H), 2.15–2.01 (m, 1H), 2.08 (s, 3H), 1.92–1.45 (m, 6H), 1.28–1.12 (m, 15H).

13C-NMR (75 MHz, CDCl3): δ = 207.1 (Cq), 159.7 (Cq), 144.6 (CH), 138.9 (CH), 121.8 (Cq), 114.6 (CH), 58.1 (CH), 51.6 (CH2), 43.7 (CH2), 34.2 (CH2), 31.1 (CH2), 29.8 (CH2), 29.7 (CH3), 29.5 (CH3), 29.4 (CH2), 29.4 (CH2), 29.3 (CH2), 29.1 (CH2), 25.8 (CH2), 24.8 (CH2), 23.8 (CH2), 19.9 (CH3).

IR (ATR): ν = 2922, 2853, 1714, 1588, 1384, 1347, 1164, 776, 731 cm⁻¹.

MS (EI) m/z (relative intensity): 344 (4) [M⁺], 252 (6), 161 (100), 133 (12), 92 (16).

HR-MS (ESI) m/z calc'd for [(C22H26N2O3)]⁺ 345.2900, found 345.2900.

Synthesis of 9-\{(3-methylpyridin-2-yl)pyrrolidin-2-yl\}nonan-2-ol (217bv)

The general procedure E was followed using 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 8-nonan-2-one (111v) (70.0 mg, 0.5 mmol). After 18 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) yielded 217bv (77 mg, 51%) as a colorless oil.

1H-NMR (300 MHz, CDCl3): δ = 8.02 (dd, J = 4.9, 1.8 Hz, 1H), 7.26 (dd, J = 7.2, 1.8 Hz, 1H),
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6.62 (dd, J = 7.2, 4.9 Hz, 1H), 4.27–4.15 (m, 1H), 3.76–3.68 (m, 1H), 3.68–3.58 (m, 1H), 3.19–3.09 (m, 1H), 2.20 (s, 3H), 2.16–2.05 (m, 1H), 1.94–1.50 (m, 5H), 1.44–1.14 (m, 13H), 1.13 (d, J = 6.4 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 159.6 (Cq), 144.6 (CH), 139.0 (CH), 121.9 (Cq), 114.6 (CH), 68.0 (CH), 58.1 (CH), 51.7 (CH2), 39.3 (CH2), 34.2 (CH2), 29.8 (CH2), 29.5 (CH2), 29.5 (CH2), 25.8 (CH2), 25.7 (CH2), 24.9 (CH2), 23.4 (CH3), 20.0 (CH3).

IR (ATR): ν = 3364, 2924, 2854, 1588, 1384, 1346, 1102, 776, 730 cm⁻¹.

MS (EI) m/z (relative intensity): 304 (5) [M⁺], 289 (5), 161 (100), 133 (12), 92 (18).

HR-MS (EI) m/z calcd for C19H32N2O⁺ 304.2515, found 304.2519.

Mechanistic studies with TEMPO (Scheme 82)

A suspension of [RuCl₂(PPh₃)₃] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), TEMPO (234 mg, 1.5 mmol), 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and 1-decene (111a) (70.1 mg, 0.5 mmol) in i-BuOH (1.0 mL) was stirred at 120 °C under N₂ for 18 h. At ambient temperature, EtOAc (5 mL) and silica (1.5 g) were added to the reaction mixture and the solvents were evaporated in reduced pressure. Purification by column chromatography on silica gel (n-hexane/EtOAc: 40/1→30/1) yielded 217ba (106 mg, 70%) as a colorless oil.

Studies with isotopically labelled [D]₄-MeOH (Scheme 83a)

A suspension of [RuCl₂(PPh₃)₃] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (243 mg, 1.5 mmol) and styrene (111o) (52.1 mg, 0.5 mmol) in [D]₄-MeOH (1.0 mL) was stirred at 120 °C under N₂ for 18 h. CuCl (50 mg), EtOAc (5 mL) and silica (1.5 g) were added to the cold reaction mixture and the solvents were evaporated in vacuo. Purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) to give [D]₄-217bo (104 mg, 78%) as a colorless oil and [D]₆-216b (118 mg, 48%) as a colorless oil. The deuterium incorporation was estimated by ¹H-NMR spectroscopy.
Studies with isotopically labelled [D]_2-MeOH (Scheme 8b)

A suspension of [RuCl_2(PPh_3)_3] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %) and 3-methyl-2-(pyrrolidin-1-yl)pyridine (216b) (81.0 mg, 0.5 mmol) in [D]_2-MeOH (1.0 mL) was stirred at 120 °C under N_2 for 18 h. EtOAc (5 mL) and silica (1.5 g) were added to the cold reaction mixture and the solvents were evaporated in vacuo. Purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded compound [D]_n-216b (65 mg, 76%) as a colorless oil. The deuterium incorporation was estimated by ^1H-NMR spectroscopy.

Studies with isotopically labelled compounds (Scheme 84)

A suspension of [RuCl_2(PPh_3)_3] (24.0 mg, 5.0 mol %), rac-BINAP (18.7 mg, 6.0 mol %), AgOTf (15.4 mg, 12 mol %), [D]_n-216b (243 mg, 1.5 mmol) and 111o (52.1 mg, 0.5 mmol) in DCE (1.0 mL) was stirred at 120 °C under N_2 for 18 h. CuCl (50 mg), EtOAc (5 mL) and silica (1.5 g) were added to the cold reaction mixture and the solvents were evaporated in vacuo. Purification by column chromatography on silica gel (n-hexane/EtOAc: 25/1→10/1) to give [D]_n-217bo (116 mg, 87%) as a colorless oil and [D]_n-216b (120 mg, 49%) as a colorless oil. The deuterium incorporation was estimated by ^1H-NMR spectroscopy.

Synthesis of 2-decylpyrrolidine (218ba)

The general procedure F was followed using 2-(2-decylpyrrolidin-1-yl)-3-methylpyridine (217ba) (151 mg, 0.5 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/MeOH: 20/1→10/1) yielded 218ba (74 mg, 70%) as a white solid. 

M.p. = 88–89 °C.

^1H-NMR (300 MHz, [d]_6-DMSO): δ = 9.34 (8H, 1H), 3.38–3.24 (8H, 1H), 3.19–3.00 (2H, 2H), 2.11–1.98 (m, 1H), 1.96–1.38 (m, 6H), 1.39–1.18 (m, 16H), 0.85 (3H, J = 6.7 Hz, 3H).

^13C-NMR (75 MHz, [d]_6-DMSO): δ = 59.3 (CH), 43.7 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 28.6 (CH_2), 26.1 (CH_2), 22.9 (CH_2), 22.0 (CH_2), 13.8 (CH_3).

IR (ATR): ν = 2919, 2850, 2744, 1461, 1385, 1030, 730 cm^{-1}.

MS (ESI) m/z (relative intensity): 210 (100) [(M+H)^+].
HR-MS (ESI) m/z calcd for [(C\textsubscript{14}H\textsubscript{29}N)H]\(^+\) 210.2373, found 210.2375.

### Synthesis of 2-(2-(triethylsilyl)ethyl]pyrrolidine (218bj)

The general procedure F was followed using 3-methyl-2-[2-(2-(triethylsilyl)ethyl]pyrrolidin-1-yl]pyridine (217bj) (152 mg, 0.5 mmol). Purification by column chromatography on silica gel (CH\textsubscript{3}Cl/MeOH: 20/1→10/1→5/1) yielded 218bj (65 mg, 61%) as a white solid.

M.p. = 52–53 °C.

\(^1\)H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.52, 3.35–3.09, 2.16–2.00, 2.00–1.69, 1.64–1.43, 0.91, 0.90–0.38\) (m, 3H, 2H, 2H, 6H, 8H).

\(^13\)C-NMR (75 MHz, [d\textsubscript{6}]-DMSO): \(\delta = 62.1, 44.1, 29.4, 26.3, 23.1, 8.0\) (CH), 7.2 (CH\textsubscript{2}), 2.7 (CH\textsubscript{3}).

IR (ATR): \(\nu = 2950, 2873, 2730, 1459, 1414, 1015, 758, 720\) cm\(^{-1}\).

MS (ESI) m/z (relative intensity): 212 (100) [M+H]\(^+\).

HR-MS (ESI) m/z calcd for [(C\textsubscript{12}H\textsubscript{23}NSi)H]\(^+\) 212.1986, found 212.1987.

### Synthesis of 2-(2-cyclohexylethyl]pyrrolidine (218bo)

The general procedure F was followed using 3-methyl-2-(2-phenethylpyrrolidin-1-yl)pyridine (217bo) (195 mg, 0.5 mmol). Purification by column chromatography on silica gel (CH\textsubscript{3}Cl/MeOH: 10/1→5/1→3/1) yielded 218bo (53 mg, 58%) as a white solid.

M.p. = 99–100 °C.

\(^1\)H-NMR (300 MHz [D\textsubscript{6}]-DMSO): \(\delta = 6.93, 3.33–3.18, 3.17–2.95, 2.12–1.96, 1.95–1.37, 1.33–1.00, 0.96–0.75\) (m, 8H).

\(^13\)C-NMR (75 MHz, [d\textsubscript{6}]-DMSO): \(\delta = 59.5, 43.8, 36.7, 33.7, 32.6, 29.8, 28.9, 26.0, 25.6, 23.0\) (CH\textsubscript{3}).

IR (ATR): \(\nu = 1917, 1851, 1575, 1588, 1448, 1412, 1027, 387\) cm\(^{-1}\).

MS (ESI) m/z (relative intensity): 182 (100) [M+H]\(^+\).

HR-MS (ESI) m/z calcd for [(C\textsubscript{12}H\textsubscript{23})N\textsubscript{2}]H\(^+\) 182.1903, found 182.1905.

### 8.3.5 Analytical Data for the Products of Ruthenium-Catalyzed ortho-C–H Halogenation of Benzamide 219

#### Synthesis of 2-bromo-N,N-diisopropylbenzamide (220a)

The general procedure G was followed using N,N-diisopropylbenzamide (219a) (103 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) yielded 220a (86 mg, 60%) as a white solid.

M.p. = 73–74 °C.

\(^1\)H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta = 7.57, 7.53, 7.53, 7.53, 7.22–7.12, 3.65–3.43, 1.56, 1.55, 1.22\) (d, J = 6.7 Hz, 3H, 3H, 3H, 3H, 2H, 2H, 3H, 3H, 3H).

\(^13\)C-NMR (75 MHz, CDCl\textsubscript{3}): \(\delta = 168.0, 140.1, 132.7, 129.3, 127.4, 126.5, 118.8, 51.1, 45.9, 20.7, 20.6, 20.5, 20.0\) (CH\textsubscript{3}).

IR (ATR): \(\nu = 2975, 2930, 1626, 1438, 1339, 1019, 770\) cm\(^{-1}\).
Synthesis of 2-bromo-N,N,3,5-tetramethylbenzamide (220b)

The general procedure G was followed using N,N,3,5-tetramethylbenzamide (219b) (177 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1) yielded 220b (175 mg, 68%) as a yellow solid.

M.p. = 103–104 °C.

1H-NMR (300 MHz, CDCl3): δ = 7.02 (s, 1H), 6.86 (s, 1H), 3.10 (s, 3H), 2.84 (s, 3H), 2.35 (s, 3H), 2.25 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ = 169.8 (Cq), 138.9 (Cq), 138.5 (Cq), 137.6 (Cq), 131.7 (CH), 125.5 (CH), 117.9 (Cq), 38.2 (CH2), 34.5 (CH2), 23.0 (CH3), 20.7 (CH3).

IR (ATR): υ = 2918, 2871, 1626, 1508, 1441, 1392, 1257, 1130, 1020, 865, 665 cm⁻¹.

MS (EI) m/z (relative intensity): 257 (17) [M⁺] (81Br), 255 (20) [M⁺] (79Br), 219 (97), 209 (100), 104 (35).

HR-MS (EI) m/z calcd for C11H14BrNO⁺ 255.0259, found 255.0249.

Synthesis of 2-iodo-N,N,3,5-tetramethylbenzamide (221b)

The general procedure G was followed using N,N,3,5-tetramethylbenzamide (219b) (177 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1) yielded 221b (224 mg, 74%) as a yellow solid.

M.p. = 82–83 °C.

1H-NMR (300 MHz, CDCl3): δ = 6.98 (s, 1H), 6.76 (s, 1H), 3.07 (s, 3H), 2.79 (s, 3H), 2.36 (s, 3H), 2.21 (s, 3H).

13C-NMR (75 MHz, CDCl3): δ = 171.3 (Cq), 143.5 (Cq), 138.0 (Cq), 138.4 (Cq), 130.3 (CH), 124.8 (CH), 94.9 (Cq), 38.3 (CH3), 34.5 (CH3), 28.4 (CH3), 20.6 (CH3).

IR (ATR): υ = 2913, 2853, 1626, 1505, 1441, 1399, 1125, 1003, 863, 663 cm⁻¹.

MS (EI) m/z (relative intensity): 303 (38) [M⁺] (81Br), 259 (100), 231 (24), 104 (20).

HR-MS (EI) m/z calcd for C11H14I NO⁺ 303.0120, found 303.0118.

Synthesis of 2-bromo-N,N-diethyl-3,5-dimethylbenzamide (220c)

The general procedure G was followed using N,N-diethyl-3,5-dimethylbenzamide (219c) (205 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1) yielded 220c (159 mg, 56%) as a colorless oil.

1H-NMR (300 MHz, CDCl3): δ = 7.02 (s, 1H), 6.85 (s, 1H), 3.79 (hex, J = 6.9 Hz, 1H), 3.31 (hex, J = 6.9 Hz, 1H), 3.19–3.05 (m, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H).
The general procedure G was followed using N,N-diethyl-3,5-dimethylbenzamide (219c) (205 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) and normal phase HPLC (n-hexane/EtOAc: 15/1→7/1) yielded 221c (179 mg, 54%) as a colorless oil.

The general procedure H was followed using N,N-diethyl-3,5-dimethylbenzamide (219c) (205 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) and normal phase HPLC (n-hexane/EtOAc: 15/1→7/1) yielded 221c (235 mg, 71%) as a colorless oil.

The general procedure G was followed using N,N-diisopropyl-3,5-dimethylbenzamide (219d) (233 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol) at 80 °C. After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 220d (277 mg, 89%) as a white solid.

M.p. = 200–201 °C.

The general procedure G was followed using N,N-diisopropyl-3,5-dimethylbenzamide (219d) (233 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol) at 80 °C. After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 220d (277 mg, 89%) as a white solid.

M.p. = 200–201 °C.

The general procedure G was followed using N,N-diisopropyl-3,5-dimethylbenzamide (219d) (233 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol) at 80 °C. After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 220d (277 mg, 89%) as a white solid.

M.p. = 200–201 °C.
Synthesis of 2-iodo-N,N-diisopropyl-3,5-dimethylbenzamide (221d)

The general procedure G was followed using N,N-diisopropyl-3,5-dimethylbenzamide (219d) (233 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 221d (251 mg, 70%) as a white solid.

The general procedure H was followed using N,N-diisopropyl-3,5-dimethylbenzamide (219d) (233 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 221d (305 mg, 85%) as a white solid.

M.p. = 195–196 °C.

1H-NMR (300 MHz, CDCl3): δ = 6.98 (s, 1H), 6.71 (s, 1H), 3.59 (hept, J = 6.8 Hz, 1H), 3.48 (hept, J = 6.8 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H).

13C-NMR (75 MHz, CDCl3): δ = 170.5 (Cq), 145.0 (Cq), 138.2 (Cq), 138.2 (Cq), 129.9 (CH), 123.8 (CH), 95.0 (Cq), 51.1 (CH), 45.8 (CH), 28.5 (CH3), 20.7 (CH3), 20.7 (CH3), 20.6 (CH3), 19.9 (CH3).

IR (ATR): ν = 2958, 2926, 1625, 1438, 1368, 1348, 1206, 864, 777, 630 cm⁻¹.

MS (El) m/z (relative intensity): 359 (40) [M⁺], 316 (48), 259 (100), 232 (40), 133 (32), 104 (32).

HR-MS (ESI) m/z calcd for [(C15H22INO)H]+: 360.0824, found 360.0817.

Synthesis of (2-bromo-3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (220e)

The general procedure G was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (219e) (203 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1→1/1) and normal phase HPLC (n-hexane/EtOAc: 3/1→2/1) yielded 220e (102 mg, 36%) as a white solid.

The general procedure H was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (219e) (203 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 2/1→1/1) and normal phase HPLC (n-hexane/EtOAc: 3/1→2/1) yielded 220e (102 mg, 36%) as a white solid.

M.p. = 68–69 °C.

1H-NMR (300 MHz, CDCl3): δ = 7.03 (s, 1H), 6.90 (s, 1H), 3.64 (t, J = 6.7 Hz, 2H), 3.31–3.08 (m, 2H), 2.36 (s, 3H), 2.26 (s, 3H), 2.00–1.83 (m, 4H).

13C-NMR (75 MHz, CDCl3): δ = 168.0 (Cq), 139.9 (Cq), 138.5 (Cq), 137.6 (Cq), 131.6 (CH), 125.3 (CH), 117.5 (Cq), 43.0 (CH2), 45.3 (CH2), 25.8 (CH2), 24.6 (CH2), 23.0 (CH2), 20.7 (CH3).

IR (ATR): ν = 2971, 2874, 1629, 1433, 1368, 1344, 1206, 1164, 1090, 790, 706, 621 cm⁻¹.

MS (El) m/z (relative intensity): 283 (30) [M⁺] (79Br), 281 (31) [M⁺] (79Br), 219 (98), 209 (100), 202 (37), 104 (38).

HR-MS (El) m/z calcd for C15H16BrNO+: 281.0415, found 281.0405.

Synthesis of (2-iodo-3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (221e)

The general procedure G was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (219e) (203 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 221e (238 mg, 72%) as a white solid.
The general procedure H was followed using (3,5-dimethylphenyl)(pyrrolidin-1-yl)methanone (219e) (203 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) yielded 221e (250 mg, 76%) as a white solid.

M.p. = 107–108 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.00, 6.76, 3.61 (\text{t, } J = 6.7 \text{ Hz, } 2\text{H}), 3.25–3.01 (\text{m, } 2\text{H}), 2.38 (\text{s, } 3\text{H}), 2.23 (\text{s, } 3\text{H}), 1.99–1.76 (\text{m, } 4\text{H}).\)

\(^1\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 169.5 (\text{C}_2), 144.7 (\text{C}_3), 138.1 (\text{C}_4), 138.5 (\text{C}_5), 130.4 (\text{CH}), 124.6 (\text{CH}), 94.7 (\text{C}_6), 48.3 (\text{CH}_2), 45.4 (\text{CH}_2), 28.4 (\text{CH}_3), 25.9 (\text{CH}_2), 24.5 (\text{CH}_2), 20.7 (\text{CH}_3).\)

IR (ATR): \(\tilde{\nu} = 2963, 2930, 1626, 1434, 1364, 1322, 1148, 1036, 816, 608 \text{ cm}^{-1} \). MS (EI) \(m/z\) (relative intensity): 329 (67) [M\(^+\)], 259 (100), 231 (34), 202 (49), 133 (37), 104 (38).

HR-MS (EI) \(m/z\) calcd for C\(_{11}\)H\(_{16}\)NO \(239.0277\), found 239.0275.

**Synthesis of (2-bromo-3,5-dimethylphenyl)(piperidin-1-yl)methanone (220f)**

The general procedure D was followed using (3,5-dimethylphenyl)(piperidin-1-yl)methanone (219f) (215 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1→4/1) and normal phase HPLC (n-hexane/EtOAc: 10/1→5/1) yielded 220f (198 mg, 67%) as a white solid.

M.p. = 107–108 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 6.99, 6.76, 3.76–3.58 (\text{m, } 2\text{H}), 3.22–3.05 (\text{m, } 2\text{H}), 2.23 (\text{s, } 3\text{H}), 1.71–1.50 (\text{m, } 5\text{H}), 1.48–1.31 (\text{m, } 1\text{H}).\)

\(^1\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 168.0 (\text{C}_2), 138.8 (\text{C}_3), 138.4 (\text{C}_4), 137.3 (\text{C}_5), 131.4 (\text{CH}), 125.2 (\text{CH}), 117.8 (\text{C}_6), 47.7 (\text{CH}_2), 38.2 (\text{CH}_2), 26.1 (\text{CH}_3), 25.3 (\text{CH}_2), 24.4 (\text{CH}_2), 23.0 (\text{CH}_2), 20.6 (\text{CH}_3).\)

IR (ATR): \(\tilde{\nu} = 2937, 2855, 1624, 1439, 1217, 1021, 792, 659 \text{ cm}^{-1} \). MS (EI) \(m/z\) (relative intensity): 297 (32) [M\(^+\)] \((^{75}\text{Br})\), 295 (34) [M\(^+\)] \((^{77}\text{Br})\), 219 (98), 209 (100), 135 (27), 104 (38).

HR-MS (EI) \(m/z\) calcd for C\(_{14}\)H\(_{18}\)BrNO \(295.0572\), found 295.0576.

**Synthesis of (2-iodo-3,5-dimethylphenyl)(piperidin-1-yl)methanone (221f)**

The general procedure G was followed using (3,5-dimethylphenyl)(piperidin-1-yl)methanone (219f) (215 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1→4/1) yielded 221f (219 mg, 62%) as a white solid.

The general procedure H was followed using (3,5-dimethylphenyl)(piperidin-1-yl)methanone (219f) (215 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1→4/1) yielded 221f (275 mg, 76%) as a white solid.

M.p. = 77–78 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.01, 6.77, 3.84–3.74 (\text{m, } 1\text{H}), 3.70–3.60 (\text{m, } 1\text{H}), 3.25–3.07 (\text{m, } 2\text{H}), 2.41 (\text{s, } 3\text{H}), 2.25 (\text{s, } 3\text{H}), 1.76–1.54 (\text{m, } 5\text{H}), 1.53–1.35 (\text{m, } 1\text{H}).\)

\(^1\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 169.8 (\text{C}_2), 143.6 (\text{C}_3), 138.2 (\text{C}_4), 138.4 (\text{C}_5), 130.3 (\text{CH}), 124.7 (\text{CH}), 95.1 (\text{C}_6), 47.8 (\text{CH}_2), 38.3 (\text{CH}_2), 28.5 (\text{CH}_3), 26.1 (\text{CH}_2), 25.3 (\text{CH}_2), 24.5 (\text{CH}_2), 20.7
Synthesis of (2-bromo-3,5-dimethylphenyl)(morpholino)methanone (220g)

The general procedure G was followed using (3,5-dimethylphenyl)(morpholino)methanone (219g) (217 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1→2/1) and normal phase HPLC (n-hexane/EtOAc: 5/1→3/1) yielded 220g (155 mg, 52%) as a white solid.

M.p. = 118–119 °C.

^1^H-NMR (300 MHz, CDCl₃): δ = 7.05 (s, 1H), 6.85 (s, 1H), 3.92–3.63 (m, 5H), 3.33–3.13 (m, 1H), 3.32–3.11 (m, 2H), 2.34 (s, 3H), 2.25 (s, 3H).

^1^3^C-NMR (75 MHz, CDCl₃): δ = 168.3 (C₆), 138.7 (C₆), 137.8 (C₆), 137.7 (C₆), 132.0 (CH), 125.5 (CH), 117.9 (C₆), 66.7 (CH₃), 66.6 (CH₂), 47.1 (CH₂), 41.9 (CH₂), 23.0 (CH₃), 20.7 (CH₃).

IR (ATR): ν = 2931, 2848, 1630, 1436, 1112, 1020, 860, 618 cm⁻¹.

MS (EI) m/z (relative intensity): 299 (16) [M⁺], 298 (100), 297 (18) [M⁺], 219 (100), 209 (98), 104 (33).

HR-MS (ESI) m/z calc’d for [(C₁₃H₁₂BrNO₂)⁺] 298.0437, found 298.0445.

Synthesis of (2-iodo-3,5-dimethylphenyl)(morpholino)methanone (221g)

The general procedure G was followed using (3,5-dimethylphenyl)(morpholino)methanone (219g) (217 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1→2/1) and normal phase HPLC (n-hexane/EtOAc: 7/1→3/1) yielded 221g (186 mg, 54%) as a white solid.

The general procedure H was followed using (3,5-dimethylphenyl)(morpholino)methanone (219g) (217 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 3/1→2/1) and normal phase HPLC (n-hexane/EtOAc: 7/1→3/1) yielded 221g (248 mg, 72%) as a white solid.

M.p. = 135–136 °C.

^1^H-NMR (300 MHz, CDCl₃): δ = 7.03 (s, 1H), 6.77 (s, 1H), 3.86–3.68 (m, 5H), 3.60–3.50 (m, 1H), 3.32–3.11 (m, 2H), 2.40 (s, 3H), 2.25 (s, 3H).

^1^3^C-NMR (75 MHz, CDCl₃): δ = 170.0 (C₆), 138.5 (C₆), 138.2 (C₆), 138.6 (C₆), 130.8 (CH), 124.9 (CH), 95.0 (C₆), 66.6 (CH₂), 66.5 (CH₃), 47.1 (CH₂), 41.8 (CH₂), 28.5 (CH₃), 20.7 (CH₃).

IR (ATR): ν = 2901, 2856, 1627, 1460, 1434, 1106, 1007, 860, 662 cm⁻¹.

MS (EI) m/z (relative intensity): 345 (30) [M⁺], 359 (100), 2313 (17), 104 (20).

HR-MS (ESI) m/z calc’d for C₁₃H₁₂INO₂⁺ 345.0226, found 345.0225.

Synthesis of 2-bromo-N,N-diisopropyl-5-methylbenzamide (220h)

The general procedure G was followed using N,N-diisopropyl-5-methylbenzamide (219h) (110 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 16 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) yielded 220h (95 mg, 64%) as a white solid.
M.p. = 162–163 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.40$ (d, $J = 8.2$ Hz, 1H), 7.03–6.94 (m, 2H), 3.61 (sept, $J = 6.7$ Hz, 1H), 3.51 (sept, $J = 6.7$ Hz, 1H), 2.29 (s, 3H), 1.57 (d, $J = 6.7$ Hz, 3H), 1.55 (d, $J = 6.7$ Hz, 3H), 1.23 (d, $J = 6.7$ Hz, 3H), 1.06 (d, $J = 6.7$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 168.3$ (C$_q$), 139.9 (C$_q$), 137.6 (C$_q$), 132.5 (CH), 130.2 (CH), 127.1 (CH), 111.4 (C$_q$), 51.1 (CH), 45.9 (CH), 20.8 (CH$_3$), 20.8 (CH$_3$), 20.6 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2960, 2928, 1626, 1441, 1337, 1044, 831, 764, 622, 459$ cm$^{-1}$.

MS (El) $m/z$ (relative intensity): 299 (5) [M$^+$] ($^{81}$Br), 297 (5) [M$^+$] ($^{79}$Br), 256 (25), 254 (25), 199 (97), 197 (100).

HR-MS (El) $m/z$ calc for C$_{14}$H$_{20}$BrNO$^+$ 297.0728, found 297.0721.

The spectral data were in accordance with those reported in the literature.$^{113}$

**Synthesis of 2-bromo-3-fluoro-N,N-diisopropylbenzamide (220i)**

The general procedure H was followed using 3-fluoro-N,N-diisopropylbenzamide (219i) (219 mg, 1.0 mmol) and NBS (356 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel ($n$-hexane/EtOAc: 5/1) yielded 220i (165 mg, 55%) as a white solid.

M.p. = 134–135 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.28$ (ddd, $J = 8.2, 7.8, 4.9, 0.8$ Hz, 1H), 7.06 (ddd, $J = 8.2, 8.2, 1.5$ Hz, 1H), 6.95 (dq, $J = 7.8, 0.8$ Hz, 1H), 3.63–3.43 (m, 2H), 1.56 (d, $J = 6.7$ Hz, 3H), 1.54 (d, $J = 6.7$ Hz, 3H), 1.21 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 6.7$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 166.9$ (d, $J_{C-F} = 2$ Hz, C$_q$), 159.2 (d, $J_{C-F} = 249$ Hz, C$_q$), 138.2 (C$_q$), 129.2 (d, $J_{C-F} = 8$ Hz, CH$_2$), 121.8 (d, $J_{C-F} = 4$ Hz, CH), 111.8 (d, $J_{C-F} = 22$ Hz, CH), 106.4 (d, $J_{C-F} = 22$ Hz, C$_q$), 51.2 (CH), 46.1 (CH), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

$^{19}$F-NMR (283 MHz, CDCl$_3$): $\delta = -105.1$–105.2 (m).

IR (ATR): $\tilde{\nu} = 2970, 2932, 2874, 1625, 1437, 1339, 1205, 1041, 790, 603$ cm$^{-1}$.

MS (El) $m/z$ (relative intensity): 303 (4) [M$^+$] ($^{81}$Br), 301 (4) [M$^+$] ($^{79}$Br), 202 (90), 200 (100), 174 (16), 172 (18), 57 (48).

HR-MS (ESI) $m/z$ calc for [C$_{13}$H$_{12}$FBrNO]$^+$ 302.0556, found 302.0551.

**Synthesis of 3-bromo-N,N-diisopropyl-[1,1'-biphenyl]-4-carboxamide (220j)**

The general procedure H was followed using 3-bromo-N,N-diisopropyl-[1,1'-biphenyl]-4-carboxamide (219j) (281 mg, 1.0 mmol) and NBS (712 mg, 4.0 mmol). After 22 h, purification by column chromatography on silica gel ($n$-hexane/EtOAc: 5/1) and normal phase HPLC ($n$-hexane/EtOAc: 15/1→1/9) yielded 220j (173 mg, 48%) as a colorless oil.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.76$ (d, $J = 1.6$ Hz, 1H), 7.57–7.49 (m, 3H), 7.47–7.39 (m 2H), 7.39–7.32 (m, 1H), 7.22 (d, $J = 7.8$ Hz, 1H), 3.68 (sept, $J = 6.7$ Hz, 1H), 3.53 (sept, $J = 6.7$ Hz, 1H), 1.59 (d, $J = 6.7$ Hz, 3H), 1.57 (d, $J = 6.7$ Hz, 3H), 1.25 (d, $J = 6.7$ Hz, 3H), 1.08 (d, $J = 6.7$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 168.1$ (C$_q$), 138.6 (C$_q$), 139.0 (C$_q$), 138.7 (C$_q$), 131.3 (CH), 128.9 (CH), 128.0 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 119.3 (C$_q$), 51.2 (CH), 46.0 (CH), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.1 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2968, 2931, 1631, 1437, 1336, 1044, 754, 696$ cm$^{-1}$. 

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MS (EI) m/z (relative intensity): 361 (10) [M⁺] (81Br), 359 (10) [M⁺] (79Br), 318 (32), 316 (33), 261 (99), 259 (100), 152 (70).

HR-MS (EI) m/z calc for C₁₀H₂₂BrNO⁺ 359.0885, found 359.0885.

Synthesis of 4-bromo-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220k)

The general procedure H was followed using N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (219k) (141 mg, 0.5 mmol) and NBS (267 mg, 1.5 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 220k (117 mg, 65%) as a white solid.

M.p. = 151–152 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.61 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 7.8 Hz, 2H), 7.51–7.37 (m, 4H), 7.36 (d, J = 2.2 Hz, 1H), 3.69 (sept, J = 6.6 Hz, 1H), 3.55 (sept, J = 6.6 Hz, 1H), 1.61 (d, J = 6.6 Hz, 3H), 1.59 (d, J = 6.6 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 168.0 (Cq), 140.8 (Cq), 140.5 (Cq), 139.4 (Cq), 133.2 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 125.1 (CH), 117.9 (Cq), 51.2 (CH), 46.0 (CH), 20.9 (CH₃), 20.7 (CH₃), 20.6 (CH₃), 20.1 (CH₃).

IR (ATR): ʋ = 2931, 2873, 1631, 1444, 1369, 1337, 786 cm⁻¹.

MS (EI) m/z (relative intensity): 361 (8) [M⁺] (81Br), 359 (8) [M⁺] (79Br), 318 (38), 316 (37), 261 (98), 259 (100), 152 (85).

HR-MS (EI) m/z calc for C₁₀H₂₂BrNO⁺ 359.0885, found 359.0882.

The spectral data were in accordance with those reported in the literature.¹¹³a

Synthesis of 4-bromo-N,N-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (220l)

The general procedure H was followed using N,N-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (219l) (148 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 220l (88 mg, 47%) as a white solid.

M.p. = 193–194 °C.

1H-NMR (300 MHz, CDCl₃): δ = 7.57 (dd, J = 8.1, 0.5 Hz, 1H), 7.44 (dt, J = 8.1, 0.5 Hz, 2H), 7.37 (dd, J = 8.2, 2.2 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 3.67 (sept, J = 6.7 Hz, 1H), 3.52 (sept, J = 6.7 Hz, 1H), 2.37 (s, 3H), 1.59 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 168.1 (Cq), 140.7 (Cq), 140.4 (Cq), 137.8 (Cq), 136.5 (Cq), 133.1 (CH), 129.6 (CH), 127.9 (CH), 126.8 (CH), 124.8 (CH), 117.5 (Cq), 51.2 (CH), 46.0 (CH), 21.1 (CH₃), 20.9 (CH₃), 20.7 (CH₃), 20.6 (CH₃), 20.1 (CH₃).

IR (ATR): ʋ = 2969, 2929, 1631, 1441, 1336, 1021, 763, 514 cm⁻¹.

MS (ESI) m/z (relative intensity): 396 (28) [(M+Na)⁺], 749 (100) [(2M+H)⁺].

HR-MS (ESI) m/z calc for [(C₂₀H₂₂BrNO)H⁺] 374.1114, found 374.1107.
Synthesis of 4-bromo-4'-fluoro-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220m)

The general procedure H was followed using 4'-fluoro-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (219m) (150 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 220m (102 mg, 54%) as a white solid.

M.p. = 156–157 °C.

1H-NMR (300 MHz, CDCl3): $\delta = 7.59$ (d, $J = 8.2$ Hz, 1H), 7.49 (dd, $J = 8.6, 8.6$ Hz, 2H), 7.33 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.30 (d, $J = 2.3$ Hz, 1H), 7.11 (dd, $J = 8.6, 8.6$ Hz, 2H), 3.66 (sept, $J = 6.6$ Hz, 1H), 3.63 (sept, $J = 6.6$ Hz, 1H), 1.58 (d, $J = 6.6$ Hz, 3H), 1.56 (d, $J = 6.6$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.6$ Hz, 3H).

13C-NMR (75 MHz, CDCl3): $\delta = 167.9$ (Cq), 162.7 (d, $^1J_{C,F} = 247$ Hz, Cq), 140.5 (Cq), 139.9 (Cq), 135.6 (d, $^1J_{C,F} = 3$ Hz, Cq), 133.2 (CH), 128.7 (d, $^1J_{C,F} = 9$ Hz, CH), 128.0 (CH), 124.9 (CH), 117.9 (Cq), 111.9 (d, $^2J_{C,F} = 22$ Hz, CH), 51.2 (CH), 46.1 (CH), 20.9 (CH3), 20.7 (CH3), 20.6 (CH3), 20.1 (CH3).

19F-NMR (283 MHz, CDCl3): $\delta = -(114.3–114.6)$ (m).

IR (ATR): $\tilde{\nu} = 2966, 2928, 1631, 1599, 1438, 1337, 1226, 849, 813$ cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 379 (9) [M$^+$Br), 377 (9) [M$^+$] (7Br), 336 (35), 334 (36), 279 (99), 277 (100), 170 (75), 135 (60).

HR-MS (EI) $m/z$ calcd for C19H21BrNO$^+$ 377.0791, found 377.0790.

Synthesis of methyl 4'-bromo-3'-(diisopropylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (220n)

The general procedure H was followed using methyl 4'-bromo-3'-(diisopropylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (219n) (170 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→4/1) yielded 220n (120 mg, 57%) as a white solid.

M.p. = 182–183 °C.

1H-NMR (300 MHz, CDCl3): $\delta = 8.08$ (dt, $J = 8.4, 1.8$ Hz, 2H), 7.62 (d, $J = 8.2$ Hz, 1H), 7.59 (dt, $J = 8.4, 1.8$ Hz, 2H), 7.41 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.38 (d, $J = 2.2$ Hz, 1H), 3.94 (s, 3H), 3.65 (sept, $J = 6.7$ Hz, 1H), 3.53 (sept, $J = 6.7$ Hz, 1H), 1.58 (d, $J = 6.7$ Hz, 3H), 1.57 (d, $J = 6.7$ Hz, 3H), 1.25 (d, $J = 6.7$ Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H).

13C-NMR (75 MHz, CDCl3): $\delta = 167.8$ (Cq), 166.7 (Cq), 143.7 (Cq), 140.7 (Cq), 139.6 (Cq), 133.4 (CH), 130.2 (CH), 129.5 (Cq), 128.2 (CH), 126.9 (CH), 125.1 (CH), 118.9 (Cq), 52.2 (CH3), 51.2 (CH), 46.1 (CH), 20.9 (CH3), 20.7 (CH3), 20.6 (CH3), 20.0 (CH3).

IR (ATR): $\tilde{\nu} = 2960, 1719, 1629, 1435, 1368, 1340, 1271, 1102, 769, 710$ cm$^{-1}$.

MS (EI) $m/z$ (relative intensity): 419 (10) [M$^+$] (81Br), 417 (10) [M$^+$] (7Br), 376 (38), 374 (38), 319 (98), 317 (100), 151 (19).

HR-MS (EI) $m/z$ calcd for C21H23BrNO$^+$ 417.0940, found 417.0934.
Synthesis of 4'-acetyl-4-bromo-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220o)

The general procedure H was followed using 4'-acetyl-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (219o) (162 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1→3/1) yielded 220o (70 mg, 34%) as a white solid.

M.p. = 203–204 °C.

1H-NMR (300 MHz, CDCl₃): δ = 8.01 (d, J = 8.2 Hz, 2H), 7.66–7.58 (m, 3H), 7.38 (dd, J = 8.2, 2.2 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 3.65 (sept, J = 6.7 Hz, 1H), 1.58 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 197.5 (Cₐ), 167.8 (Cₐ), 143.8 (Cₕ), 140.7 (Cₕ), 139.5 (Cₕ), 136.3 (Cₕ), 133.4 (CH), 129.0 (CH), 128.2 (CH), 127.1 (CH), 125.1 (CH), 119.0 (Cₕ), 51.3 (CH), 46.1 (CH), 26.7 (CH₃), 20.9 (CH₃), 20.7 (CH₃), 20.6 (CH₃), 20.0 (CH₃).

IR (ATR): ν = 2982, 2934, 1677, 1629, 1451, 1367, 1397, 1036, 767, 602 cm⁻¹.

MS (EI) m/z (relative intensity): 403 (11) [M⁺] (81Br), 401 (11) [M⁺] (79Br), 360 (43), 358 (43), 303 (99), 301 (100), 151 (18), 43 (41).

HR-MS (EI) m/z calcd for C₂₁H₂₁BrNO₂⁺ 401.0990, found 401.0990.

Synthesis of 3'-acetyl-4-bromo-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (220p)

The general procedure H was followed using 3'-acetyl-N,N-diisopropyl-[1,1'-biphenyl]-3-carboxamide (219p) (162 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→4/1) yielded 220p (93 mg, 46%) as a white solid.

M.p. = 159–160 °C.

1H-NMR (300 MHz, CDCl₃): δ = 8.11 (t, J = 1.6 Hz, 1H), 7.93 (dt, J = 7.8, 1.6 Hz, 1H), 7.72 (dq, J = 7.6, 1.1 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.52 (dd, J = 7.8, 7.6 Hz, 1H), 7.41 (dd, J = 8.2, 2.3 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 3.65 (sept, J = 6.7 Hz, 1H), 3.53 (sept, J = 6.7 Hz, 1H), 2.63 (s, 3H), 1.58 (d, J = 6.7 Hz, 3H), 1.57 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.7 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ = 197.8 (Cₐ), 167.8 (Cₐ), 140.6 (Cₕ), 140.0 (Cₕ), 139.8 (Cₕ), 137.7 (Cₕ), 133.4 (CH), 131.5 (CH), 129.2 (CH), 128.2 (CH), 127.8 (CH), 126.7 (CH), 125.1 (CH), 124.7 (Cₕ), 118.7 (Cₕ), 51.2 (CH), 46.1 (CH), 26.8 (CH₃), 20.9 (CH₃), 20.7 (CH₃), 20.6 (CH₃), 20.0 (CH₃).

IR (ATR): ν = 2982, 2934, 1677, 1629, 1451, 1367, 1397, 1036, 767, 602 cm⁻¹.

MS (EI) m/z (relative intensity): 403 (11) [M⁺] (81Br), 401 (11) [M⁺] (79Br), 360 (43), 358 (43), 303 (98), 301 (100), 151 (15).

HR-MS (EI) m/z calcd for C₂₁H₂₁BrNO₂⁺ 401.0990, found 401.0991.

Synthesis of 5-(5'-acetylthiophen-2-yl)-2-bromo-N,N-diisopropylbenzamide (220q)

The general procedure H was followed using 3-(5'-acetylthiophen-2-yl)-N,N-diisopropylbenzamide (219q) (165 mg, 0.5 mmol) and NBS (178 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 4/1→3/1) yielded 220q (76 mg, 37%) as a white solid.
Experimental Section

M.p. = 181–183 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.62$ (d, $J = 4.0$ Hz, 1H), 7.58 (d, $J = 8.2$ Hz, 1H), 7.43 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.40 (d, $J = 2.2$ Hz, 1H), 7.29 (d, $J = 4.0$ Hz, 1H), 3.62 (sept, $J = 6.7$ Hz, 1H), 3.53 (sept, $J = 6.7$ Hz, 1H), 2.54 (s, 3H), 1.59 (d, $J = 6.7$ Hz, 3H), 1.55 (d, $J = 6.7$ Hz, 3H), 1.24 (d, $J = 6.7$ Hz, 3H), 1.07 (d, $J = 6.7$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 190.5$ (C$_q$), 167.3 (C$_q$), 150.3 (C$_q$), 143.8 (C$_q$), 140.9 (C$_q$), 133.6 (CH), 133.3 (CH), 133.0 (C$_q$), 127.0 (CH), 124.6 (CH), 124.0 (CH), 119.5 (C$_q$), 51.3 (CH), 46.1 (CH), 26.5 (CH$_3$), 20.9 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2977, 2936, 1653, 1621, 1435, 1340, 1281, 1021, 827, 796, 599$ cm$^{-1}$.

MS (EI) $m$/z (relative intensity): 409 (10) [M$^+$] (Br), 407 (10) [M$^+$] (Br), 366 (40), 364 (40), 309 (100), 307 (100), 185 (14).

HR-MS (ESI) $m$/z calcd for [(C$_{19}$H$_{29}$BrNO$_2$S)H]$^+$ 408.0627, found 408.0620.

Synthesis of 2-iodo-$N,N$-diisopropylbenzamide (212a)

The general procedure H was followed using $N,N$-diisopropylbenzamide (219a) (103 mg, 0.5 mmol) and NIS (225 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) and normal phase HPLC (n-hexane/EtOAc: 19/1→9/1) yielded 212a (88 mg, 53%) as a white solid.

M.p. = 188–189 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.76$ (dd, $J = 8.0, 1.0$ Hz, 1H), 7.34 (ddd, $J = 7.6, 7.5, 1.0$ Hz, 1H), 7.11 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.00 (ddd, $J = 8.0, 7.5, 1.6$ Hz, 1H), 3.63–3.38 (m, 2H), 1.58 (d, $J = 6.8$ Hz, 3H), 1.54 (d, $J = 6.8$ Hz, 3H), 1.25 (d, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 169.8$ (C$_q$), 144.2 (C$_q$), 139.3 (CH), 129.4 (CH), 128.2 (CH), 125.2 (C$_q$), 51.2 (CH), 46.0 (CH), 20.7 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (neat): $\tilde{\nu} = 2967, 2929, 2181, 1581, 1398, 1012, 771$ cm$^{-1}$.

MS (EI) $m$/z (relative intensity): 331 (7) [M$^+$], 288 (27), 230 (100), 202 (21), 43 (23).

HR-MS (EI) $m$/z calcd for C$_{13}$H$_{14}$INO$^+$ 331.0433, found 331.0414.

The spectral data were in accordance with those reported in the literature.$^{113a}$

Synthesis of 2-iodo-$N,N$-diisopropyl-5-methylbenzamide (212h)

The general procedure H was followed using $N,N$-diisopropyl-3-methylbenzamide (219h) (217 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 10/1) and normal phase HPLC (n-hexane/EtOAc: 19/1→9/1) yielded 212h (219 mg, 64%) as a white solid.

M.p. = 161–162 °C.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.63$ (d, $J = 8.0$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 6.82 (dt, $J = 8.0, 0.7$ Hz, 1H), 3.58 (sept, $J = 6.7$ Hz, 1H), 3.49 (sept, $J = 6.7$ Hz, 1H), 2.27 (s, 3H), 1.57 (d, $J = 6.7$ Hz, 3H), 1.54 (d, $J = 6.7$ Hz, 3H), 1.25 (d, $J = 6.7$ Hz, 3H), 1.05 (d, $J = 6.7$ Hz, 3H).

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 169.9$ (C$_q$), 144.0 (C$_q$), 139.0 (CH), 138.4 (C$_q$), 130.4 (CH), 126.5 (CH), 88.0 (C$_q$), 51.2 (CH), 45.9 (CH), 20.9 (CH$_3$), 20.8 (CH$_3$), 20.7 (CH$_3$), 20.6 (CH$_3$), 20.0 (CH$_3$).

IR (ATR): $\tilde{\nu} = 2966, 2928, 1621, 1441, 1337, 1012, 834, 763, 621, 455$ cm$^{-1}$.

MS (EI) $m$/z (relative intensity): 345 (11) [M$^+$], 302 (23), 245 (100), 216 (16), 90 (22).

HR-MS (ESI) $m$/z calcd for [(C$_{14}$H$_{15}$NO)$^+$] 346.0668, found 346.0662.
The spectral data were in accordance with those reported in the literature.\(^\text{179}\)

**Synthesis of 2-iodo-\(N,N\)-diisopropyl-4,5-dimethylbenzamide (219v)**

The general procedure \(H\) was followed using \(N,N\)-diisopropyl-3,4-dimethylbenzamide (219v) (233 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 221v (187 mg, 52\%) as a white solid. M.p. = 106–107 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.55\) (s, 1H), 6.94 (s, 1H), 3.62 (sept, \(J = 6.7\) Hz, 1H), 3.49 (sept, \(J = 6.7\) Hz, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 1.58 (d, \(J = 6.7\) Hz, 3H), 1.56 (d, \(J = 6.7\) Hz, 3H), 1.26 (d, \(J = 6.7\) Hz, 3H), 1.06 (d, \(J = 6.7\) Hz, 3H).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 170.0\) (C\(_q\)), 141.8 (C\(_q\)), 139.7 (CH), 138.4 (C\(_q\)), 137.0 (C\(_q\)), 126.8 (CH), 88.3 (C\(_q\)), 51.1 (CH), 45.8 (CH), 20.8 (CH\(_3\)), 20.7 (CH\(_3\)), 20.6 (CH\(_3\)), 19.3 (CH\(_3\)).

IR (ATR): \(\tilde{\nu} = 2970, 2929, 1623, 1435, 1359, 1322, 1043, 817, 609\) cm\(^{-1}\).

MS (El) \(m/z\) (relative intensity): 359 (10) [M\(^+\)], 316 (28), 259 (100), 232 (17), 104 (13).

HR-MS (El) \(m/z\) calcd for \(C_{14}H_{22}INO^+\) 359.0746, found 359.0745.

**Synthesis of 3-fluoro-2-iodo-\(N,N\)-diisopropylbenzamide (219i)**

The general procedure \(H\) was followed using 3-fluoro-\(N,N\)-diisopropylbenzamide (219i) (219 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1) yielded 221i (128 mg, 36\%) as a white solid. M.p. = 124–125 °C.

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.32\) (ddd, \(J = 8.0, 5.2, 0.7\) Hz, 1H), 7.00 (ddd, \(J = 8.0, 7.6, 1.5\) Hz, 1H), 6.93 (dd, \(J = 7.6, 1.0\) Hz, 1H), 3.62–3.43 (m, 2H), 1.60 (d, \(J = 6.6\) Hz, 3H), 1.56 (d, \(J = 6.6\) Hz, 3H), 1.26 (d, \(J = 6.6\) Hz, 3H), 1.07 (d, \(J = 6.6\) Hz, 3H).

\(^13\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 168.6\) (d, \(^2\)J\(_{C-F} = 2\) Hz, C\(_q\)), 161.8 (d, \(^1\)J\(_{C-F} = 246\) Hz, C\(_q\)), 146.4 (d, \(^3\)J\(_{C-F} = 8\) Hz, C\(_q\)), 130.3 (d, \(^3\)J\(_{C-F} = 8\) Hz, CH), 121.4 (d, \(^4\)J\(_{C-F} = 3\) Hz, CH), 114.8 (d, \(^2\)J\(_{C-F} = 24\) Hz, CH), 76.5 (d, \(^2\)J\(_{C-F} = 26\) Hz, C\(_q\)), 51.3 (CH), 46.1 (CH), 20.8 (CH\(_3\)), 20.7 (CH\(_3\)), 20.6 (CH\(_3\)), 20.0 (CH\(_3\)).

\(^19\)F-NMR (283 MHz, CDCl\(_3\)): \(\delta = -(90.8–90.9)\) (m).

IR (ATR): \(\tilde{\nu} = 2967, 2930, 1620, 1435, 1340, 1203, 1041, 788, 604\) cm\(^{-1}\).

MS (El) \(m/z\) (relative intensity): 349 (10) [M\(^+\)], 306 (28), 249 (100), 218 (18), 43 (16).

HR-MS (El) \(m/z\) calcd for \(C_{13}H_{12}FNO^+\) 349.0339, found 349.0339.

**Synthesis of 4-iodo-\(N,N\)-diisopropylbenzo[d][1,3]dioxole-5-carboxamide (221w)**

The general procedure \(H\) was followed using 4-iodo-\(N,N\)-diisopropylbenzo[d][1,3]dioxole-5-carboxamide (219w) (249 mg, 1.0 mmol) and NIS (450 mg, 2.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 5/1) yielded 221w (277 mg, 73\%) as a white solid. M.p. = 149–150 °C.

**Synthesis of 4-iodo-\(N,N\)-diisopropyl-[1,1'-biphenyl]-3-carboxamide (221k)**

The general procedure H was followed using \(N,N\)-diisopropyl-[1,1'-biphenyl]-3-carboxamide (219k) (141 mg, 0.5 mmol) and NIS (338 mg, 1.5 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 221k (130 mg, 64%) as a white solid.

**M.p. = 171–172 °C.**

**\(^1\)H-NMR (300 MHz, CDCl\(_3\))**: \(\delta = 7.84\) (d, \(J = 8.2\) Hz, 1H), 7.53 (dt, \(J = 7.0, 2.0\) Hz, 2H), 7.43 (dt, \(J = 7.0, 2.0\) Hz, 2H), 7.36 (dt, \(J = 7.0, 1.3\) Hz, 1H), 7.32 (d, \(J = 2.2\) Hz, 1H), 7.23 (dd, \(J = 8.2, 2.2\) Hz, 1H), 3.65 (sept, \(J = 6.7\) Hz, 1H), 3.52 (sept, \(J = 6.7\) Hz, 1H), 1.60 (d, \(J = 6.7\) Hz, 3H), 1.58 (d, \(J = 6.7\) Hz, 3H), 1.28 (d, \(J = 6.7\) Hz, 3H), 1.06 (d, \(J = 6.7\) Hz, 3H).

**\(^{13}\)C-NMR (75 MHz, CDCl\(_3\))**: \(\delta = 169.6\) (C\(_\beta\)), 144.5 (C\(_\gamma\)), 141.4 (C\(_\delta\)), 139.6 (CH), 139.4 (C\(_\epsilon\)), 128.9 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 124.3 (CH), 90.8 (C\(_\alpha\)), 51.2 (CH), 46.0 (CH), 20.8 (CH\(_3\)), 20.7 (CH\(_3\)), 20.6 (CH\(_3\)), 20.0 (CH\(_3\)).

**IR (ATR): \(\tilde{\nu} = 2967, 2930, 1622, 1444, 1337, 1207, 785, 608\) cm\(^{-1}\).**

**MS (EI) m/z (relative intensity): 407 (15) [M\(^+\)], 364 (35), 307 (100), 276 (25), 152 (45).**

**HR-MS (EI) m/z calcld for C\(_{19}\)H\(_{32}\)I\(\text{NO}^+\) 407.0746, found 407.0727.**

**Synthesis of 4-iodo-\(N,N\)-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (221i)**

The general procedure H was followed using \(N,N\)-diisopropyl-4'-methyl-[1,1'-biphenyl]-3-carboxamide (219i) (148 mg, 0.5 mmol) and NIS (225 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 221i (145 mg, 68%) as a white solid.

**M.p. = 208–210 °C.**

**\(^1\)H-NMR (300 MHz, CDCl\(_3\))**: \(\delta = 7.82\) (d, \(J = 8.2\) Hz, 1H), 7.43 (dt, \(J = 8.1, 1.8\) Hz, 2H), 7.30 (d, \(J = 2.2\) Hz, 1H), 7.26–7.19 (m, 3H), 3.65 (sept, \(J = 6.6\) Hz, 1H), 3.52 (sept, \(J = 6.6\) Hz, 1H), 2.37 (s, 3H), 1.60 (d, \(J = 6.6\) Hz, 3H), 1.57 (d, \(J = 6.6\) Hz, 3H), 1.27 (d, \(J = 6.6\) Hz, 3H), 1.06 (d, \(J = 6.6\) Hz, 3H).

**\(^{13}\)C-NMR (75 MHz, CDCl\(_3\))**: \(\delta = 169.8\) (C\(_\beta\)), 144.5 (C\(_\gamma\)), 141.4 (C\(_\delta\)), 139.6 (CH), 137.8 (C\(_\epsilon\)), 136.6 (C\(_\zeta\)), 129.6 (CH), 128.0 (CH), 126.7 (CH), 124.1 (CH), 90.4 (C\(_\alpha\)), 51.2 (CH), 46.0 (CH), 21.1 (CH\(_3\)), 20.8 (CH\(_3\)), 20.7 (CH\(_3\)), 20.7 (CH\(_3\)), 20.0 (CH\(_3\)).

**IR (ATR): \(\tilde{\nu} = 2968, 2929, 1627, 1440, 1335, 1034, 762, 515\) cm\(^{-1}\).**

**MS (ESI) m/z (relative intensity): 382 (82) [M+H]\(^+\), 444 (37) [M+Na]\(^+\), 843 (100) [(2M+H)\(^+\)].**

**HR-MS (ESI) m/z calcld for [(C\(_{20}\)H\(_{36}\)I\(\text{NO})H]^+ 382.0975, found 382.0970.**
Synthesis of 2-iodo-\(N,N\)-diisopropyl-5-(naphthalen-1-yl)benzamide (221x)

The general procedure H was followed using \(N,N\)-diisopropyl-3-(naphthalen-1-yl)benzamide (219x) (166 mg, 0.5 mmol) and NIS (225 mg, 1.0 mmol). After 22 h, purification by column chromatography on silica gel (n-hexane/EtOAc: 20/1→10/1) yielded 221x (134 mg, 59%) as a white solid.

M.p. = 161–162 °C.

\(^{1}\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.91 \text{ (d, } J = 8.2 \text{ Hz, 1H), 7.89 \text{ (d, } J = 8.2 \text{ Hz, 1H), 7.86 \text{ (d, } J = 8.6 \text{ Hz, 1H), 7.82 \text{ (d, } J = 8.6 \text{ Hz, 1H), 7.50 \text{ (ddd, } J = 8.2, 7.0 \text{ Hz, 1H), 7.46 \text{ (ddd, } J = 8.0, 7.0, 1.5 \text{ Hz, 1H), 7.38 \text{ (ddd, } J = 7.6, 7.5, 1.5 \text{ Hz, 1H), 7.37 \text{ (dd, } J = 7.5, 1.1 \text{ Hz, 1H), 7.25 \text{ (dd, } J = 2.2, 2.1 \text{ Hz, 1H), 7.15 \text{ (dd, } J = 8.2, 2.1 \text{ Hz, 1H), 3.77 \text{ (sept, } J = 6.6 \text{ Hz, 1H), 3.51 \text{ (sept, } J = 6.6 \text{ Hz, 1H), 1.61 \text{ (d, } J = 6.7 \text{ Hz, 3H), 1.51 \text{ (d, } J = 6.7 \text{ Hz, 3H), 1.33 \text{ (d, } J = 6.7 \text{ Hz, 3H), 1.09 \text{ (d, } J = 6.7 \text{ Hz, 3H).}}\)

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 169.6 \text{ (C}_{q} \text{), 144.2 \text{ (C}_{q} \text{), 141.0 \text{ (C}_{q} \text{), 139.3 \text{ (CH), 138.3 \text{ (C}_{q} \text{), 133.7 \text{ (C}_{q} \text{), 131.1 \text{ (CH), 128.4 \text{ (CH), 128.2 \text{ (CH), 127.4 \text{ (CH), 126.9 \text{ (CH), 126.3 \text{ (CH), 126.0 \text{ (CH), 125.5 \text{ (CH), 125.3 \text{ (CH), 91.0 \text{ (C}_{q} \text{), 51.4 \text{ (CH), 46.0 \text{ (CH), 20.9 \text{ (CH}_{2} \text{), 20.7 \text{ (CH}_{3} \text{), 20.6 \text{ (CH}_{3} \text{), 20.1 \text{ (CH}_{3} \text{) (One C}_{q} \text{ is invisible).}}\)

IR (ATR): \(\tilde{\nu} = 2968, 2933, 1624, 1439, 1368, 1331, 1119, 1038, 1011, 778 \text{ cm}^{-1} \).

MS (ESI) \(m/z\) (relative intensity): 458 [(M+H)\(^{+}\)] (46), 915 [(2M+H)\(^{+}\)] (100).

HR-MS (ESI) \(m/z\) calcd for [(C\(_{25}\)H\(_{18}\)F\(_{3}\)NO)H]\(^{+}\) 458.0975, found 458.0968.

Studies with isotopically labelled [D\(_{2}\)-MeOH (Scheme 90a)

A mixture of \(N,N\)-diisopropylbenzamide (219a) (103 mg, 0.5 mmol), Ru\(_{3}\)(CO)\(_{12}\) (10.5 mg, 3.3 mol %) and AgO\(_2\)C(1-Ad) (20 mg, 20 mol %) in DCE (2.0 mL) and [D\(_{2}\)-MeOH (0.2 mL) was stirred at 100 °C under N\(_{2}\) for 16 h. The mixture was then allowed to cool to ambient temperature, diluted with EtOAc (5 mL), filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, the product was purified by column chromatography on silica gel (n-hexane/EtOAc: 4/1) to yield a mixture 219a and [D\(_{2}\]-219a (93 mg, 90%) as a white solid. The deuterium incorporation was estimated to be 33% by \(^{1}\)H-NMR spectroscopy.

Studies with isotopically labelled compound [D\(_{2}\]-250 (Scheme 90b)

A mixture of \(N,N\)-diisopropylbenzamide (219a) (205 mg, 1.0 mmol), NBS (356 mg, 2.0 mmol),
Ru$_3$(CO)$_{12}$ (21.1 mg, 3.3 mol %), AgO$_2$C(1-Ad) (57.4 mg, 20 mol %) and [D]$_1$-250 (200 mg, 2.0 mmol) in DCE (3.0 mL) was stirred at 120 °C under N$_2$ for 16 h. The mixture was then allowed to cool down to ambient temperature, diluted with EtOAc (5 mL), filtered through a short pad of silica gel and eluted with EtOAc (50 mL). After removing the solvent under reduced pressure, the product was purified by column chromatography on silica gel (n-hexane/EtOAc: 10/1→5/1) to give [D]$_1$-220a (164 mg, 57%) as a white solid and [D]$_2$-219a (79 mg, 38%) as a white solid. The deuterium incorporation was estimated by $^1$H-NMR spectroscopy.

**Kinetic isotope effect studies by parallel experiments (Scheme 91)**

A mixture of benzamide 219a or [D]$_2$-219a (1.0 mmol), NBS (356 mg, 2.0 mmol), Ru$_3$(CO)$_{12}$ (21.1 mg, 3.3 mol %), AgO$_2$C(1-Ad) (57.4 mg, 20 mol %) and the internal standard 1,3,5-tri-tert-butylbenzene (246 mg, 1.0 mmol) in DCE (8.0 mL) was stirred at 120 °C under N$_2$. For three hours, an aliquot (0.2 mL) was collected every fifteen minutes and submitted to GC analysis to determine the conversion.

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### Abbreviations

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Nationality: Chinese

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