Investigations towards the design, synthesis and application of new sulfur-based transfer reagents

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Ein Patent zu den in der Arbeit synthetisierten Verbindungen und zu deren synthetischer Anwendbarkeit wurde von der Universität Göttingen eingereicht (DE102018211606.7).

Hiermit versichere ich, dass ich die eingereichte Dissertation selbständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, sowie Zitate kenntlich gemacht habe.

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Bernd Waldecker

Abbreviation

Å	Ångstrom (10^{-10}m)	ESI-MS	Electrospray Ionisation Mass Spectrometry
ACM	Alkyne cross metathesis	*et al.*	et alia
ADIMET	Acyclic diyne metathesis polymerization	EtOAc	Ethyl acetate
Ar	generic arene	EtOH	Ethanol
Bn	Benzyl	^{18}F	Fluorine-18
Boc	*tert*-Butyloxycarbonyl protecting group	g	gram
BuLi	Butyllithium	GC-MS	Gas Chromotography Mass Spectrometry
Bz	Benzoyl	HRMS	High Resolution Mass Spectrometry
cald.	calculated	hυ	Light irradiation
cat.	catalytic	IR	Infrared spectroscopy
Cbz	Carboxybenzyl	*i*Pr	*iso*-propyl
CF_3	Trifluoromethyl group	J	Joule
CoA	Coenzyme A	*J*	Coupling constant
CPPA	Cycloparaphenyleneacetylene	K	Kelvin
CuAAC	Copper-catalyzed azide-alkyne cycloaddition	KAPA	Potassium 3-aminopropylamide
DBCO	dibenzylcyclooctyne	KB cell	Subline of tumor cell line HeLa
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene	L	Ligand
DCE	1,2-Dichloroethane	LDA	Lithium diisopropylamide
DCM	Dichloromethane	*m*	*meta*
DDQ	2,3-Dichlor-5,6-dicyano-1,4-benzochinon	M	Metal
DIPEA	N,N-Diisopropylethylamine	M	Molar (Mold m^{-3})
DMAP	4-Dimethylaminopyridine	*m*CPBA	*meta*-Chloroperoxybenzoic acid
DMF	N,N-dimethylformamide	MeCN	Acetonitrile
DMP	Dess–Martin periodinane	MOF	Metal−organic framework
DNA	Deoxyribonucleic acid	MS	Molecular sieves
EBX	EthynylBenziodoXolone	NEt_3	Triethylamine
ECHC	4-epoxycyclohexenylmethyl-3,4-epoxycyclo-hexenyl carboxylate	NMR	Nuclear Magnetic Resonance
EI	Electron Ionisation	Nu	Nucleophile
equiv.	equivalents	*o*	*ortho*

p	*para*
P388 cells	Leukaemia cell line
PBS buffer	Phosphate-buffered saline
PET	Positron emission tomography
Ph	Phenyl
PMB	4-Methoxybenzyl
ppm	parts per million
PPTS	Pyridinium p-toluenesulfonate
Pr	Propyl
q	quartet (NMR)
quant.	quantitative
R	Generic substituent
RCAM	Ring-Closing Alkene Metathesis
RNA	Ribonucleic acid
ROM	ring opening metathesis
rt	Room temperature
RuAAC	ruthenium-catalyzed azide-alkyne cycloaddition
s	singlet (NMR)
SAM	S-(Adenosylmethionin)
T	Temperature
t	Time
TAMRA	Tetramethylrhodamine
TBAX	Tetra-*n*-butylammonium salt
TES	Triethylsilyl
*t*Bu	*tert*-butyl
TBS	*tert*-Butyldimethylsilyl ether
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofurane
TIPS	Triisopropyl
TMS	Trimethylsily
X	Generic heteroatom
X-ray	X-ray crystallography
Y	Generic substituent
Z	Generic heteroatom
δ	Chemical shift
λ	wavelength

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1 General Part

1.1 Introduction

Alkynylation is an important reaction class to incorporate a C_2-unit into organic molecules. Similarly, the majority of the utilized building blocks in nature such as acetyl-CoA, shikimic acid or mevalonic acid are C_2-units or a multiples of it.[1] As a result, many natural and bioactive compounds are constructed by a repetitive introduction of these units. Furthermore, alkynes are very versatile groups for further functionalization (compare Chapter 1.2.3). Therefore, it is not surprising that in the years that in the years 1997–2009 methods for the introduction of carbon units to molecules, such as alkylation, acylation or C-C-bond formation, including alkynylation were some of the most frequently used reactions in innovative chemistry, such as library synthesis, lead optimization, process chemistry and bioactive compounds synthesis (Figure 1).[2]

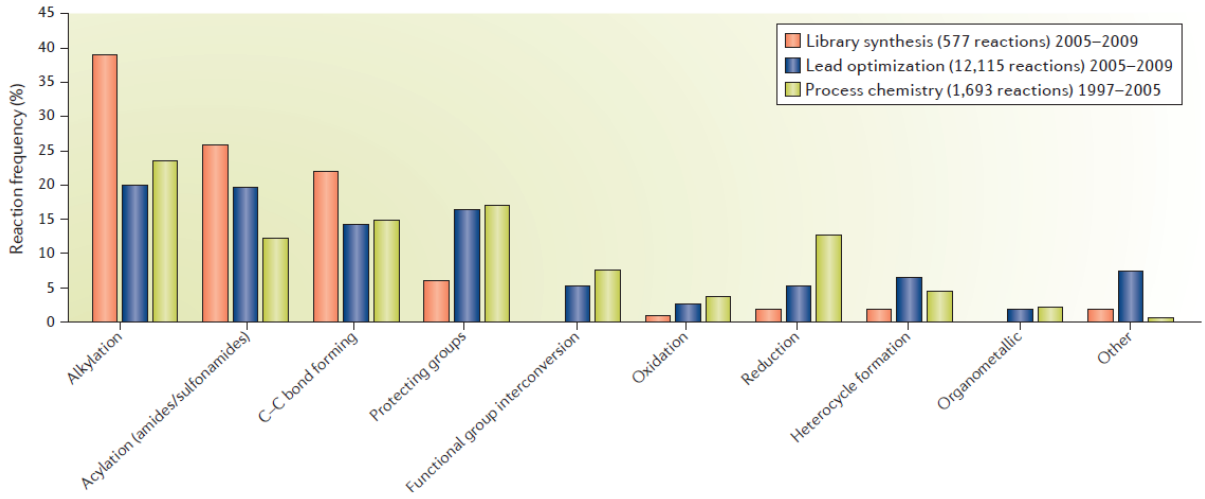


Figure 1 Reaction types used in library synthesis (GlaxoSmithKline (GSK): 2005–2009), lead optimization (AstraZeneca, GSK and Pfizer: 2005–2009) and process chemistry for the synthesis of candidate drugs (AstraZeneca, GSK and Pfizer: 1997–2005).2

However, the introduction of alkyne moieties into organic molecules is clearly limited by the structural features of this functional group, e.g. the strong tendency to react as a nucleophile due to easy deprotonation. Therefore, new methodologies, which open new reaction pathways, are required for these purposes. These processes could in turn facilitate the synthesis of new drug candidates and allow the preparation of new compounds and materials. The aim of this work is to consider alternative possibilities for the incorporation of this versatile building block, to avoid harsh reaction conditions and to enable the functionalization of complex highly functionalized molecules, thus, offering a new instrument for the chemist's toolbox of introducing alkynes.

1.2 The alkyne group

1.2.1 General properties of alkynes

Alkynes are highly energetic, linear compounds. The characteristic structural element of this functional group is the triple bond. From a formal viewpoint, it consists of a σ-bond formed by the overlap of two axial sp-hybridized orbitals of two carbon atoms, and two orthogonal π-bonds, formed by unhybridized p-orbitals (Figure 2).[3]

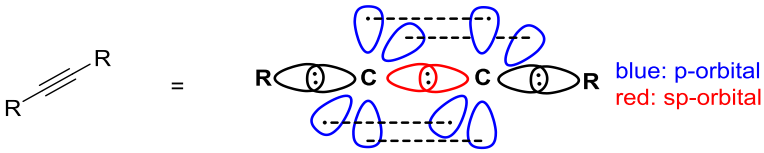


Figure 2 Schematic representation of the triple bond in alkynes.

A variety of different reactions can be applied towards the synthesis of alkynes on laboratory scale (compare Chapter 1.2.2).[4a] In contrast, on an industrial level alkynes are mainly synthesized by homologation of short terminal alkynes like acetylene or propyne. The latter can be accessed by common procedures like the calcium carbide process or cracking methods from oil, coal or gas.[3,4b,c] With a pKa of around 25, terminal alkynes are considerably easier to deprotonate, when compared with alkenes or alkanes. Consequently, the resulting acetylides react normally as nucleophiles and can be used for a variety of substitution or addition reactions (compare Chapter 1.2.3). Nowadays, many natural products are known to contain alkyne moieties.[5] Often these compounds show interesting biological activities like the antibiotic (-)-marasin (**1**)[6] or the natural antifeedant tonghaosu (**2**) (Figure 3).[7]

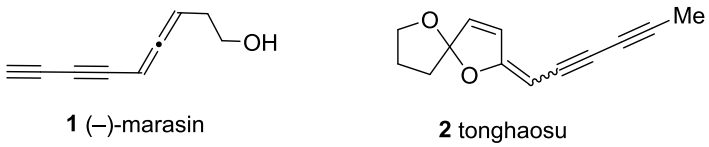


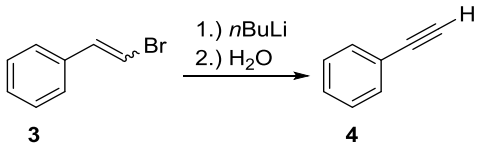
Figure 3 Alkyne containing natural products (–)-marasin (**1**) and tonghaosu (**2**).

Furthermore, alkynes are applied in many different research fields, such as in the synthesis of organic electronics,[8] in medicinal chemistry[9] or in the functionalization of metal organic frameworks (MOFS).[10] Additionally, alkynes are known to be biorthogonal and can be introduced to complex biological molecules and systems.[11]

1.2.2 Synthesis of alkynes in a laboratory scale

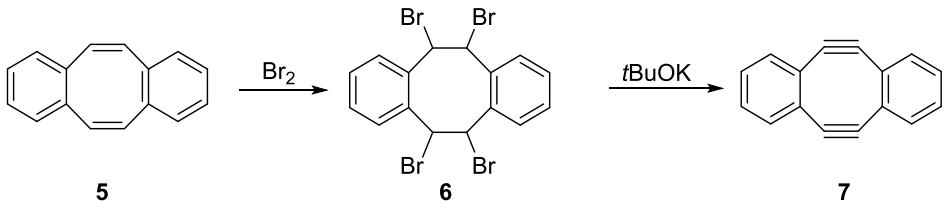
1.2.2.1 Synthesis of alkynes by elimination

Elimination is a classical, widely used method for the formation of an alkyne moiety in the laboratory. Commonly used methods are the dehydrohalogenation of haloalkenes, the twofold dehydrohalogenation of dihaloalkanes or the elimination reactions of alkenes with heteroatom-containing substituents.[12] An early example for the dehydrohalogenation of haloalkenes was given by the synthesis of phenylacetylene (**4**) from (2-bromovinyl)benzene (**3**) using a strong base like *n*BuLi (Scheme 1).[13]



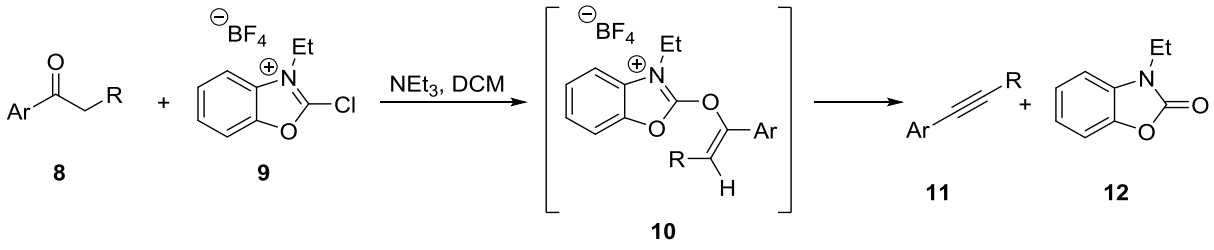
Scheme 1 Synthesis of alkynes by dehydrohalogenation of haloalkenes.[13]

Dihaloalkanes can easily be synthesized by the addition of bromine to alkenes. In a publication by Wong *et al*., the tetrabromide **6** was obtained by the reaction of cyclooctatetraene **5** with elemental bromine. Afterwards, the cyclic dialkyne **7** was synthesized by a four-fold dehydrobromination with the base potassium *tert*-butoxide (Scheme 2).[14]



Scheme 2 Synthesis of alkynes by fourfold dehydrohalogenation.[14]

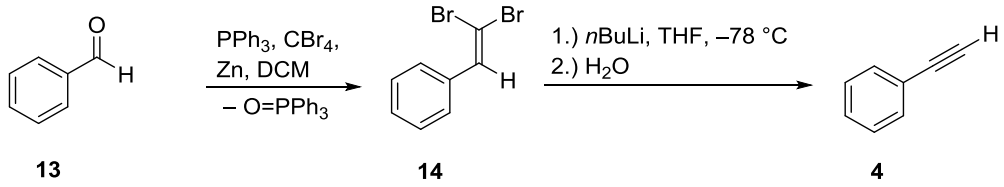
Another example for the synthesis of alkynes via elimination reactions was given by Tsuji and coworkers. Enoles of the type **10** were synthesized from ketones **8** and 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**9**) in the presence of NEt_3 (Scheme 3). Subsequently, a set of different alkynes was obtained from the intermediate **10** by the elimination of 3-ethylbenzoxazol-2(3*H*)-one (**12**).[15]



Scheme 3 Synthesis of alkynes employing 2-chloro-3-ethylbenzoxazolium salt (**9**).[15]

1.2.2.2 The Corey-Fuchs reaction

The Corey-Fuchs reaction is a two-step reaction sequence, which can be used to furnish alkynes. In their publication, Corey and Fuchs[16] reported a method consisting initially preparing 1,1-dibromoolefins from aldehydes as reported by Ramirez[17] with a consequent Fritsch-Buttenberg-Wiechell (FBW) rearrangement[18] to synthesize alkynes. For example, this methodology was utilized by Corey and Fuchs to afford phenylacetylene (**4**) from benzaldehyde (**13**) (Scheme 4).[16] The latter was treated with a mixture of triphenylphosphine, tetrabromomethane and zinc to synthesize the dibromide **14**. Afterwards, the dibromide **14** was transformed to phenylacetylene (**4**) upon reaction with *n*BuLi.



Scheme 4 Synthesis of phenylacetylene (**4**) by Corey and Fuchs.[16]

The dibromoolefination also proceeds in the absence of Zn. For the mechanism of the latter reaction, an initial attack of triphenylphosphine to tetrabromomethane is proposed (Figure 4).[19] This results in the formation of the carbanion **15** and the phosphonium salt **16**, which are in equilibrium with the phosphonium salt **17**. Subsequently, a second triphenylphophine molecule debrominates the phosphonium salt **17** to form the ylide **18**. Therefore, a minimum of two equivalents of triphenylphosphine is necessary to conduct the reaction.[19c] The ylide **18** undergoes a Wittig-type reaction and attacks the aldehyde **14** to offer the zwitterionic structure **19**. The latter undergo a ring closure to form the oxaphosphetane **20** and in the next step the desired dibromide **21** is formed by cycloreversion, eliminating triphenylphosphine oxide. A strong base such as *n*BuLi or LDA is applied in the subsequent Fritsch-Buttenberg-Wiechel rearrangement, which furnishes alkyne **23**.[20] In the peculiar case of R = H, the resulting acetylene **23** is attacked by a second equivalent of the base affording the corresponding lithiated alkyne **23**. Afterwards, phenylacetylene (**4**) is obtained after protonation.

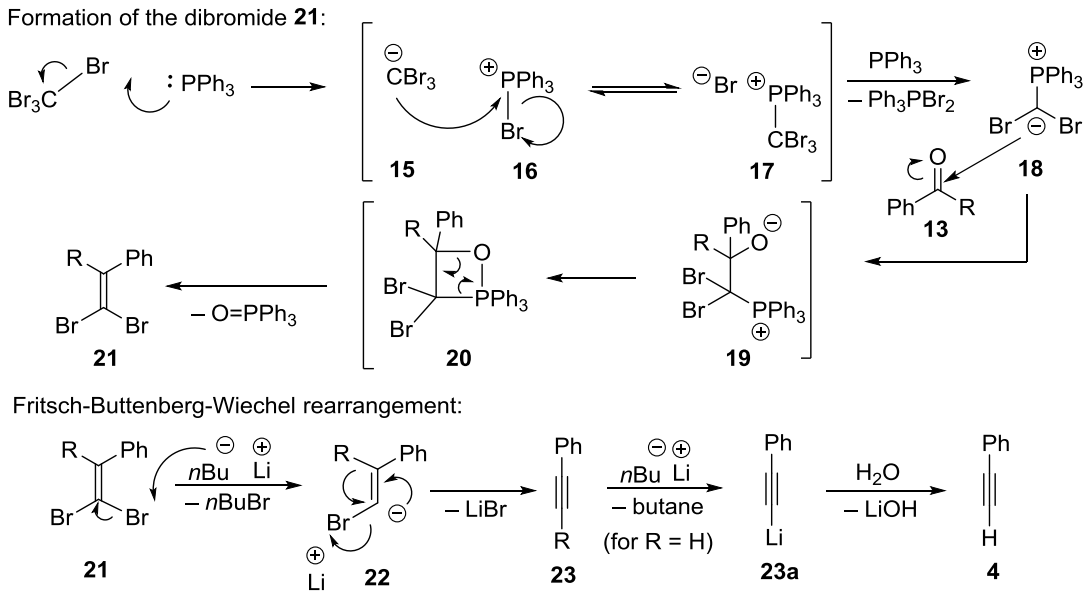
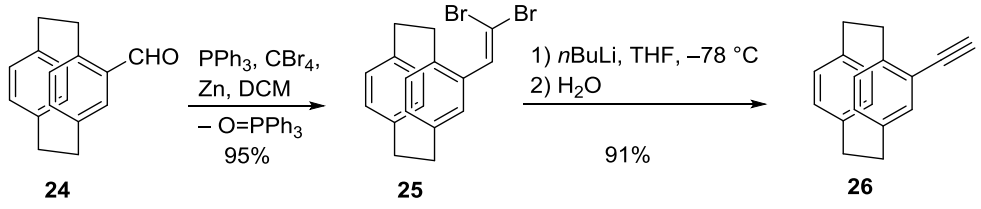


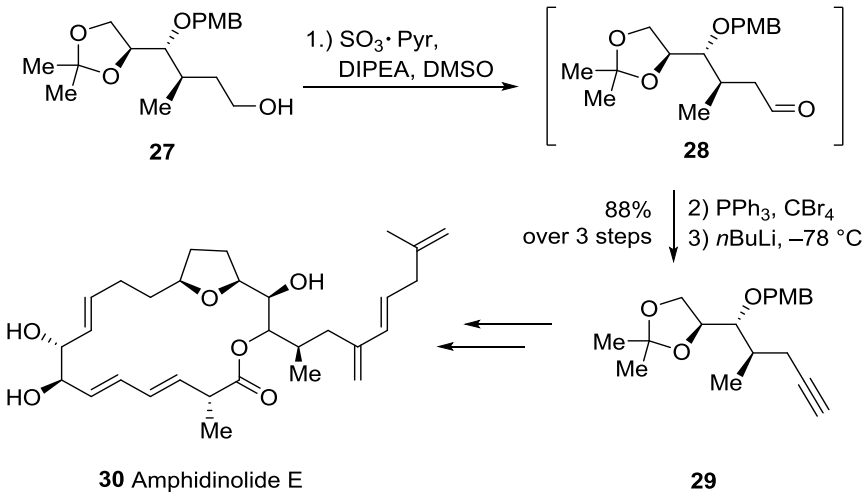
Figure 4 Proposed mechanism of the Corey-Fuchs reaction.[19,20]

This methodology was utilized by Clément *et al.* to afford (±)-4-ethynyl[2.2]paracyclophane (**26**) in 86% overall yield (Scheme 5).[21] Compound **26** is an interesting target in coordination chemistry.[22] The aldehyde **24** was treated with a mixture of triphenylphosphine, tetrabromomethane and zinc to synthesize the dibromide **25**. Afterwards, the dibromide **25** was converted to (±)-4-ethynyl[2.2]paracyclophane (**26**) with *n*BuLi.



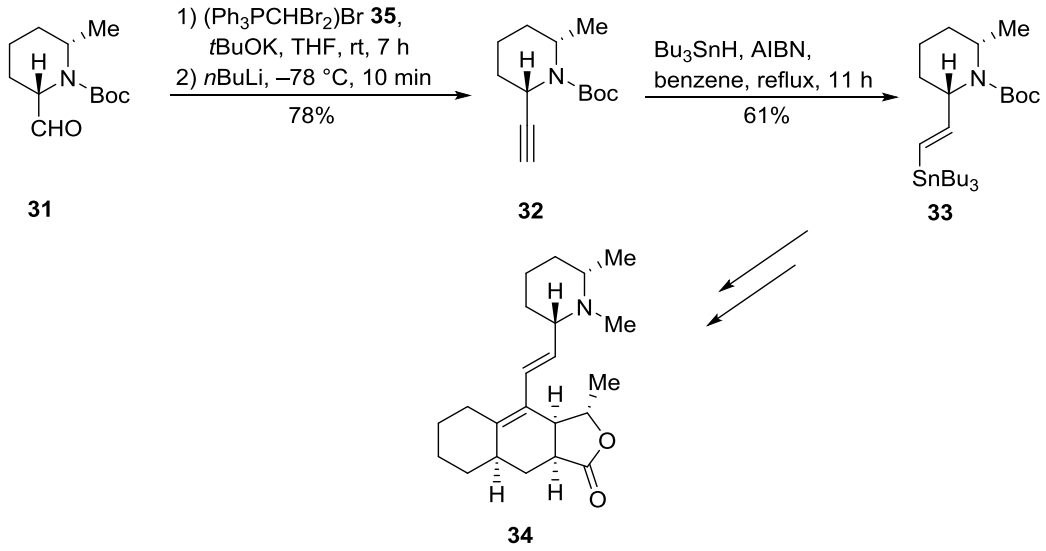
Scheme 5 Synthesis of (±)-4-ethynyl[2.2]paracyclophane (**26**) by Clément *et al*.[21]

Another example of a Corey-Fuchs reaction, which illustrates the relevance of this transformation in the synthesis of intermediates for the preparation of complex molecules such as Amphidinolides, was presented by Roush and coworkers.[23] Amphidinolides are a group of macrolides isolated from the dinoflagellate *Amphidinium.* Many representatives of this family demonstrate a potent antitumor activity and are therefore interesting targets for total synthesis.[24] In their synthesis of the macrolide Amphidinolide E (**30**), the authors used a three-step sequence to build up the alkyne **29**. Initially, the alcohol **27** was oxidized under Parikh-Doering conditions. The resulting aldehyde **28** was treated with the ylide **18**, formed from a reaction of tetrabromomethane with triphenylphosphine. Finally, the desired alkyne **29** was obtained by workup with *n*BuLi in a total yield of 88% over three steps. After this, Amphidinolide E (**30**) was synthesized from the intermediate **29** (Scheme 6).



Scheme 6 Synthesis of Amphidinolide E by Roush and coworkers utilizing the Corey-Fuchs reaction.[23]

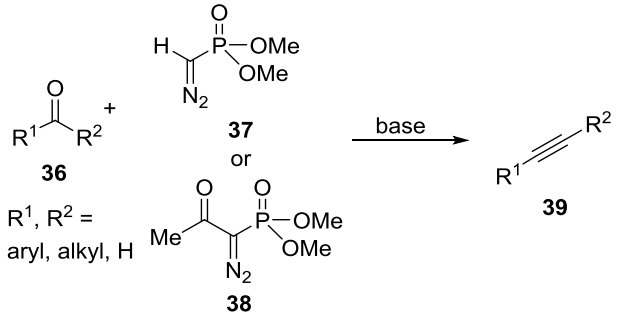
Wong and coworkers used a Fritsch-Buttenberg-Wiechell rearrangement in their synthesis of alkaloide Himbacine (**34**) (Scheme 7).[25] The latter is a muscarinic receptor antagonist and, consequently, possesses a large potential to find application in the treatment of Alzheimer's disease or other neurodegenerative disorders.[26] Accordingly, the Boc-protected piperidine **31** was treated with the ylide formed from deprotonation of the phosphonium salt **35** with potassium *tert*-butoxide, before addition of *n*BuLi to obtain the alkyne **32** in a high yield of 78% over two steps. The alkyne **32** with a piperidine moiety was then converted though a radical hydrostannylation to the corresponding stannane **33**, which was incorporated via Stille coupling into the lactone core of the Himbacine framework.



Scheme 7 Synthesis of Himbacine (**34**) by Wong and coworkers.[25]

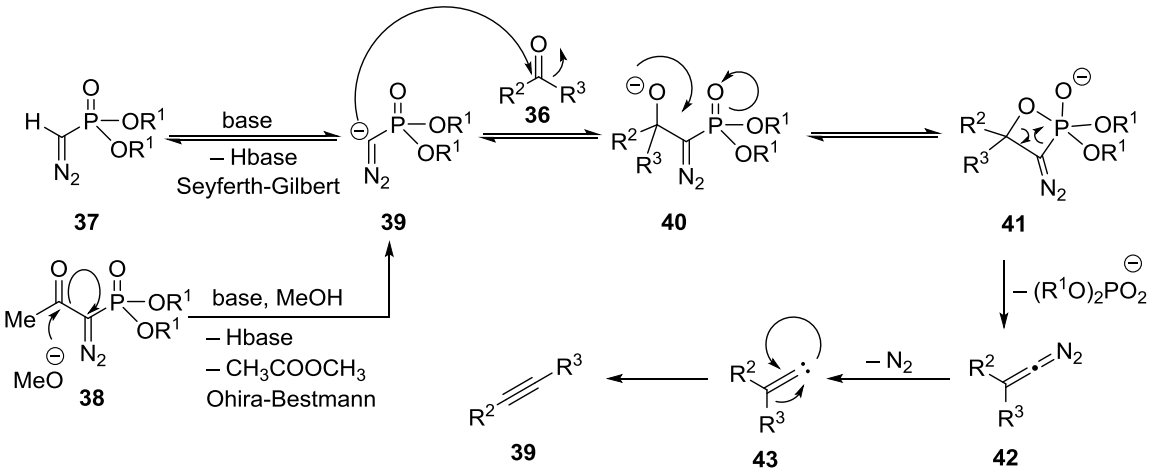
1.2.2.3 The Seyferth-Gilbert homologation

The Seyferth-Gilbert homologation[27] and the corresponding Ohira-Bestmann modification[28] are common methods to introduce alkynes into organic molecules. Similarly to the Corey-Fuchs reaction, aldehydes and ketones are used as starting materials. These are treated with dimethyl (diazomethyl)phosphonate (**37**) or dimethyl 1-diazo-2-oxopropylphosphonate (**38**) and a base to obtain terminal and internal alkynes (Scheme 8).



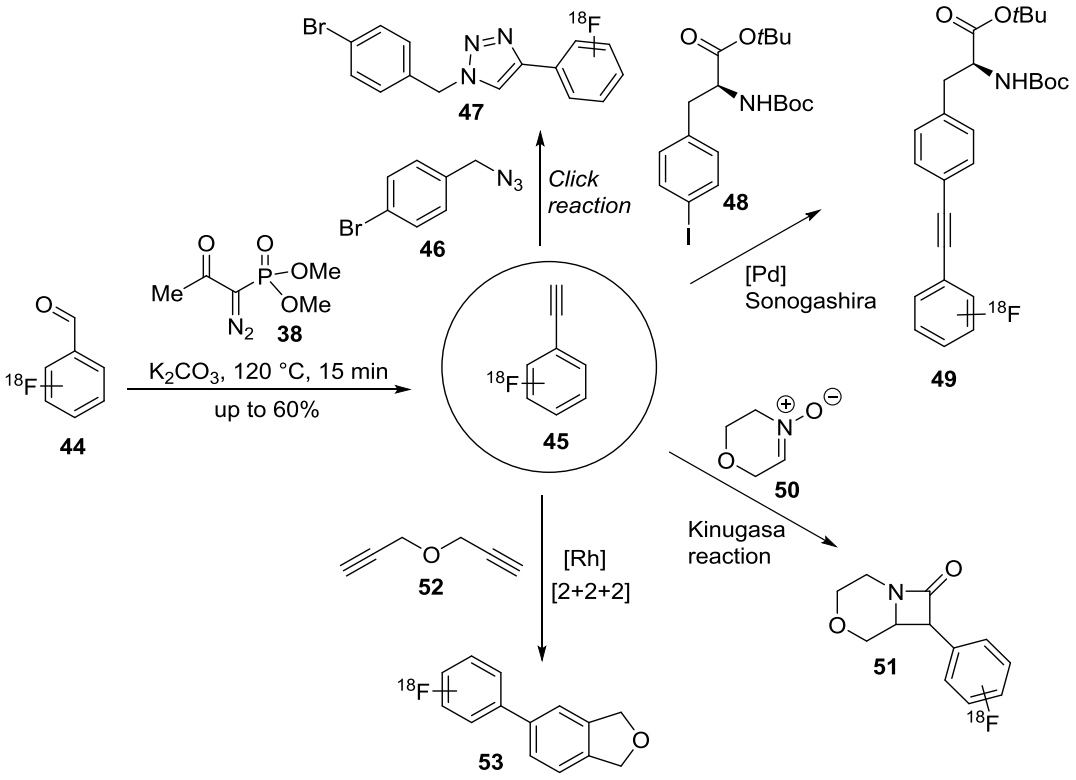
Scheme 8 General reaction scheme of the Seyferth-Gilbert homologation and the Ohira-Bestmann modification.

A mechanism was proposed by Gilbert *et al.*[29]. First, the deprotonated Seyferth-Gilbert reagent **39** is formed by deprotonation of dimethyl (diazomethyl)phosphonate (**37**) with a strong base in the unmodified Seyferth-Gilbert homologation or by retro-Claisen-type cleavage of the acetyl group in dimethyl 1-diazo-2-oxopropylphosphonate (**38**) (the Ohira-Bestmann variation). In the latter case a base is required although milder bases can be used than in the unmodified Seyferth-Gilbert homologation. As a consequence, a number of base-sensitive compounds can be applied in the Ohira-Bestmann-variation. Afterwards, the deprotonated Seyferth-Gilbert reagent **39** attacks the aldehyde or ketone **36** to form the alkoxide **40**. Subsequently, the alkoxide **40** cyclizes to the oxaphosphetane **41**. A dimethyl phosphate anion is then eliminated to form the diazoalkene **42**, which is followed by elimination of nitrogen from the latter. As a result, the carbene **43** is formed. Finally, the desired alkyne **39** can be obtained by an 1,2-migration of one of the substituents in **43** (Scheme 9).



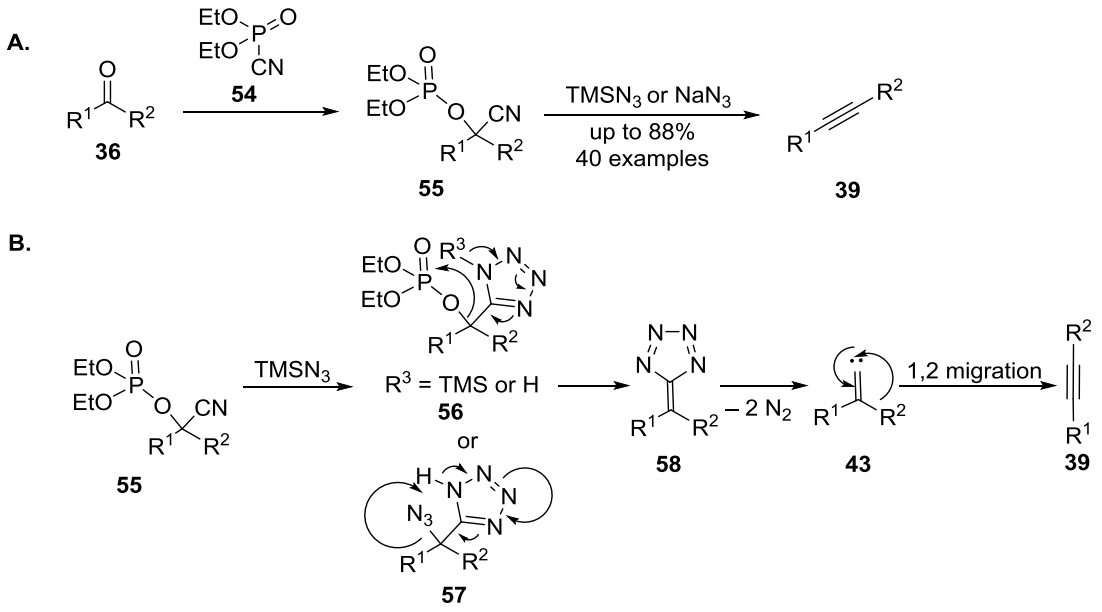
Scheme 9 Proposed mechanism of the Seyferth-Gilbert homologation and the Ohira-Bestmann modification.[29]

Recently, Neumaier and coworkers reported an application of an Ohira-Bestmann homologation in the synthesis of ^{18}F-labeled building blocks for positron emission tomography (PET).[30] PET is a methodology to visualize processes on molecular level of ^{18}F-labeled compounds in clinical diagnostics, utilizing the positron emission of radioactive decay of ^{18}F. Because of the low half-time of ^{18}F (110 min), it is necessary to use reliable and fast reactions. In their synthesis, the authors utilized the labeled benzaldehydes **44** and the Ohira-Bestmann-reagent **38** for the synthesis of the labeled alkynes **45** in high radiochemical yields of up to 60% in only 15 min. Finally, these labeled alkynes were transformed applying common synthetic methods to biologically interesting compounds. Thus, the triazol **47** was synthesized by a "click reaction" (see below in Chapter 1.2.3.1), the protected amino acid **49** was obtained using Sonogashira coupling, the β-lactam **51** – via the Kinugasa reaction and the phthalan **53** through a rhodium catalyzed [2+2+2]-cyclization (Scheme 10).



Scheme 10 Synthesis of ^{18}F-labeled alkynes **45** and their further derivatization to different biologically interesting compounds by Neumaier and coworkers.[30]

An interesting modification of the Seyferth-Gilbert homologation was presented by Harusawa and coworkers.[31] First, the authors synthesized cyanohydrin-*O*-phosphates **55** from the reaction of aldehydes and ketones with diethyl phosphorocyanidate (**54**). Alkynes of the type **39** were then obtained under very mild conditions through reaction of **55** with $TMSN_3$ or NaN_3 in high yields of up to 88% (Scheme 11). No additional base was necessary. Thus, challenging functionalized compounds, which could not be accessed in high yields or in high selectivity by other variations, could be prepared. In line with their mechanistic studies, the authors suggest the initial formation of either tetrazolylphosphate **56** or azidotetrazole **57**. Afterwards, fragmentation by the elimination of either diethyl phosphoric or hydrazoic acid derivatives leads to the tetraazafulvene **58**. Subsequently, an elimination of two nitrogen molecules from **58** affords the carbene **43**, which then undergoes a 1,2-migration to form the desired product **39**.



Scheme 11 Modification of Seyferth-Gilbert homologation as reported by Harusawa and coworkers. A. General reaction scheme. B. Proposed mechanism of the reaction.[31]

1.2.3 Reactivity of alkynes

The versatility of alkynes is based on the low oxidation state of the carbon atoms and the resulting possibility for further functionalization to a multiplicity of other functional groups. Hydrofunctionalisations are one of the most famous reactions (Figure 5). Typical examples are hydrogenations and the addition of halogens or hydrogen halides.[32] Furthermore, reactions such as hydroborations,[33] hydrosilylations,[34] hydrostannylations[35a] as well as additions of alcohols, thiols, amines, etc.[35b] are commonly used. In general, it possible to obtain the *cis* or *trans* products from addition reactions. Therefore, a catalyst is normally applied in an addition to obtain a defined stereoselectivity and to prevent overreaction. An illustrative example is the well-known Lindlar catalyst, which can be utilized for the hydrogenation of alkynes to alkenes. In case of this catalyst system, lead acetate is applied to poison the catalyst partially, preventing over reaction.[36] Besides, with double addition reactions alkanes can be accessed from alkynes.[3] The hydration of alkynes affords aldehydes or ketones[37] and 1,2-diketones are accessible via the *Wacker*-Oxidation.[38] In contrast, the oxidation with strong oxidants like potassium permanganate leads to the formation of acids.[39] Another reaction commonly applied towards alkynes is the synthesis of aromatic systems by [2+2+2]-cyclization.[40] Furthermore, alkynes can be used in a variety of other cycloadditions such as the Diels-Alder-reaction.[41] Lastly, substituted 1,2,3-triazoles can be obtained from 1,3-dipolar cycloaddition of azides and alkynes ("*click* reaction", see Chapter1.2.3.1).

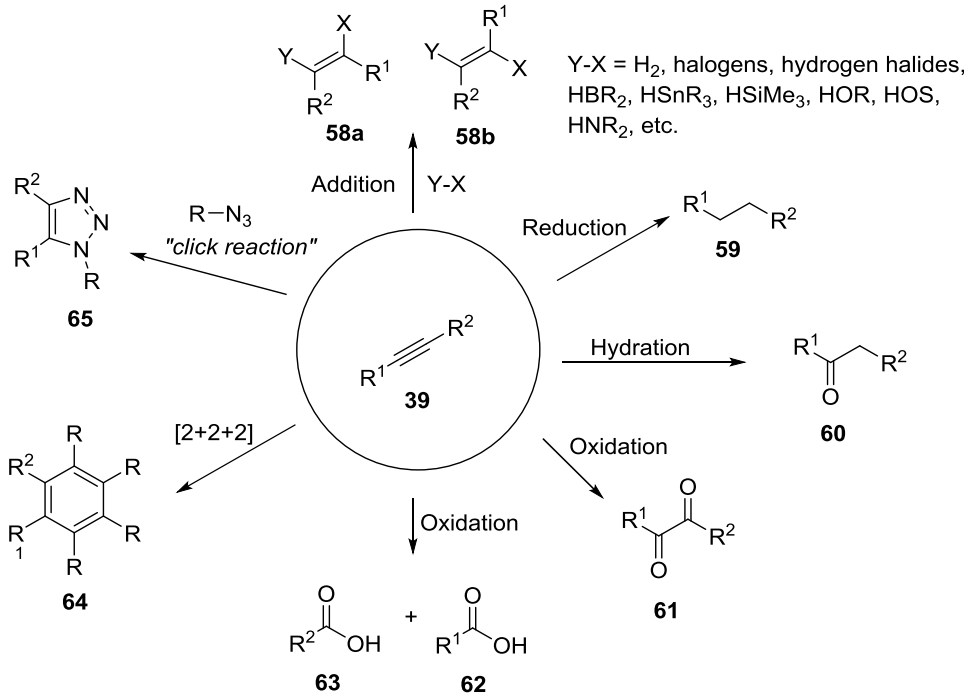


Figure 5 Selected products of alkynes common derivatization.

Furthermore, it should be mentioned that there are several methods for the modification of alkynes that can be applied in the synthesis of complex structures. Such famous reactions as the alkyne *zipper* reaction[42] that is used for the transformation of internal to terminal alkynes or alkyne metathesis[43] for the synthesis of polymeric, cyclic or terminal alkynes (Figure 6).

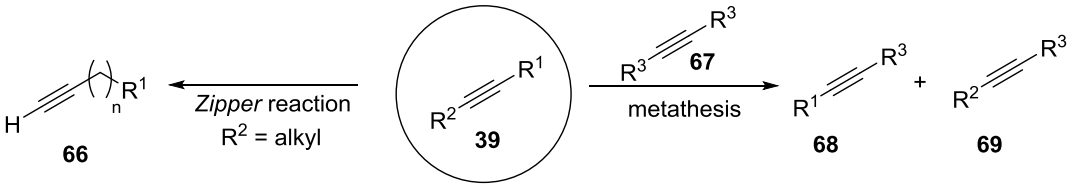
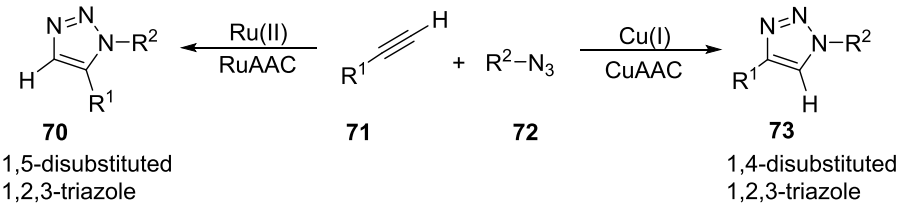


Figure 6 Common methods to modify alkynes.

1.2.3.1 Azide-alkyne cycloaddition ("*click* chemistry")

The term "*click* chemistry" was introduced by Sharpless and coworkers in 2001.[44] Accordingly, a *click*-reaction should fulfill several requirements such as a high functional-group tolerance, mild and simple reaction conditions, an easy reaction work-up and the usage of environmental friendly or no solvents. Furthermore a high reaction yield, stereoselectivity, a broad substrate scope and a minimum of byproducts should be achieved.

Nowadays, the metal catalyzed 1,3-dipolar Huisgen cycloaddition for the formation triazoles from alkynes and azides is strongly related to the term *click* chemistry.[45] The utilization of a metal catalyst in this reaction allows a significant reduction in temperature and affords the products with higher regioselectivity, when compared to the uncatalyzed Huisgen cycloaddition. Therefore, it fulfills nearly all the requirements of a click reaction. Particularly, the use of either copper of ruthenium catalysts for this reaction have emerged as powerful synthetic tools. These two systems elegantly either afford 1,4- (**73**) or 1,5- disubstituted triazoles (**70**) with high selectivity. (Scheme 12).



Scheme 12 Schematic reaction scheme of the copper- and the ruthenium-catalyzed *click* reactions.

In the proposed mechanism of the copper-catalyzed azide-alkyne cycloaddition (CuAAC, Figure 7A), the alkyne **71** and the copper catalyst initially form a π-complex **74**.[46] Subsequent reaction with an additional molecule of copper catalyst affords the π-copper complex **75** of the copper acetylide. This complex coordinates the azide resulting in the formation of the intermediate **76**. Subsequently, an internal rearrangement leads to the 6-membered metallacycle **77**. The latter undergoes a ring contraction to afford the intermediate **78**. Finally, the product **73** and the initial copper catalyst are obtained after protonolysis.

In the mechanism of ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC, Figure 7B), an initial ligand exchange of the spectator ligands of the catalyst with the alkyne **71** and the azide **72** affords the complex **80**.[47] Subsequent regioselective oxidative coupling leads to the formation of the ruthenabicycle **81**, which undergoes a reductive elimination to furnish the complex **82**. Finally, the product **70** is obtained and the catalyst is regenerated through ligand replacement.

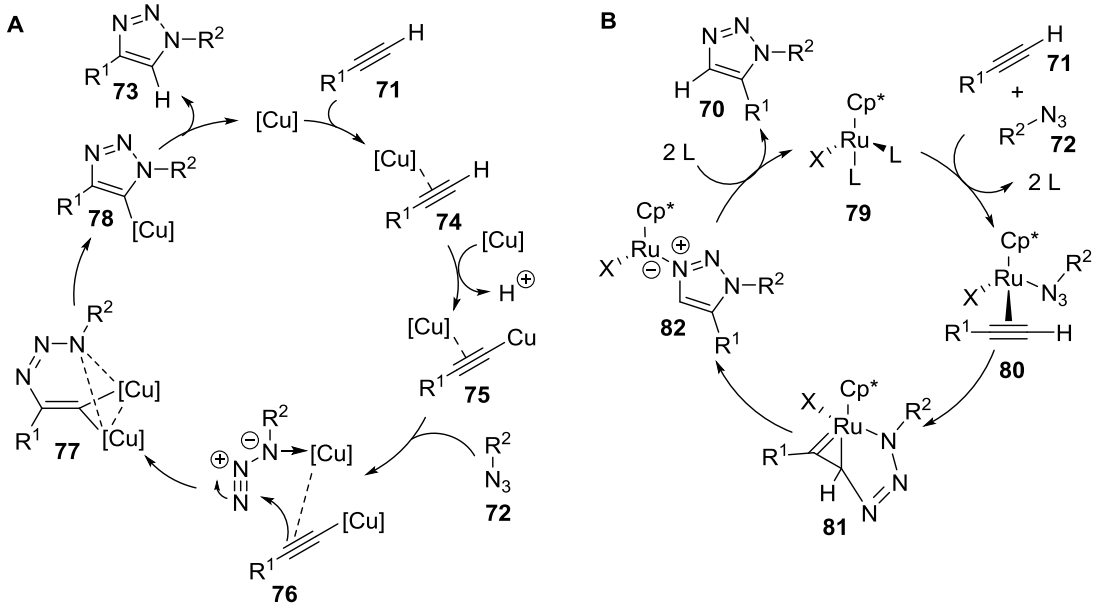
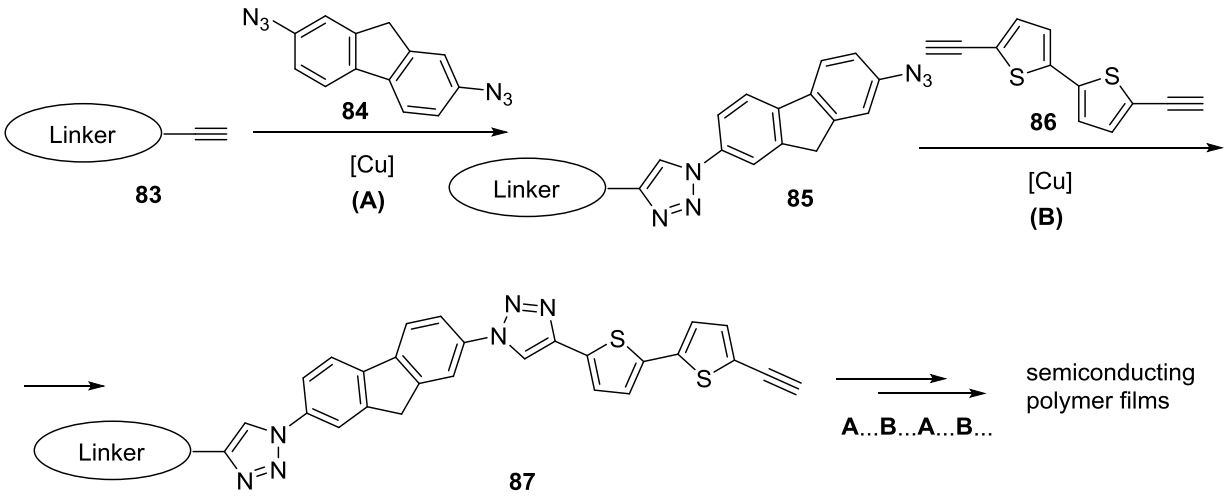


Figure 7 Proposed mechanisms for (**A**) the copper-catalyzed (CuAAC)[46] and (**B**) the ruthenium-catalyzed (RuAAC)[47] *click* reactions.

In their publication from 2011, Nesterov and coworkers gave an illustrative example for the utilization of alkynes in organic electronics.[48] They synthesized surface-bound semiconducting polymers with interesting spectroscopic and electronic properties. In the functionalization process, the polymer-bonded alkyne **83** was treated successively with the diazide **84** and the dialkyne **86** in a copper-mediated 1,3-dipolar cycloaddition (Scheme 14). After 34 steps, the solutions of compounds **84** and **86** were re-used without any significant loss of reactivity, thus illustrating the economic use of materials for the reported transformation.



Scheme 13 Synthesis of surface-immobilized semiconducting polymers by Nesterov and coworkers.[48]

Recently, Mirkin and coworkers used DNA functionalized with dibenzylcyclooctyne (DBCO) to cover the surface of nanoparticles of a zirconium-based metal organic framework (MOF) (Figure 8A).[49] The MOF-DNA conjugates **90** were obtained from the copper-free *click reaction* of the DBCO-labeled DNA **89** and azide group-containing metal organic-frameworks **88** (Figure 8B). Driving force of the reaction is the release of ring strain of the DNA-bounded alkynes. Later, the influence of the variation of the DNA length and the utilization of fluorescent DNA-residues was investigated in order to gain insight into the cell uptake of these compounds and to give important information towards drug delivery processes in cells.

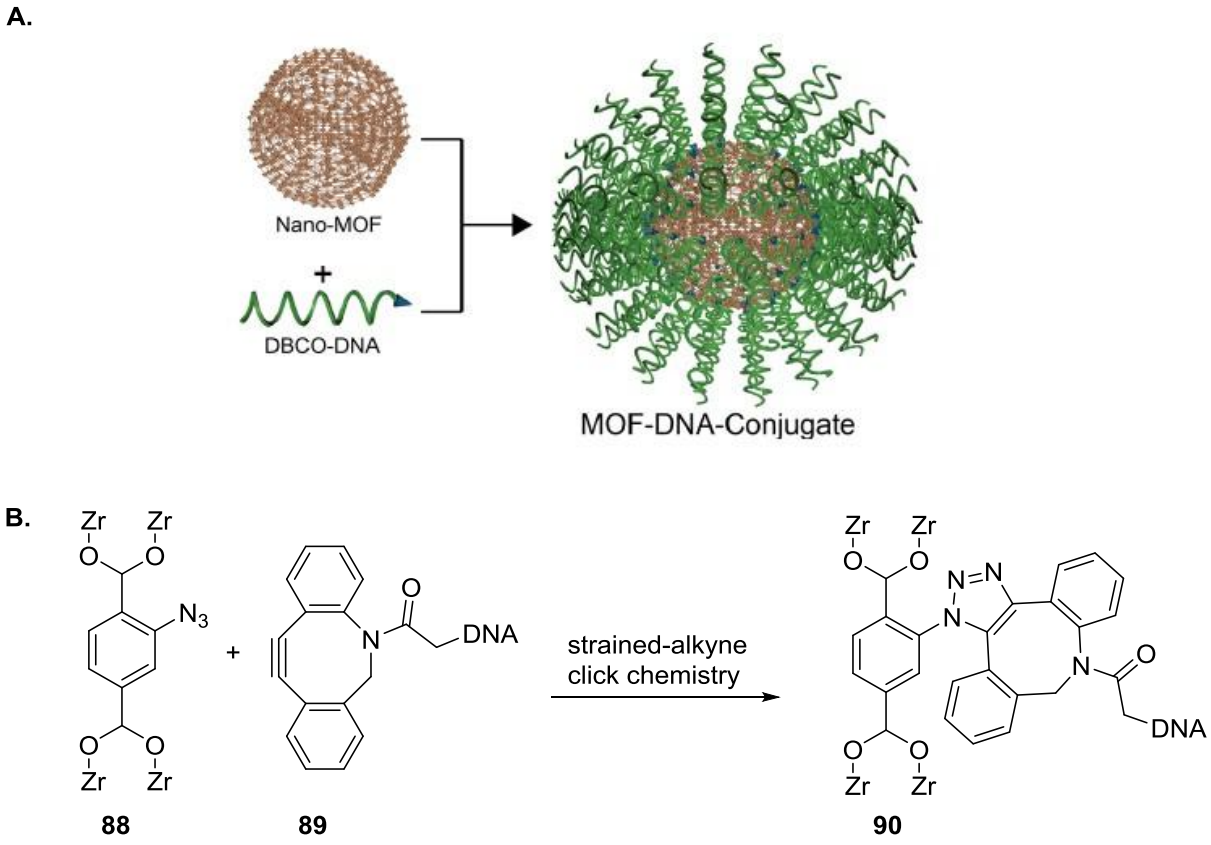


Figure 8 Schematic surface attachment of DBCO-DNA to the Nano-MOF-surface (**A**) and reaction of DBCO-functionalized DNA **89** and azide-containing Nano-MOF **88**. (**B**).[49]

1.2.3.2 [2+2+2] Cyclization

The [2+2+2]-cyclization was first described by Reppe and coworkers in 1948 and over the years has become a versatile tool in the synthesis of complex molecules.[50] Nowadays, polysubstituted cyclic molecules, such as pyridines or benzenes, can be easily accessed from this condensation reaction. A variety of unsaturated molecules, such as alkynes, alkenes, nitriles or isonitriles, can be applied as starting materials and the reaction tolerates other functional groups, including alcohols, amines, esters and halogens (Figure 9A).[51] The cobalt complex [$CpCo(CO)_2$] (**92**, Figure 9B) is a commonly used precatalyst in the [2+2+2]-cyclization, but also other cobalt, iridium, nickel or ruthenium catalysts can be applied.[52]

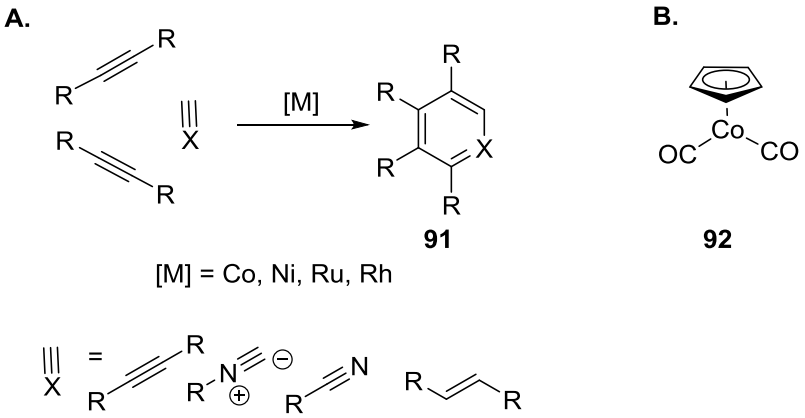


Figure 9 (**A**) General reaction scheme of the [2+2+2]-cycloaddition of alkynes and (**B**) the commonly used catalyst [$CpCo(CO)_2$] (**92**).

Two general mechanisms have been proposed for the cobalt-catalyzed [2+2+2] synthesis of benzene from acetylene (Figure 10).[51] In both, the metal catalyst is coordinated by two alkynes and the 5-membered intermediate **94** is subsequently formed through an oxidative addition. This intermediate **94** is then coordinated by another alkyne molecule, forming the intermediate **95**. Two reaction pathways have been proposed from this intermediate to yield benzene. In the first case, the alkyne inserts into the carbon-metal bond of **95** to form the intermediate **96**, and reductive elimination follows to form complex **98**. Alternatively, it has been proposed that the intermediate **97** is initially formed by a [4+2]-cycloaddition, which after isomerization affords the intermediate **98**. Finally, release of benzene regenerates the catalyst.

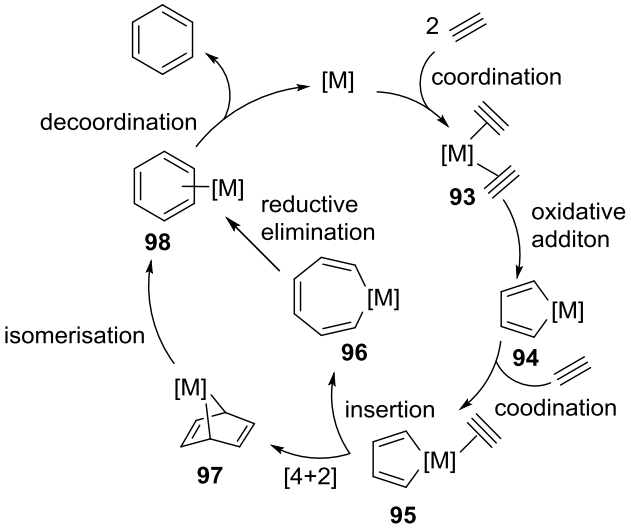
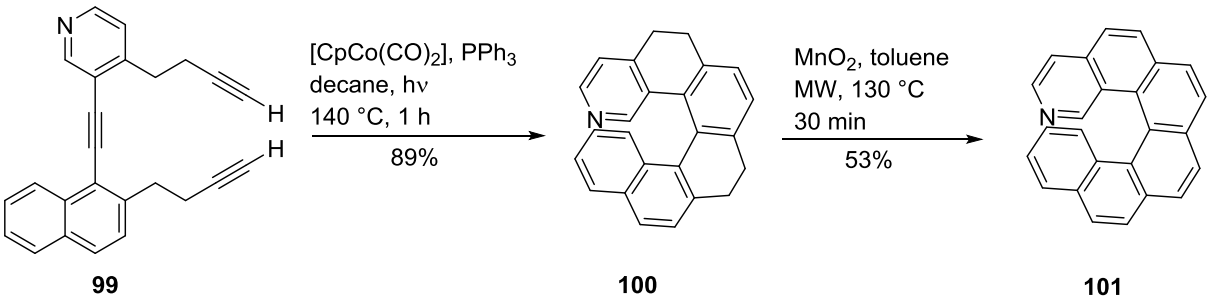


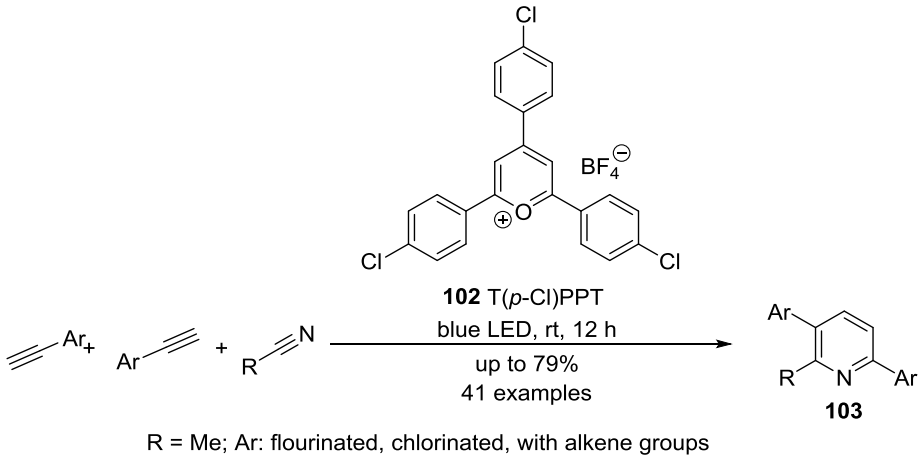
Figure 10 Proposed mechanism for the [2+2+2]-cyclization.[51]

Stará, Starý and coworkers have used a cobalt catalyzed [2+2+2]-cycloaddition in their synthesis of pyridohelicenes **101** (Scheme 14).[53] These helically chiral structures can be potentially applied in variety of fields of chemistry including coordination chemistry[54] and material science.[55] Initially, the partially saturated helicene **100** was synthesized by a [$CpCo(CO)_2$]-catalyzed [2+2+2]-cyclization of the triyne **99**. In a second step, the compound **100** was completely aromatized to the pyridohelicene **101** in a microwave-assisted oxidation with manganese dioxide. This class of compounds was relatively unexplored before due to synthesis limitations regarding the basic pyridine group.



Scheme 14 Pyridohelicene synthesis by Stará, Starý and coworkers.[53]

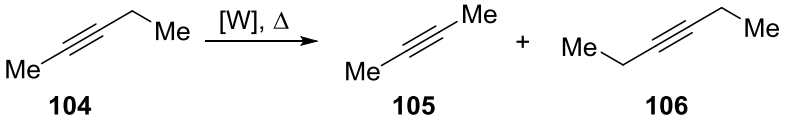
Another recent example of a [2+2+2] cyclization was presented by Wang and coworkers in the synthesis of 2,3,6-trisubstituted pyridines of the type **103** (Scheme 15).[56a] Pyridines **103** were synthesized in the reaction of alkylsubstituted cyanides and terminal arylalkynes under mild conditions. The chlorinated pyrylium salt **102** [T(*p*-Cl)PPT] was utilized as a photocatalyst under visible light irradiation, and variously substituted pyridines were accessed in yields of up to 79%. The authors proposed a single-electron-transfer process[56b] as a key mechanistic step of the reaction.



Scheme 15 Synthesis of 2,3,6- trisubstituted pyridines **103** by Wang and coworkers.[56]

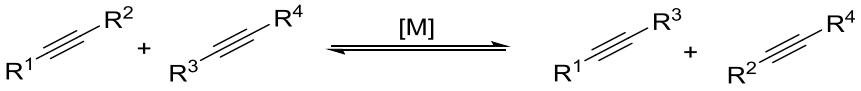
1.2.3.3 Alkyne metathesis

In the year 1968 Penella and coworkers observed that under high temperatures and in the presence of a tungsten catalyst, pent-2-yne (**104**) disproportionates affording a mixture of but-2-yne (**105**) and hex-3-yne (Scheme 16).[57] This observed reactivity was the foundation of the alkyne metathesis reaction, which is nowadays a powerful and versatile tool in the synthesis of complex molecules.



Scheme 16 Observations by Penella and coworkers towards the metal-catalyzed disproportionation of pent-2-yne (**104**).[57]

The alkyne metathesis is defined as a reaction where the alkylidyne constituents of two acetylene molecules are statistically redistributed in the presence of a metal catalyst (Scheme 17).



Scheme 17 Schematic reaction scheme for the alkyne metathesis.

Modern catalysts for the metathesis of alkynes comprise the systems based on molybdenum, such as the catalyst **107** or the bench stable precursor **108** (Figure 11). These catalysts distinguish themselves through a high stability, activity and selectivity in combination with a high functional group tolerance with respect to many common functional groups.[58]

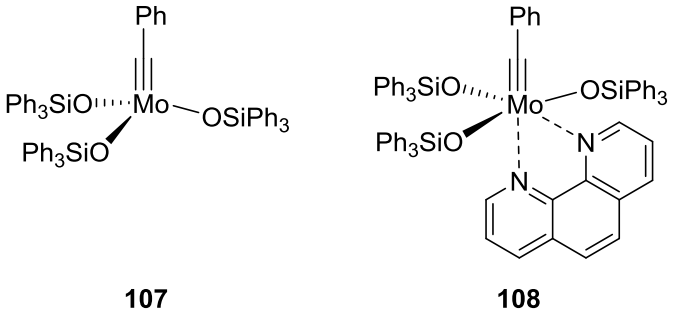


Figure 11 Common catalysts utilized in the alkyne metathesis.

A mechanism for the alkyne metathesis was proposed by Katz and coworkers.[59] Initially, the metallacyclobutane **111** is formed by a [2+2]-addition of the catalyst and the alkyne. A subsequent isomerization leads to the formation of the metallacyclobutane **112**. Finally, the catalyst **114** and the new alkyne **113** are obtained through a cycloelimination (Figure 12).

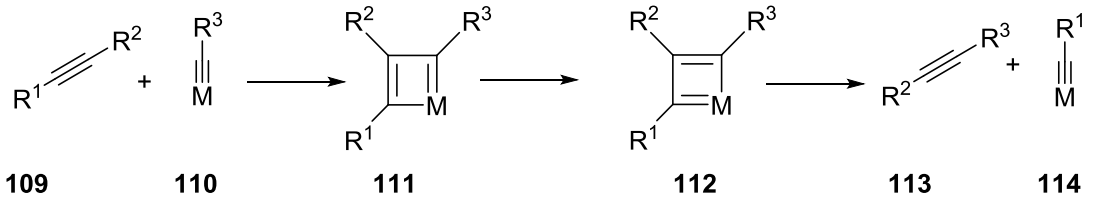


Figure 12 Proposed mechanism for the alkyne metathesis.[59]

Nowadays, other reaction formats of the alkyne metathesis rather than alkyne cross metathesis (ACM) are the focus of investigations. Ring closing metathesis (RCAM), which can be applied in the synthesis of cyclic alkynes or cyclic oligomers of dialkynes, is extensively investigated. Furthermore, polymerization techniques such as acyclic diyne metathesis polymerization (ADIMET) and ring opening polymerization are of high interest in the field of material science (Figure 13).[58a,60]

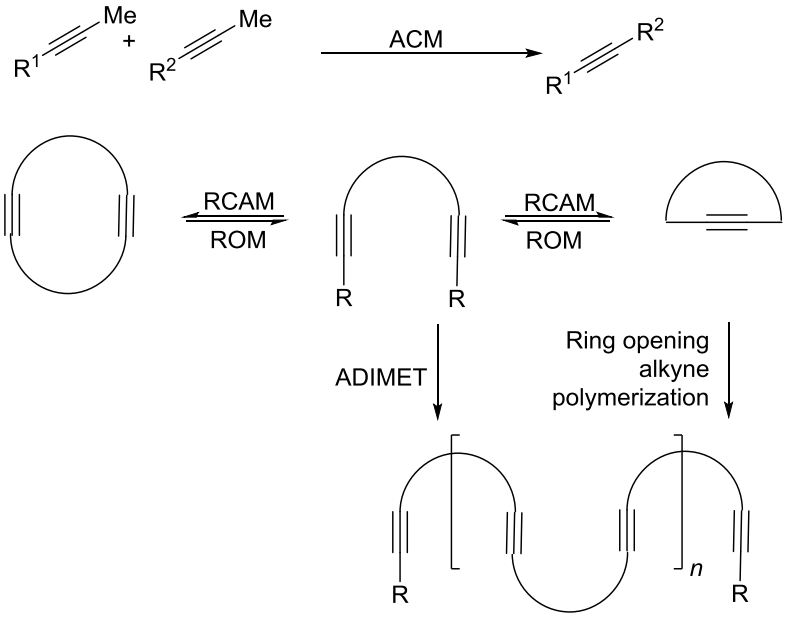
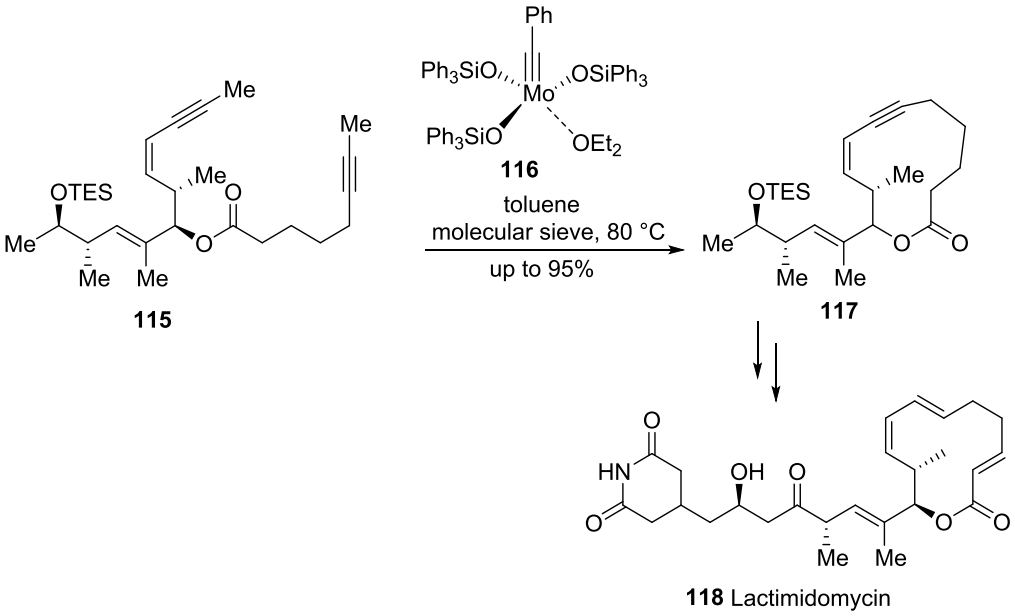


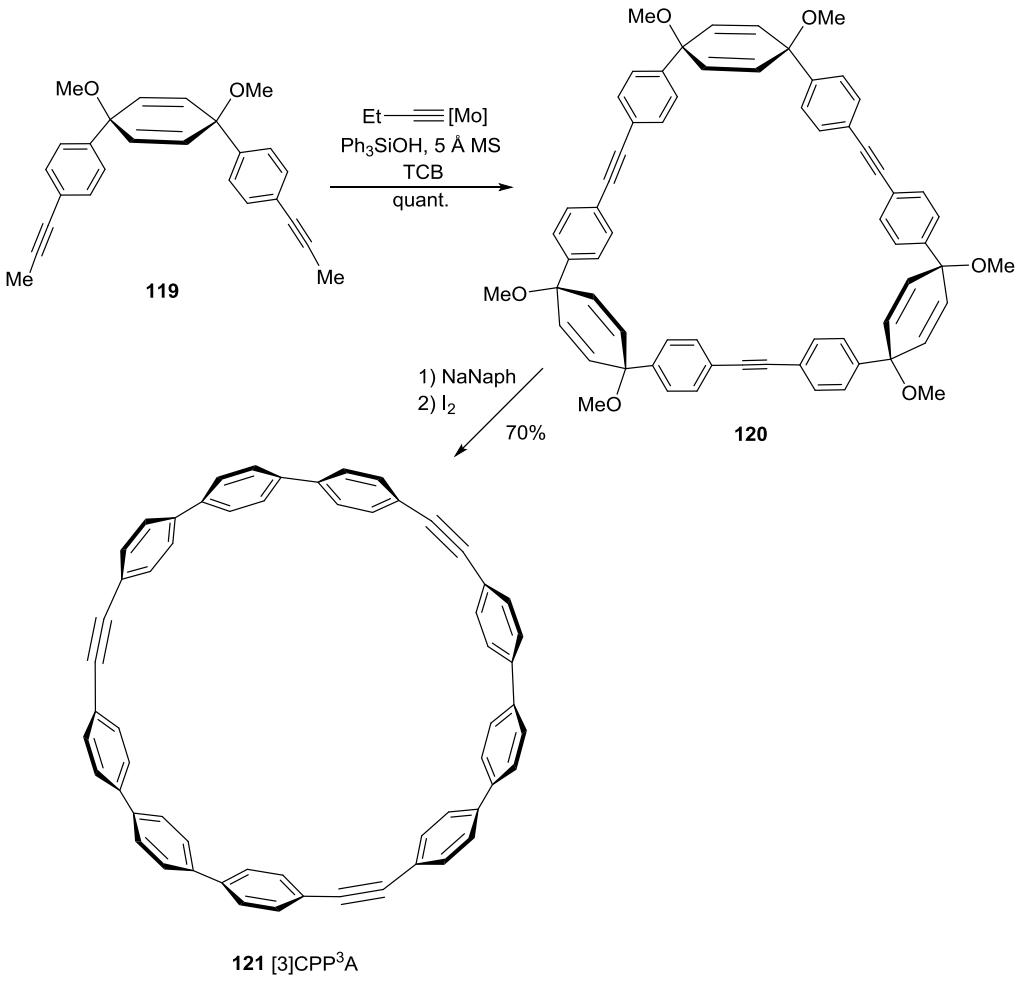
Figure 13 Typical reaction formats of alkyne metathesis: alkyne cross metathesis (ACM), ring closing metathesis (RCAM), ring opening metathesis (ROM), acyclic diyne metathesis polymerization (ADIMET) and the ring opening polymerization.[60]

Fürstner *et al.* presented a descriptive example for alkyne metathesis in the first total synthesis of Lactimidomycin (**118**) (Scheme 18).[61] The latter exhibits anti-cancer activity in combination with a low cytotoxicity towards mammals and inhibits cell migration. Therefore, this macrolide is an attractive synthesis target. A high yielding ring closing alkyne metathesis (RCAM) was used as key step in the synthesis of the cyclic enyne **117** from the dialkyne **115**. For this reaction, the molybdenum (VI) catalyst **116** was selected due to its strong Lewis acidity and resulting high reactivity. Afterwards, the cyclic alkyne **117** was transferred to Lactimidomycin (**118**). This methodology was also applied in the synthesis of a variety of biologically interesting derivatives.[62]



Scheme 18 First synthesis of Lactimidomycin **118** by Fürstner and Micoine utilizing ring closing alkyne metathesis (RCAM).[59]

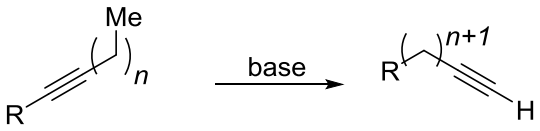
An example of the formation of oligomers employing RCAM towards the synthesis of precursors of cycloparaphenyleneacetylene (CPPA) was published by Moore and coworkers (Scheme 19).[63] CPPA's are completely conjugated molecular belts with interesting photophysical and electronic properties and capable of forming host-guest complexes. Therefore, they are intriguing targets in the field of supramolecular chemistry and material science. The compound **120** was synthesized through a high yielding macro-cyclization utilizing a molybdenum (VI) pre-catalyst. Molecular sieves were used to remove the byproduct but-2-yne, providing a driving force for the reaction. Afterwards, the desired compound [3]CPP^{3}A **121** was obtained by a sodium naphthalenide-mediated reductive aromatization. Additionally, the potential application of CPPA **121** as a polymer linker applying the copper-free *click*-reaction with methyl azide as well as the physical properties of its host-guest complexes with C_{70} fullerene were examined



Scheme 19 Synthesis of [3]CPP^{3}A **121** by Moore and coworkers.[63]

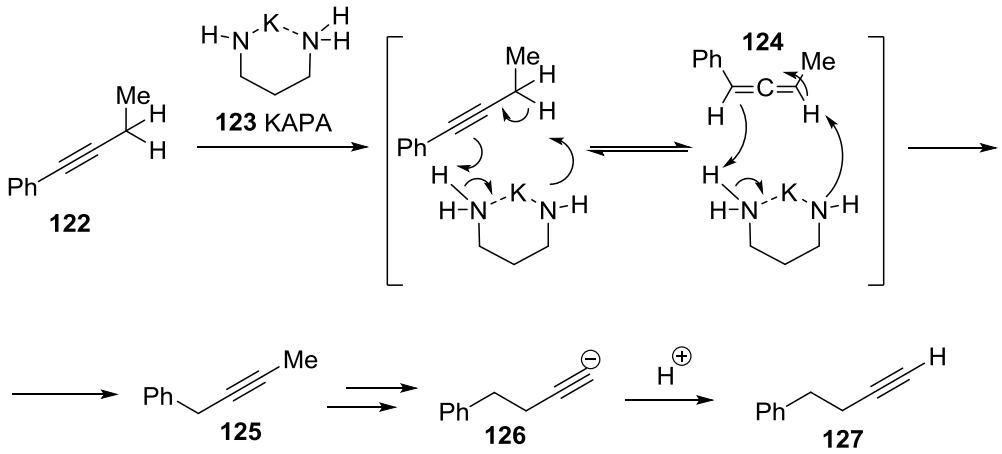
1.2.3.4 Alkyne zipper reaction

The alkyne zipper reaction is a prototropic migration of an internal triple bond under the action of superbases producing metallated derivatives of terminal acetylenes (Scheme 20).[42]



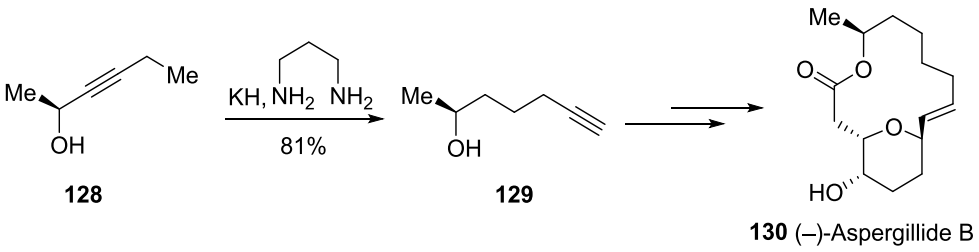
Scheme 20 Schematic scheme of the zipper reaction.[42]

This general reactivity was already described in the end of the 19th century, but the full synthetic potential of the transformation was revealed in 1975 with the discovery of potassium 3-aminopropylamide (KAPA, **123**) as an efficient base/acid system.[64] KAPA allows the reaction to proceed at ambient temperature and in short reaction times. It fulfills a dual role as a base and an acid in the reaction mechanistic pathway. Initially, a KAPA mediated isomerization of the alkyne **122** leads to the formation of the allene **124** (Scheme 21). Afterwards, a second isomerization by KAPA affords the regioisomer **125**. This prototropic migration continues further until the terminal acetylide **126** is formed. The final deprotonation is rather easy and represents the thermodynamic driving force of the reaction. A subsequent protonation leads to the formation of the final product **127**. [64a]



Scheme 21 Proposed mechanism for the KAPA-catalyzed zipper reaction[64a]

An example of a zipper reaction was given by Trost *et al.* for the synthesis of (-)-Aspergillide B (Scheme 22).[65] The class of the Aspergillide macrolactones shows biological activity against leukemia and human breast cancer. Representatives share the characteristic tetrahydropyran motif. Trost and coworkers used 1,3-diaminopropane to convert the internal alkyne **128** to its terminal isomer **129** by a zipper reaction in a yield of 81%. The latter was used to synthesize the desired (–)-Aspergillide (**130**).



128 **129** **130** (–)-Aspergillide B

Scheme 22 Utilization of an alkyne zipper reaction in the synthesis of (–)-Aspergillide B **130** by Trost and coworkers.[65]

1.2.4 Incorporation of alkyne moieties into organic molecules

1.2.4.1 Nucleophilic substitution with acetylides

Acetylides, one of the oldest known family of organometallic compounds, are salts of metals and deprotonated alkynes.[66] The first synthesis of silver acetylides was already reported in 1865.[67] Deprotonated alkynes are isoelectronic to cyanide and carbon monoxide and can be described as pseudohalogenides. The metal salts show similar stoichiometry and magnetic properties compared to related cyanide compounds.[68] Today a variety of metal acetylides is known in literature and include lithium,[69] sodium,[70] zinc,[71] silver[66] or copper acetylides.[72] Acetylides act as nucleophiles and, therefore, can be utilized in nucleophilic substitution or addition reactions. Transition metal analogs, like silver or copper acetylides, tend to be explosive and should be only handled in solution of a limited concentration and with special precautions. Nevertheless, when handled accordingly these salts are quite stable.[66,73] In solution acetylides tend to form dimers, oligomers or polymers.[73,74] In general, acetylides react with electrophiles. Among others, nucleophilic substitution or addition reactions with different carbon-based electrophiles such as ketones or aldehydes, alkyl halides, imines, activated acids or the Michael-addition to α,β-unsaturated carbonyl compounds are common examples (Figure 14).[3]

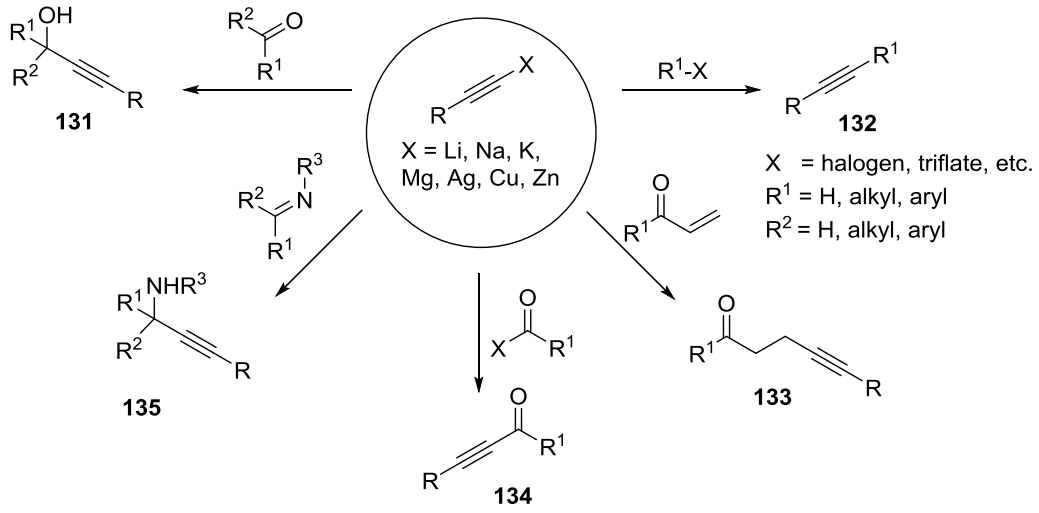
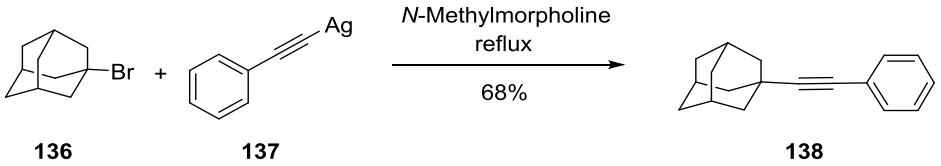


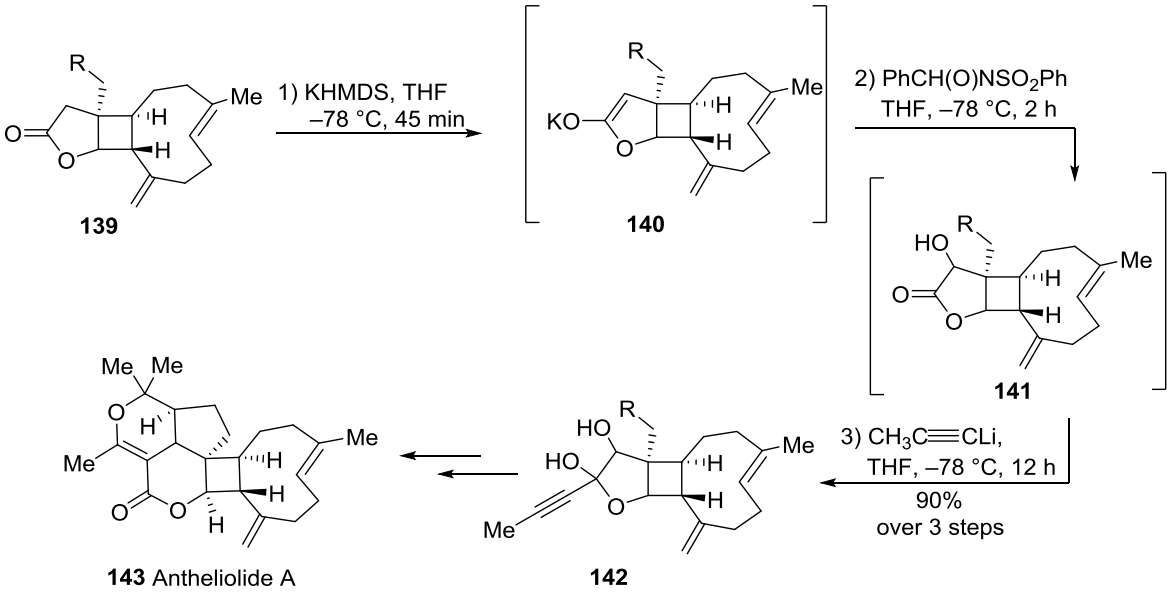
Figure 14 Typical reactions of acetylides with different electrophiles.[3]

An example of a nucleophilic substitution with acetylides was given by Williams *et al.*[75] The adamantyl bromide (**136**) was refluxed in *N*-methylmorpholine with silver(I) acetylide (**137**) to offer the alkyne **138** (Scheme 23). This illustrates the enhanced stability of silver acetylides in contrast to other organosilver(I) compounds.



Scheme 23 Synthesis of adamantyl-alkynes with silver (I) acetylides by Williams *et al.*[75]

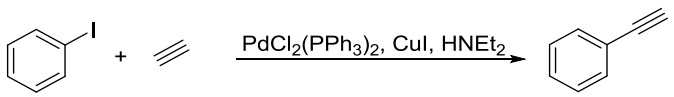
Another example of a typical addition reaction with acetylides was reported by Corey and coworkers as a step in the total synthesis of Antheliolide A (**143**).[76] This naturally occurring compound was first isolated from the marine coral *Anthelia glauca*.[77] Furthermore, it is a synthetically challenging molecule with multiple stereo centers and a complex arrangement of functional groups. In the synthesis by Corey and coworkers, the lactone **139** was transferred to hemiacetal **142** in a three step reaction sequence. First, the intermediate enolate **140** was generated by addition of potassium bis(trimethylsilyl)amide as a base. Subsequently, the Davis oxaziridine was added, generating the intermediate lactone **141**. Finally, nucleophilic attack of the lactone **141** with lithium acetylide afforded the hemiacetal **142**, which was later utilized to synthesize Antheliolide A (**143**) (Scheme 24).



Scheme 24 Synthesis of Antheliolide A (**143**) by Corey and coworkers.[76]

1.2.4.2 The Sonogashira reaction

In their groundbreaking publication of 1975, Sonogashira and coworkers described their own modification of the Stephans-Castro coupling of an aryl iodide with terminal alkynes.[78] They reported a cross-coupling reaction utilizing a palladium catalyst in combination with a copper co-catalyst and an amine base (Scheme 25). Particularly important was that this protocol could overcome the use of shock-sensitive copper acetylides, which were necessary in previous protocols.



Scheme 25 Coupling of aryliodides with acetylene described by Sonogashira and coworkers.[78]

In general, the Sonogashira coupling can be performed under mild conditions, tolerating moisture and commonly used functional groups. Thus, the Sonogashira-reaction is an established and versatile tool for the introduction of alkyne moieties.[19a]

A typical cross-coupling mechanism has been proposed for this transformation (Figure 15).[79] Initial oxidative addition of the aryl halide to the palladium(0) catalyst **A** affords the intermediate **B**. In a second catalyst cycle, the terminal alkyne is activated through the coordination of the copper co-catalyst **G** to the triple bond. The resulting alkyne π-complex **F** is deprotonated by the base to form the copper acetylide **E**, which substitutes the counterion of the intermediate **B** through a transmetalation step. A subsequent *cis/trans*-isomerization results in the formation of the complex **D**, which can undergo a reductive elimination to furnish the product and the initial palladium(0) complex.

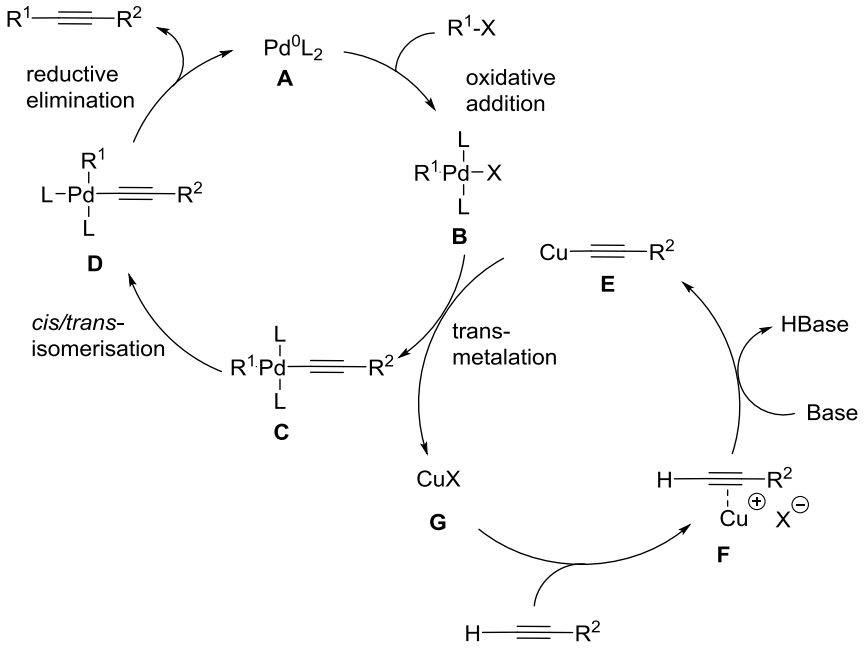
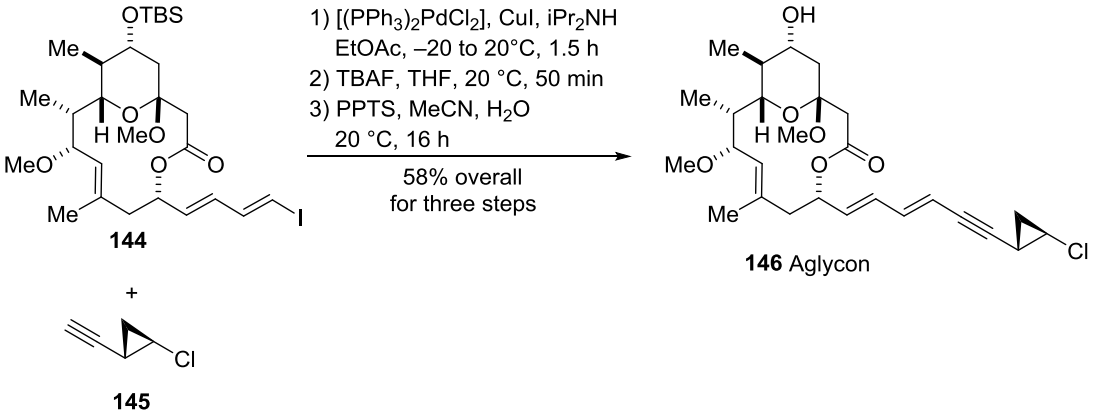


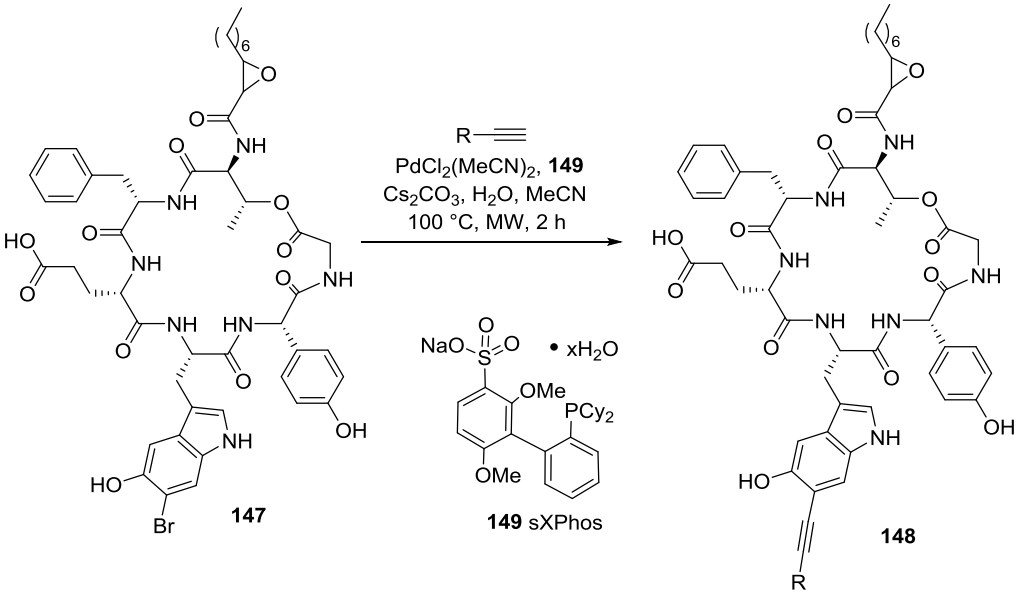
Figure 15 Proposed mechanism for the copper co-catalyzed Sonogashira coupling.[79]

Paterson *et al.* applied a late stage Sonogashira coupling in the first synthesis of the Callipeltoside Aglycon.[80] Callipeltosides are an interesting class of natural macrolide polyketides isolated from the marine sponge *Callipelte sp*., which show activity in the proliferation of KB and P388 cells. The key structural feature of these polyketides is the *trans*-chlorocyclopropane ring adjacent to a dienyne moiety. Exactly this functionality of the molecule was addressed by Paterson and coworkers. Aglycon (**146**) was obtained through a high yielding Sonogashira coupling of the iodide **144** and the chlorocyclopropane-substituted alkyne **145**, which was followed by deprotection of the TBS protective group (Scheme 26).



Scheme 26 Synthesis of Aglycon (**146**) by Paterson *et al.*[80]

Recently, a copper-free Sonogashira coupling was used in the functionalization of unprotected halotryptophans and halotryptophan containing peptides in water as a solvent. In their publication from 2017, Corr and coworkers presented this elegant methodology utilizing the water soluble Buchwald catalyst sXphos (**149**) (Scheme 27).[81] Among others, the 6-bromocystargamide (**147**) smoothly underwent alkynylation to afford the corresponding product **148** in a microwave-assisted reaction. This methodology made these compounds accessible for labeling experiments and illustrates the potential of the Sonogashira coupling in the alkynylation of complex biological molecules.



Scheme 27 Functionalization of bromocystargamide (**147**) employing a copper-free Sonogashira reaction.[81]

1.2.4.3 Electrophilic umpolung

The term "umpolung" is used to describe a process in which the polarity and reactivity of a structural unit (synthon) used for synthetic transformations is changed.[82] Similarly, in the case of electrophilic group transfer, a compound is transformed into an electron acceptor, which contains a structural unit that acts naturally as an electron donor. Consequently, where conventionally the positively polarized residue X would possess affinity to a nucleophile and Z to an electrophile, in the case of an umpolung the now positively polarized structural group Z is attacked by a nucleophile (Figure 16). Common methods to access this reactivity are the introduction of neighboring electron withdrawing or delocalizing groups like halides, hypervalent iodine moieties or chalcogen salts. Groups which can be transferred as electrophiles in this way include the trifluoromethyl,[83] azide,[84] cyanide[85] or acetylide functionality.[66] In the several following representative examples of electrophilic group transfer, reactivities of different functional groups are given. Due to the large amount of publications in this field, these examples will mainly focus on reactions where no additional catalyst is needed.

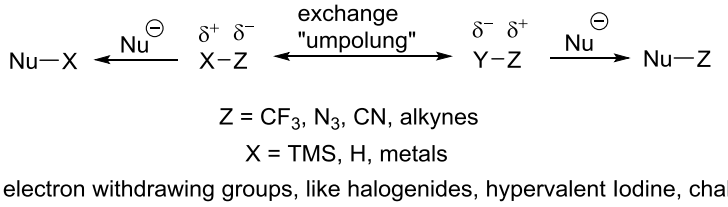


Figure 16 The principle of electrophilic group transfer by umpolung.

1.2.4.3.1 Halogen compounds

Halides are the simplest reagents imaginable to design an electrophilic group transfer. The utilization of these compounds would produce a minimum of waste. Nevertheless, to the best of our knowledge, no significant reactivity towards umpolung with nucleophiles is known for halogen azides, trifluoromethyl halides and halogen cyanides. Bromotrifluoromethane is usually transferred as corresponding zinc, aluminum or phosphorous nucleophiles or can be applied in metal-catalyzed radical transformations.[86] Furthermore, cyanogen halogenides are extremely toxic reagents that should only be handled under special precautions and the showed just a low applicability in the electrophilic-functionalization of complex molecules.[87,88] Only a few examples for the utilization of haloalkynes in pure electrophilic transformations are known,[89] yet they are commonly used in transition metal-catalyzed reactions.[90]

1.2.4.3.2 Hypervalent iodine λ³ compounds

Hypervalent iodine compounds are a class of reagents that can be utilized for electrophilic group transfer. The first representation of these compounds was reported already in 1886 by C. J. Willgerodt.[91] Later, in 1951, the hypervalent structure of these compounds was proposed by G. C. Pimentel and R. E. Rundel (Figure 17).[92]

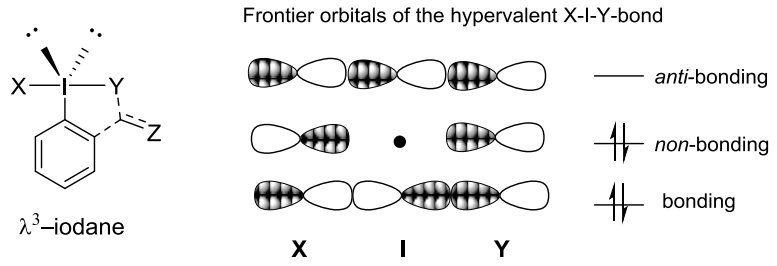
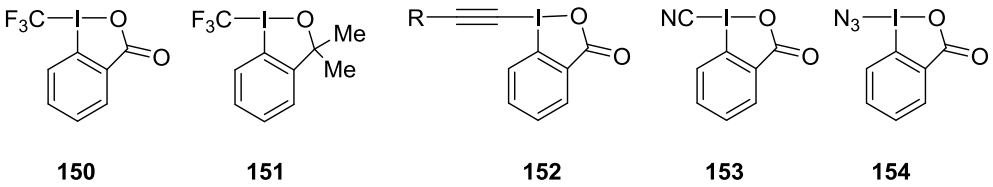


Figure 17 Characteristic structure of λ³-iodine compounds and frontier orbitals of the hypervalent bond.

Polyvalent λ³ iodine reagents exhibit pseudotrigonal bipyramidal geometry, where three substituents are arranged in a nearly T-shaped geometry around the central iodine-atom. Two lone pairs and one heteroatomic substituent are located in the equatorial positions. Likewise, a (3C-4e)-bond is present in the apical position and is formed by the non-hybridized 5p-orbital of the iodine and two adjacent substituents. As a result, the bonds of these substituents to the iodine are much longer and weaker compared to those in the equatorial position. The unique ability of hypervalent iodine reagents for electrophilic group transfer is directly related to this property. In many regards hypervalent I(III) reagents behave more like transition metal complexes than atoms of other lighter main group equivalents. As such, they are able to undergo characteristic reactions of transition metals such as oxidative addition, reductive elimination or ligand exchange.[93] Most of these compounds can be synthesized from rather simple starting materials and thus, are easy accessible. However, it should be noted that these compounds should be handled with reasonable precautions, since several examples demonstrate an explosive nature at elevated temperatures or are shock sensitive.[94]

In the last two decades, a variety of different benziodoxolones and benziodoxoles were introduced and utilized for electrophilic group transfer in ground-breaking works by the groups of Togni, Waser or Zhdankin. In this regard, compounds **150**–**154** must be highlighted (Figure 18). They were utilized in the trifluoromethylation,[94] alkynylation,[95] azidation[96] and cyanation[97] of various nucleophiles

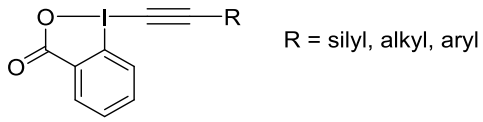


150 **151** **152** **153** **154**

Figure 18 Modern polyvalent λ3 iodine reagents.

Alkynylation with Iodine(III) Reagents

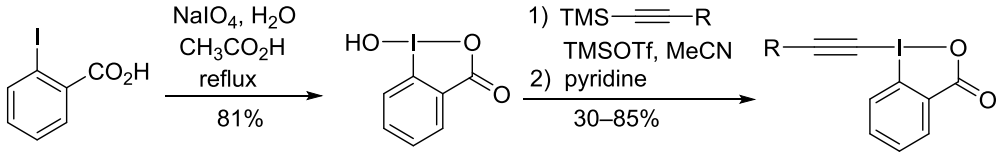
Alkyne-substituted benziodioxolones (EBX reagents, Figure 19) are a group of electrophilic transfer reagents that deserve to be highlighted.[95] These compounds were initially synthesized by Ochiai, Shira[98] and Zhdankin[99] and later introduced as electrophilic transfer reagent by Waser and coworkers.[100]



152

Figure 19 EBX-based electrophilic alkynylation reagents.

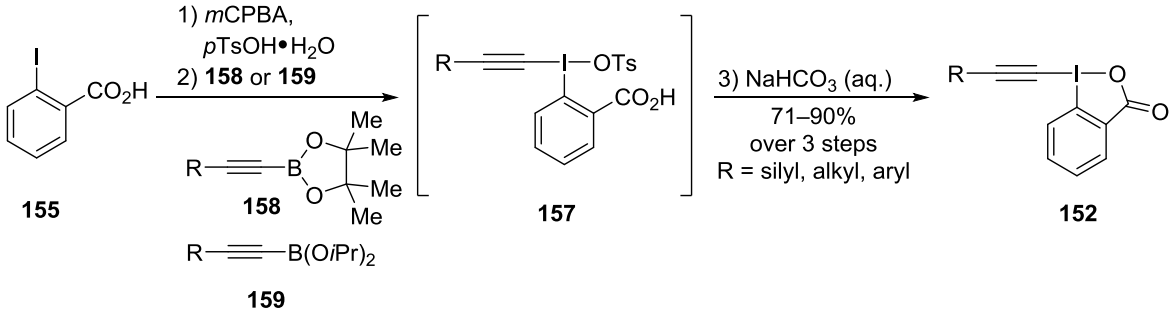
In their synthesis, Zhdankin and coworkers oxidized iodobenzoic acid (**155**) with sodium periodate. Afterwards the resulting compound **156** was activated by TMSOTf and subsequently treated with a TMS-protected alkyne. After basic work up with pyridine, the desired compound **152** was obtained (Scheme 28).[99] Later, this procedure was scaled up by Waser and Brand.[95a,101]



155 **156** **152**

Scheme 28 Synthesis of the EBX-reagents by Zhdankin and coworkers.[99,101]

In their seminal paper of 2012, Olofsson and Bouma showed that these alkynylation reagents are also easily accessible in a one-pot synthesis.[102] In their protocol, iodobenzoic acid **155** was oxidized by *m*CPBA and activated by *p*TsOH. After substitution with either boronic esters **158** or **159** and cyclization with sodium bicarbonate, the desired compound **152** was obtained in yields of up to 90% (Scheme 29).



155 **158** **159** **157** **152**

Scheme 29 Synthesis of the EBX-reagents by Olofsson and Bouma.[102]

Recent calculations carried out by Waser and coworkers indicated that the mechanism of alkynylation with hypervalent iodine reagents is nearly independent from the character of the iodine backbone and instead depends highly on the nature of the employed nucleophiles and the substituent on the alkyne-moiety.[103] If an iodine reagent with electron donating substituent is applied in the reaction with a sulfide, the authors propose that the reaction proceeds via the concerted transition state **160a**, from which internal α-addition results in the formation of intermediate **161a.** Elimination offers the desired product. On the other hand, the application of reagents with an electron withdrawing substituents proceeds through concerted transition state **160b** and leads to the formation of **161b** through internal β-addition. Afterwards, α-elimination gives the carbene **162**, which can undergo a 1,2-shift to afford the desired product (Figure 20). Based on labeling experiments, Waser and coworkers concluded that in the case of the Ph-EBX and TIPS-EBX reagent both mechanisms are competing.[103]

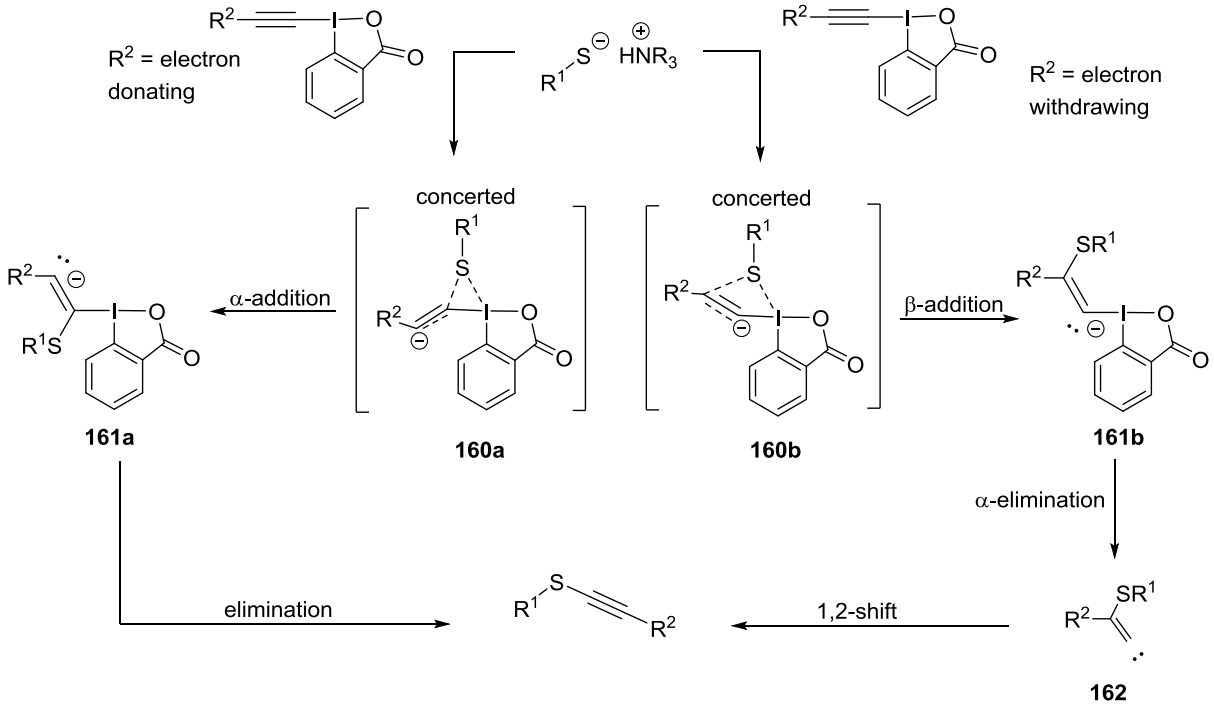


Figure 20 Proposed mechanism for the electrophilic transfer of alkynes by EBX-reagents.[103]

Several studies have been carried out towards the functionalization of different nucleophiles with the reagent **152** and the structurally similar alkynyl(phenyl)iodonium salts. Alkynes were transferred successfully to sulfides and carbothioic S-acids.[104] Furthermore, it was possible to alkynylate sulfonamides,[105] azlactones[106] and β-ketoesters.[107] Moreover, the alkynylation of H-phosphi(na)tes and secondary phosphine oxides was conducted (Figure 21).[108] In summary, all reactions were conducted without additional metal catalyst in good to excellent yields, illustrating these reagents as useful tools for the functionalization of pharmaceutical products and other complex molecules.

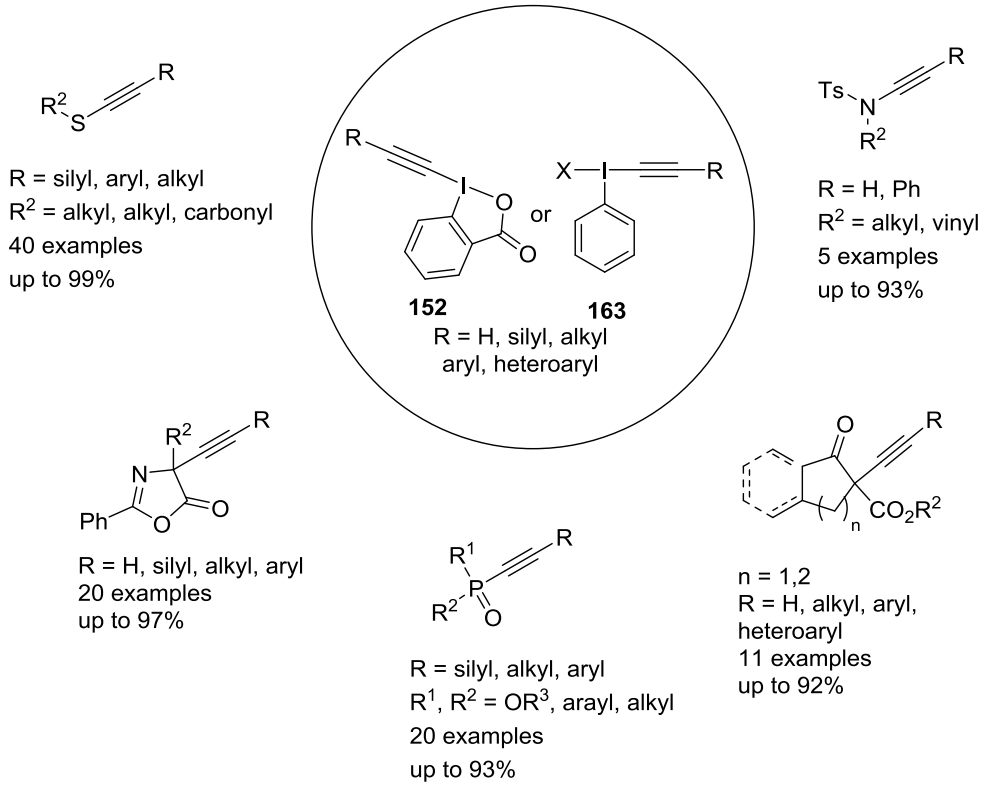
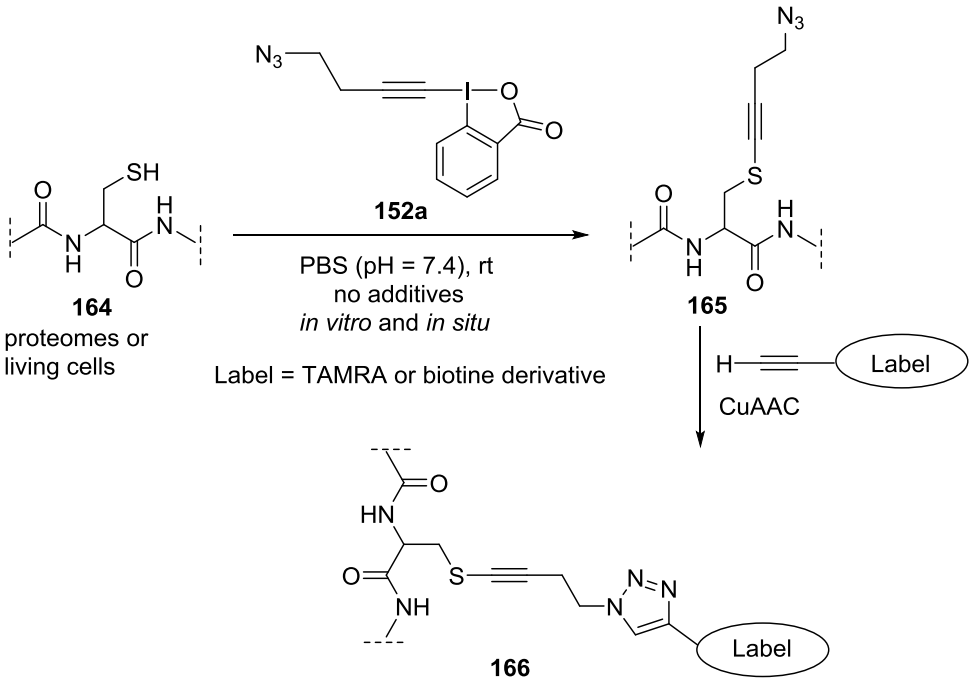


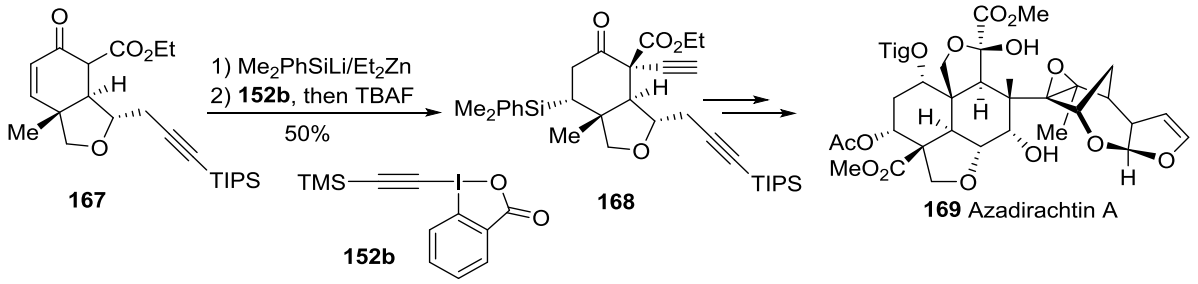
Figure 21 Typical reaction products of the direct, uncatalyzed alkynylations of nucleophiles by EBX-reagents.

In 2015, Adibekian, Waser *et al.* showed the great potential for the utilization of alkyne-substituted benziodoxoles in proteomic profiling of cysteine residues for drug discovery.[109] The authors investigated the applicability of the reagent **152a** towards proteomes and living cells in aqueous phosphate buffered saline (PBS). Terminal cysteines of protein structures were functionalized selectively with the azide-substituted reagent **152a**. Afterwards, these activated cysteine residues were utilized in the copper (I)-catalyzed "*click*"azide-alkyne cycloaddition (CuAAC) with alkyne-substituted TAMRA or biotin derivatives (Scheme 30). Moreover, this methodology was successfully applied for the investigation of the proteomic targets of the potential anticancer agent curcumin.[110]



Scheme 30 Labeling of cysteine moieties of proteomes or living cells by alkynylation with hypervalent iodine compounds followed by CuAAC.[109]

Furthermore, EBX reagents have been employed as useful tools in the synthesis of complex molecules. Luo, Yang and coworkers utilized TMS-EBX in their investigations towards the synthesis of Azadirachtin derivatives.[111] Azadirachtines are triterpenoids, which show anti-insect properties in combination with a low toxicity towards mammals.[112] The authors conducted the alkynylation of compound **167** in a two-step procedure. Firstly, the β-ketoester **167** underwent *Michael* addition by addition of the *in situ* formed dimethyl(phenyl)silyl zincate, before alkynylation by the reagent **152b** Finally, deprotection by TBAF afforded the desired building block **168** (Scheme 31).



Scheme 31 Synthetic study towards Azadirachtin A (**169**) ultilizing an alkynylation with the reagent **152b**, as reported by Luo, Yang and coworkers.[111]

1.3 Chalcogen salts as transfer reagents

In nature, SAM [*S*-(adenosylmethionine)] is a common methylation reagent in the biosynthesis of several important compounds.[113] For example, 23S ribosomal RNA (rRNA) **171** originates from methylation by SAM **170** (Figure 23).[114] Accordingly, the possibility of using chalcogen salts as transfer reagents for the synthesis has been known for a long time. However, these reactions are normally catalyzed by enzymes and proceed through radical pathways.

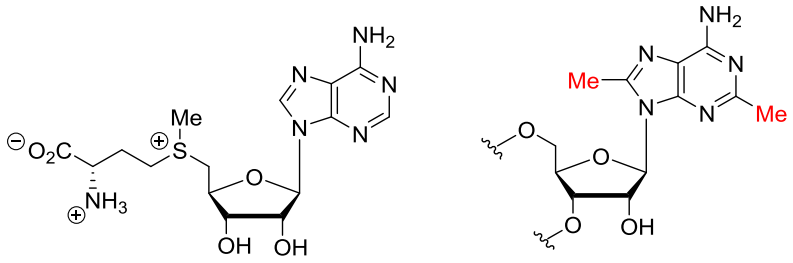
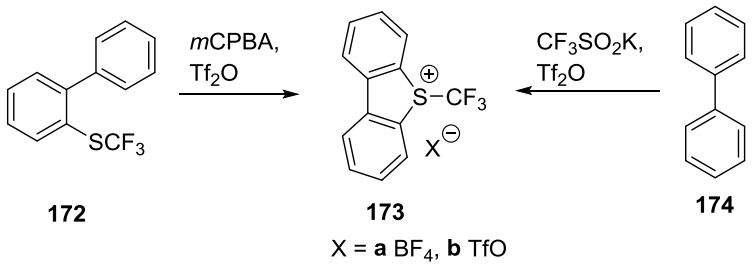


Figure 22 The electrophilic methylation reagent *S*-(adenosylmethionine) (SAM) **170** and methylated 23S ribosomal RNA **171**.[114]

1.3.1 Umemoto reagent

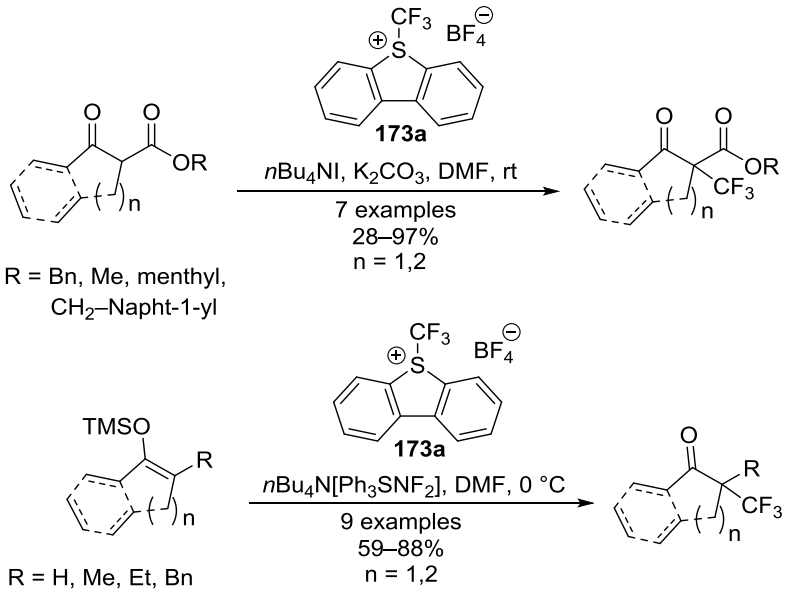
(Trifluoromethyl)dibenzosulfonium salts are a well-known class of electrophilic transfer reagents, which were introduced by Umemoto and coworkers.[115] These reagents show a high potential for electrophilic group transfer and better thermal stability in comparison to their hypervalent iodine equivalents.[116] They can be accessed in a straightforward reaction sequence from the corresponding biaryl sulfide **172** with *m*CPBA as oxidant under activation by triflic anhydride,[117] or in the reaction of biphenyl (**174**) with potassium trifluoromethanesulfinate and triflic anhydride (Scheme 32).[118]



Scheme 32 Common synthetic methods for the Umemoto reagent **173**.[117,118]

Investigations towards the mechanism of trifluoromethylation with dibenzothiophenium salts are still ongoing; however, presumably the mechanism strongly depends on the nature of the utilized nucleophile.[119] There is no evidence for the participation of CF_3-cation. Moreover, when certain nucleophiles, such as enolates, are used, radical trapping experiments indicate a SET-process.[120]

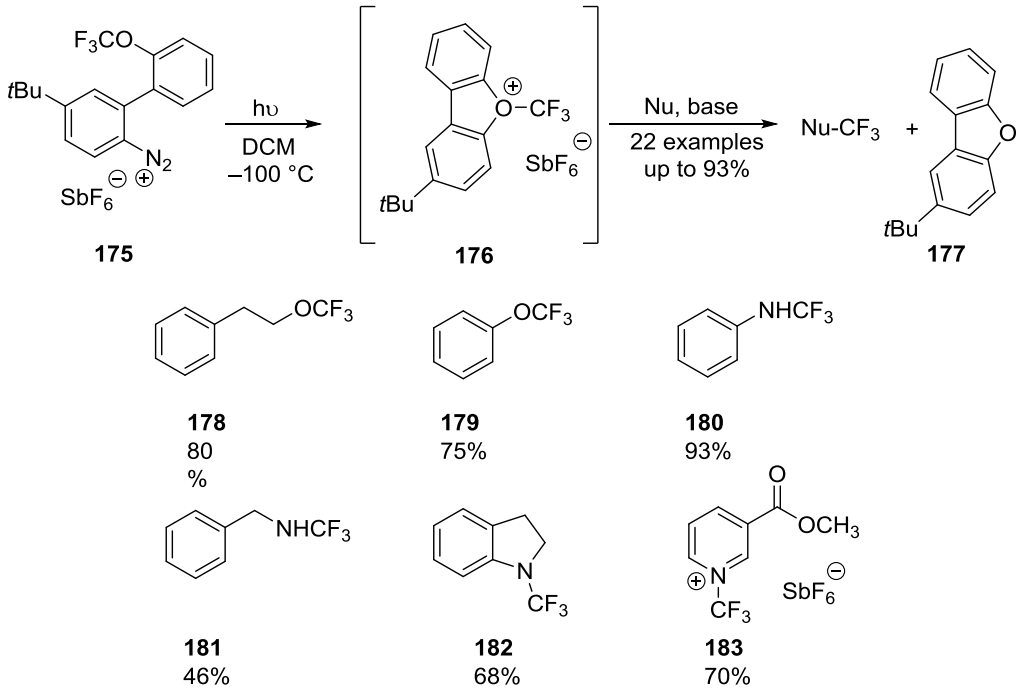
In 2003, Cahard and Ma reported the ability of the Umemoto reagent to trifluoromethylate different nucleophiles.[121] β-Ketoesters were functionalized under mild reaction conditions utilizing TBAI as a phase transfer catalyst. Additionally, in a fluoride-mediated trifluoromethylation trimethylsilyl enolates were converted to α-trifluoromethyl ketones in good yields (up to 88%) employing the dibenzothiophenium salt **173a** (Scheme 33).



Scheme 33 Trifluoromethylation of β-ketoesters and silyl enol ethers with the Umemoto reagent **173a**, as reported by Cahard and Ma.[121]

In addition, Umemoto and coworkers synthesized the thermally unstable dibenzofuranium salt **176** and employed it in the trifluoromethylation of different nucleophiles.[122] The dibenzofuranium salt **176** was synthesized *in situ* from the diazonium salt **175** at –100 °C in a light-induced *Sandmeyer* reaction (Scheme 34). Although it was not possible to isolate this highly reactive reagent, the presence of the desired compound **176** was confirmed by NMR experiments at low temperature, and a half-time of around 4.5 h at -60 °C for the hexafluoroantimonate(V)-salt **176** was determined.

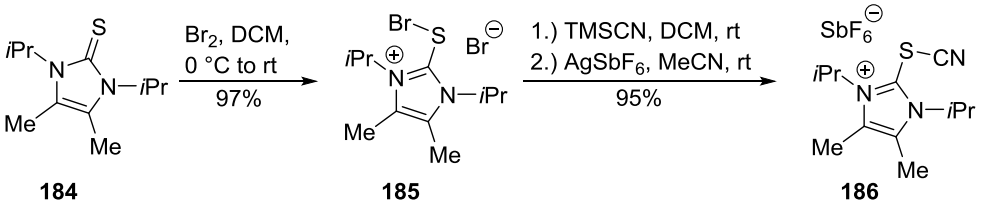
The unique reactivity of this reagent was demonstrated through trifluoromethylation of more challenging substrates. Among others, the aliphatic ether **178** and phenol ether **179** were functionalized in high yields. Furthermore, it was possible to functionalize different anilines and amines (Scheme 34). Pyridine derivatives were transformed to the corresponding pyridinium salts in good yields, as was showcased by the synthesis of the nicotine derivative **183**. For comparison, only low yields could be achieved for the trifluoromethylation of phenols with hypervalent iodine compounds, probably due to radical reaction pathways.[123] Therefore, the authors suggest that a CF_3-cation must be transferred in the reaction. The wide substrate scope of the reagent **176** illustrates its huge potential. Nevertheless, its challenging synthesis and difficult handling are clearly limiting factors in its applications.



Scheme 34 Synthesis of the dibenzofuranium salt **176** and the utilization in the trifluoromethylation of *N*- and *O*-based nucleophiles by Umemoto and coworkers.[122]

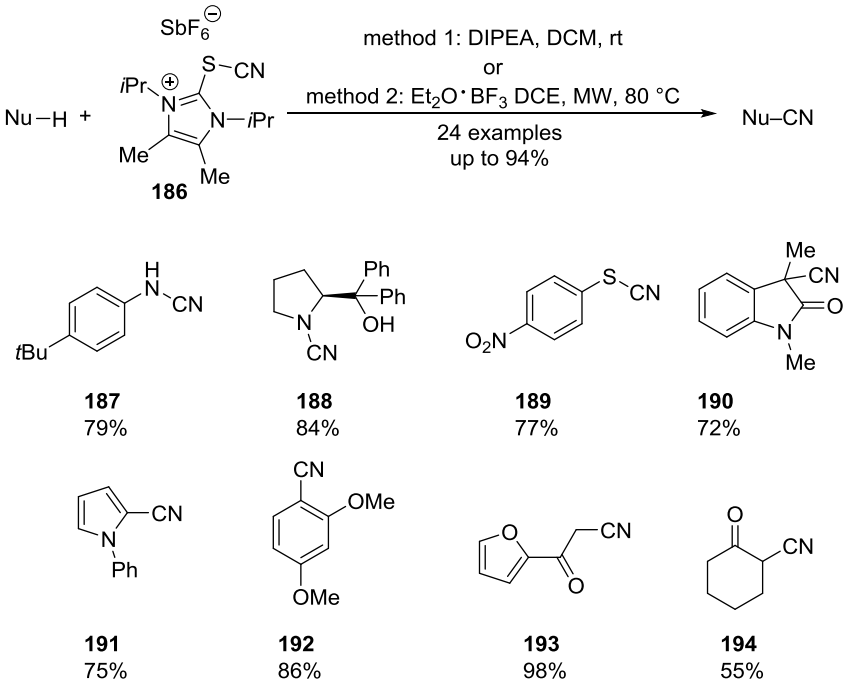
1.3.2 Thioimidazolium salts

A thioimidazolium-based transfer reagent was presented recently by Alcarazo *et al.*[124] In a straightforward procedure the thiourea **184** was transformed to the dibromide **185** via bromination with elemental bromine. Afterwards, a bromide atom was substituted by a cyanide group derived from TMSCN. Subsequent counterion exchange applying silver hexafluoroantimonate afforded the thioimidazolium salt **186** in an excellent yield of 95% (Scheme 35).



Scheme 35 Synthesis of the thioimidazolium salt **186**.[124]

The thioimidazolium salt **186** was used in the electrophilic cyanation of different nucleophiles. Two different methods were developed for the transfer reaction. Cyanamides, thiocyanates and β-amido- or ketonitriles were obtained in good to excellent yields using DIPEA as a base. The indole **191** and the dimethoxybenzonitrile **192** were prepared in a microwave-assisted reaction with a catalytic amount of boron trifluoride etherate as a Lewis acid. This method was also applied in the synthesis of the furan derivative **193** and the ketone **194** from the corresponding TMS-enolate and enamine, respectively (Scheme 36). These results highlight the broad applicability of the new reagent **186** towards electrophilic cyanation.



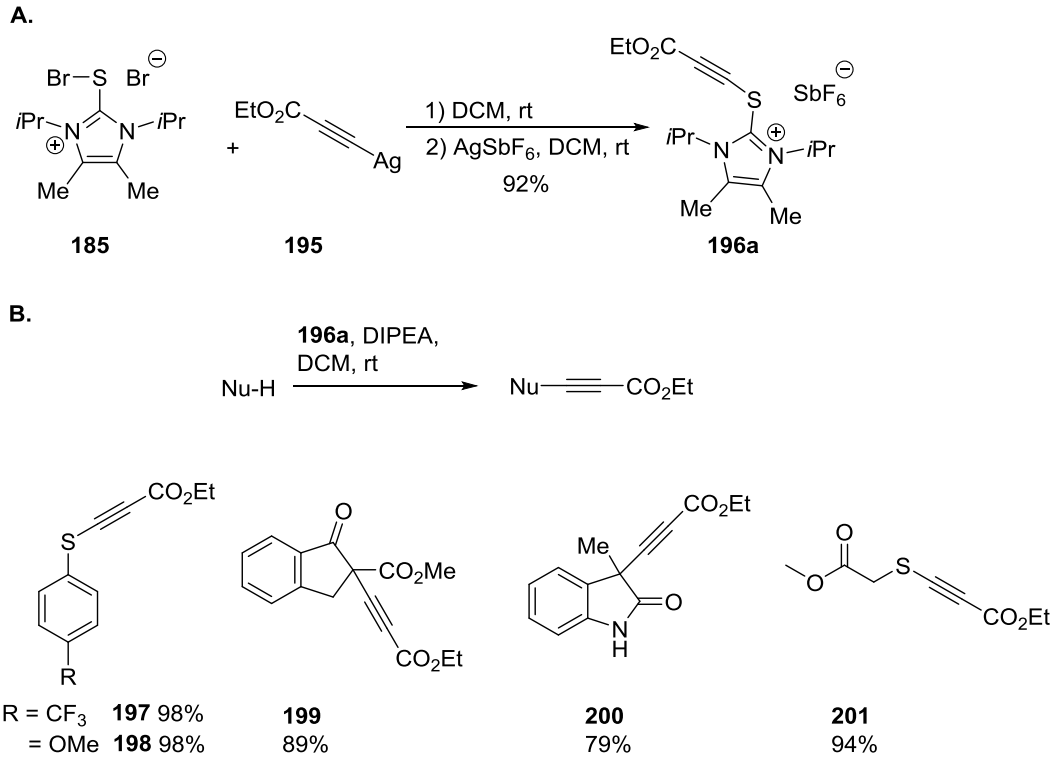
Scheme 36 Cyanation of *N*-, *C*- and *S*-based nucleophiles by the thioimidazolium salt **186**.[124]

2 Design of the project

2.1 State of research

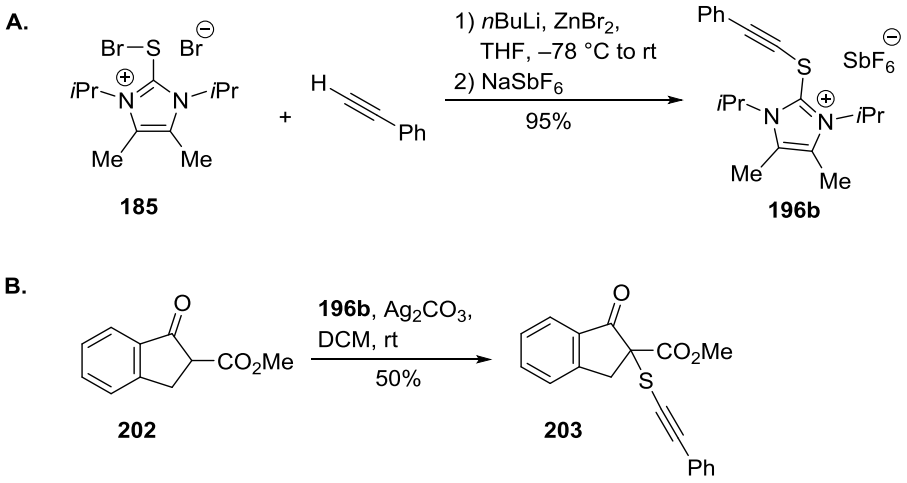
2.1.1 Alkyne-transferring reagents formerly developed in the Alcarazo group

In their seminal publication of 2015, Alcarazo and coworkers presented the imidazolium-based alkyne transfer reagent **196a** in line with the methodology applied for the formerly described cyanation reagent **186**.[124] **196a** was easily accessible in a high yield of 92% employing the reaction of dibromide **185** with silver acetylide **195** (Scheme 37A). Moreover, it was shown that compound **195** is capable of alkynylateing different nucleophiles such as thiols, ketoesters or amides in high yields of up to 98% (Scheme 37B).



Scheme 37 (**A**) Synthesis of new thioimidazolium salts for alkynylation by Alcarazo and coworkers. (**B**) Substrate scope of the alkynylation.[125]

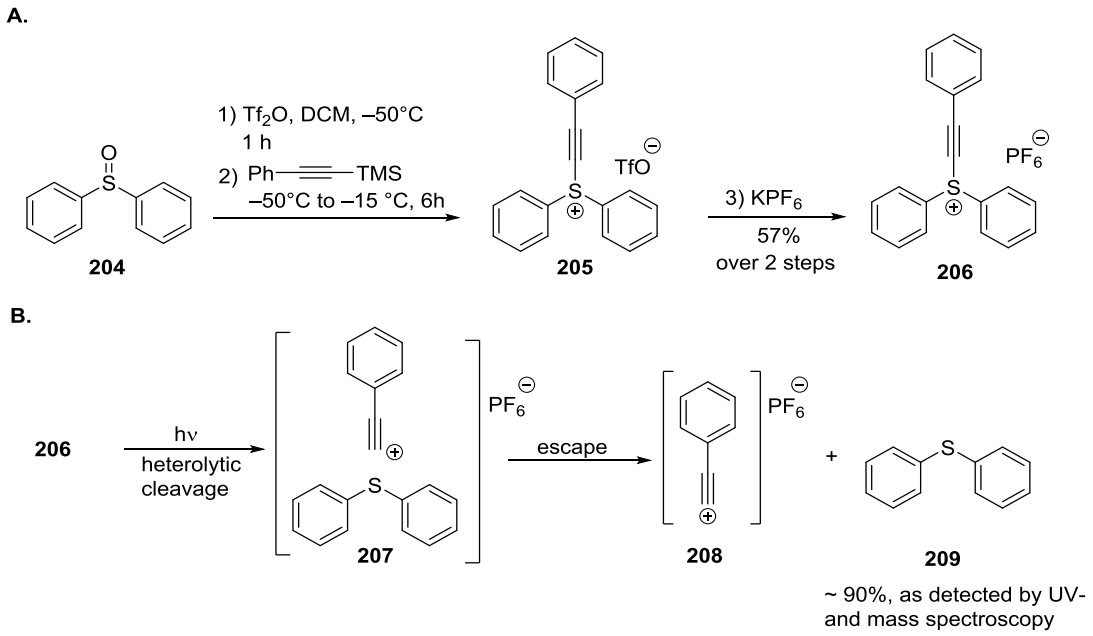
This desired reactivity was only observed for reagents with an electron withdrawing substituent on the alkyne moiety. The phenyl-substituted thioimidazolium salt **196b** could be synthesized from dibromide **185** and a corresponding alkynyl zincate in a high yield (95%). Interestingly, in attempted reactions with the β-ketoester **202** this alkynylating reagent exclusively formed the thioalkynylated derivative **203** as the main product instead of the targeted compound (Scheme 38). Undoubtedly, this unexpected reactivity demands further investigation.



Scheme 38 Synthesis of a new phenyl-substituted thioimidazolium salt **196b** and observed thioalkynylation of cyclic β-ketoester **202**.[124]

2.1.2 Alkyne-based cationic polymerization initiators developed by Liska *et al.*

In 2009, Liska *et al.* reported the synthesis and utilization of diphenylsulfonium- and -iodonium salts as initiators for cationic polymerization reactions of 4-epoxycyclohexenyl-methyl-3,4-epoxycyclohexenyl carboxylate (ECHC).[125] In a straightforward procedure, diphenyl sulfoxide **204** was treated successively with triflic anhydride and 1-phenyl-2-trimethylsilylacetylene to afford the compound **205**. After counterion exchange with potassium hexafluorophosphate, the targeted diphenylsulfonium salt **206** was obtained (Scheme 39A). Subsequent steady state photolysis experiments revealed that the main decomposition pathway of these complexes is a heterolytic cleavage of the ethynyl carbon-sulfur bond (Scheme 39B). It was assumed that this is a direct consequence of the lower strength of the sulfur-alkyne bond. Thus, we considered the utilization of the salts **205** and **206** as potential transfer reagents that could possibly offer different reactivity to imidazolium-based system described above.



Scheme 39 (**A**) Synthesis of a new dibenzothiophenium-based initiator for cationic polymerization. (**B**) The mechanism for decomposition of the dibenzothiophenium salts, as proposed by Liska *et al.*[125]

2.2 Project aims

The very recently discovered thioalkynylation with thioimidazolium-based reagents will be further investigated in collaboration with Dr. J. Peña and Dr. G. Talavera. The main focus of this study will be the introduction of differently substituted alkynes. Furthermore, suitable conditions will be examined to enhance the efficiency of the thioalkynylation protocol. The products obtained from these transformations will also be employed in further derivatization reactions (Figure 23).

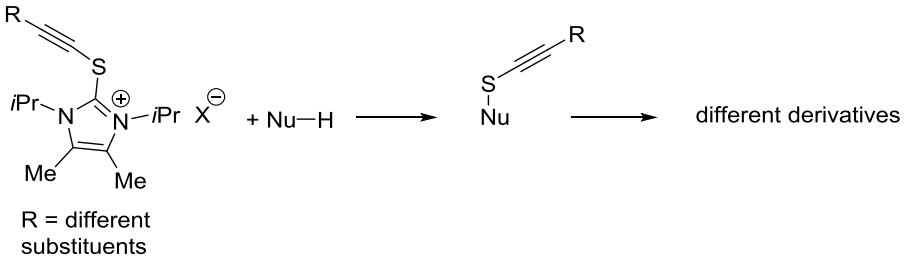


Figure 23 Proposed application of thioimidazolium reagents in the thioalkynylation of different nucleophiles with a perspective of further derivatization.

Additionally, based on the results of Liska and coworkers,[125] the potential of diphenylsulfonium salts will be investigated as a platform for the transfer of alkynes or other functional groups. This approach will be evaluated in addition to the modification of derivatives with a dibenzothiophenium backbone. Although the dibenzothiophene backbone is already present in the commercially available Umemoto reagent (compare Chapter 1.3.1), to the best of our knowledge, no derivatives have been employed for the transfer of alkyne groups. One reason for this could be the complex synthesis of this reagent. The transfer of electron-rich or neutral alkyne groups could not be achieved with the previously developed thioimidazolium system. Therefore, these sulfur-based reagents could be considered as an alternative or complementary to the commercially available hypervalent iodine (EBX) reagents and/or other common methods to introduce alkynes to organic molecules (Figure 24).

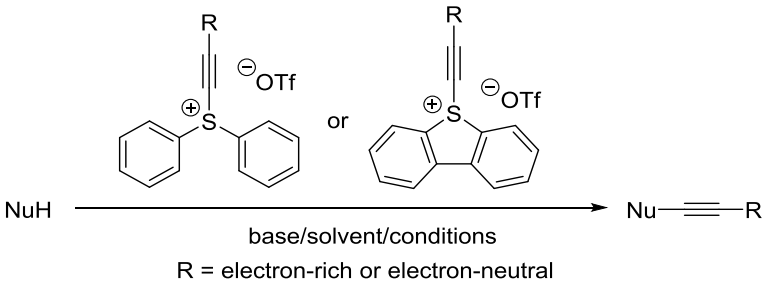


Figure 24 Proposed application of diphenylsulfonium- and dibenzothiophenium-reagents in the alkynylation of different nucleophiles.

Electrophilic transfer reagents are valuable tools for the insertion not only of alkyne moieties into complex molecules, but of other functional groups as well. Particularly the thioimidazolium-based transfer reagents have a high potential to serve as a general platform for the umpolung of functional groups, as demonstrated by the recent results of Alcarazo and coworkers discussed above. [124] Based on the success in establishing the thioimidazolium framework as a basis for very potent cyanating reagents, investigations on the ability of these reagents to facilitate the transfer of various functional groups will be conducted. In this connection, the most interesting targets are perfluoroalkylated molecules, as many pharmaceutically active or agrochemically useful compounds include fluorine-containing groups.[126] Accordingly, one part of the project will be the synthesis of reagents containing trifluoromethyl- or trifluoroethylene groups followed by investigation of their reactivity as group transfer reagents (Figure 25). These compounds are considered as a potential alternative or complement to commercially available systems developed by groups of Togni and Umemoto.[122,123]

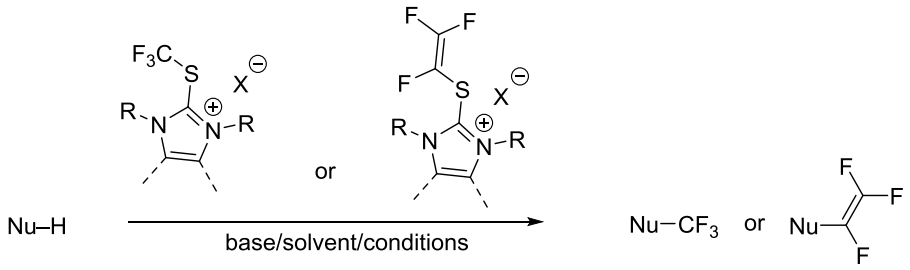


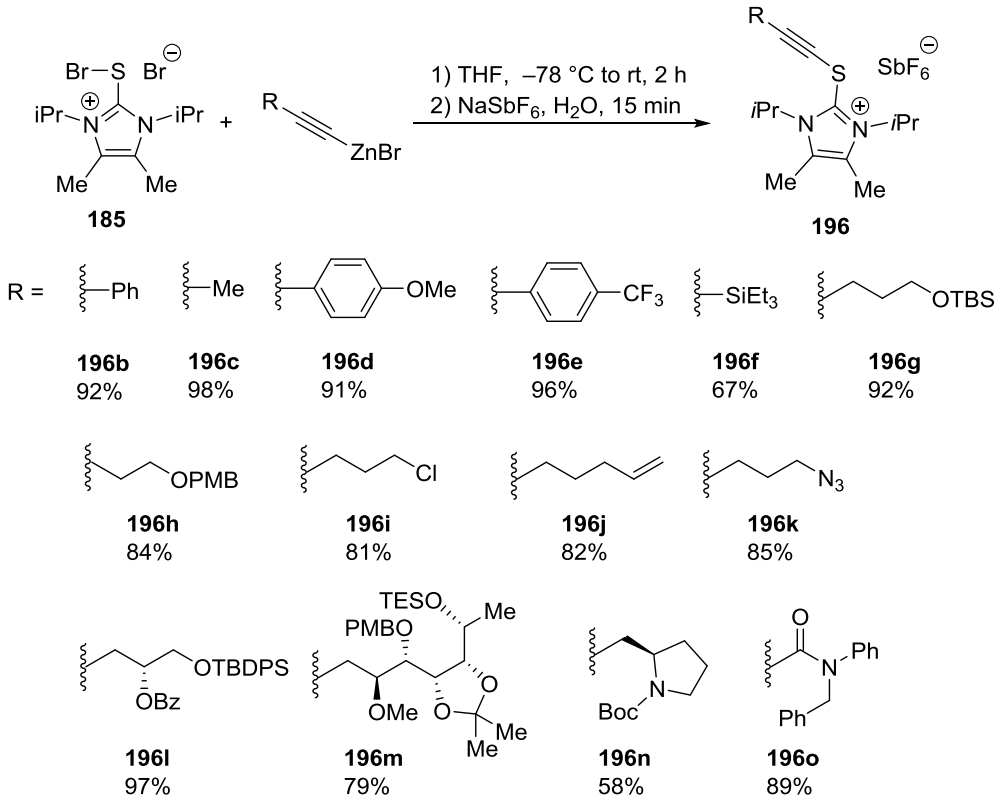
Figure 25 Proposed application of new thioimidazolium-based fluorine-containing transfer reagents.

3 Results and discussion

3.1 Further development of the newly discovered thioalkynylation reaction

3.1.1 Synthesis of new thioimidazolium-based alkynylation reagents

The great interest in discovering new ways to introduce alkynes is spurred by the versatility of application and further derivatization possibilities of this functional group (compare Chapter 1.2.3). To begin with, the reactivity of harder and stronger nucleophiles, such as Grignard reagents, should thoroughly be studied in the reaction of either potential thioalkynylation or alkynylation with imidazolium salts (compare Scheme 37 and Scheme 38 in Chapter 2.1.1). For this purpose, a new series of prospective alkyne transfer reagents with electron donating or neutral substituents on the alkyne moiety was synthesized in collaboration with Dr. G. Talavera and Dr. J. Peña. Beginning with terminal alkynes, the corresponding zincates were prepared by deprotonation with *n*BuLi followed by transmetalation with zinc bromide. Subsequent addition of the dibromide **185** furnishes the desired alkyne reagents **196b**–**196o** in good to very good yields, tolerating a variety of different functional groups. Thus, compounds **196d** and **196e** with substituted aromatic residues were synthesized in yields of up to 96%, TBS- and PMB-protected reagents **196g** and **196h** were prepared in excellent yields of up to 92% as well, and challenging structures like the chloride **196i**, enyne **196j** or azide **196k** were obtained in yields of 81%, 82% and 85%, respectively. Additionally, complex reagents **196i**–**196n** with a set of various protecting groups like TES, PMB, Bz, etc. were successfully prepared. Besides this, it was possible to synthesize the reagent **196o** in good yield of 89% from the corresponding amide (Scheme 40).



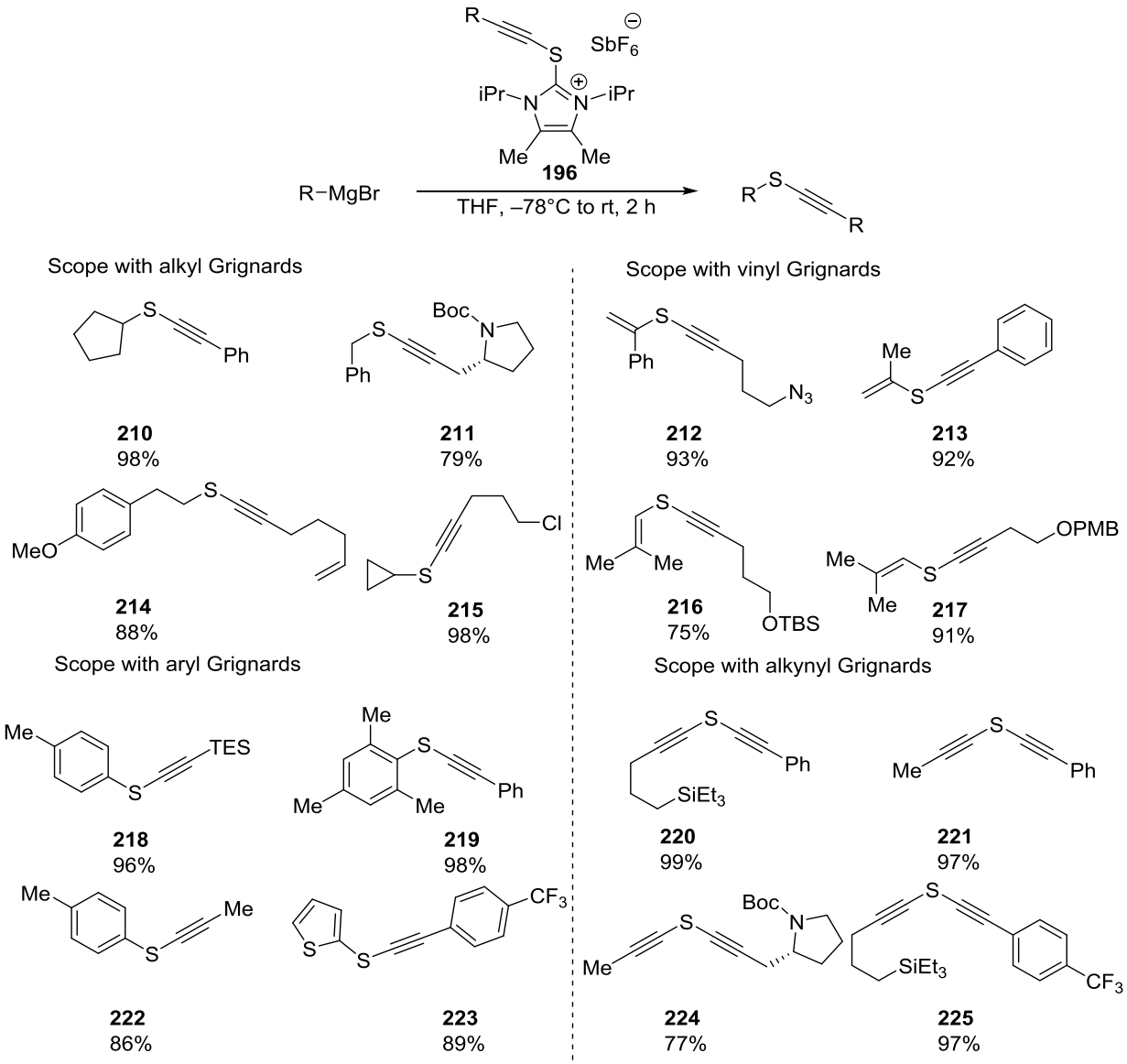
Scheme 40 Different imidazolium reagents prepared in cooperation with Dr. G. Talavera and Dr. J. Peña.

3.1.2 Scope and limitations of the transfer reaction

It was shown that organomagnesium reagents react with compounds **196** in an electrophilic thioalkynylation fashion as indicated above in Chapter 2.1.1 (Scheme 38B), smoothly affording the corresponding alkynyl sulfides **210**–**225**, however, with better efficiency (Scheme 41). This reaction was utilized to synthesize a set of alkynyl sulfides in excellent yields. These results correspond to the formerly observed reactivity with weaker nucleophiles like β-ketoesters. With the established methodology, it was possible to perform reactions with alkyl, vinyl, aryl and alkynyl Grignards to generate a variety of different products.

The alkylsulfide **210** was obtained in a virtually quantitative yield (98%). Furthermore, more challenging alkylsulfides, such as Boc-protected propargylpyrrolidine **211**, compounds **214** and **215** were synthesized in 79, 88 and 98% yield, respectively. The enyne **212** was obtained in a yield of 93%, thus demonstrating that azide groups are tolerated by the reaction procedure. The isopropenylalkyne **213** was prepared in a yield of 92%. Moreover, it was proven that this methodology is efficient in the presence of commonly used alcohol protecting groups with the synthesis of the enynes **216** and **217** in 75 and 91% yield, respectively.

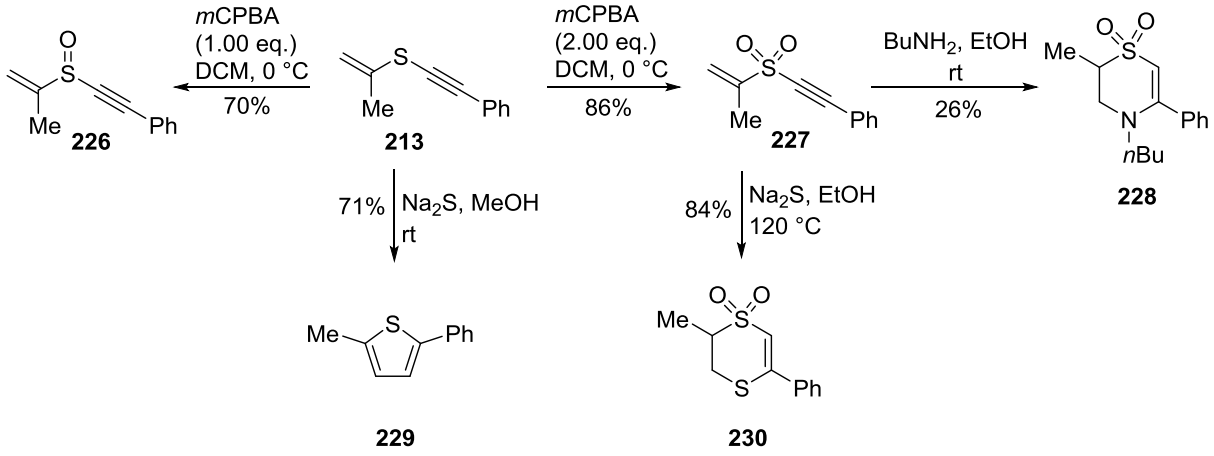
Furthermore, it was possible to obtain the TES-substituted arylsulfide **218** in an excellent yield of 96%, thus illustrating the compatibility with silicon-based alkyne protective groups. The arylsulfides **219** and **222** were prepared in 98 and 86% yield, respectively. Heteroaromatic Grignard reagents could be used as well, which was demonstrated by the synthesis of the alkyne **223** in a yield of 89%. Additionally, a series of structurally interesting dialkynyl derivatives was synthesized. In a reaction of the compound **196b** with a TES-protected Grignard reagent, the sulfide **220** was obtained in virtually quantitative yield (99%). The sulfide **221** was synthesized in an excellent yield (97%), whereas the sulfide **224** in a good yield (77%). Besides, trifluoromethyl groups are tolerated in this reaction, as was demonstrated by the successful preparation of diyne **225** (97% yield).



Scheme 41 Different disulfides prepared in cooperation with Dr. G. Talavera and Dr. J. Peña.

3.1.3 Further derivatization of the synthesized sulfides

A set of illustrative examples of transformed products was prepared starting from the vinylsulfide **213** in order to emphasize the applicability of this alkynsulfides for further modification (Scheme 42). Accordingly, the sulfide **213** was converted to the sulfoxide **226** and to the sulfone **227** upon reaction with one or two equivalents of *m*CPBA, in good yields of 70 and 86%, respectively. The sulfone **227** was further functionalized under mild conditions to the cyclic enamine **228** in a Michael-type reaction in a yield of 26%. Apart of these functionalizations, the cyclization of the sulfone **227** with Na_2S at elevated temperature gave access to the cyclic sulfide **230** (84% yield). Finally, the sulfide **213** was cyclized with Na_2S at ambient temperature into the thiophene **229** in a yield of 71%.

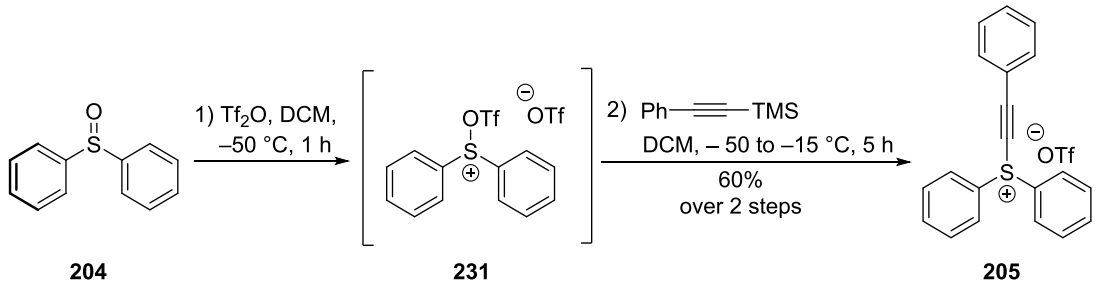


Scheme 42 Further derivatization of the synthesized sulfides.

3.2 The diphenylsulfonium-based reagent

3.2.1 Synthesis of the diphenylsulfonium reagent

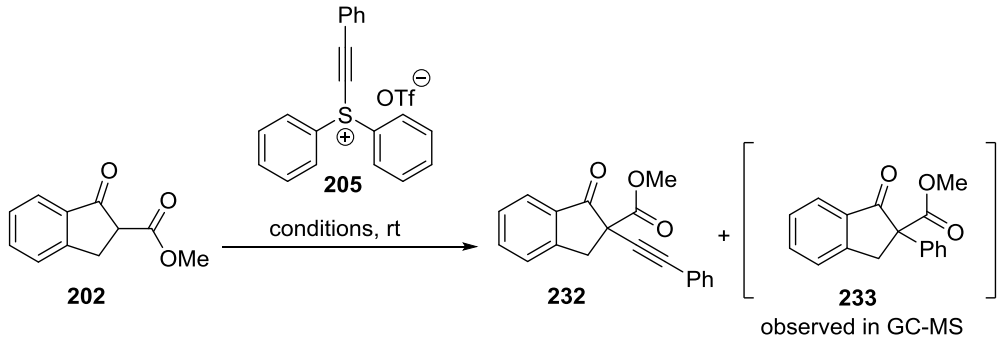
The inability of thioimidazolium salts to transfer electron-rich alkyne groups to nucleophiles was discussed above. To overcome this limitation, the possibility to utilize diphenylsulfonium salts as reagents for the alkynylation of nucleophiles based on the research of Liska and coworkers[125] should be investigated. According to our optimized protocol, the intermediate sulfonium salt **231** was obtained by treatment of commercially available phenyl sulfoxide **204** with triflic anhydride. Subsequently, the final sulfonium salt **205** was synthesized from the intermediate **231** in a reaction with 1-phenyl-2-trimethylsilylacetylene in a yield of 60% (Scheme 43).



Scheme 43 Synthesis of the diphenylsulfonium salt **205**.

3.2.2 Scope and limitations of the transfer reaction

After the optimization of synthesis of the salt **205**, reactions with the β-ketoester **202** were performed in order to study the activity of this reagent towards nucleophiles (Table 1 and Scheme 44). With common bases for transfer reactions like DIPEA, K_2CO_3 or K_3PO_4 in dichloromethane as a solvent, the product **232** was obtained in low yields lying in the range of 7–14% (entries 1 and 2). Neither changing the solvent to the more polar acetonitrile nor applying the reagent **205** in excess did significantly increase the efficiency of the reaction. Reducing the reaction time or adding the base and reagent at –78 °C did not improve the product yield as well.

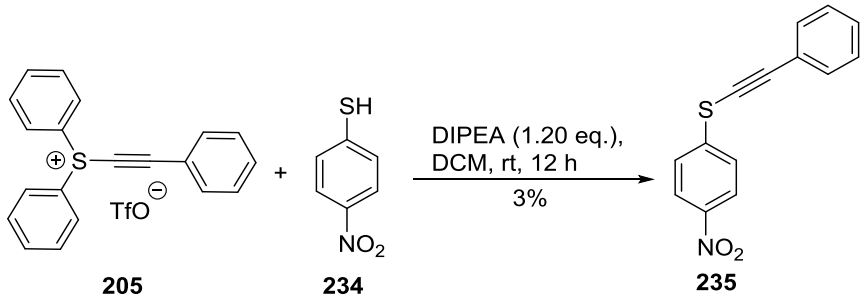


Scheme 44 Reaction of β-ketoester **202** with the diphenylsulfonium salt **205**.

Table 1 Alkynylation of the β-ketoester **202** with the diphenylsulfonium salt **205**: screening for the conditions at ambient temperature.

Entry	Equiv. 205	Base	Equiv.	Solvent	Time (h)	Yield (%)	Comment
1	1.20	DIPEA	1.10	DCM	12	7	
2	1.20	K_2CO_3	1.05	DCM	2	9	
3	1.50	K_2CO_3	1.05	MeCN	12	9	
4	1.50	K_2CO_3	1.10	DCM	50	13	
5	1.50	K_3PO_4	1.05	DCM	12	14	
6	1.50	DIPEA	1.05	DCM	2	11	
7	1.20	DIPEA	1.00	DCM	2	8	–78 °C to rt

Furthermore, the reaction with other nucleophiles like thiols did not lead to essential improvements. Nonetheless, for the reaction of the thiophenol **234** with the reagent **205** and DIPEA as a base, the desired product **235** was obtained in 3% yield (Scheme 45).



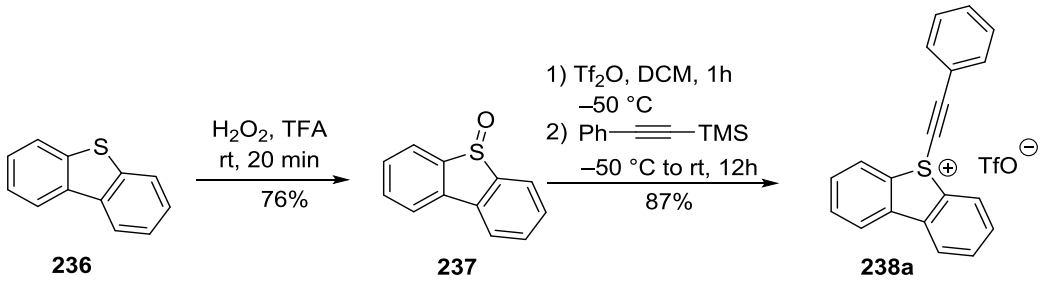
Scheme 45 Reaction of the thiol **234** with the diphenylsulfonium salt **205**.

An explanation could be the direct decomposition of the reagent **205** because of its low stability under basic conditions. Moreover, other decomposition pathways are possible, as already discussed in the publication of Liska and coworkers.[125] Thus reported on the formation of an unstable phenyl cation under the reaction conditions. As such, this illustrates that the nucleophile can also attack the phenyl cation, and indeed, the phenyl-substituted by-product was detected in GC-MS.

3.3 Searching for new dibenzothiophene-based reagents

3.3.1 Synthesis of the dibenzothiophene-based reagents

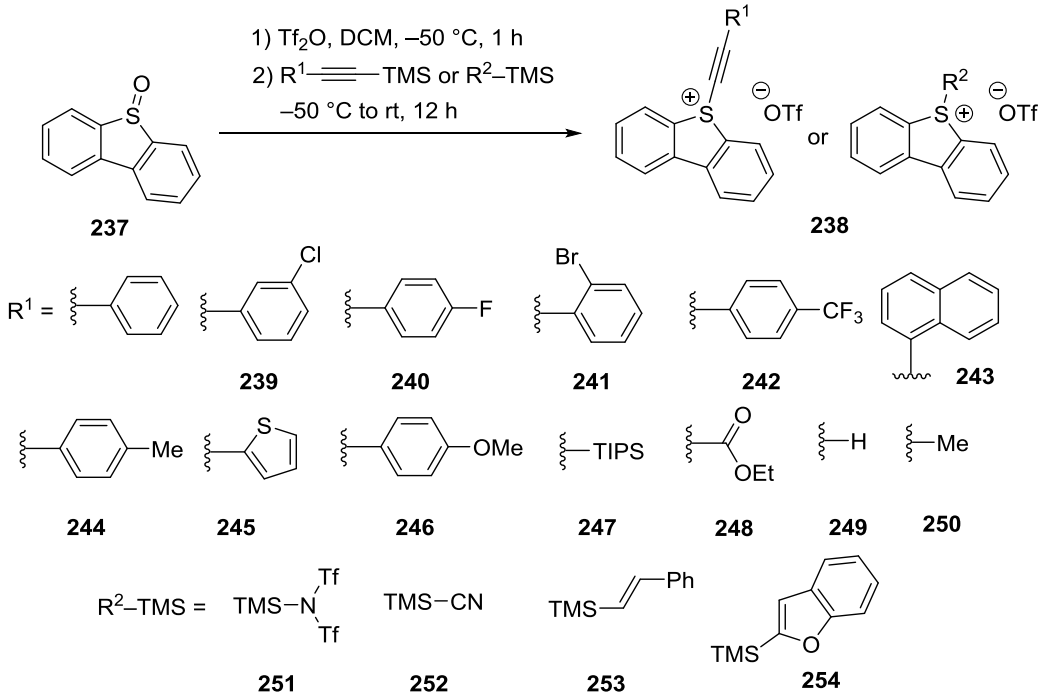
As a consequence, we decided to address the problem of undesired side reactions through an additional modification of the backbone of the reagent. Thus, the well-known trifluoromethylation reagent – Umemoto reagent **173** – has a dibenzothiophene backbone (compare Chapter 1.3.1). Very probably, a dibenzothiophene-based alkynilating reagent should enhance the reactivity by enabling the charges to be localized in a larger conjugated system. On one hand, it should lower the frontier orbitals energies of the reagent and make the compound easier accessible for the nucleophilic attack. On the other hand, it should make the compound more stable due to the rigid backbone and the inclusion of the sulfur atom in the bigger aromatic system. Therefore, the methodology from Liska and coworkers[125] was employed to synthesize a new kind of dibenzothiophene-based reagent. In the straightforward synthesis, commercially available dibenzothiophene (**236**) was oxidized by hydrogen peroxide to the corresponding sulfoxide **237** in a yield of up to 76%.[127] Afterwards, the latter was activated by triflic anhydride and subsequently converted to the desired compound **238a** with 1-phenyl-2-trimethylsilylacetylene in 87% yield (Scheme 46).



Scheme 46 Synthesis of a new dibenzothiophenium-based reagent **238a**.

3.3.2 Expanding the scope towards different dibenzothiophenium salts

A set of differently substituted dibenzothiophenium salts **238** was synthesized from the corresponding trimethylsilyl-protected alkynes and other TMS-bearing compounds to investigate the scope and limitations of this methodology (Scheme 47).



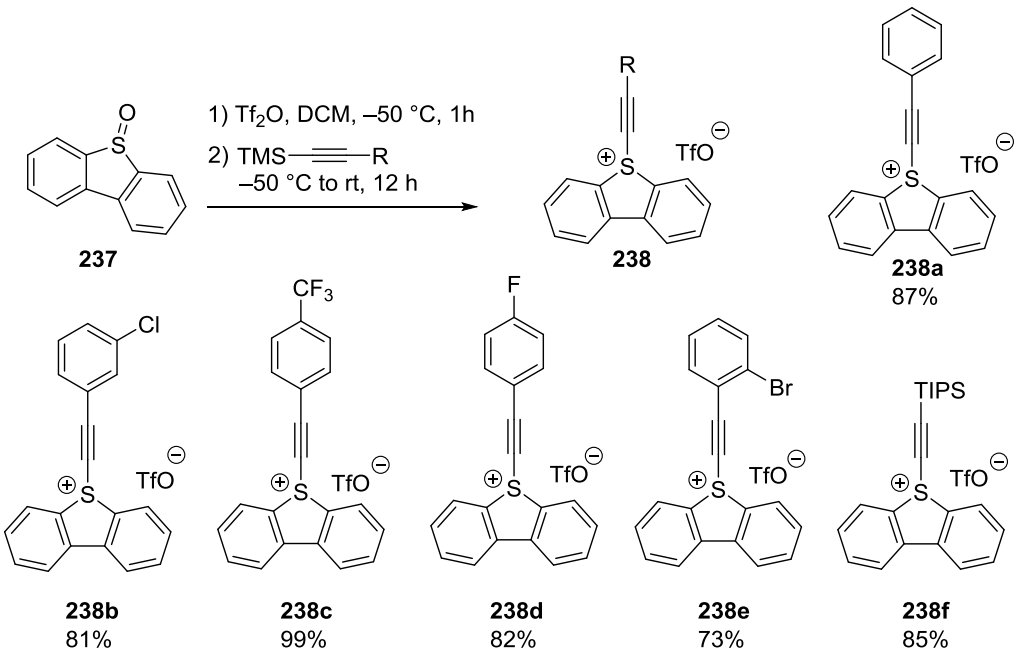
Scheme 47 Attempted syntheses towards different dibenzothiophene-based reagents using various TMS-protected alkynes and other TMS-decorated molecules.

The reaction was working with different arylsubstituted alkynes. Thus, the reagents **238b**–**238f** were smoothly obtained in the reaction with the alkynes **239**, **242**, **240**, **241** and **247**, respectively, in 81, 99, 82, 73 and 85% isolated yield, respectively (

Table **2** and Scheme 48). The same reactivity was observed for the reaction with the alkyne **244** as well, yet it appeared to be impossible to isolate the product **238h** of an acceptable purity after several attempts. On the other hand, the reactions of the alkyne **243**, TMS-protected acetylenes **245**, **246**, **248**, **250** decorated with stronger coordinating functional groups and the trimethylsilylacetylene (**249**) led to the complete decomposition of the material. Presumably, the intermediately formed product underwent further reaction with rather active electron rich alkynes. Alternatively, activated dibenzothiophene **238** may be attacked by electron rich TMS sources to another reaction center, followed by direct decomposition of the resulting intermediates.

Table 2 Attempted syntheses of differently substituted alkynylating reagents of type **238**.

Entry	Product	R	Yield (%).	Comments
1	**238a**	phenyl	87	
2	**238b**	3-chlorophenyl	81	
3	**238c**	4-trifluoromethylphenyl	99	
4	**238d**	4-fluorophenyl	82	
5	**238e**	2-bromophenyl	73	
6	**238f**	TIPS	85	
7	**238g**	1-naphthyl	0	decomposition
8	**238h**	4-methylphenyl	77	purity ~ 80–90%
9	**238i**	2-thienyl	0	decomposition
10	**238j**	4-methoxyphenyl	0	decomposition
11	**238k**	ethoxycarbonyl	0	decomposition
12	**238l**	H	0	decomposition
13	**238m**	methyl	0	decomposition



Scheme 48 Substrate scope for the synthesis of novel dibenzothiophenium reagents **238**.

The structures of the selected salts **238** were unambiguously established by X-ray diffraction analysis (Figure 29). Crystals suitable for X-ray diffractometry of the reagent **238f** were obtained by slowly cooling down of a boiling, saturated toluene solution to rt. Furthermore, crystals of the reagent **238a** were grown by slow evaporation of a saturated DCM solution. As expected, both compounds show a pyramidal geometry of the central sulfur atom (the sum of angles around S1 is 302.3° for reagent **238f** and 294.6° for the salt **238a**). The bonds between S1 and the neighboring carbons of the dibenzothiophene backbone [S1–C3 = 1.7897(1) Å in compound **238a** and S1–C3 = 1.7933(8) Å in **238f**] are lengthened due to the partial loss of the aromaticity, as compared to the parent dibenzothiophene (1.740 Å).[128a] This is a direct consequence of the reduction of the bonding order of the corresponding bond between sulfur and carbon in a dibenzothiophene backbone in **238**. Besides, a strong coordination of the oxygen of the triflate counterion towards the sulfur-atom was observed. This can be interpreted as a consequence of the enhanced Lewis acidity of sulfur atom, resulting in a significant shortening of interatomic distances [O1–S1 = 3.157(1) Å in the salt **238a** and O1–S1 2.972(2) Å in compound **238f**] in comparison to the corresponding sum of the Van-der-Waals-radii (3.32 Å).[129b]

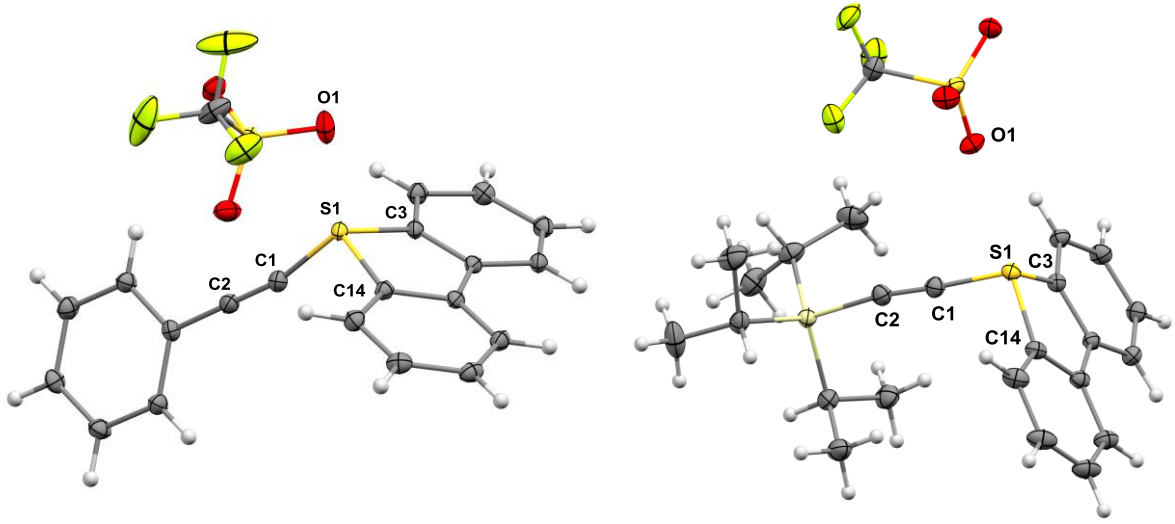


Figure 26 Molecular structures of compound **238a** (left side) and **238f** (right side) in the crystal. Thermal ellipsoids at 50% probability, the numbering does not correspond to the IUPAC rules. Selected bond lengths, distances (Å) and angles (°): Compound **238a**: O1–S1 = 3.157(1), S1–C3 = 1.7878(1), S1–C14 = 1.7897(1), S1–C1 = 1.6871(1), C3-S1-O1 = 179.0(1); Compound **238f**: S1–O1 = 2.972(1), S1–C3 = 1.7933(8), S1–C14 = 1.7935(8), S1–C1 = 1.6980(9), C6-S1-O1 = 177.3(1).

Apart from TMS-protected alkynes, several other TMS-decorated molecules **251**–**254** (Scheme 47) were tested toward the synthesis of further dibenzothiophene-derived potential transfer reagents (Table 3). Whereas only decomposition products of the dibenzothiophene were obtained in the reaction with the TMS-sulfonamide **251**, with TMS-cyanide (**252**) the corresponding reagent **238o** was successfully synthesized in 83% yield. Also the β-trimethylsilylstyrene (**253**) was transferred to the dibenzothiophenium backbone. The reagent **238p** was isolated with minor impurities in a yield around 87%. In contrast, the use of 2-(trimethylsilyl)benzofurane (**254**) led to a complete decomposition of the reaction partners.

Table 3 Attempted syntheses of further dibenzothiophene-derived potential transfer reagents.

Entry	Product	TMS-R	Yield (%)	Comment
1	**238n**	TMS-N(Tf)$_2$	0	decomposition
2	**238o**	TMS-cyanide	83	–
3	**238p**	(*E*)-trimethyl(styryl)silane	~87	contain impurities
4	**238q**	TMS-benzofuran-2-yl	0	decomposition

Furthermore, the structure of compound **238p** was confirmed by X-ray crystal structure analysis (Figure 27). Single crystals suitable for X-ray diffraction were grown from over-layering a solution of the salt **238q** in DCM with Et_2O. As in the previously discussed above structures, the bond length C9–S1 with 1.780(2) Å is longer than in dibenzothiophene (1.740 Å)[128a] This is attributed to the partial loss of aromaticity in the dibenzothiophene backbone as well. The distance between the carbon atoms C1–C2 of the alkene moiety with 1.333(3) Å is comparable to the length of a C=C double bond in unsubstituted styrene in the solid phase [1.3245(2) Å].[128c] A significant shortening of interatomic distance C1–O1 [3.069(3) Å vs. the sum of the Van-der-Waals-radii of 3.22 Å][128b] may be occurs due to the support of a strong hydrogen bonding C1–H···· O1.

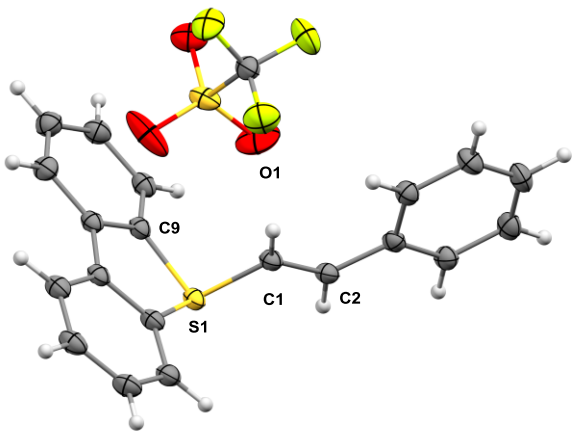
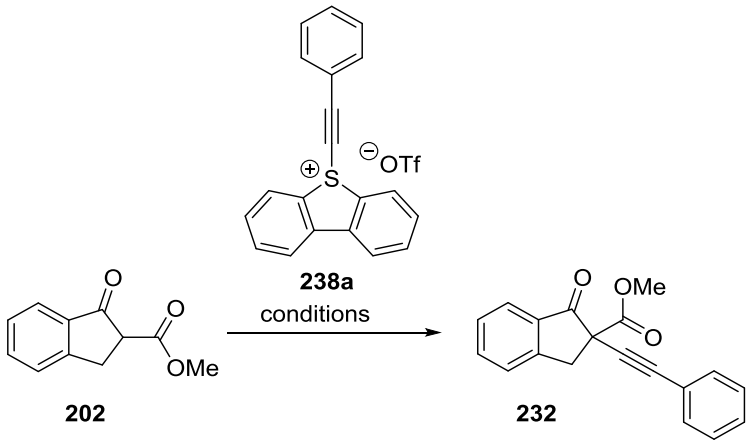


Figure 27 Molecular structure of compound **238q**. Thermal ellipsoids at 50% probability. Selected bond lengths and distances (Å): C1–C2 = 1.333(3), C1–O1 = 3.069(3), C9–S1 = 1.780(2), C1H–O1 = 3.069(3).

3.3.3 Optimization of the reaction conditions

The reactivity of the reagents **238** was investigated by example of ethynylation of the β-ketoester **202** with the reagent **238a** (Scheme 49 and Table 4). As believed, higher yields of compound **232** were observed for the reaction with the salt **238a** as compared to the diphenylsulfonium salt **205** (*cf.* Scheme 44 and Table 1). Compound **232** was isolated in up to 61% yield when applying Cs_2CO_3 or DIPEA as base and 1.20 equivalents of the reagent **238a** in DCM (entries 1, 2). However, thus obtained product was contaminated with 10% of starting material as inseparable impurity. No unreacted β-ketoester **202** was observed, when the amount of the reagent **238a** was increased to 1.50 equivalents while employing DIPEA as a base (entry 3). The same results were observed with Cs_2CO_3 (entries 4 and 5). Furthermore, no significant influence of the solvent was found, as the reaction exhibited similar efficiency utilizing MeCN, toluene and THF (entries 6–9). Surprisingly, no reaction was observed when silver carbonate was used as a base (entry 10). Solely starting material was isolated, when the reaction was run without a base in MeCN (entry 11). The yield increased up to 69% by lowering the reactants concentration by factor 2 (entries 12 and 13). The dropwise addition of the reagent solution utilizing DIPEA as a base afforded the desired product **232** in 62% yield (entry 14). Finally, a screening of the temperature in the range from 40 to 70 °C (entries 15–20) revealed that 60 °C was the optimal one giving **232** in the best yield of 79% (entry 18).



Scheme 49 Alkynylation of the β-ketoester **202** with the reagent **238a** as a test reaction.

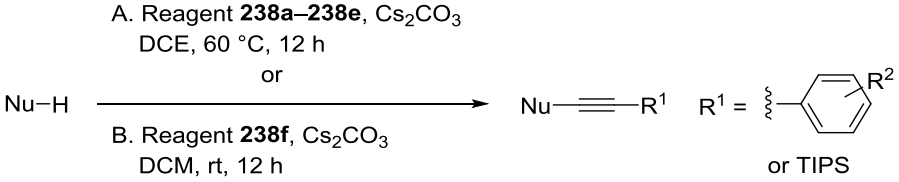
Table 4 Alkynylation of the β-ketoester **202** with the dibenzothiophenium salt **238a**: screening for the better conditions.

Entry	Equiv.	Base	Solvent	T (°C)	Concentration.	Yield (%)	Comment
1	1.20	Cs_2CO_3	DCM	rt	0.14 *M*	57	+10% SM*
2	1.20	DIPEA	DCM	rt	0.14 *M*	61	+10% SM
3	1.50	DIPEA	DCM	rt	0.14 *M*	58	–
4	1.50	Cs_2CO_3	DCM	rt	0.14 *M*	58	–
5	1.50	Cs_2CO_3	DCM	rt	0.07 *M*	67	–
6	1.20	Cs_2CO_3	MeCN	rt	0.14 *M*	67	+10%SM
7	1.20	Cs_2CO_3	THF	rt	0.14 *M*	58	–
8	1.20	Cs_2CO_3	Toluene	rt	0.14 *M*	52	Isolated 40% SM
9	1.50	Cs_2CO_3	MeCN	rt	0.14 *M*	66	–
10	1.20	Ag_2CO_3	DCM	rt	0.14 *M*	0	Isolated only SM
11	1.20	–	MeCN	rt	0.14 *M*	0	Isolated only SM
12	1.50	Cs_2CO_3	MeCN	rt	0.07 *M*	69	–
13	1.50	Cs_2CO_3	DCM	rt	0.07 *M*	67	–
14	1.50	DIPEA	DCM	rt	0.07 *M*	62	Reagent solution added dropwise
15	1.50	Cs_2CO_3	DCE	40	0.07 *M*	71	–
16	1.50	Cs_2CO_3	DCE	50	0.07 *M*	73	–
17	1.50	Cs_2CO_3	DCE	55	0.07 *M*	66	–
18	**1.50**	**Cs_2CO_3**	**DCE**	**60**	**0.07** *M*	**79**	–
19	1.50	Cs_2CO_3	DCE	65	0.07 *M*	74	–
20	1.50	Cs_2CO_3	DCE	70	0.07 *M*	69	–

*SM = starting material **202**.

3.3.4 Scope and limitations of the transfer reaction

Reactions with *N*-, *S*,- *C*- and *P*-benchmark nucleophiles were performed to demonstrate the scope of this transfer reaction (Scheme 50). The reactions with the reagents **238a–238e** were performed under the optimized conditions described above (A), but the excess of used reagent **238f** could be reduced to 1.20 equivalents, whereas all reactions with this salt were conducted at room temperature (B).



Scheme 50 Applied reaction conditions for the investigations towards the alkynylation of nucleophiles with newly developed reagents **238**.

Additionally, all reactions with thiols were accomplished at room temperature because of the possibility of disulfide formation. Different aliphatic and aromatic, electron rich and electron poor thiols were functionalized (Figure 28). For example, the products **255** and **256** were obtained in a yield of 70 and 67%, respectively, by reacting (4-methoxyphenyl)methanethiol with reagents **238f** or **238a**. respectively. In addition, upon treatment with the salts **238f** or **238a**, ethyl 2-mercaptoacetate was converted into sulfides **257** or **258** in 87 or 91% yield, respectively. The reaction of 4-nitrobenzenethiol with the reagent **238f** resulted in the formation of product **259** with a yield of 76%. With 4-methoxybenzenethiol, compound **260** was received from the reaction with the reagent **238f** in 73% yield, whereas the transfer of a phenylacetylene moiety from reagent **238a** appeared to be slightly less efficient, as the product **261** in a yield of 64%. The examined conversions of naphthalene-1-thiol into the corresponding thioether **262** using the reagent **238a** (49% yield), of benzo[*d*]thiazole-2-thiol into compound **263** employing the salt **238f** (99% yield), of thiobenzoic acid into the corresponding ester **264** (66% yield) and of protected cysteine into its derivative **266** using the same reagent (80%) appeared to be successful as well. On the other hand, no product formation was observed in the attempted alkynylations of the latter two starting materials with the reagent **238a**. Unfortunately, all attempts to synthesize the bromide **267** or the selenoether **268** failed. Presumably, both products possess a low stability and decompose under the reaction conditions.

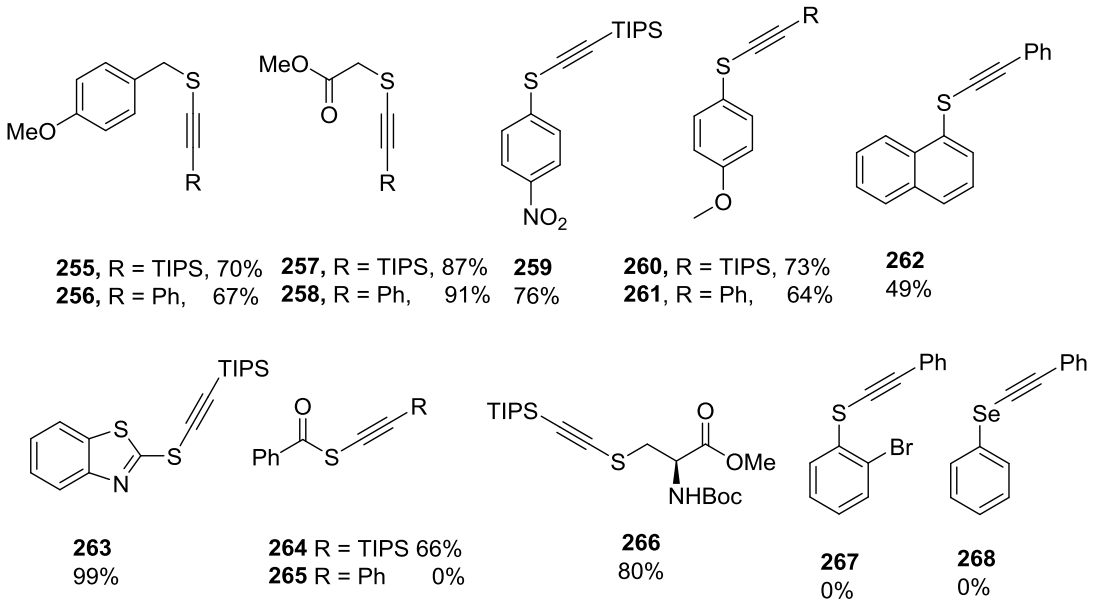


Figure 28 Reaction scope of the transfer reaction with different sulfur-based nucleophiles**.**

Also twofold-activated methyne compounds were examined as nucleophiles in the alkynylation reaction (Figure 29). The β-ketoester **202** was functionalized under the optimizing reaction conditions with the reagents **238a**–**238f**. This reaction tolerates a wide range of substituents on the aromatic ring upon transferring arylacetylene moieties. Thus, the products **232** (79% yield) **269** (79% yield), **270** (74% yield), **271** (65% yield) and **272** (81% yield) were obtained in the reactions of compound **202** with reagents **238a**, **238e**, **238c**, **238d** and **238b**, respectively. The TIPS-substituted reagent **238f** appeared to be synthetically useful in alkynylation of several twofold-activated methyne compounds such as cyclic β-ketoester **202**, its analogue 2-phenyl-1*H*-indene-1,3(2*H*)-dione or ring-opened 2-cyano-3-phenylpropanoate. Reactions with **238f** afforded acetylenes **273**–**275** in 88, 95 and 79% isolated yield. Surprisingly, the attempted preparation of the closest analogue of the latter – ring opened β-ketoester **277** from methyl 2-methyl-3-oxo-3-phenylpropanoate – failed because of unknown reasons. Likewise, only solely starting material was isolated in the reaction of the reagent **238f** with methylated Meldrum's acid. Most probably, this is a result of enhanced acidity of Meldrum's acid: the two carbonyl groups in the six-membered ring are better conjugated and exert stronger electron-withdrawing effect. As result, this compound is 8 orders of magnitude more C–H acidic than the closely related dimethyl malonate. On the other hand, products like compounds **278**, **279** or **280** could not be synthesized from single activated starting materials with low C–H acidity applying elaborated methodology as well. Following the HSAB-concept, the generated nucleophiles are presumably too hard, what led to a decomposition of the reagent instead.

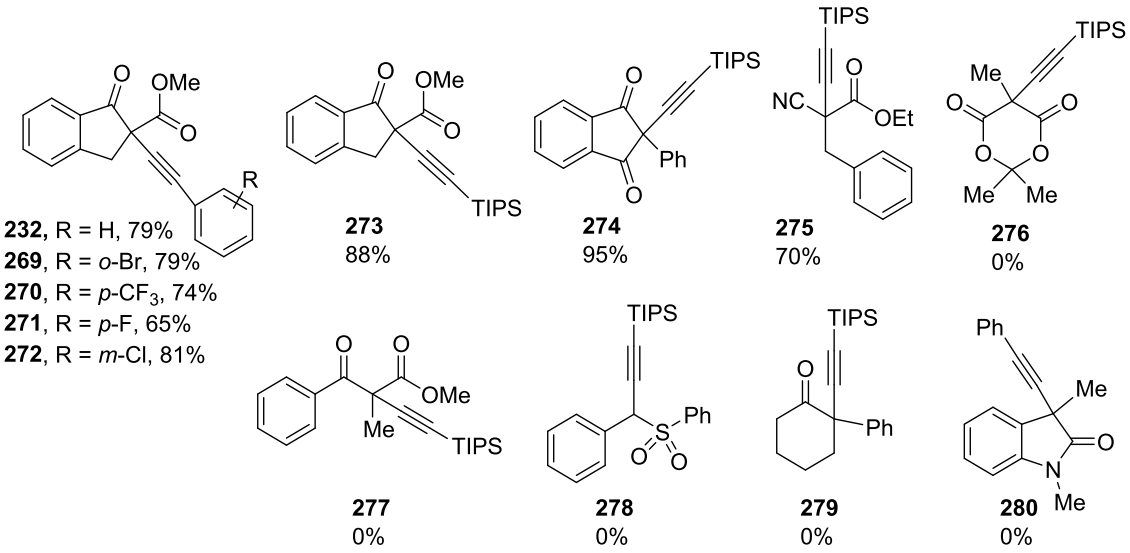


Figure 29 Reaction scope of the alkyne transfer reaction with different carbon-based nucleophiles.

Among nitrogen-based nucleophiles, sulfonamides were working in the alkyne transfer reaction as well (Figure 30). Thus, *N*,4-dimethylbenzenesulfonamide was functionalized with the salts **238a** and **238f** affording products **282** and **281** in 55 and 67% yield, respectively. Derivatives of differently substituted anilines were also alkynylated in good yields. Proceeding from the tosylated anilines, the compound **283** (77% (bsrm, 55%) yield), **284** (50% yield), **285** in a of (61% yield) and **286** (53% yield) were successfully synthesized, thus demonstrating the reaction tolerance towards ethoxycarbonyl, methoxy and iodine substituents on an aniline aromatic moiety.

Sulfonamides with other structural motifs were probed as well. Accordingly, compound **287** was obtained in a yield of 60%, and the derivatives of camphorsulfonic acid **288** and **289** – in a yield of 60% and 58%, respectively. Furthermore, the pharmacologically active compounds and veterinary antibiotic Sulfadimidine[129] was selectively converted to the alkyne **290** in a yield of 60%. A completely new reactivity, which, as far as we know, has not yet been described in the literature, was found upon the functionalization of diamides with alkyne transfer reagents. Naphthalimide and phthalimide were transformed into their *N*-alkynylated derivatives **291** and **292** in 60 and 33% yield, respectively. In contrast, maleimide or succinimide could not be functionalized with the reagent **238f**. This looks surprising, as structural differences between compounds **292** and **293** seem to be negligible. On the other hand, the general degree of conjugation in a molecule drops in the sequence **291**→**292**→**293**→**294**. This could result in dropping in stability of the products and lead to decomposition under the reaction conditions. A number of other cyclic and open-chained functionalized amides, such as the compounds **295**–**296**, could not be synthesized as well. Most likely, only compounds with a Lewis basicity that lie within a certain range can be alkynylated with the dibenzothiophenium reagents. This is in line with HSAB-concept and the reported results on the reactivity of amides with the hypervalent iodine equivalent TIPX-EBX.[105] As well, the *tert*-amine **298** was not obtained due to the expected low stability of the product.

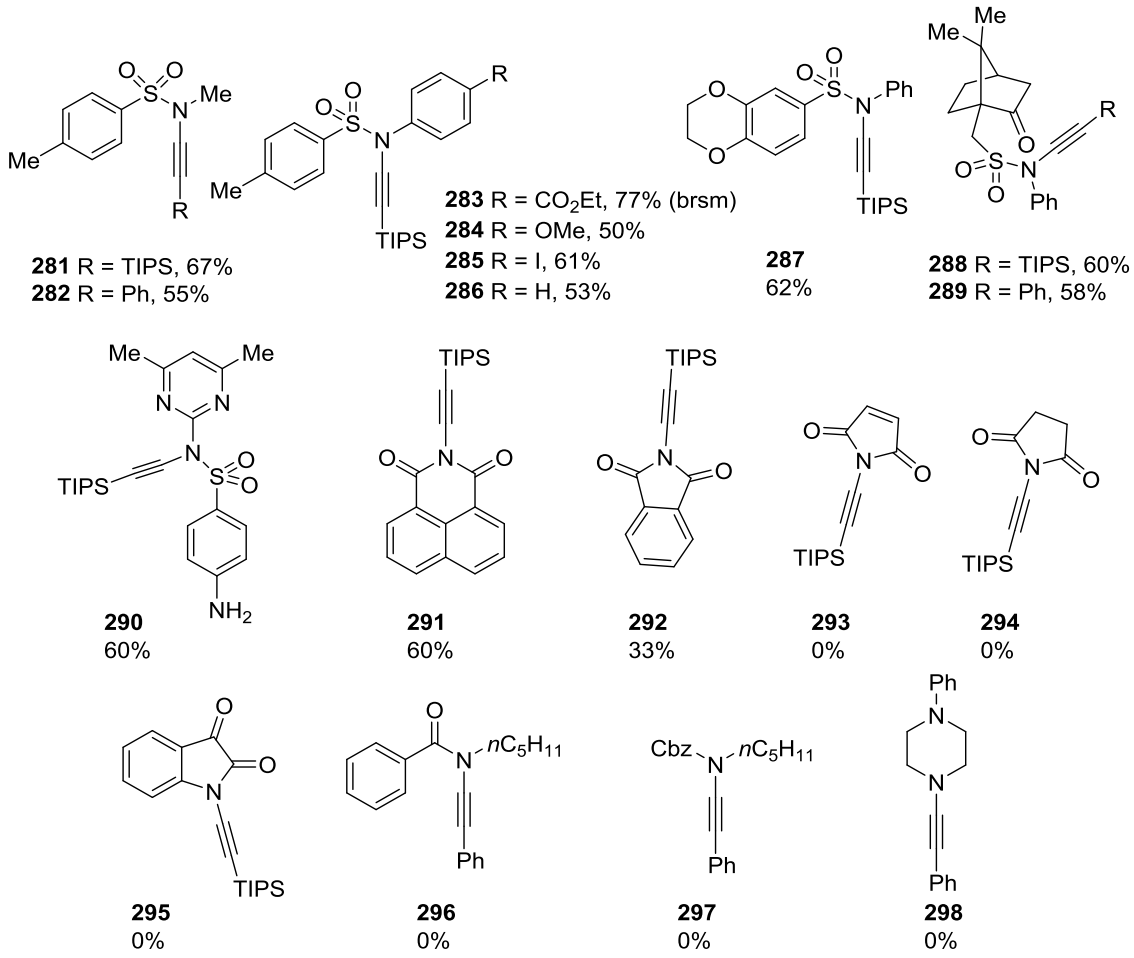


Figure 30 Reaction scope of the alkyne transfer reaction with different nitrogen-based nucleophiles.

In contrast to amines, alcoholates did not react with these reagents **238** in the desired manner. Neither benzylic (**299** and **300)** nor phenolic ethers **301** and **302** could be synthesized with the newly developed transfer reagents (Figure 31). Presumably, salts **238** only react properly with soft nucleophiles, while alcoholates can act on the reagent in an undesirable position, forming unstable products.

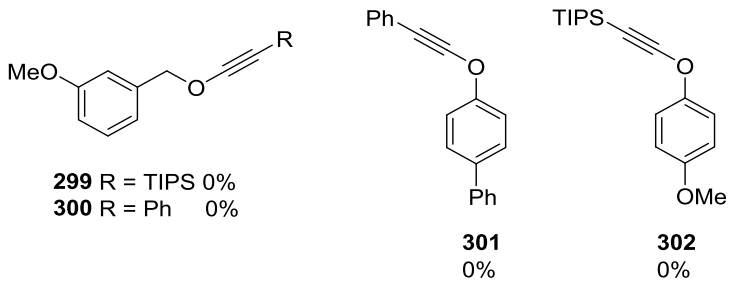


Figure 31 Attempted alkynylation of different alcoholates with reagents **238**.

The posphonium salt **303** was synthesized by the direct ethynylation of triphenylphosphine with the reagent **238f** in a yield of 88% without additional base (Figure 32). Also the diyne **304** could be obtained from the reaction of the salt **238f** with 1-ethynyl-4-methoxybenzene after deprotonation with and *n*BuLi in a yield of 19%. In contrast, the reaction of the enol ether **306** and the Grignard reagent **308** with reagents **238f** or **238a**, respectively, did not afford the desired product **305** and **307**, respectively. The alkynylated indole derivatives **309** and **310** and the dimethoxybezene derivative **311** were not accessed under base-free conditions as well, even in microwave-assisted reactions. Furthermore, in the attempted alkynylations with the salt **238a**, the products **312** and **314** could not be obtained from enamine **313** or from Grignard reagent **315**, respectively. As indicated above, only specific nucleophiles appeared to be functionalized with the elaborated system.

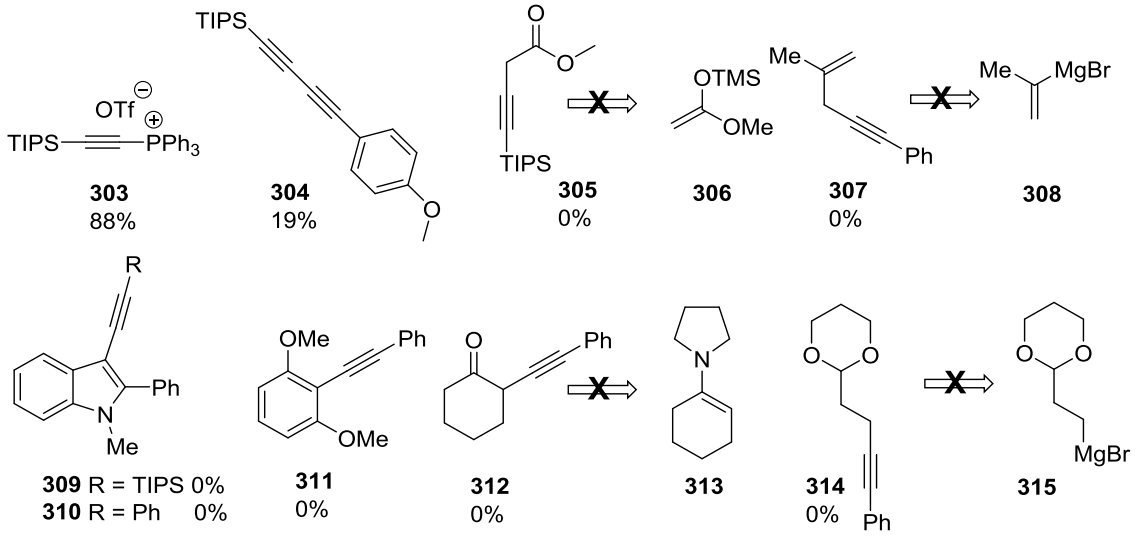


Figure 32 Reaction scope of the transfer reaction with selected various nucleophiles.

To verify structural identity of the selected representative products, their single crystals suitable for X-ray diffraction were grown by slow evaporation of a saturated solution in DCM or hexane. The results of X-ray crystal structure analysis are presented in Figure 33.

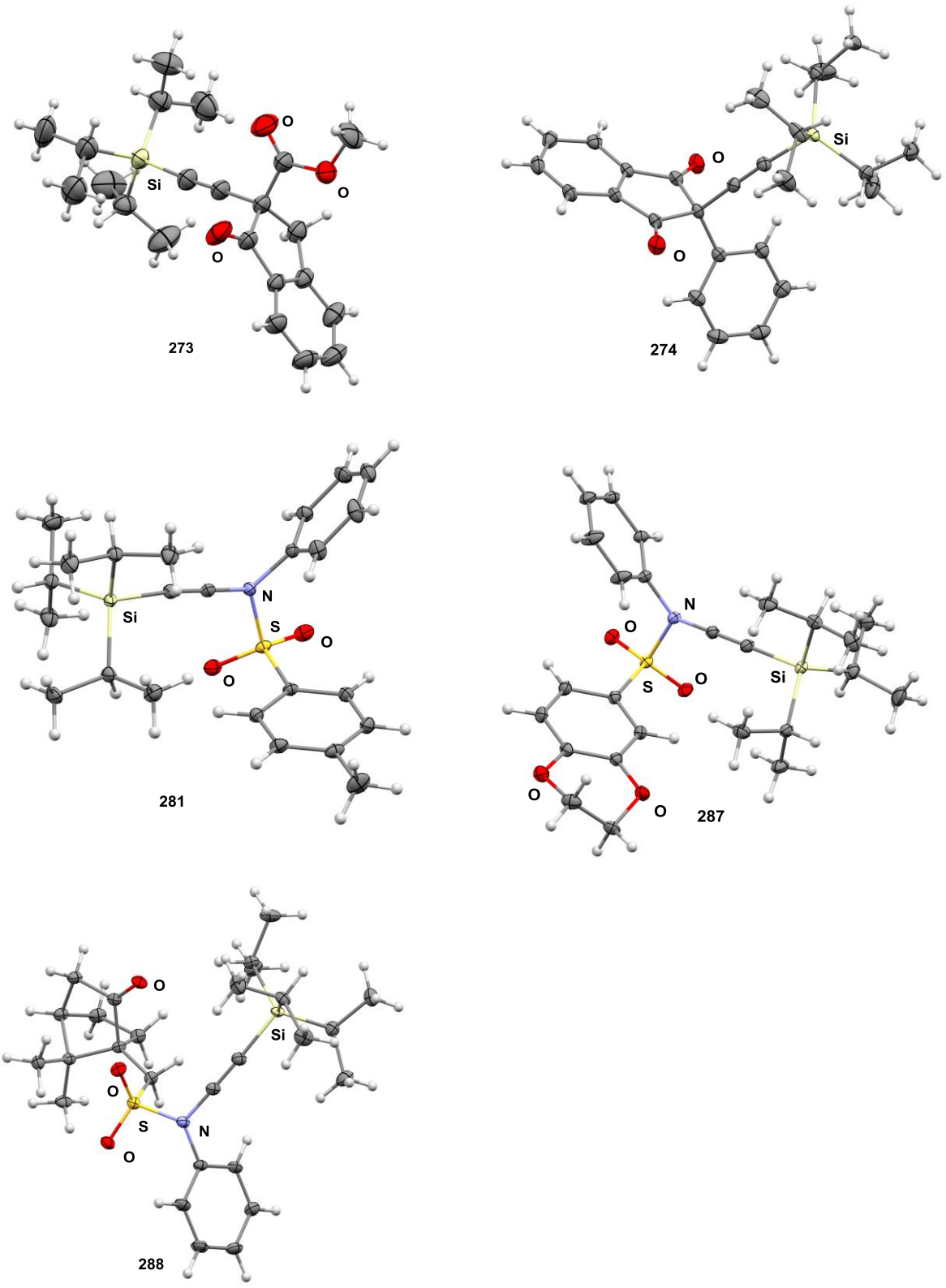
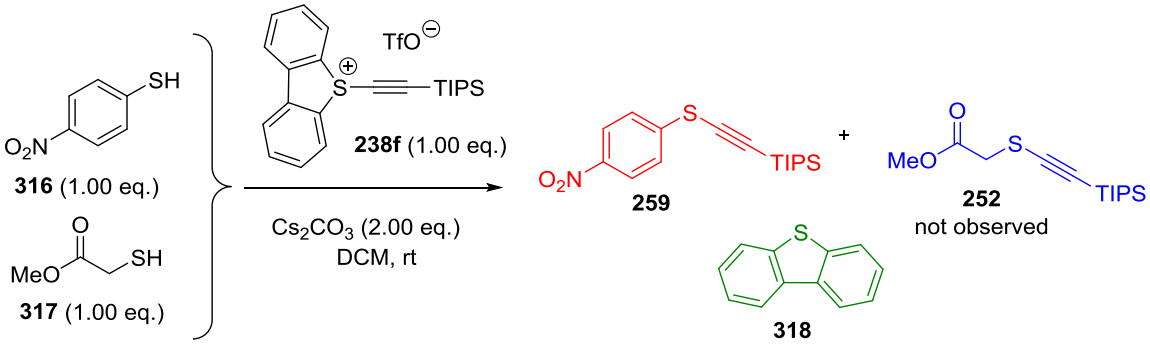


Figure 33 Molecular structure of the alkynylated compounds **273** (top left), **274** (top right), **281** (middle left), **287** (middle right) and **288** (bottom). Thermal ellipsoids at 50% probability.

3.3.5 Comparison of the new reagents with TIPS-EBX

It is known that hypervalent iodine compounds can undergo a strong exothermic decomposition; some of them even show explosive nature.[130] Hence, estimation of decomposition energy of the compound **238a** and **238f** by differential scanning calorimetry (DSC) was performed to compare with the values for corresponding hypervalent iodine reagents. With 449 $J \cdot g^{-1}$, the decomposition energy of the phenyl reagent was around 100 $J \cdot g^{-1}$ lower than that of Ph-EBX **152c**. Moreover, the decomposition of dibenzothiophenium salts **238** appeared to be a non-explosive slow process. [131]

Furthermore, competition experiments with NMR monitoring were performed applying equimolar mixtures of aromatic thiol **316** and the aliphatic thiol **317** with either the reagent **238f** or the commercially available TIPX-EBX **152d**. When the reagent **238f** was used under basic conditions, the thioether **259** was formed selectively (Scheme 51 and Figure 34).



Scheme 51 Competition reaction of a 1:1 mixture of the thiol **316** and **317** with the dibenzothiophenium salt **238f**.

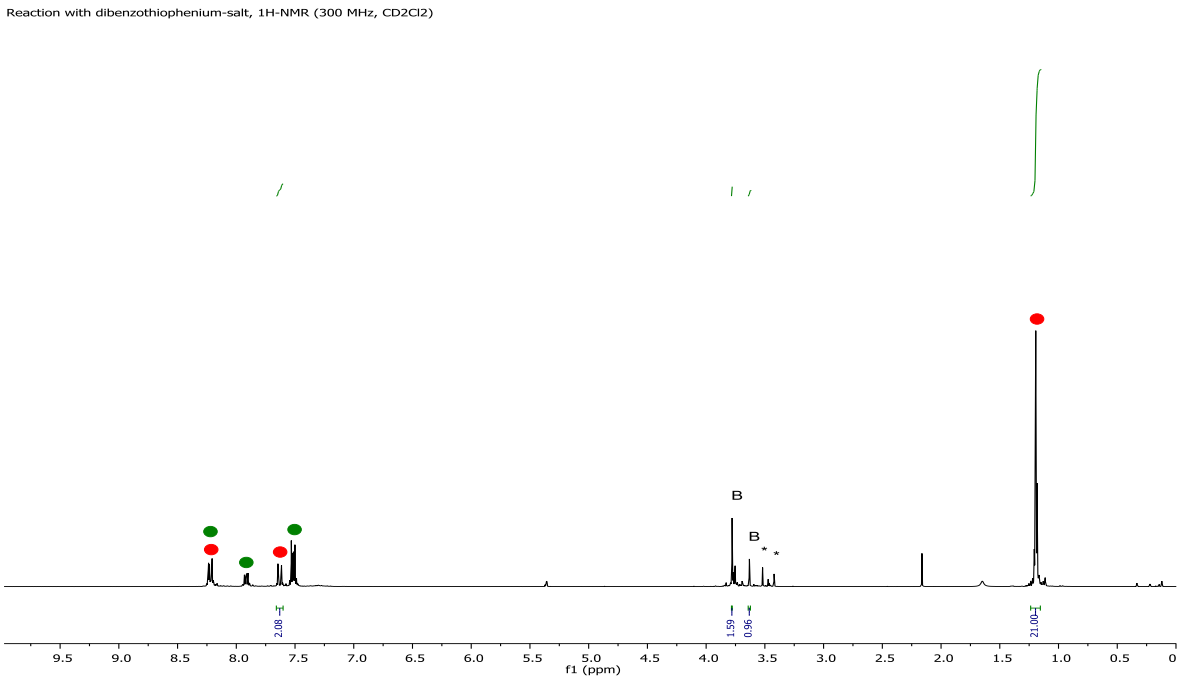
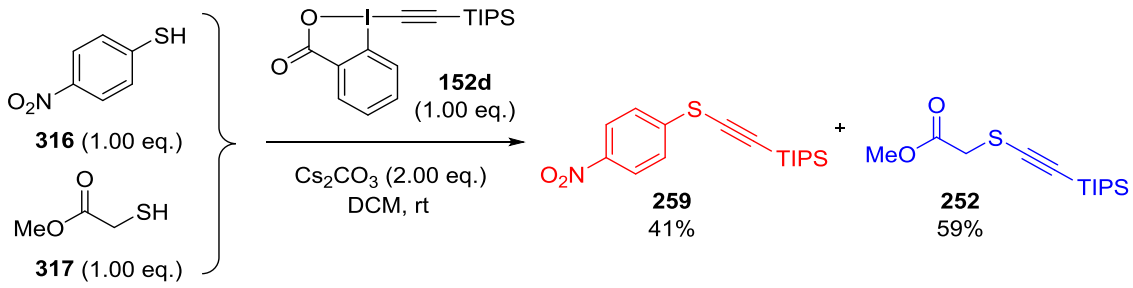


Figure 34 ^{1}H NMR spectrum of the reaction mixture obtained from dibenzothiophenium salt **238f** and equimolar mixture of thiols **316** and **317**.

Under the same conditions, a 40:60 mixture of both products was obtained with the commercially available TIPS-EBX **152d** instead, favoring the formation of the thioether **252** (Scheme 52 and Figure 35). This result could be explained by the enhanced reactivity of the iodine reagent **152d** in comparison to **238f** and, as result, unselectively in the alkynylation. Therefore, this proves that the new dibenzothiophenium reagents can be a valuable alternative to iodine-based reagents, especially in research fields were high selectivity is required, i.e. the late stage functionalization of challenging and complex substrates. Besides, the products can easy be purified due to the stability of the formed byproduct dibenzothiophene **318** and its high solubility in most organic solvents.



Scheme 52 Competition reaction of a 1:1 mixture of the thiol **316** and **317** with TIPX-EBX **152d**.

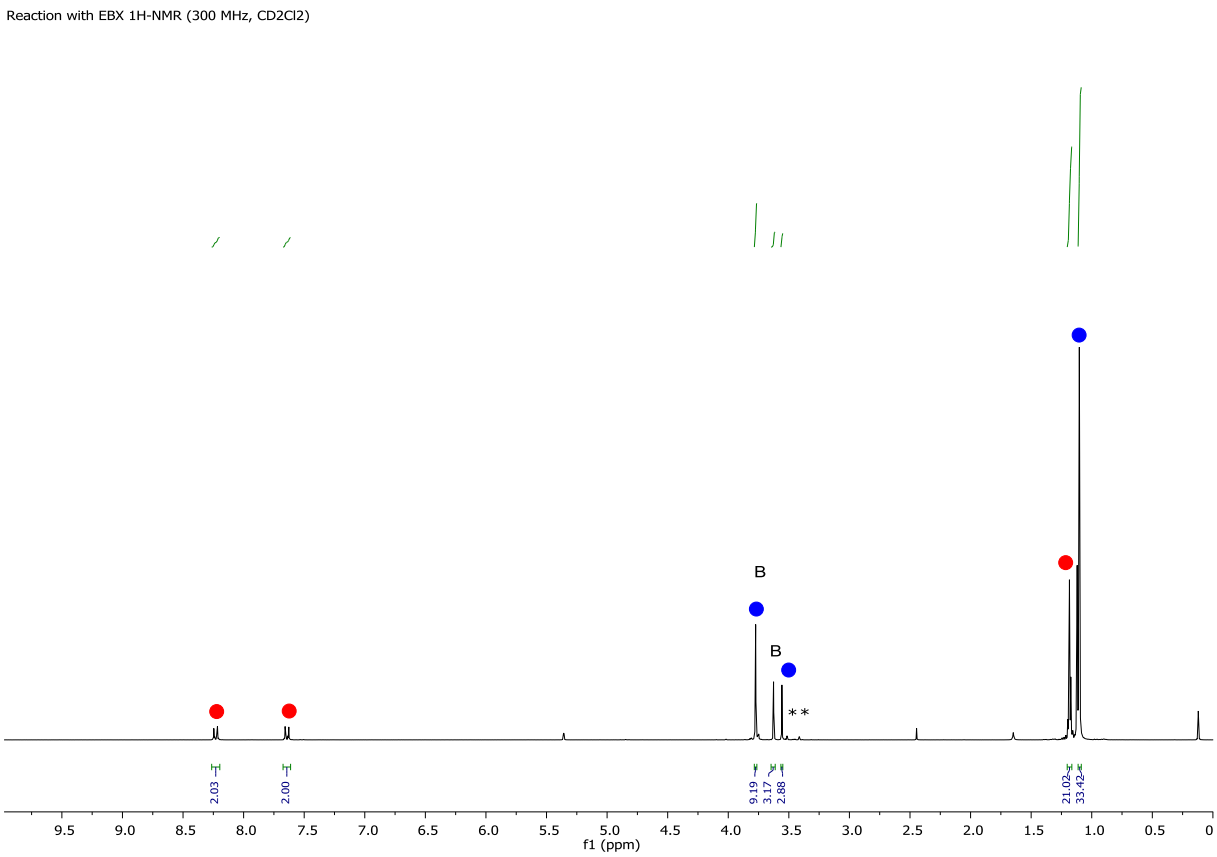
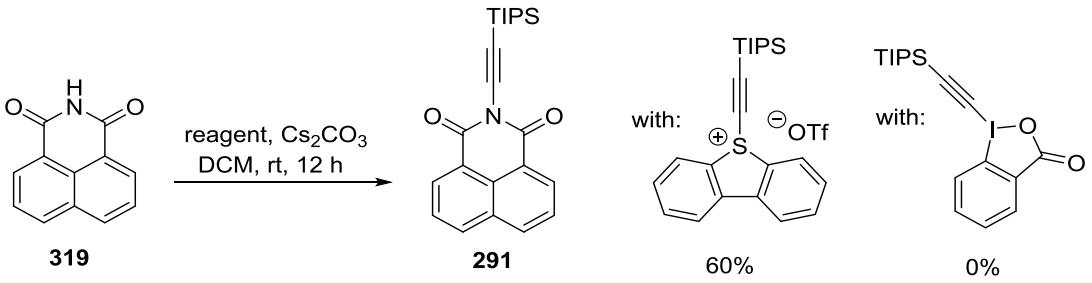


Figure 35 ^{1}H NMR spectrum of the reaction mixture obtained from dibenzothiophenium-salt **152d** and equimolar mixture of thiols **316** and **317**.

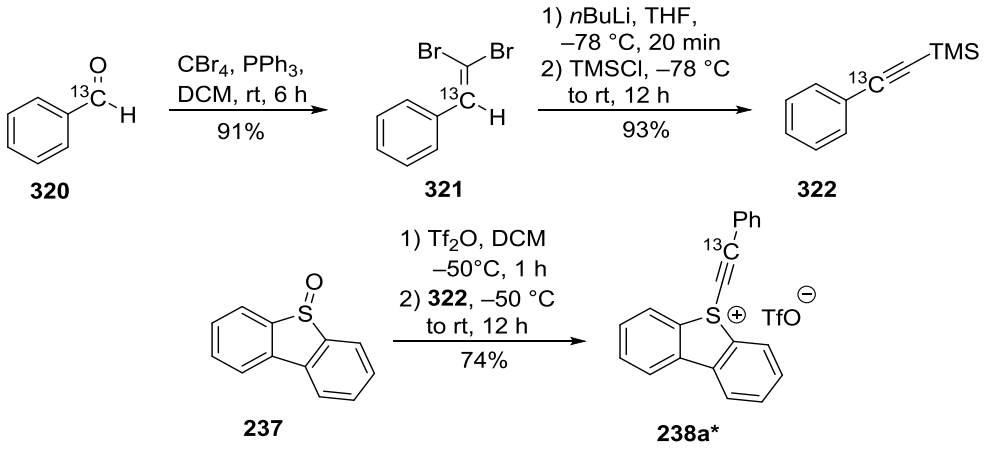
In several cases, the new reagents **238** demonstrate a reactivity which differs from those of the hypervalent iodine compounds. For example, the reagent **238f** allows functionalization of naphthalimide **319**, which, to the best of our knowledge, was not achieved applying the commercially available TIPS-EBX **152d**. In our hands, when the reaction of reagent **152d** with the naphthalimide **319** was performed under the developed reaction conditions, only the unreacted naphthalimide **319** was re-isolated from the reaction mixture, whereas 60% of the desired product **291** was isolated upon employment of the reagent **238f** (Scheme 53).



Scheme 53 Reaction of naphthalimide **319** with the newly developed dibenzothiophene reagent **238f**, as compared to the commercially available TIPS-EBX reagent **152d**.

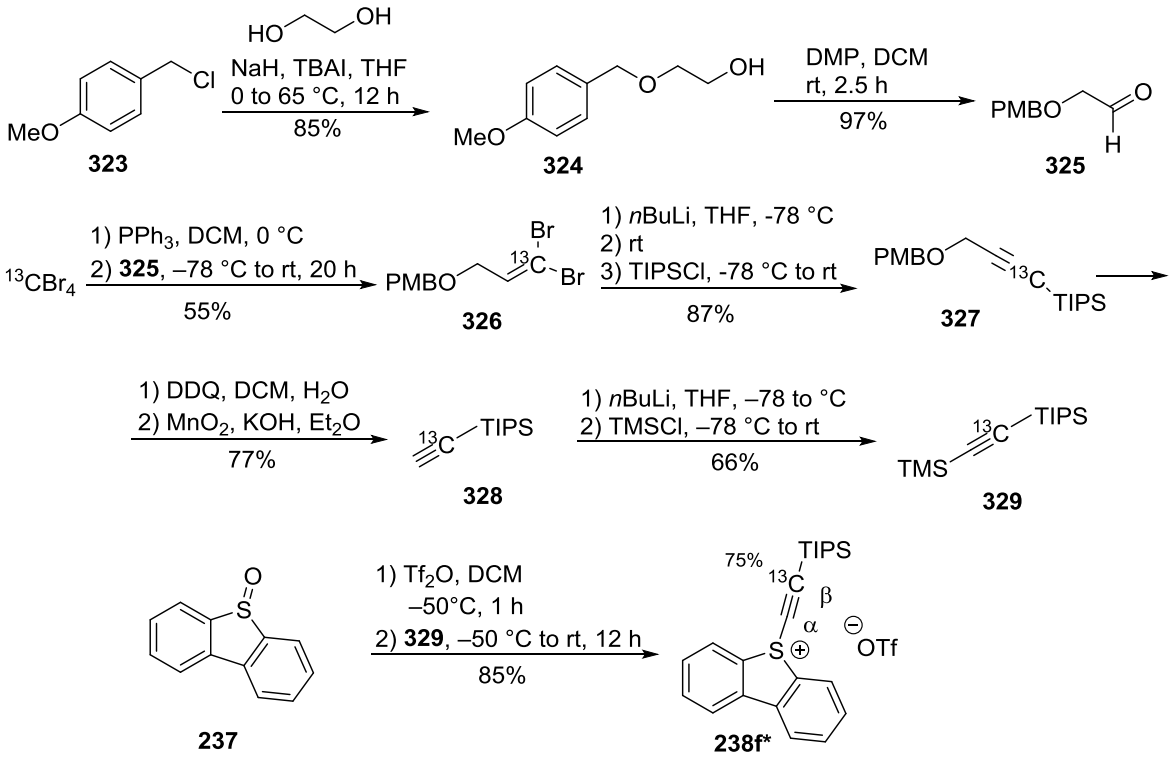
3.3.6 Investigations towards mechanistic rationalization of the transfer reaction

Experiments with ^{13}C-labeled substrates were performed addressing further investigations on the mechanism of the transfer reaction. Basing on the results of former investigations by Waser *et al*,.[104] we suggest that the reagent **238a** and **238f** could react in different ways, as compared to the corresponding hypervalent iodine reagents. Therefore, labeled equivalents of reagent **238a** (Scheme 54) and reagent **238f** were synthesized. Initially, the ^{13}C-labeled alkyne **322** was prepared over two steps using a *Corey-Fuchs* reaction according to a protocol by Yoshikai *et al*..[132] In the first step, ^{13}C-labeled benzaldehyde **320** was treated with tetrabromomethane and triphenylphosphine to synthesize the dibromide **321** in a yield of 91%. Subsequently, the alkyne **322** was obtained by treatment of the dibromide **321** with *n*BuLi followed by the addition of trimethylsilyl chloride in 93% yield. Finally, the desired labeled compound **238a*** was received by the activation of the sulfoxide **237** with triflic anhydride and subsequent nucleophilic substitution with the alkyne **322** (63% overall yield).



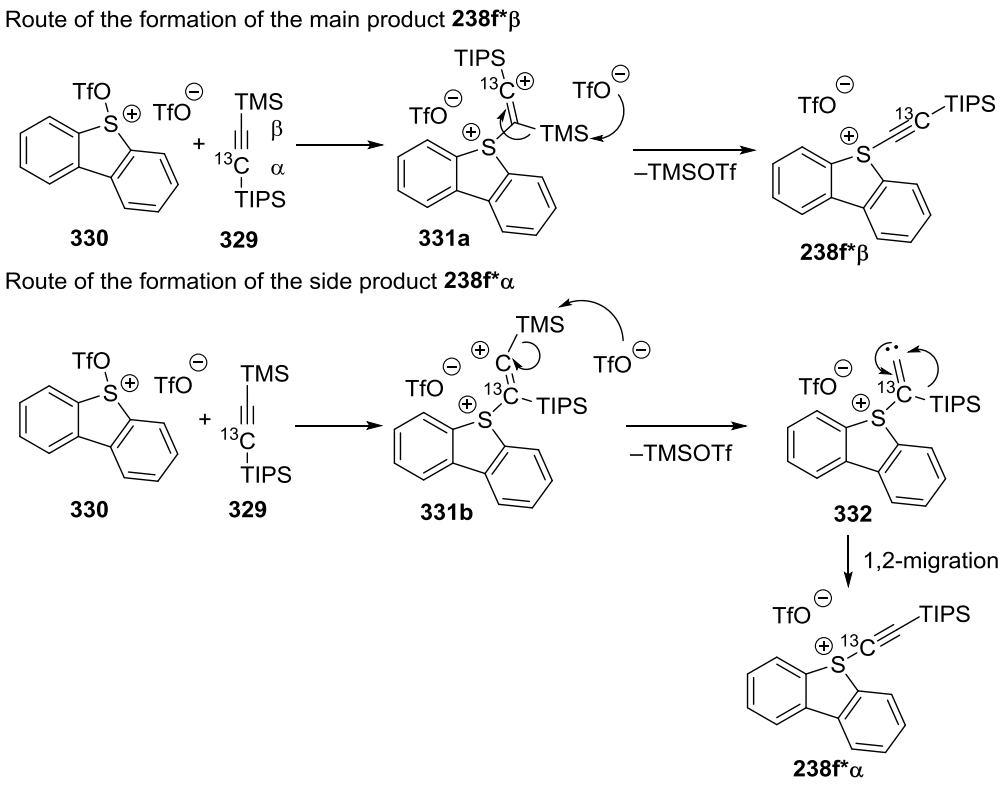
Scheme 54 Synthesis of the labeled reagent **238a***.

In addition, the labeled reagent **238f*** was synthesized according to a protocol by Waser *et al.* (Scheme 55).[160] First, ethylene glycol was protected with a *p*-methoxybenzyl group in a yield of 85%. The resulting alcohol **324** was oxidized by *Dess-Martin* periodinane to the corresponding aldehyde **325** in 97% yield. The latter was converted to the alkyne **327** by a *Corey-Fuchs* reaction: the dibromide **326** was synthesized in a yield of 55% with labeled tetrabromomethane and triphenylphosphine. Afterwards, alkyne **327** was obtained in a yield of 87% by treatment of **326** with *n*BuLi and subsequent quenching the reaction with TIPS chloride. The *p*-methoxybenzyl group in **327** was first oxidatively deprotected with DDQ, and the resulting propagylic alcohol was cleaved using manganese dioxide to obtain the unprotected alkyne **328** in a total yield of 77% over two steps. The terminal alkyne **328** was protected with TMS chloride (66% yield). Finally, the sulfoxide **237** was activated by triflic anhydride, and the desired labeled transfer reagent **238f*** was synthesized in the reaction with the labeled alkyne **329** in a yield of 85%.



Scheme 55 Synthesis of the labeled TIPS-substituted dibenzothiophenium reagent **238f***.

Unexpectedly, an isotopic scrambling was observed in the final step of the synthesis of the reagent **238f***. An enrichment of 75% was obtained for the desired position instead of the expected ratio of 20:1. To our delight, after completion of the reaction, the isotopic ratio did not changed anymore, as was proven in NMR experiments over 3 days (Experimental part 5.7). Furthermore, the consistency of this result was proven by a second synthesis attempt. Consequently, this observation must have a mechanistic reason. Our suggestion is that it could be a direct result of the direction in which the alkyne attacks the reactive intermediate **330** (Scheme 56).Accordingly to this, both **α** and **β** carbon atoms of the alkyne **329** (in respect to the TIPS moiety) possess similar reactivity and can attack the sulfonium salt **330**. After initial attack with the carbon atom in **β**-position, the carbenium ion **331a** would be formed, which would undergo an elimination to form the product **238f*β**. Alternatively, if sulfonium intermediate is attacked by the carbon atom in **α**-position, the resulting carbenium ion **331b** would undergo an elimination to form the terminal carbene **332**. Afterwards, the isomer **238f*α** would be obtained by a 1,2-migration. However, an attack of **α** carbon atom should be less favored because of the bigger steric bulk of the TIPS group, what explains the observed isotopic distribution.



Scheme 56 Proposed mechanism of the formation of unexpected label distribution in TIPS-substituted dibenzothiophenium reagent **238f***.

Reactions of the labeled reagents **238a*** and **238f*** with different nucleophiles were performed (Figure 36 and Scheme 57). The product **256*** was obtained from the reaction of (4-methoxyphenyl)methanethiol with **238a***. This could be a result of a direct attack of the alkyne to the **α**-position of the reagent, followed by an elimination of dibenzothiophene moiety (pathway **A**). Another possibility would be a **β**-attack of the thiol with a subsequent 1,2-migration of the thiogroup (*cf.* Scheme 57, pathway **B**). The compound **286*** with alternative label distribution was exclusively obtained for the reaction with *N*-tosylanilide and reagent **238a*.** A plausible explanation would be a **β**-attack of the amide to the transfer reagent and concomitant 1,2-migration of a phenyl group. In case of the product **232***, the **α**- and **β**-position in the corresponding product were equally labeled. An explanation could be a **β**-attack on the transfer-reagent with subsequent 1,2-migration. Both substituents should be able to undergo the following 1,2-migration with a similar probability because of the very similar migratory aptitudes for *tert*-butyl and phenyl groups. Nevertheless, the possibility of an **α**-attack of the nucleophile towards the reagent cannot be completely excluded.

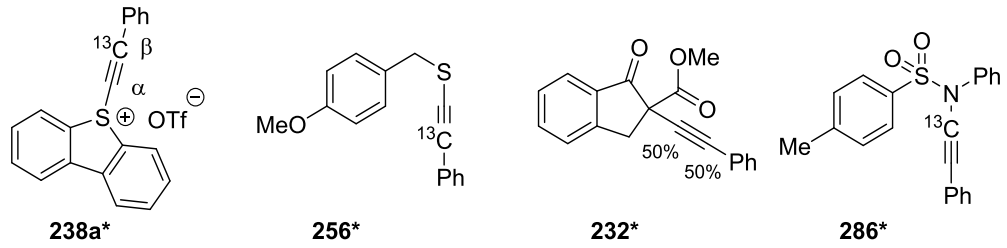
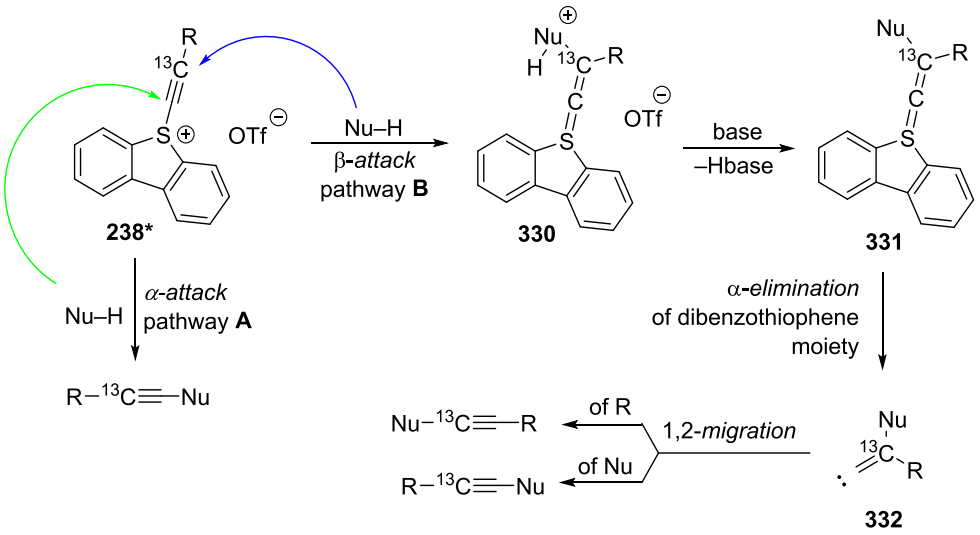


Figure 36 Results of the alkynylations experiments with labeled compound **238a***.



Scheme 57 Proposed mechanism for the transfer reaction.

However, no ^{13}C scrambling was observed for the reactions with the reagent **238f***: solely the compounds **255***, **273*** and **281*** were selectively obtained (Figure 37). Most likely, the steric bulk of the TIPS group favors a direct **α**-attack of the nucleophiles, thus resulting in the formation of the observed products.

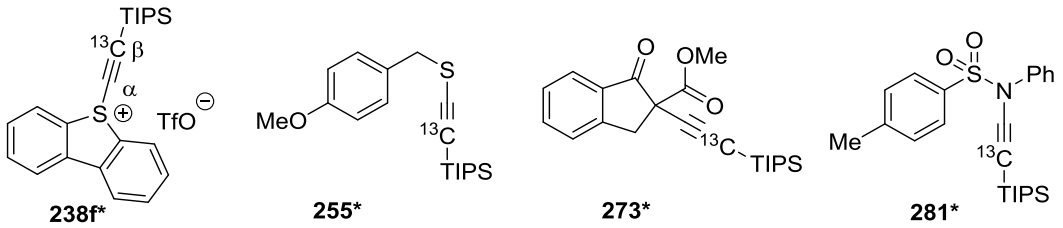


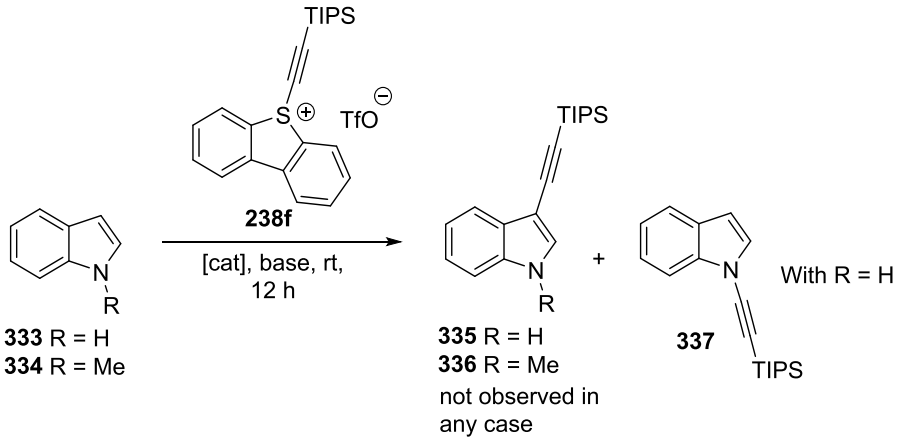
Figure 37 Results of the experiments with labeled compound **238f***.

Calculations regarding the mechanism are conducted in collaboration with Dr. R. Mata, which are currently ongoing. These will give a better understanding and a deeper insight towards the mechanism of the transfer reaction.

3.3.7 Investigation towards metal-catalyzed reactions

3.3.7.1 Investigations towards reactions with metal-based Lewis acids

As reported by Waser et al.,[133] indoles can be functionalized with alkynes applying gold- and silver-based metal catalysts. Normally, these catalysts enhance the reactivity of the alkyne reagent towards the attack of nucleophiles by coordination of the reagents as Lewis acids. Hence, newly prepared transfer reagents **238** were tested in the alkynylation of indoles in the presence of metal-based Lewis acids. Unexpectedly, no reactivity was observed for the functionalization of the 3-position in indoles. Instead, the indole **337** was selectively obtained (Scheme 58).



Scheme 58 Attempted metal-catalyzed functionalization of indoles with the salt **238f**.

First, chloro(triphenylphosphine)gold(I) and silver hexafluoroantimonate(V) were tested as catalysts in presence of different bases. *N*-Functionalized indole **337** was obtained from indole (**333**) in 38% yield with cesium carbonate as base and DCM as solvent (Table 5, entry 1). On the contrary, only the unreacted indole **333** was obtained using stronger bases such as potassium phosphate, tetrabutylammonium acetate or potassium acetate (entries 2–4). This result could originate from the fast decomposition of the reagent in the presence of these bases. The yield of product **337** decreased to 23% at an elevated temperature of 60 °C (entry 5), probably because of limited thermal stability of the reagent. Furthermore, only the unreacted starting material was re-isolated, if *N*-methylindole **334** was used instead of indole (**333**) (entry 6). A slightly reduced yield (23–25%) of the *N*-alkynylated product **337** was observed *via* the addition of silver chloride (entries 7–9), whereas varying of the solvent had no significant influence on the isolated yield, unlike the absence of a base (entry 10). If platinum(II) chloride was used as a catalyst, neither utilizing bases like *N*,*N*-diisopropylethylamine or cesium carbonate (entries 11 and 12), nor running the reaction at higher temperatures without addition of base (entry 13) led to any product formation. No product formation was observed with gold(III) chloride as well (entry 14). A final control experiment showed that the reaction proceeds even without additional Lewis acid in a yield of 30% (entry 16). The low yields of indole **333** can be attributed to its reduced stability as well as partial decomposition during the purification process.

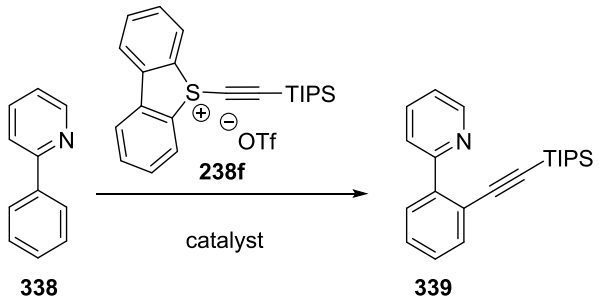
Table 5 Screening of conditions for the alkynylation of indoles **333**, **334** with the dibenzothiophenium salt **238f**.

Entry	Catalyst	Additive	Base	Solvent	Yield (%)	Comments
1	$AuClPPh_3$	$AgSbF_6$	Cs_2CO_3	DCM	**38**	*N*-alkynylated product **337**
2	$AuClPPh_3$	$AgSbF_6$	K_3PO_4	DCM	0	Isolated starting material **333**
3	$AuClPPh_3$	$AgSbF_6$	TBAOAC	DCM	0	Isolated starting material **333**
4	$AuClPPh_3$	$AgSbF_6$	KOAC	DCM	0	Isolated starting material **333**
5	$AuClPPh_3$	$AgSbF_6$	Cs_2CO_3	DCE	23	Reaction at 60 °C
6	$AuClPPh_3$	$AgSbF_6$	Cs_2CO_3	DCM	0	*N*-Methylindole **334** as a substrate; re-isolated
7	AgCl	–	Cs_2CO_3	DCM	23	*N*-alkynylated product **337**
8	AgCl	–	Cs_2CO_3	Et_2O	25	*N*-alkynylated product **337**
9	AgCl	–	K_2CO_3	THF	23	*N*-alkynylated product **337**
10	AgCl	–	–	DCM	0	Isolated starting material **333**
11	$PtCl_2$	–	Cs_2CO_3	DCM	0	No reaction
12	$PtCl_2$	–	DIPEA	DCM	0	Reaction at 60°C, Isolated starting material **333**
13	$PtCl_2$	–	–	DCE	0	Reaction at 80 °C, Isolated starting material **333**
14	$AuCl_3$	–	Cs_2CO_3	DCM	0	No reaction
15	$AuCl_3$	–	–	DCM	0	*N*-Methylindole as a substrate
16	–	–	Cs_2CO_3	DCM	30	+ Isolated starting material **333**

Summarizing the results discussed above, it can be concluded that the utilization of a Lewis acid only slightly influences the formation of *N*-alkynylated product **337** in this reaction, whereas the C–H bond alkynylation of indoles with the reagent **238f** was not detected.

3.3.7.2 Investigations towards directing group based C–H-alkynylation with metal catalysts

The TIPS-EBX reagent **152d** is reported to be applied in rhodium- or iridium-catalyzed C–H-alkynylation of 2-phenylpyridine (**338**).[134] In this regard, commercially available catalysts and additives were examined in the reaction with the reagent **238f** (Scheme 59).



Scheme 59 Attempted metal-catalyzed C–H alkynylations of 2-phenylpyridine (**338**).

Only traces of the desired product **339** were detected in alkynylations utilizing $[RhCp^*Cl_2]_2$, silver hexafluoroantimonate(V) or zinc triflate as a catalyst (Table 6, entries 1 and 2). An increase in temperature (entries 3 and 4) to 80 °C resulted in formation of the desired product in up to 34% yield. No formation of the product was observed with $[IrCp^*Cl_2]_2$ and silver hexafluoroantimonate(V) (entry 5). With acetonitrile as a solvent (entry 6), 4% of the product was isolated. Traces of the product were obtained when $MnBr(CO)_5$ and dicyclohexylamine (entry 7) were used as a catalytic system.[135] Variation of the dilution or equivalents of the catalyst components (entries 8–12) did not lead to an increase of the product yield. From the results of the mass spectrometric analysis it can be concluded that a large amount of the starting material **338** in the reaction under investigation was acting as a base. Therefore, an external base would be necessary to achieve complete conversion.

Table 6 Screening of the conditions for C–H alkynylation of 2-phenylpyridine (**338**) with the reagent **238f**.

Entry	Catalyst	Additive	Solvent	T (°C)	Yield (%)
1	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DCM	rt	Traces of the product **339**
2	$[RhCp^*Cl_2]_2$ (2%)	$Zn(OTf)_2$ (10%)	DCE	rt	SM* + traces of the product **339**
3	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DCE	80	34
4	$[RhCp^*Cl_2]_2$ (2%)	$Zn(OTf)_2$ (10%)	DCE	80	32
5	$[IrCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (10%)	DCM	rt	0 (SM)
6	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	MeCN	80	4
7	$MnBr(CO)_5$	$HNCy_2$ (20%)	DCE	80	Traces of the product **339**
8	$[RhCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (10%)	DCE	80	Mixture of SM and product
9	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DCE (twice diluted)	80	24
10	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (20%)	DCE	80	Mixture of SM and product
11	$[RhCp^*Cl_2]_2$ (8%)	$AgSbF_6$ (10%)	DCE	80	Mixture of SM and product
12	$[RhCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (5%)	DCE	80	Mixture of SM and product

*SM = Starting material **338**.

Consequently, the effect of different bases on the reaction was investigated (Table 7). The reaction was performed in DCM at ambient temperature or in DCE at 80 °C. By using rhodium and iridium catalysts in combination with cesium carbonate, only starting material **338** or traces of the product **339** were observed (entries 1–3). The same result was obtained when tetrabutylammonium acetate was used (entry 4). Furthermore, a complete decomposition of the starting material was observed with cesium pivalate as a base (entry 5). Similarly, only starting material **338** was isolated when potassium phosphate or water were used (entries 6 and 7). No conversion was observed by utilizing potassium pyrophosphate (entry 8). The same result was obtained from the reaction with pyridine or 2,6-lutidine (entries 9 and 10), whereas employment of 2,6-di-*tert*-butylpyridine led to formation of the desired product in 4% yield (entry 11). Variation of the temperature or the equivalents of the base resulted in solely traces of product (entries 12 and 13). The same holds true for the reaction catalyzed by bromopentacarbonylmanganese(I) in the presence of stoichiometric quantity of dicyclohexylamine (entry 14). Strong bases like DMAP or DIPEA (entries 15 and 16) led to traces of the desired product **339** as well. Starting material was re-isolated for the utilization of 1,8-bis(*N*,*N*-dimethylamino)naphthaline (proton sponge, entry 17). At last, DBU (entry 18) completely decomposed the alkynylating agent **238f.**

Table 7 Screening of conditions for the C–H alkynylation of 2-phenylpyridine (**338**) with the reagent **238f** in the presence of an additional base.

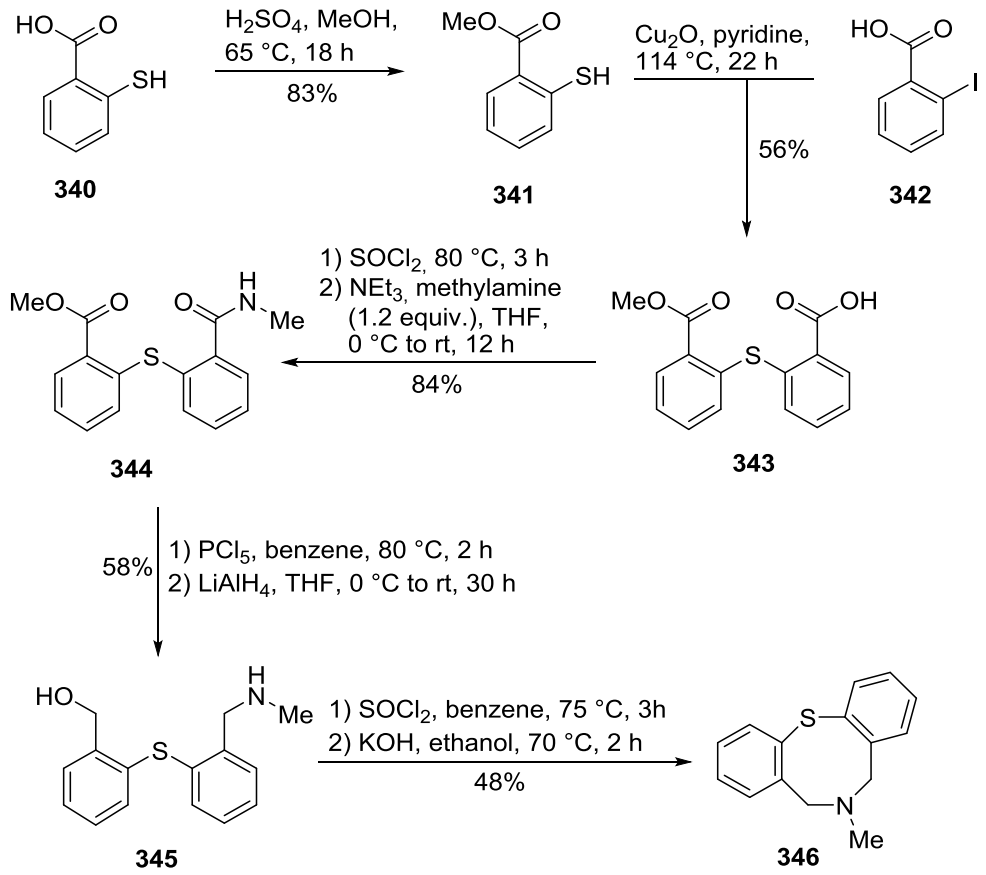
Entry	Catalyst	Additive	Base	Solvent	T (°C)	Yield(%)/ Comment
1	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Cs_2CO_3	DCM	rt	0 (SM*)
2	$[IrCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (10%)	Cs_2CO_3	DCM	rt	0 (SM)
3	$[RhCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (5%)	Cs_2CO_3 (2.00 equiv.)	DCE	80	Traces of the product **339**
4	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	TBAOAc	DCM	rt	0 (SM)
5	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Cesium pivalate	DCE	80	Decomposition of **238f**
6	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	K_3PO_4	DCE	rt	Traces of the product **339**
7	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	H_2O	DCE	80	Traces of the product **339**
8	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	$K_4P_2O_7$	DCE	rt	SM
9	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Pyridine	DCE	80	SM
10	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Lutidine	DCE	80	SM
11	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	2,6-Di-*tert*-butylpyridine	DCE	80	Product **339** (4%)
12	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	2,6-Di-*tert*-butylpyridine	DCE	rt	Traces of the product **339**
13	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	2,6-Di-*tert*-butylpyridine (0.50 eq)	DCE	rt	Traces of the product **339**
14	$MnBr(CO)_5$		$HNCy_2$	DCE	80	Traces of the product **339**
15	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DMAP	DCE	80	Traces of the product **339**
16	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DIPEA	DCE	80	Traces of the product **339**
17	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Proton sponge	DCE	rt	0 (SM)
18	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DBU	DCE	80	Decomposition of **238f**

*SM = Starting material **338**.

In summary, the application of an additionally base did not improve the product yield. The problem seems to be the low stability of the reagent **238f** in the presence of different bases. Correspondingly, the decomposition caused by a base is faster than the desired transfer towards the phenylpyridine (**338**). Presumably, an internal base such as in EBX-systems might help to improve the efficiency.

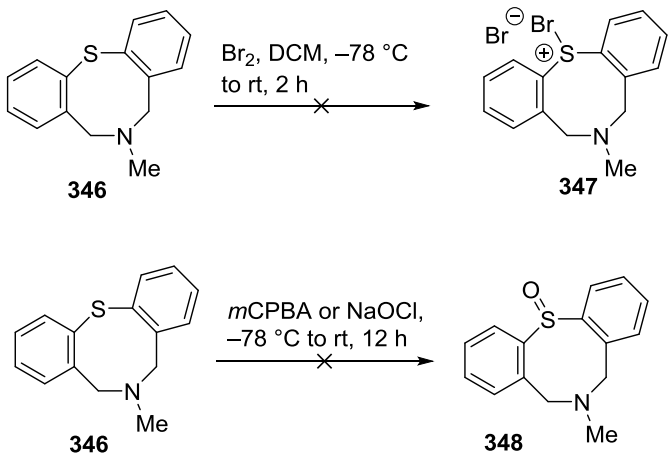
3.3.8 Synthesis attempts towards a system with internal base

In analogy to EBX-reagents **152**, a synthesis of a compound with an internal basic amine moiety was attempted in order to increase the stability of the reagents **238** by a chelating effect. Also it is possible that this amine acts as base in transfer reactions. An additional advantage of such a reagent would be a reduction of waste by avoiding any external base, if the compound is reusable like the dibenzothiophene system. Thus, an equivalent of the diphenylsulfide with a coordinating group in the backbone was synthesized utilizing a modified literature procedure (Scheme 60).[136] Starting from the acid **340**, esterification with methanol led to the corresponding ester **341** in 83% yield. Subsequently, the ester **341** was transformed into the unsymmetrical diary sulfide **343** by an Ullmann-type reaction with copper(I) oxide as catalyst (56% yield). Then, compound **343** was converted to the corresponding amide **344** in a two-step procedure in a yield of 84%. Afterwards, the amide **344** was activated by phosphorus pentachloride and reduced to the aminoalcohol **345** with lithium aluminum hydride in a yield of 58% over two steps. Finally, compound **345** was chlorinated using thionyl chloride to enable the cyclization towards the cyclic thioether **346**.



Scheme 60 Synthesis of the cyclic aminosulfide **346**.

It is known that oxidation of the thioether **346** with H_2O_2 affords the respective sulfone, whereas reaction with $NaIO_4$ furnishes the corresponding *N*-Oxide.[136] Within our synthetic goal, the bromination of the compound **346** was investigated. Surprisingly, in the attempted reaction with bromine a complete decomposition of the starting material **346** was observed. The same results were obtained upon oxidation of **346** with *m*CPBA or with sodium hypochlorite (Scheme 61).



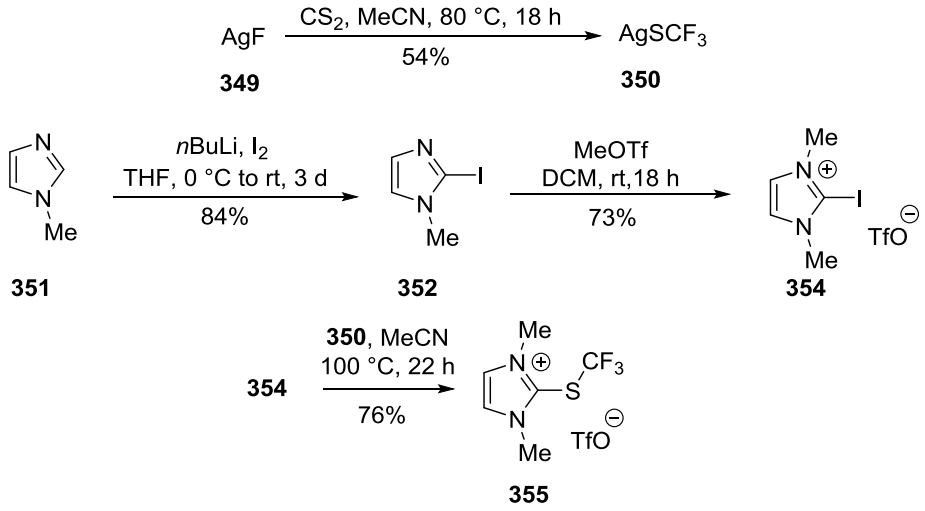
Scheme 61 Investigations towards the activation of the cyclic aminosulfide **346**.

After such a daunting result, no further synthetic investigations were conducted on this potential transfer reagent backbone.

3.4 Investigations towards potential trifluoromethylation reagents based on the thioimidazolium backbone.

3.4.1 Synthesis of the new potentially trifluoromethylating reagent 355

To further expand the observed reactivity of the thioimidazolium based reagents different fluorine bearing compounds were synthesized. A new family of potentially useful trifluoromethylation reagent was synthesized in a straightforward reaction sequence. At first, the silver thiolate **350** was prepared in a good yield of 54% following the published protocol.[137] Then, the iodinated imidazole **352** was obtained in a high yield (84%) by treating methylimidazol **351** with *n*BuLi and subsequent reaction with iodine. Afterwards, compound **352** was methylated to afford the imidazolium salt **354** in a yield of 73%.[138] Finally, nucleophilic substitution in the imidazolium salt **354** via treatment with the silver thiolate **350** in a microwave-assisted reaction offered the desired product **355** in a yield of 76% (Scheme 62).



Scheme 62 Synthesis of a new potential trifluoromethylation reagent **355**.

The structural identity of the compound **355** was confirmed by X-ray crystallography (Figure 38). Single crystals suitable for X-ray diffraction were grown by overlayering a saturated solution of the reagent **355** in MeCN with diethyl ether. As expected, the structure of the compound shows an angular geometry of C–S–CF_3 with an angle of 97.3(9)°. With 2.913(2) Å, the S3–O1 bond is significantly shortened as compared to the corresponding sum of Van-der-Waals radii (3.32 Å[128b]), thus illustrates a strong coordinative bonding between the Lewis-acidic sulfur atom and the oxygen atom of the triflate counterion. Furthermore, with a bond length of 1.747(3) Å the S1-C2 bond shows clearly the characteristics of a single bond.[139]

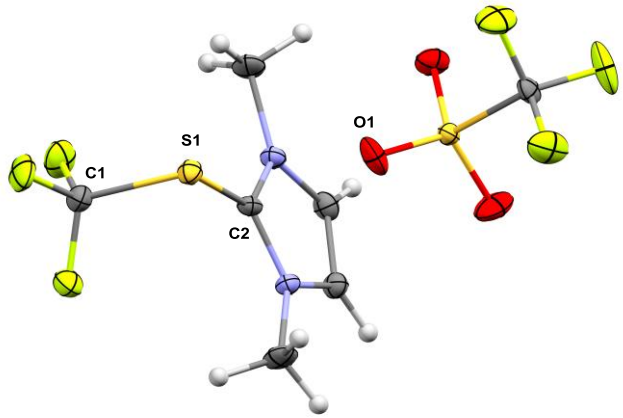
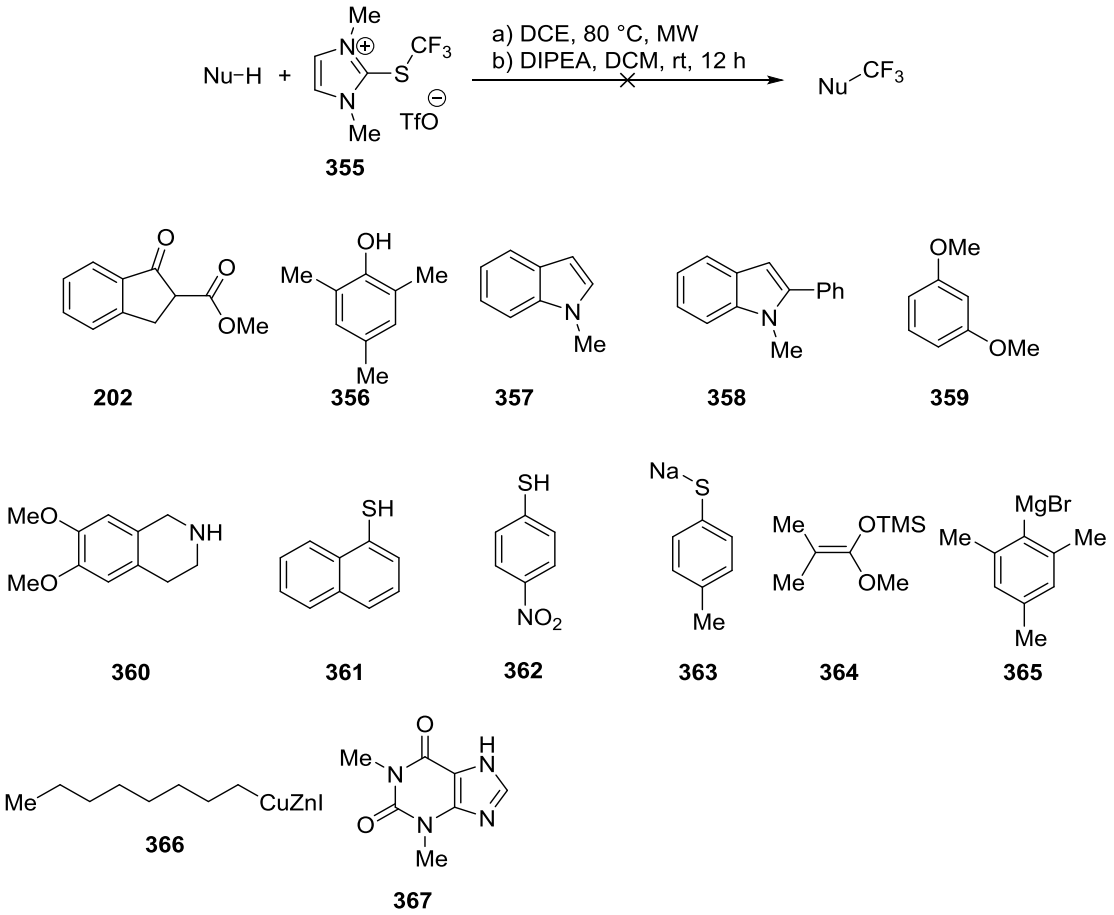


Figure 38 Molecular structure of reagent **355**. Thermal ellipsoids at 50% probability. Selected bond lengths and distances (Å): S1–O1 = 2.913(2), C2–S1 = 1.747(3); angle of the sulfide moiety (°): C1–S1–C2 = 97.29(2).

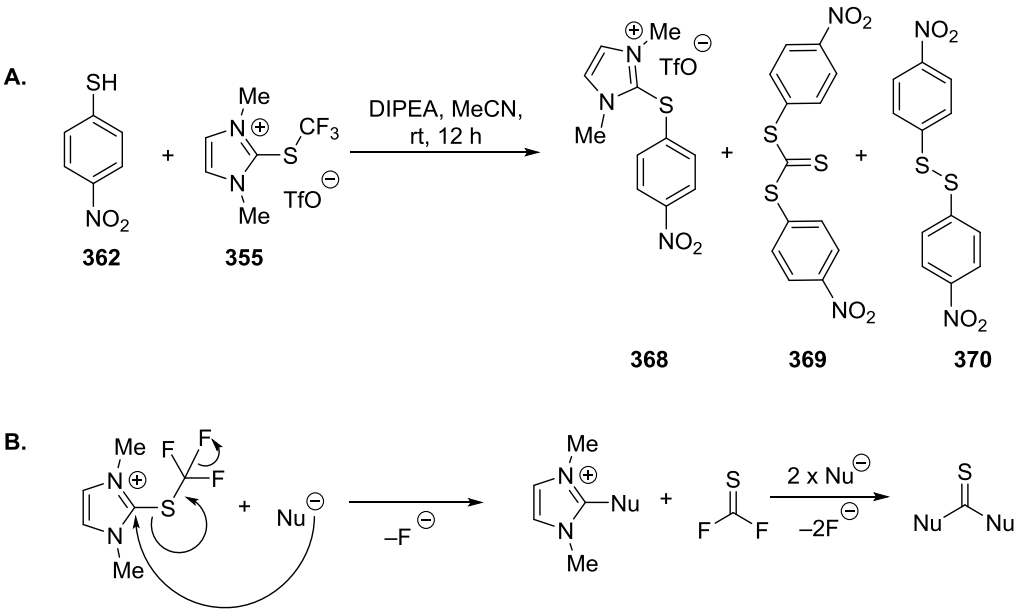
3.4.2 Investigations towards reactions with different nucleophiles

The reactivity of newly prepared compound **355** with respect to various nucleophiles has been investigated to understand its synthetic utility. Unfortunately, in contrast to hypervalent iodine compounds[94] or Umemoto reagent,[119] no nucleophiles were reacting with the salt **355** in the desired way (Scheme 63). Only the starting material could be isolated from the reactions with β-ketoester **202**, 2,4,6-trimethylphenol (**356**), electron-rich aromatics like 1-methylindole (**357**), 1,3-dimethoxybenzene (**359**) or *sec*-amine **360**, all of which were successively cyanated with the previously developed reagent **186** (*cf.* Scheme 36).[124] The modification of the reaction conditions such as temperature, solvent and reaction time did not lead to any observable reactivity as well. When stronger nucleophiles like Grignard reagent **365** or zincate **366** were utilized, a complete decomposition of the salt **355** was observed. The reaction with enol ether **364** also did not lead to the formation of the expected product. Another possibility would be the transfer of a trifluoromethyl radical. But only starting material was obtained employing theophylline **367** as a nucleophile in combination with a radical initiator.[140]



Scheme 63 Investigations towards the reaction of the thioimidazolium-based reagent **355** with different nucleophiles.

Only with thiols **361**, **362** any reactivity was observed. However, instead of the desired product, an inseparable mixture of trithiocarbonates **369** and the corresponding disulfides **370** was obtained (Scheme 64A). An explanation of this undesired reaction pathway could consist in the initial attack of the imidazolium moiety in α-position to the sulfur atom with a sulfur nucleophilic center of thiol **362** (Scheme 64B). The released carbonothioic difluoride could undergo a subsequent attack of additional thiols to form the observed product. The side product of this reaction, the thioimidazolium salt **368**, was crystallized, and the structural identity was confirmed by X-ray crystallography (Figure 39).



Scheme 64 (**A**) Reaction of thiol **362** with the new thioimidazolium reagent **355** and (**B**) proposed mechanistic rationalization of the results.

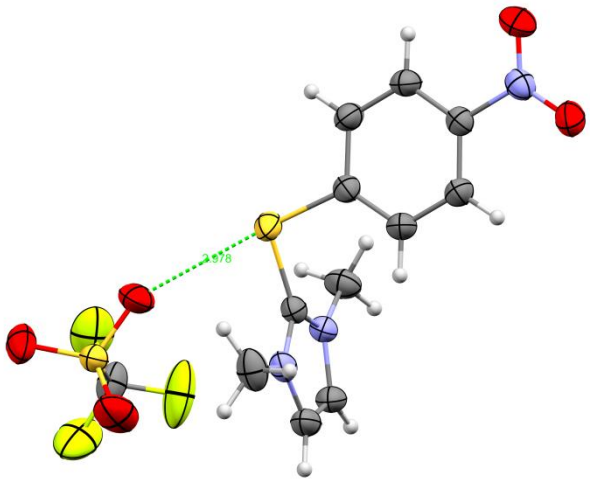
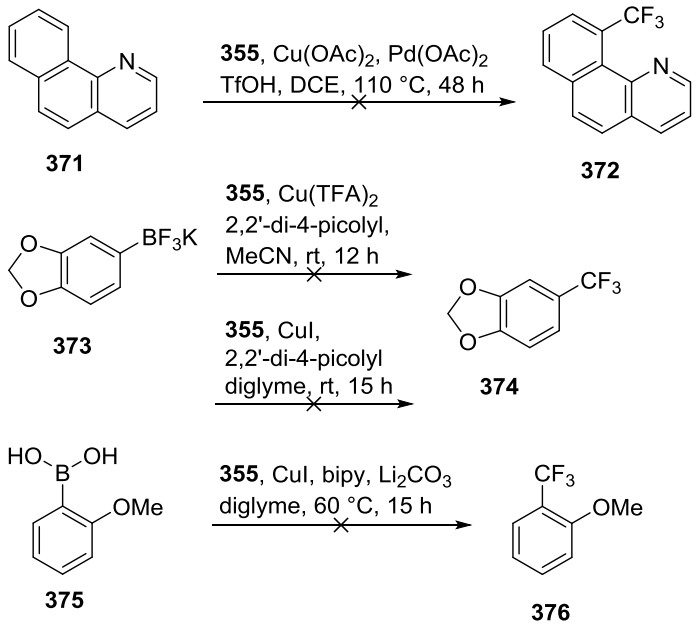


Figure 39 Molecular structure of side product **368**. Thermal ellipsoids at 50% probability.

3.4.3 Investigations towards metal-catalyzed reactions

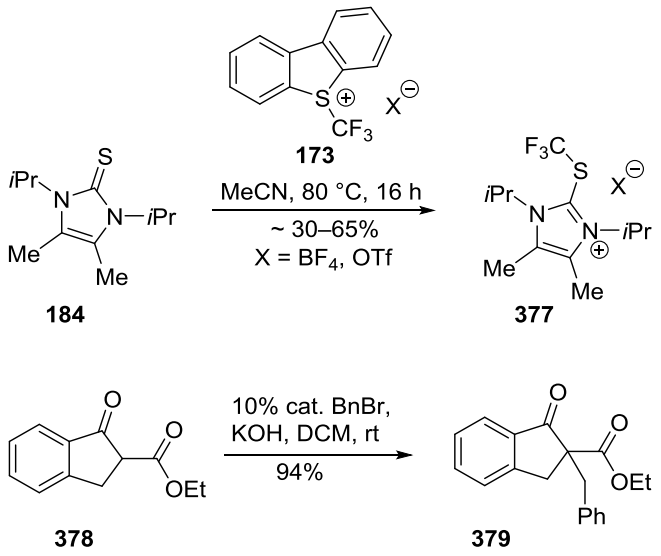
Several examples of metal-catalyzed trifluoromethylation reactions have been reported in literature using group transfer reagents.[141] Regarding this, copper salts seem to be an excellent choice for stabilizing trifluoromethyl radicals.[142] Test reactions with different copper catalysts and starting materials were examined (Scheme 65). In no case any reactivity towards trifluoromethylation was observed. Following a publication by Huang, Weng *et al.*,[143] the reaction of benzo[*h*]quinoline (**371**) with the reagent **355** was probed applying copper trifluoroacetate and palladium acetate as catalyst; unfortunately, the unreacted quinoline **371** was re-isolated. The same result was obtained by employing trifluroborate **373** as a substrate: neither copper iodide nor $Cu(TFA)_2$[143] appeared to be a suitable catalyst for the desired reaction. Furthermore, only starting material was obtained using boronic acid **375** and copper iodide/bipy as a catalyst.[144] Summarizing these experimental results, this indicates that reagent **355** exhibit no expected reactivity with copper catalysts under the investigated conditions.



Scheme 65 Investigations towards metal-catalyzed reactions with reagent **355**.

3.4.4 Application of thioimidazolium salts as phase transfer catalyst by Mizuta and coworkers

During our investigations, a thioimidazolium-based reagent similar to **355** was published by Mizuta *et al.*,[145] who trifluoromethylated the thiourea **184** using the commercially available Umemoto reagent **173** to obtain the corresponding imidazolium salts **377** in good yields (Scheme 66). The authors utilized the resulting imidazolium salts as phase transfer catalysts in the alkylation of different compounds possessing an active methylene moiety, whereas applying of the compounds **377** for the trifluoromethylation of nucleophiles was not examined.



Scheme 66 Synthesis of a new thioimidazolium-based reagent **377** by Mizuta and coworkers and its application as phase transfer catalyst.

Based on preliminary NMR studies, the authors suggest that in the beginning of the reaction carbanion **380** is formed by deprotonation of the β-ketoester **378** with potassium hydroxide. The low solubility of this carbanion would normally lead to a low reaction rate. They assumed that the reactive imidazolium intermediate **377d** is formed *via* counterion exchange. This complex is more soluble and allows achieving higher reaction rate of the alkylation reaction. A subsequent attack of benzyl bromide with the imidazolium salt-stabilized carbanion **377d** would release the product **379** and the imidazolium salt **377e**, which undergoes the cycle again (Figure 40).

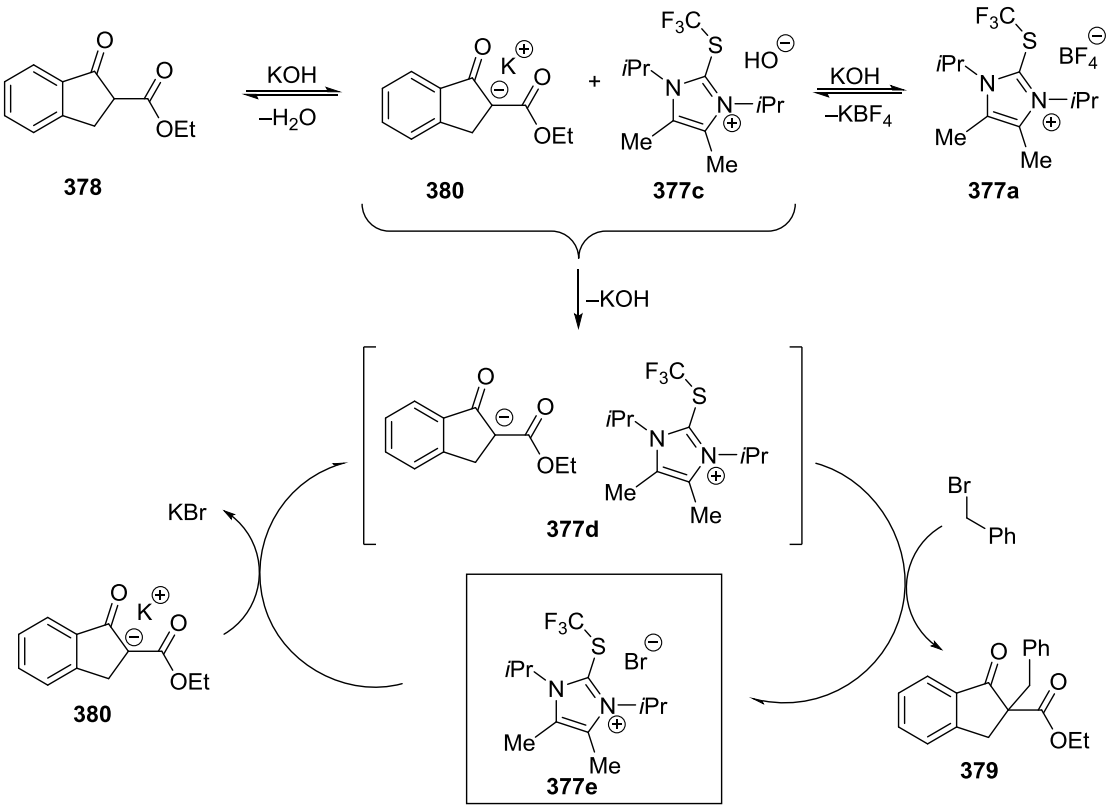


Figure 40 Mechanism for the phase transfer catalysis as proposed by Mizuta and coworkers.

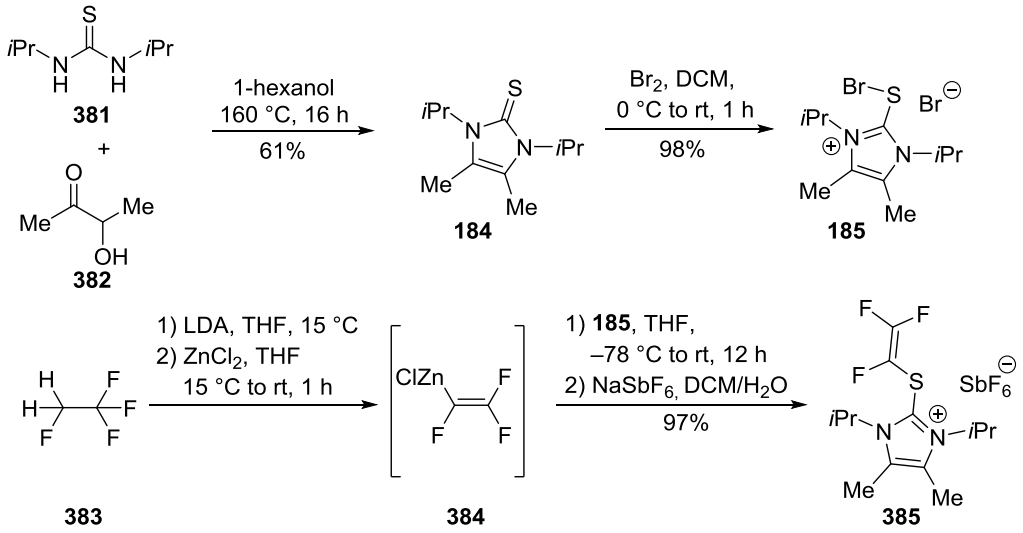
Considering the chosen substrates and reaction conditions, it can be assumed that Mizuta and coworkers were also interested in the trifluoromethylation instead of the presented phase-transfer catalysis. As a result of the high similarity to the presented results, no further resources were spent on this project part.

3.5 Investigations towards a new trifluoroethylenating reagent

3.5.1 Synthesis of the new reagent 385

An imidazolium-based fluorinated alkene derivative would be another desirable synthesis target. To the best of our knowledge, no metal-free alkenylation method for the functionalization of nucleophiles with transfer reagents by umpolung was reported. However, fluorinated alkenes could be useful tools in the synthesis of partly fluorinated heteroaromatics or other perfluoroalkylated molecules.

In fact, it was possible to synthesize the corresponding alkene reagent **385** (Scheme 63). First, the imidazothione **184** was synthesized by the condensation of acetoin (**381**) and 1,3-diisopropylthiourea (**382**) in a yield of 61%. Subsequent bromination of the reagent **184** led to the corresponding dibromide **185** in a yield of 98%. The formation of the zincate **384** was accessed by dehydrofluorination of tetrafluoroethane **383**, deprotonation initiated by LDA and subsequent transmetalation with zinc chloride.[146] The concentration of the zincate **384** was determined by a method of *Knochel* and coworkers.[147] After reaction of zincate **384** with the dibromide **185**, a counterion exchange with sodium hexafluoroantimonate(V) was performed to obtain the desired product **385** in a yield of 97%.



Scheme 67 Synthesis of a new potential trilfluoroethylating reagent **385**.

Single crystals of the compound **385** suitable for X-Ray diffraction were obtained by slow evaporation of a saturated solution of the compound in DCM. The expected structural connectivity was confirmed (Figure 41). Similarly to the compound **355**, the structure of the compound **385** shows an angular geometry C1–S1–C3 with an angle value of 99.50(1)°. Similarly as in chase for compound **355**, the S1-C3 bond is with 1.749(3) Å in the range of a single bond.

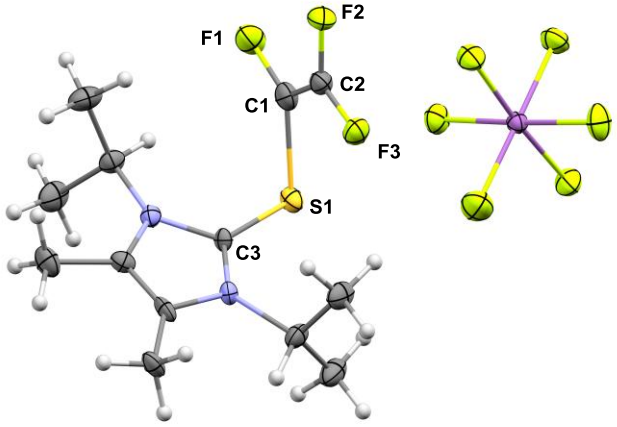
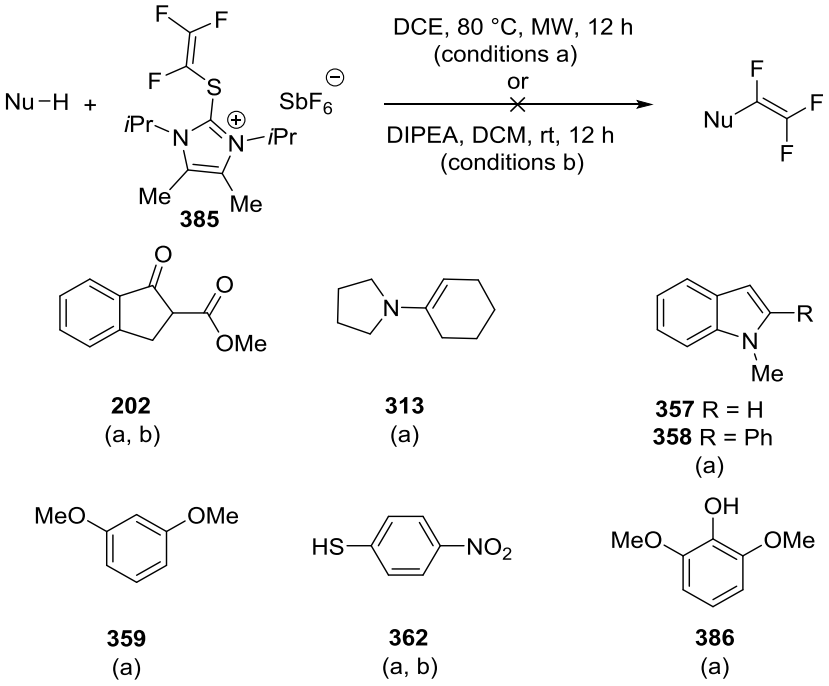


Figure 41 Molecular structure of compound **385**. Thermal ellipsoids at 50% probability. Selected bond lengths and distances (Å): C1-C2 1.316(4), S1-C1 1.721(9), S1-C3 1.749(3); angle of the sulfide moiety (°): C1–S1–C3 = 99.50(1).

3.5.2 Investigations towards reactions with different nucleophiles

No electrophilic transfer of the trifluoroethylene group was observed in the course of investigations of the reactivity of the reagent **385** under various conditions (Scheme 68). In fact, only unreacted starting material was isolated in the reactions with the *beta*-keto ester **202**, indole derivatives **357** and **358**, and the dimethoxyphenol **386**. The reaction with the thiol **362** led to a complete decomposition of the reagent **385**. Furthermore, reactivities of 1,3-dimethoxybenzene (**359**) and the enamine **313** were tested in a microwave-assisted reaction with reagent **385** without any additional base. Likewise, only the starting materials were isolated.

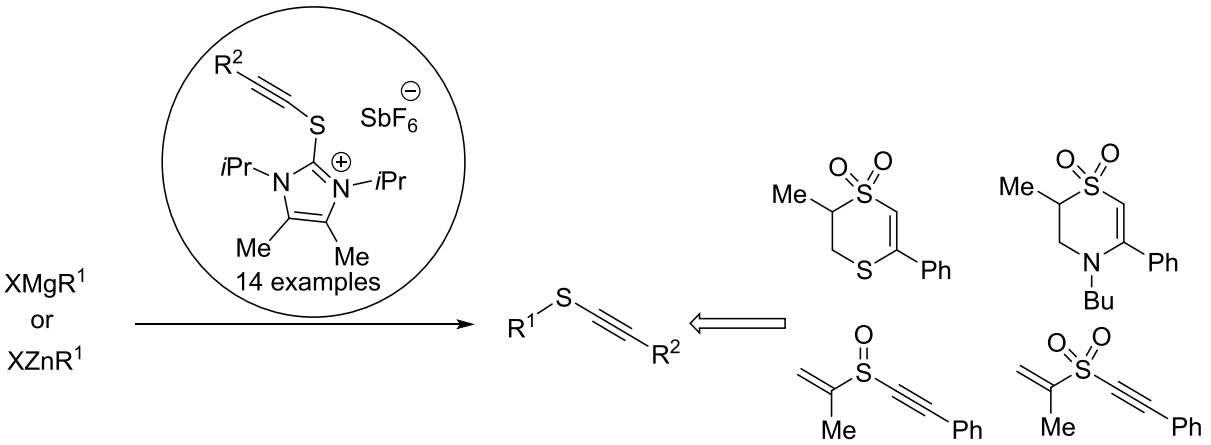


Scheme 68 Investigations towards the reactivity of the reagent **385** with different nucleophiles.

The further study of the chemistry of the salt **385** remains a matter of the nearest future. In this regards, most interesting would be reactions with metal-catalysts or/and the possible radical transfer of the ethylene-group.

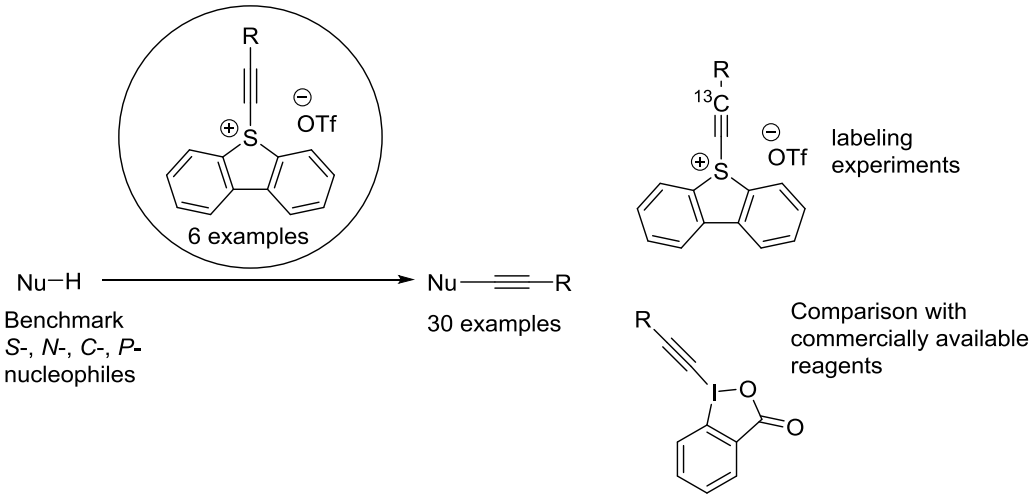
4 Summary

In collaboration with the colleagues Dr. G. Talavera and Dr. J. Peña, the recently discovered thioalkynylation reaction was further investigated. A set of different alkyne reagents was prepared, and their reactivity towards thioalkynylation with Grignard reagents and zincates was examined. The products of these reactions were used for further derivatization, thus enabling easy access to different kind of compounds such as sulfones or sulfoxides (Scheme 69).



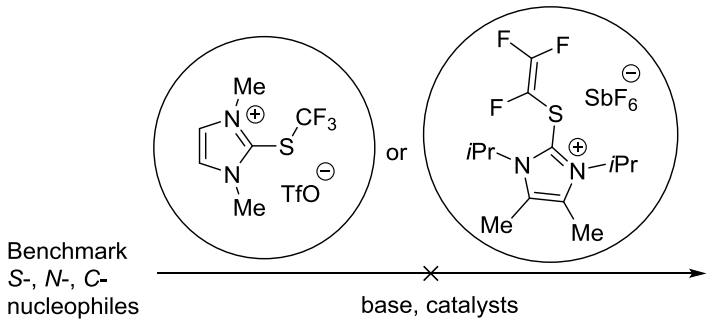
Scheme 69 Results of the investigations towards the thioalkynylation with thioimidazolium-based alkyne transfer reagents.

Additionally, a set of new dibenzothiophenium-based alkynylation reagents was prepared and their structural identity was confirmed by X-ray crystallography. The versatile reactivity of the new reagents was demonstrated in their reactions with benchmark *C*-, *S*-, *N*- and *P*-nucleophiles (Scheme 70). Straightforward experiments applying ^{13}C-labeled reagents were proceeded to give a first insight in the reaction mechanism. Finally, the reagents were directly compared with their commercially available EBX analogues highlighting them as powerful and safe alternative to hypervalent iodine reagents.



Scheme 70 Results of the investigations towards the synthesis of a new set of dibenzothiophenium-based alkyne transfer reagents.

The thioimidazolium salt **355** and the salt **385** were synthesized in a straightforward reaction sequence. Their structural identity was confirmed by spectral methods as well as by X-ray crystallography. Moreover, the reactivity of these compounds in the reaction with benchmark nucleophiles was investigated as well (Scheme 71), albeit with negative results. For reagent **355**, an unexpected decomposition process was observed affording the product **368**, which structure was confirmed by crystallographic study.



Scheme 71 Results of the investigations towards synthesis and application of thioimidazolium-based fluorine-containing transfer reagents.

5 Experimental

5.1 General remarks

Unless otherwise stated, all reactions were carried out in flame-dried glassware under nitrogen atmosphere. Solvents were dried by an MBraun MB-SPS-800 solvent purification system (tetrahydrofuran, diethyl ether, toluene, pentane, dichloromethane, acetonitrile) or by distillation with appropriate drying agents. The water content of the solvent was determined by Karl Fischer titrator TitroLine R 7500 KF trace from SI Analytics. Reactions were monitored by thin layer chromatography (TLC) polygram SIL G/UV254 from Macherey Nagel, UV irradiation (λ = 254 nm) and/or phosphomolybdic acid or $KMnO_4$ dip. Flash chromatography was performed on Macherey Nagel 60 (40–63 μm) silica gel.

Chemicals: Unless otherwise stated, all reagents were used as received from commercial suppliers (ABCR, Acros Organics, Alfa Aesar, Chempur GmbH, J and K Scientific, Sigma Aldrich, Thermo Fisher Scientific, Tokyo Chemical Industry). 1-(trifluoromethyl)-4-[2-(trimethylsilyl)ethynyl]-benzene,[148] 1-chloro-3-[2-(trimethylsilyl)ethynyl]-benzene,[149] 1-bromo-2-[2-(trimethylsilyl)ethynyl]-benzene,[150] 1-fluoro-4-[2-(trimethylsilyl)ethynyl]-benzene,[151] trimethyl[2-[tris(1-methylethyl)silyl]-ethynyl]-silane,[152] *N*-(4-methoxyphenyl)-4-methyl-benzenesulfonamide and *N*-(4-Iodophenyl)-4-methyl-Benzenesulfonamide,[153] α-cyano-benzenepropanoic acid ethyl ester,[154] 2,3-dihydro-1-oxo-1*H*-Indene-2-carboxylic acid methyl ester,[155] 1,3-diisopropyl-4,5-dimethyl-1,3-dihydro-2H-imidazole-2-thione[124] were prepared according to the literature reports. Compounds **196d**-**196n**, **210**-**212**, **214**-**221**, **223**-**225** were prepared and analyst by Dr. G. Talavera and Dr. J. Peña.

NMR: NMR spectra were recorded on a Bruker AV600, AV500, AV400, DPX300, Varian Mercury 300 or Varian Inova 500. The ppms of ^{1}H- and ^{13}C-NMR-spectras were measured relative to TMS. Coupling constants (*J*) were given in Hz. All NMR solvents were used as received from commercial suppliers.

Mass analysis: Mass spectrometry analysis was performed by the department of mass spectrometry of the chemistry department of the Georg-August University utilizing a Finnigan MAT 95 (70 eV, EI), Finnigan LCQ (ESI) and APEX IV 7T FTICR, Bruker Daltonic (HRMS).

Single crystal X-ray diffraction analysis: Data collection was done on a *Bruker D8 Venture* four-circle-diffractometer from *Bruker AXS GmbH*; used detector: *Photon II* from *Bruker AXS GmbH*; used X-ray sources: microfocus *IμS* Cu/Mo from *Incoatec GmbH* with mirror optics *HELIOS* and single-hole collimator from *Bruker AXS GmbH*.

Used programs: *APEX3 Suite* (v2017.3-0) and therein integrated programs *SAINT* (Integration) und *SADABS* (Absorption correction) from *Bruker AXS GmbH*; structure solution was done with *SHELXT*, refinement with *SHELXS*[156] ; OLEX[2] was used for data finalization.[157]

Special Utilities: *SMZ1270* stereomicroscope from *Nikon Metrology GmbH* was used for sample preparation; crystals were mounted on *MicroMounts* or *MicroLoops* from *MiTeGen*; for sensitive samples the *X-TEMP 2 System* was used for picking of crystals;[158] crystals were cooled to given temperature with *Cryostream 800* from *Oxford Cryosystems.*

IR: FT-IR spectra were measured by the utilization of a FT/IR-4100 (Jasco). The wavenumbers ($\tilde{\nu}$) were recorded in cm^{-3}.

Differential scanning calorimetry (DSC): The DSC measurements were performed in a Mettler-Toledo TGA/DSC 3+ , using the method *25_650_20K/min_N2 –b*.

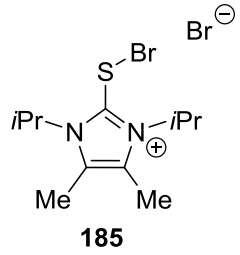
5.2 Reactions towards the newly discovered thioalkynylation reaction

5.2.1 Synthesis of new thioimidazolium-based alkynylation reagents

General procedure A (GPA)

To a solution of a terminal alkyne (0.50 mmol, 1.00 equiv.) in THF (2 mL) was added *n*BuLi (1.6 M in hexanes, 1.05 equiv.) at -78 ºC. After stirring for 1 hour, a solution of $ZnBr_2$ (1.05 equiv.) in THF (1 M) was added at -78 ºC and the whole mixture stirred for another hour. Then the dibromide **185** (1.00 equiv.) was added in one portion to the reaction mixture at -78ºC and after 30 minutes the reaction was let to warm up to room temperature. The solvents were removed *in vacuo* to afford a crude mixture which was washed with dry diethyl ether (3x) and pentane (2x). The obtained solid was dissolved in DCM (0.1M) and treated with an aqueous solution of $NaSbF_6$ (3.00 equiv.). Extraction of the aqueous layer with DCM (3x) and subsequent removal of all solvents *in vacuo* afforded the desired products as white to pale yellow-orange solids.

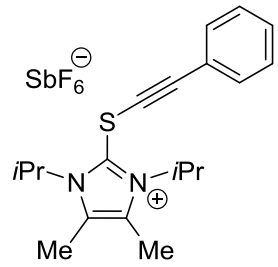
Synthesis of the compound 2-(bromothio)-1,3-diisopropyl-4,5-dimethyl-1*H*-imidazol-3-ium bromide (**185**)



185

To a solution of 1,3-diisopropyl-4,5-dimethyl-1,3-dihydro-2*H*-imidazole-2-thione (4.00 g, 18.8 mmol, 1.00 equiv.) in DCM (20 mL) was added bromine (0.97 mL, 18.8 mmol, 1.00 equiv.) at 0 °C and the solution was stirred for 1 h at 0°°C and 2 h at rt. The solvent was removed under reduced pressure and the residue was washed with ether (2 x 20 mL) to afford the desired compound **185** as orange solid (6.90 g, 18.5 mmol, 98%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 3.81 (6 H, s), 2.27 ppm (6 H, s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 127.8, 33.8, 9.7 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 783, 855, 1032, 1230, 1372, 1429, 1490, 1624, 2944. **HRMS**: calcd. for $C_7H_{12}N_2BrS$ $[M]^+$ = 234.9898; found = 234.9899. Analytical data corresponded to those described in the literature.[124]

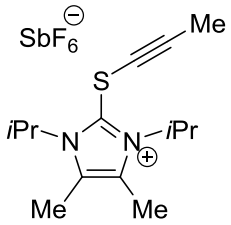
Synthesis of 1,3-diisopropyl-4,5-dimethyl-2-((phenylethynyl)thio)-1*H*-imidazol-3-ium hexafluoro-antimonate(V) (**196b**)



196b

Using the general procedure GPA, compound (**196b**) was prepared from phenyl acetylene (1.70 mL, 15.3 mmol), *n*BuLi (10 mL, 16.0 mmol), $ZnBr_2$ (3.62 g, 16.0 mmol) and dibromide **185** (5.70 g, 15.3 mmol). The desired compound was obtained as pale white solid (7.7 g, 92%). **^{1}H NMR** (500 MHz, $CDCl_3$,) δ = 7.28 – 7.47 (5 H, m), 5.31 (2 H, hept., *J* = 7.0 Hz),. 2.43 (6 H, s), 1.73 ppm (12 H, d, *J* = 7.0 Hz). **^{13}C NMR** (126 MHz, $CDCl_3$,) δ = 132.0, 131.0, 130.0, 129.8, 128.5, 120.4, 95.3, 69.2, 53.7, 20.7, 10.0 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 653, 691, 754, 906, 1114, 1219, 1378, 1459, 1618, 2943, 2996. **HR-MS**: calcd. for $C_{19}H_{25}N_2S$ $[M]^+$ =313.1732; found = 313.1732.

Synthesis of 1,3-diisopropyl-4,5-dimethyl-2-(prop-1-yn-1-ylthio)-1*H*-imidazol-3-ium hexafluoro-antimonate(V) (**196c**)



196c

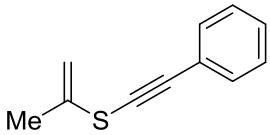
Using the general procedure GPA, compound **196c** was prepared from propynyl lithium (29.6 mg, 0.64 mmol), $ZnBr_2$ (151.3 mg, 0.67 mmol) and dibromide **185** (238.8 mg, 0.64 mmol). The desired compound was obtained as pale yellow solid (307.9 mg, 99%); **^{1}H NMR** (300 MHz, $CDCl_3$,) δ = 5.15 (2 H, hept, *J* = 7.1 Hz), 2.35 (6 H, s), 1.90 (3 H, s), 1.63 ppm (12 H, d, *J* = 7.1 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 131.1, 130.8, 94.4, 58.5, 53.7, 20.9, 10.1, 4.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 652, 754, 844, 1065, 1136, 1164, 1219, 1321, 1371, 1458, 1615, 2943, 2994. **HR-MS**: calcd. for $C_{14}H_{23}N_2S$ $[M]^+$ = 251.1577; found = 251.1576.

5.2.2 Synthesis of sulfides

General procedure B (GPB)

The thioalkynyl imidazolium salt (0.05 – 0.25 mmol) was dissolved in THF (0.2M) at the indicated temperature and the Grignard reagent solution (1.00 equiv.) was added dropwise. After 2 h a saturated aqueous NH_4Cl solution was added and reaction mixture was extracted with EtOAc (3x15mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the volatiles were removed under vacuum. Purification of the crude product by flash chromatography on silica gel (hexane/EtOAc) afforded the desired substances.

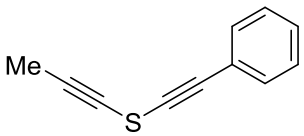
Synthesis of (phenylethynyl)(prop-1-en-2-yl)sulfane (**213**)



213

Using the general procedure GPB, compound **213** was prepared from isopropenylmagnesium bromide (0.5 M in THF, 1.80 mL, 0.85 mmol) and compound **196b** (496 mg, 0.90 mmol). The Grignard reagent was added at -78ºC. Flash chromatography purification (hexane/EtOAc 9/1) afforded **213** as a pale yellow oil (155 mg, 99%).**^{1}H NMR** (300 MHz, $CDCl_3$,) δ = 7.41–7.54 (2 H, m), 7.28–7.38 (3 H, m), 5.30–5.42 (1 H, m), 5.23 (1 H, q, *J* = 1.5 Hz), 2.09 ppm (3 H, dd, *J* = 1.5, 0.8 Hz). **^{13}C NMR** (75 MHz, CDCl,) δ = 136.9, 131.7, 128.6, 128.5, 123.2, 111.3, 98.7, 75.9, 22.0 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 693, 736, 751, 801, 917, 1028, 1072, 1175, 1263, 1357, 1444, 1490, 1596, 1687, 2186, 2922, 3027, 3057. **HRMS**: calcd. for $C_{11}H_{10}S$ $[M]^+$ = 174.0501; found = 174.0503.

Synthesis of (phenylethynyl)(prop-1-yn-1-yl)sulfane (**221**)



221

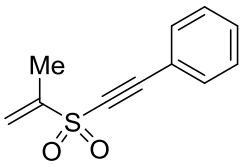
Using the general procedure GPA, compound **221** was prepared from propynylmagnesium bromide (0.5 M in THF, 1.08 mL, 0.51 mmol) and the compound **196b** (297 mg, 0.54 mmol). The Grignard reagent was added at -78ºC. Flash chromatography purification (hexane/EtOAc 9/1) afforded **221** as a pale yellow oil (85.4 mg, 97%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.43–7.52 (2 H, m), 7.28–7.36 (3 H, m), 2.00 ppm (3 H, s,). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 132.0, 129.0, 128.5, 122.5, 94.5, 92.5, 73.1, 60.8, 5.2 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 729, 803, 905, 1014, 1260, 1443, 1487, 2252, 2853, 2924, 2959. **HRMS**: calcd. for $C_{11}H_8S$ $[M]^+$ = 172.0345; found = 172.0346.

5.2.3 Synthesis of derivatization products of the synthesized sulfides

Synthesis of ((prop-1-en-2-ylsulfinyl)ethynyl)benzene (**226**)

To a solution of the compound **213** (110 mg, 0.63 mmol, 1.00 equiv.) in DCM (6.5 mL) was slowly added *m*CPBA (141 mg, 0.63 mmol, 1.00 equiv.) over 1 h. The solution was stirred for another 12 h at 0 °C. Then the white solid was removed by filtration and the solution was washed with a saturated aqueous solution of NaS_2O_3, a saturated aqueous solution of $NaHCO_3$ and water. Afterwards the solution was dried over $MgSO_4$, the solvent was removed by evaporation and the residue was purified by flash-chromatography (hexane/ether : 3/2) to afford the product as yellow oil (81 mg, 68 %).**^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.50-7.52 (1 H, m); 7.41-7.44 (1 H, m), 7.34-7.37 (2 H, m), 5.92 (1 H, m_C), 5.67 (1 H, m_C), 2.22 ppm (3 H, dd *J* = 1.1). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 148.5, 132.2, 130.5, 128.5, 120.0, 118.3, 101.0, 84.6, 14.7 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 527, 534, 629, 688, 756, 921, 1066, 1442, 1487, 1636, 2159, 2956, 3082. **HRMS**: calcd. for $C_{11}H_{10}SO$ $[M+H]^+$ = 191.0525; found = 191.0528.

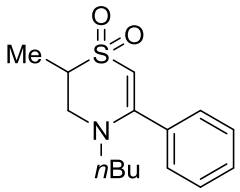
Synthesis of ((prop-1-en-2-ylsulfonyl)ethynyl)benzene (**227**)



227

To a solution of the compound **213** (305 mg, 1.75 mmol, 1.00 equiv.) in DCM (6.5 mL) was slowly added *m*CPBA (141 mg, 3.68 mmol, 2.00 equiv.) over 1 h. The solution was stirred for another 12 h at 0 °C and 1 h at rt. Then the white solid was removed by filtration and the solution was washed with a saturated aqueous solution of NaS_2O_3, a saturated aqueous solution of $NaHCO_3$ and water. Afterwards the solution was dried over $MgSO_4$, the solvent was removed by evaporation and the residue was purified by flash-chromatography (hexane/ether : 3/2) to afford the product as colorless oil (309 mg, 86 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = , 6.30 (1 5.81 (1 H, m_C), 2.26 ppm (3 H, dd, *J* = 0.5, 0.8 Hz)**^{13}C NMR** (125 MHz, $CDCl_3$) δ = 146.3, 132.9, 131.7, 128.8, 124.9, 117.8, 93.0, 83.1, 16.1 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 531, 633, 684, 726, 756, 846, 923, 952, 1127, 1220, 1319, 1444, 1488, 1636, 2177, 3061. **HRMS**: calcd. for $C_{11}H_{10}O_2S$ $[M+H]^+$ = 207.0474; found = 207.0472.

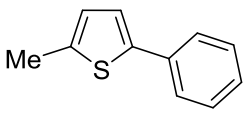
Synthesis of 4-butyl-2-methyl-5-phenyl-3,4-dihydro-2*H*-1,4-thiazine 1,1-dioxide (**228**)



228

To a solution of butan-1-amine (48.9 mg, 0.67 mmol, 2.00 eq,) in methanol (7 mL) was added a solution of the compound **227** (69.0 mg, 0.33 mmol, 1.00 equiv.) in one drop at RT. The solution was stirred for 20 h at rt and added then to a saturated aqueous solution of $NaHCO_3$. The aqueous solution was extracted three times with DCM, the combined organic phases were dried over $MgSO_4$ and the solvent was removed by evaporation. Flash chromatography (hexane/EE+ 1% NEt_3: 3/1 to 1/1) afford the desired product as white solid (22 mg, 26%). **^{1}H NMR** (300 MHz, $CDCl_3$,) δ = 7.29-7.38 (3 H, m), 7.20-7.26 (2 H, m), 4.93 (1 H, s), 3.57-3.74 (2 H, m), 3.09-3.20 (1 H, m), 2.90-2.95 (2 H, m), 1.37 (5 H, m_C), 1.03 (2 H, hex, *J* = 7.6 Hz), 0.68 ppm (3 H, t, *J* = 7.2 Hz). **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 155.3, 135.7, 129.4, 128.5, 127.7, 95.1, 52.4, 52,3, 50.8, 30.7, 13.6, 9.8 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 510, 536, 563, 666, 693, 728, 769, 1042, 1079, 1110, 1162, 1216, 1260, 1315, 1364, 1376, 1442, 1465, 1551, 1579, 2859, 2918, 2983, 3071; **HRMS**: calcd. for $C_{15}H_{21}NO_2S$ $[M+H]^+$ = 280.1366; found = 280.1367.

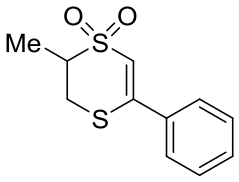
Synthesis of 2-methyl-5-phenylthiophene (**229**)



229

To a solution of compound **213** (60.1 mg, 0.34 mmol, 1.00 equiv.) in EtOH (10 mL) was added $Na_2S{\cdot}9H_2O$ (82.0 mg, 0.34 mmol, 1.00 equiv.). The reaction mixture was stirred under microwave irradiation for 20h at 120 °C. Water was added to the reaction mixture and the reaction mixture was extracted by EtOAc. The combined org. phases were washed with brine and the solvent was removed *in vacuo*. Column chromatography (hexane) afforded the desired product as white solid (41.4 mg, 70%). **^{1}H NMR (**300 MHz, $CDCl_3$, ppm) δ = 7.50–7.62 (2 H, m), 7.30–7.43 (2 H, m), 7.20–7.29 (1 H, m), 7.11 (1 H, d, *J* = 3.5 Hz), 6.73 (1 H, dq, *J* = 3.4, 1.1 Hz), 2.51 ppm (3 H, d, *J* = 1.1 Hz). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 141.8, 139.4, 134.6, 128.7, 126.9, 126.0, 125.4, 122.8, 15.5 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 682, 747, 798, 900, 944, 1026, 1072, 1210, 1259, 1440, 1468, 1496, 1596, 2851, 2913, 3020, 3056. **HRMS**: calcd. for $C_{11}H_{10}S$ $[M^+]$ = 174.0530; found = 174.0494**.** Analytical data corresponded to that described in the literature.[159]

Synthesis of 2-methyl-5-phenyl-2,3-dihydro-1,4-dithiine 1,1-dioxide (**230**)



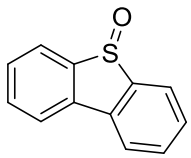
230

To a solution of sodium sulfide nonahydrate (316 mg, 1.32 mmol, 2.00 equiv.) in methanol (10 mL) was added a solution of the compound **227** (135 mg, 0.66 mmol, 2.00 equiv.) in one drop at rt. The solution was stirred for another 15 min at rt and then was added to a water/ice-mixture. Afterwards the suspension was extracted three times with DCM. The combined organic phases were dried over $MgSO_4$ and the solvent was removed by evaporation. After purification by flash chromatography (hexane/ether : 1/1) the product was isolated as white solid (132 mg, 84%).**^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.35-7.50 (5 H, m), 6.54 (1 H, s), 3.52 (1 H, s), 3.50 (1 H, d, *J* = 1.4 Hz), 3.30-3.40 (1 H, m), 1.55 ppm (3 H, d, *J* = 3.4 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 150.2, 130.8, 128.9, 126.7, 119.0, 51.0, 32.5, 11.2 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 513, 540, 573, 642, 691,.702, 746, 774, 821, 915, 943, 1026, 1072, 1098, 1118, 1220, 1267, 1293, 1445, 1489, 1556, 3018. **HRMS**: calcd. for $C_{11}H_{12}O_2S_2$ $[M+H]^+$ = 241.0351; found = 241.0343.

5.3 Synthesis of new diphenylsulfane and dibenzothiophene based reagents

5.3.1 Synthesis of starting materials

Synthesis of dibenzo[*b*,*d*]thiophene 5-oxide (**237**)



237

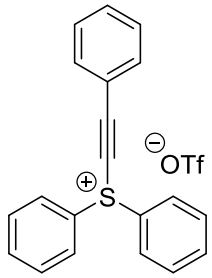
Compound **237** was synthesized according to a modified literature procedure.[127] To a suspension of dibenzothiophene (2.00 g, 10.9 mmol, 1.00 equiv.) in TFA (8 mL) was added dropwise H_2O_2 (1.24 mL, 30 %, 1.20 equiv.) at 0 °C. Afterwards the reaction was allowed to warm up to r.t. Upon complete consumption of the starting material (monitored by TLC), the reaction was stirred for additional 20 mininutes and then neutralized with H_2O (ca. 100 mL) to precipitate a white solid. The solid was washed with H_2O (ca. 30 mL) and dried *in vacuo*. The crude product was then purified by column chromatography using DCM/MeOH (50:1; R_F = 0.5) as the eluent. Removal of the solvents *in vacuo* afforded **237** as a white solid (1.66 g, 8.26 mmol, 76 %). Analytical data corresponded to that described in the literature.[127] **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.95 (ddd, *J* = 7.6, 1.2, 0.6 Hz, 2 H), 7.76 (ddd, *J* = 7.7, 1.2, 0.6 Hz, 2 H), 7.56 (td, *J* = 7.6, 1.2 Hz, 2 H), 7.46 ppm (td, *J* = 7.5, 1.2 Hz, 2 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.11, 137.02, 132.50, 129.49, 127.46, 121.91 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3055, 1591, 1578, 1477, 1443, 1220, 1124, 1066, 1042, 1020, 987, 947, 871, 762, 750, 712, 691, 650, 613, 579, 569, 554, 506. **HR-MS** for $C_{12}H_8OS$: calc.: 200.03, found: 200.0293 $[M]^+$ (EI-HRMS).

5.3.2 Synthesis of transfer reagents

General procedure C (GPC)

These compounds were synthesized by the modification of a literature procedure.[125] Triflic anhydride (1.00 equiv.) was slowly added at -50 °C to a solution of the sulfoxide (1.00 equiv.) in dry DCM (8 mL/mmol). The reaction was stirred for 1 h at that temperature and then a solution of the desired TMS-alkyne (1.00 equiv.) in DCM (1 mL/mmol) was added dropwise. After this, the reaction was slowly warmed to -15 °C and stirred for another 6 h at this temperature. Removal of the solvents *in vacuo* afforded crude salts, which were washed with dry Et_2O (5 x 3 mL/mmol) and dry pentane (2 x 3 mL/mmol) to obtain the desired products as a powder.

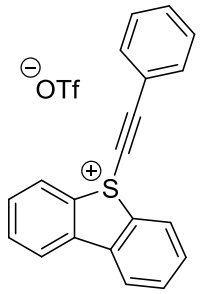
Synthesis of diphenyl(phenylethynyl)sulfonium trifluoromethanesulfonate (**205**)



205

Using the general procedure GPC, compound **205** was prepared from diphenylsulfoxid (0.77 g, 3.83 mmol, 1.00 equiv.), trifluoromethanesulfonic anhydride (0.65 ml, 3.83 mmol, 1.00 equiv.) and 1-phenyl-2-trimethylsilylacetylene (0.44 g, 2.50 mmol, 1.25 equiv.). The product was obtained as an orange resin (1.03 g, 2.30 mmol, 60%). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 8.21 8.18 (m, 4 H), 7.80-7.79 (m, 2 H); 7.74 7.68 (m, 6 H), 7.61 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.48 (tt, *J* = 7.9, 1.4 Hz, 2 H) ppm.**^{13}C-NMR** (126 MHz, $CDCl_3$): δ [ppm] = 135.1, 133.9, 133.4, 132.0, 129.8, 129.2, 128.0, 117.0, 111.6 ppm. **^{19}F-NMR** (282 MHz, $CDCl_3$): δ [ppm] = -78.1. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3088, 3063, 2182, 2102, 1474, 1446, 1305, 1259, 1222, 1028, 1012, 997, 932, 872, 842, 744, 681, 660, 634, 587, 572, 535, 514, 501. **HR-MS** for $C_{20}H_{15}S^+$: calc.: 287.0889; found: 287.0894 $[M]^+$ (ESI-HRMS).

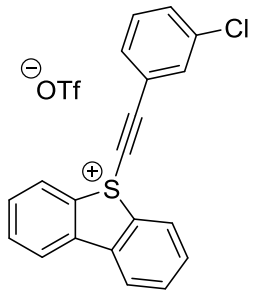
Synthesis of 5-(phenylethynyl)-5*H*-dibenzo[*b,d*]thiophen-5-ium trifluoromethanesulfonate (**238a**)



238a

Using the general procedure GPC, compound **238a** was prepared from **237** (0.77 g, 3.83 mmol, 1.00 equiv.), Tf_2O (0.65 mL, 3.83 mmol, 1.00 equiv.) and trimethyl-(phenylethynyl)silane (0.75 ml, 3.83 mmol, 1.00 equiv.), obtaining after washing a white powder (1.52 g, 3.59 mmol, 94%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.43 (ddd, *J* = 8.1, 1.1, 0.5 Hz, 2 H), 8.20 (ddd, *J* = 7.8, 1.3, 0.5 Hz, 2 H), 7.95 (ddd, *J* = 7.5, 1.1 Hz, 2 H), 7.80 (ddd, *J* = 8.1, 7.5, 1.3 Hz, 2 H), 7.72 – 7.62 (m, 2 H), 7.63 – 7.51 (m, 1 H), 7.50 – 7.35 ppm (m, 2 H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ = 139.6, 135.6, 134.2, 133.5, 132.7, 130.5, 129.5, 128.9, 125.0, 117.8, 108.2, 64.4 ppm. **^{19}F NMR** (376 MHz, CD_2Cl_2) δ = -78.74 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3104, 3088, 3065, 3011, 2174, 2121, 2090, 1593, 1574, 1484, 1462, 1449, 1441, 1427, 1257, 1221, 1156, 1151, 1073, 1059, 1026, 998, 952, 936, 884, 867, 785, 760, 702, 689, 658, 635, 612. **HR-MS** calc. for $C_{20}H_{13}S$: 285.0732; found: 285.0740 $[M]^+$ (ESI-HRMS).

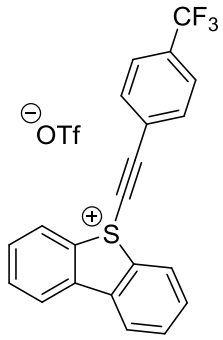
Synthesis of 5-((3-chlorophenyl)ethynyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate (**238b**)



238b

Using the general procedure GPC, compound **238b** was prepared from **237** (1.15 g, 5.75 mmol, 1.00 equiv.), Tf_2O (0.96 mL, 5.75 mmol, 1.00 equiv.) and , 1-chloro-3-[2-(trimethylsilyl)ethynyl]-benzene (1.26 g, 5.75 mmol, 1.00 equiv.), obtaining after washing a white powder (2.18 g, 4.65 mmol, 81%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.46 (ddd, *J* = 8.1, 1.1, 0.5 Hz, 2 H), 8.20 (ddd, *J* = 7.9, 1.3, 0.5 Hz, 2 H), 7.95 (ddd, *J* = 7.5, 1.1 Hz, 2 H), 7.81 (ddd, *J* = 8.1, 7.5, 1.3 Hz, 2 H), 7.63 – 7.51 (m, 3 H), 7.38 ppm (t, *J* = 8.2 Hz, 1 H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ = 139.7, 135.6, 135.3, 133.7, 133.6, 132.8, 132.5, 130.9, 130.4, 129.2, 125.0, 119.7, 105.6, 66.0 ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -78.78 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 1587, 1447, 1247, 1218, 1146, 1025, 905, 791, 753, 633. **HR-MS** calc. for $C_{20}H_{12}ClS$: 319.0348; found: 319.0345 $[M]^+$ (ESI-HRMS).

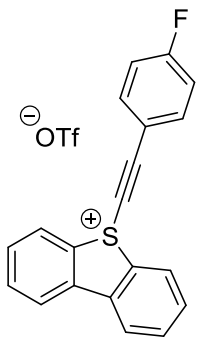
Synthesis of 5-((4-(trifluoromethyl)phenyl)ethynyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethane-sulfonate (**238c**)



238c

Using the general procedure GPC, compound **238c** was prepared from **237** (0.50 g, 2.50 mmol, 1.00 equiv.), Tf_2O (0.42 mL, 2.50 mmol, 1.00 equiv.) and 1-(trifluoromethyl)-4-[2-(trimethylsilyl)ethynyl]-benzene (0.60 g, 2.50 mmol, 1.00 equiv.), obtaining after washing a pale yellow powder (0.89 g, 2.50 mmol, quant.).**^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.49 (ddd, *J* = 8.1, 1.1, 0.5 Hz, 2 H), 8.20 (ddd, *J* = 7.8, 1.3, 0.5 Hz, 2 H), 7.96 (ddd, *J* = 7.5, 1.1 Hz, 2 H), 7.87 – 7.77 (m, 4 H), 7.67 ppm (dt, *J* = 8.2, 0.7 Hz, 2 H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ = 139.8, 139.7, 135.7, 134.6, 134.1, 132.8, 130.2, 129.3, 126.4 (q, *J* = 3.8 Hz), 125.0, 121.8, 119.2, 105.1 ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -63.80, -78.82 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3094, 2185, 1450, 1405, 1319, 1247, 1153, 1066, 1025, 849, 755, 703, 635, 612. **HR-MS** calc. for $C_{21}H_{12}F_3S$: 353.0606; found: 353.0607 $[M]^+$ (ESI-HRMS).

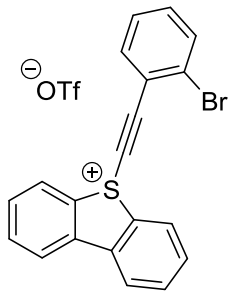
Synthesis of 5-((4-fluorophenyl)ethynyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate (**238d**)



238d

Using the general procedure GPC, compound **238d** was prepared from **237** (0.37 g, 1.87 mmol, 1.00 equiv.), Tf_2O (0.32 mL, 3.90 mmol, 1.00 equiv.) and 1-fluoro-4-[2-(trimethylsilyl)ethynyl]-benzene (0.36 g, 1.87 mmol, 1.00 equiv.), obtaining after washing a pale yellow powder (0.65 g, 1.44 mmol, 77%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.42 (d, *J* = 8.2 Hz, 2 H), 8.20 (ddd, *J* = 7.7, 1.1Hz, 2 H), 7.94 (dt, *J* = 7.7, 0.9 Hz, 2 H), 7.79 (dt, *J* = 8.0, 1.1, 2 H), 7.72 – 7.67 (m, 2 H), 7.14 – 7.08 (m, 2 H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ = 166.1 (d, *J* = 287.8 Hz), 139.6, 137.9 (d, *J* = 10.0 Hz), 135.6, 132.7, 130.4, 129.0, 125.0, 117.5 (d, *J* = 20.7 Hz), 114.1 (d, *J* = 3.5 Hz), 107.1, 64.5 (d, *J* = 2.3 Hz) ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -78.87, -102.44 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3087, 3066, 2972, 2868, 2180, 2133, 2112, 1598, 1506, 1482, 1465, 1449, 1427, 1282, 1255, 1242, 1221, 1151, 1114, 1077, 1062, 1026, 999, 875, 842, 822, 798, 842, 822, 797, 765, 706, 669, 634, 612. **HR-MS** calc. for $C_{20}H_{12}FS$: 303.0638; found: 303.0630 $[M]^+$ (ESI-HRMS).

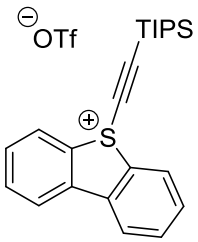
Synthesis of 5-((2-bromophenyl)ethynyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate (**238e**)



238e

Using the general procedure GPC, compound **238e** was prepared from **237** (0.78 g, 3.90 mmol, 1.00 equiv.), Tf_2O (0.66 mL, 3.90 mmol, 1.00 equiv.) and 1-bromo-2-[2-(trimethylsilyl)ethynyl]-benzene (0.60 g, 3.90 mmol, 1.00 equiv.), obtaining after washing a pale yellow powder (1.45 g, 2.83 mmol, 73%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.46 (ddd, *J* = 8.1, 1.1, 0.5 Hz, 2 H), 8.20 (ddd, *J* = 7.9, 1.3, 0.5 Hz, 2 H), 7.96 (ddd, *J* = 7.5, 1.1 Hz, 2 H), 7.82 (ddd, *J* = 8.1, 7.5, 1.3 Hz, 2 H), 7.77 – 7.72 (m, 1 H), 7.65 - 7.59 (m, 1 H), 7.44 – 7.37 ppm (m, 2 H).**^{13}C NMR** (126 MHz, CD_2Cl_2) δ = 139.7, 135.7, 135.3, 133.7, 133.6, 132.8, 132.5, 130.9, 130.4, 129.2, 125.0, 119.6, 105.6, 66.0 ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -78.77 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3091, 1576, 1447, 1270, 1248, 1222, 1149, 1025, 868, 754, 702, 634, 612, 571, 515, 420. **HR-MS** calc. for $C_{20}H_{12}BrS$: 362.9843; found: 362.9838 $[M]^+$ (ESI-HRMS).

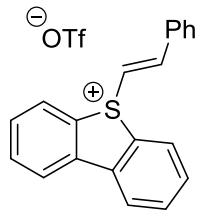
Synthesis of 5-((triisopropylsilyl)ethynyl)-5*H*-dibenzo[*b,d*]thiophen-5-ium trifluoromethanesulfonate (**238f**)



238f

Using the general procedure GPC, compound **238f** was prepared from **237** (2.00 g, 10.0 mmol, 1.00 equiv.), Tf_2O (1.68 mL, 10.0 mmol, 1.00 equiv.) and trimethyl[2-[tris(1-methylethyl)silyl]ethynyl]-silane (3.14 mL, 10.0 mmol, 1.00 equiv.), obtaining after washing a white powder (4.36 g, 8.47 mmol, 85%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.33 (ddd, *J* = 8.1, 1.0, 0.5 Hz, 2 H), 8.20 (ddd, *J* = 7.8, 1.3, 0.5 Hz, 2H), 7.94 (dt, *J* = 7.7, 1.1 Hz, 2 H), 7.82 (ddd, *J* = 8.6, 8.1, 1.3 Hz, 2 H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ = 139.6, 135.5, 132.7, 131.1, 128.4, 125.1, 118.6, 78.9, 18.6, 11.5 ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -78.77 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =2945, 2924, 2865, 1461, 1448, 1273, 1249, 1226, 1154, 1130, 1072, 1062, 1029, 997, 966, 921, 880, 822, 767, 757, 704, 685, 657, 636, 614, 605,. **HR-MS** calc. for $C_{23}H_{29}SiS$: 365.1754; found: 365.1754 $[M]^+$ (ESI-HRMS).

Synthesis of (*E*)-5-styryl-5*H*-dibenzo[*b,d*]thiophen-5-ium trifluoromethanesulfonate (**238p**)

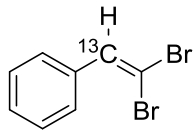


238p

Using the general procedure GPC, compound **238p** was prepared from dibenzothiophene sulfoxide **237** (0.40 g, 2.00 mmol, 1.00 equiv.), trifluoromethanesulfonic anhydride (0.34 ml, 2.00 mmol, 1.00 equiv.) and trimethyl-(styryl)-silane (0.44 g, 2.50 mmol, 1.25 equiv.). The product was obtained as a green powder (0.76 g, 1.74 mmol, 87%). **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 8.49 (d, *J* = 15.0 Hz, 1H), 8.25 (dd, *J* = 18.3, 7.9 Hz, 4H), 7.98 – 7.91 (m, 2H), 7.82 – 7.74 (m, 2H), 7.66 – 7.59 (m, 2H), 7.50 (dt, *J* = 14.3, 7.0 Hz, 3H), 6.33 (d, *J* = 15.0 Hz, 1H) ppm. **^{13}C-NMR** (125 MHz, CD_2Cl_2): δ [ppm] = 155.0, 139.2, 134.44, 132.6, 132.4, 131.6, 130.0, 129.3, 129.0, 128.5, 124.0, 111.5 ppm. **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ [ppm] = -78.8 ppm. **IR (ATR)**: $\tilde{\nu}$ (cm^{-1}) = 3487. 3084, 3054, 1598, 1569, 1484, 1448, 1430, 1251, 1221, 1150, 1075, 1025, 1000, 967, 856, 748, 704, 688, 633, 586, 571, 514. **HR-MS** for $C_{20}H_{15}S^+$: calc.: 287.0889; found: 287.0886 $[M]^+$ (ESI-HRMS).

5.3.3 Synthesis of labeled reagents

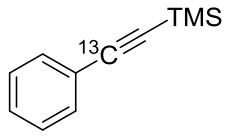
Synthesis of (2,2-dibromovinyl-1-^{13}C)benzene (**321**)



321

For the synthesis of (2,2-dibromovinyl-1-^{13}C)benzene a slightly modified literature procedure was used.[132] To a solution of CBr_4 (3.33 g, 10.0 mmol, 2.00 equiv.) and PPh_3 (5.25 g, 20.0 mmol, 4.00 equiv.) in DCM (20 mL) was added dropwise a solution of labeled benzaldehyde (0.50 mL, 5 mmol, 1.00 eq, 20% enriched) in DCM (6 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt and subsequently the reaction mixture was filtered through a short pad of silica. The solvent was removed under reduced pressure and after column chromatography (pure hexane) the labeled product could be obtained as colorless oil (1.14 g, 4.35 mmol, 87%). Analytical data corresponded to those described in the literature.[132]

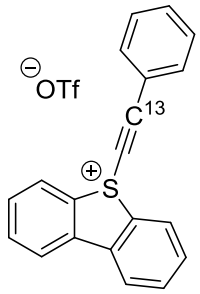
Synthesis of compound trimethyl(phenylethynyl-2-^{13}C)silane (**322**)



322

For the synthesis of labeled trimethyl(phenylethynyl-2-^{13}C)silane a slightly modified literature procedure was used.[132] To a solution of the dibromide **321** (1.14 g, 4.35 mmol, 1.00 equiv.) in THF (30 mL) was added *n*BuLi (2.5 M in hexane, 4.35 mL, 10.9 mmol, 2.50 equiv.) at -78 °C. The solution was stirred for 1 h at -78 °C and subsequently TMSCl (1.18 g, 10.9 mmol, 2.50 equiv.) was added to the reaction mixture. The reaction mixture was warmed up to rt and stirred for another hour at this temperature. A saturated aqueous solution of NH_4Cl was added and the reaction mixture was extracted with diethylether (2 x 20 mL). The combined org. phases were dried over Na_2SO_4 and after purification by flash chromatography the desired product could be obtained as colorless oil (550 mg, 3.16 mmol, 73%). Analytical data corresponded to those described in the literature.[132]

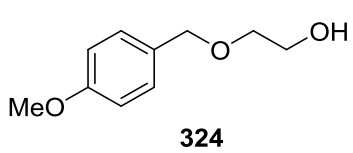
Synthesis of labeled 5-(phenylethynyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate (**238a***)



238a*

Using the general procedure GPC, compound **238a*** was prepared from **237** (674 mg, 3.34 mmol, 1.00 equiv.), Tf_2O (0.56 mL, 3.34 mmol, 1.00 equiv.) and trimethyl(phenylethynyl-2-^{13}C)silane (582 mg, 3.34 mmol, 1.00 equiv.), obtaining a white powder (1.26 g, 2.99 mmol, 90%) after washing. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.60 (d, *J* = 8.6 Hz, 2 H), 8.21 (d, *J* = 8.2 Hz, 2 H), 7.94 (dd, *J* = 8.2, 7.8 Hz, 2 H), 7.78 (dd, *J* = 8.5, 7.8 Hz, 2 H), 7.63 (d, *J* = 7.9 Hz, 2 H), 7.55 (tt, *J* = 7.9, 1.7 Hz, 1 H), 7.40 (d, *J* = 7.9 Hz, 2 H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ = 139.6, 135.6, 134.2, 133.5, 132.7, 130.5, 129.5, 129.1, 125.0, 117.9, 108.2 (^{13}C-enriched), 64.4, ppm. **^{19}F NMR** (287 MHz, CD_2Cl_2) δ = -78.79 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3106, 3086, 2175, 2143, 1484, 1449, 1442, 1427, 1258, 1221, 1157, 1072, 1059, 1028, 998, 952, 936, 905884, 867, 785, 861, 734, 702, 761, 734, 702, 689, 659, 635,612. **HR-MS** calc. for $C_{20}H_{13}S$: 285.0732; found: 285.0730 $[M]^+$ (ESI-HRMS)

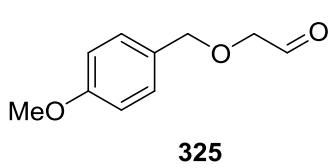
Synthesis of the compound 2-((4-methoxybenzyl)oxy)ethan-1-ol (**324**)



324

For the synthesis of compound **324** a slightly modified literature procedure was used.[160] To a solution of glycol (11.4 mL, 228 mmol, 6.00 equiv.) in THF (65 mL) was added dropwise NaH (60%, 1.35 g, 33.8 mmol, 1.00 equiv.) at 0 °C. After stirring for 15 min at 0 °C TBAI (1.25 g, 3.38 mmol, 0.10 equiv.) was added, followed by the dropwise addition of the chloride (4.60 ml, 33.8 mmol, 1.00 equiv.). The mixture was stirred at 65 °C for 12 h and subsequently s saturated aqueous solution of NH_4Cl (150 mL) was added to the reaction mixture. The organic phase was extracted with diethylether and the combined organic phases were dried over Na_2SO_4. After flash chromatography (hexane: EtOAc = 1:1) the desired product could be obtained as yellow oil (5.24 g, 28.7 mmol, 85%). Analytical data corresponded to those described in the literature.[160]

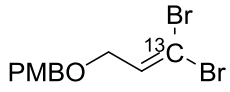
Synthesis of 2-((4-methoxybenzyl)oxy)acetaldehyde (**325**)



325

For the synthesis of **325** a slightly modified literature procedure was used.[100] To a solution of the alcohol **324** (630 mg, 3.60 mmol, 1.00 equiv.) in DCM (27 mL) was added DMP (1.59 mmol, 3.90 mmol, 1.00 equiv.) and the suspension was stirred for 2.5 h at rt. A saturated aqueous solution of $NaHCO_3$ (30 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (30 ml) was added to the reaction mixture and the resulting biphasic mixture was stirred for 10 min until a clear mixture occurred. The layers were separated and the organic phase was washed with water (30 mL) and brine (30 mL). The organic phases were dried over Na_2SO_4. After removal of the solvent under reduced pressure the desired product could be obtained as yellow oil (630 mg, 3.49 mmol, 97%). Analytical data corresponded to those described in the literature.[100]

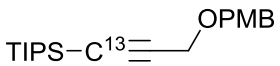
Synthesis of 1-(((3,3-dibromoallyl-3-^{13}C)oxy)methyl)-4-methoxybenzene (**326**)



326

For the synthesis of labeled **326** a slightly modified literature procedure was used.[100] To a solution of labeled CBr_4 (950 mg, 2.86 mmol, 1.00 equiv.) in DCM (12 mL) was added a solution of PPh_3 (1.55 g, 5.83 mmol, 2.00 equiv.) in DCM (9 mL) with a syringe pump over 30 min at 0 °C. The solution was stirred for another 15 min at 0 °C and then cooled to -78 °C. Subsequently a solution of the aldehyde **325** (630 mg, 3.49 mmol, 1.20 equiv.) was added with a syringe pump to the reaction mixture at -78 °C. The solution was stirred for another 12 h, slowly warming up to rt. A saturated aqueous solution of $NaHCO_3$ (30 ml) was added to the reaction mixture. Phases were separated and the aqueous phase was extracted by DCM (3 x 20 mL). The combined org. phases were washed water (30 mL), brine (30 mL) and dried over Na_2SO_4. After column chromatography (pure hexane) the product could be obtained as colorless oil (530 mg, 1.58 mmol, 55%). Analytical data corresponded to those described in the literature.[100]

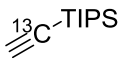
Synthesis of labeled labeled triisopropyl(3-((4-methoxybenzyl)oxy)prop-1-yn-1-yl)silane (**327**)



327

For the synthesis of labeled **327** a slightly modified literature procedure was used.[100] To a solution of the dibromide **326** (530 mg, 1.58 mmol, 1.00 equiv.) in THF (10.5 mL) was added *n*BuLi (2.5 M in hexane, 1.40 mL, 3.48 mmol, 2.20 equiv.) at -78 °C and the solution was stirred for 1 h at -78 °C. The solution was warmed up to rt and stirred for another hour at this temperature. Then the solution was cooled back to -78 °C and TIPSCl (0.44 mL, 2.05 mmol, 1.30 equiv.) was added. The reaction mixture was stirred for 12 h, slowly was warming up to rt. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After flash chromatography the desired product could be isolated as colorless oil (456 mg, 1.37 mmol, 87%). Analytical data corresponded to those described in the literature.[100]

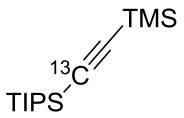
Synthesis of (ethynyl-^{13}C)triisopropylsilane (**328**)



328

For the synthesis of labeled compound **328** a slightly modified literature procedure was used.[100] To a suspension of the ether **327** (472 mg, 1.42 mmol, 1.00 equiv.) in DCM (10 mL) and water (1 mL) was added DDQ (484 mg, 2.13 mmol, 1.50 equiv.) at 0 °C and the reaction was stirred for 15 in at 0 °C and 3 h at rt. Then a saturated aqueous solution of $NaHCO_3$ (30 mL) was adding to the reaction mixture and the reaction mixture was extracted by DCM (3 x 15 mL). The combined org. phases were washed with brine (2 x 30 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was dissolved in diethylether (25 mL). Manganese dioxide (1.85 g, 21.3 mmol, 15.00 equiv.) and potassium hydroxide (599 mg, 10.7 mmol, 7.50 equiv.) were added to reaction in four portions over 3 h. Afterwards the reaction mixture was stirred for another 4 h at rt. The excess of manganese dioxide was removed by filtration over a short pad of silica. Column chromatography (pentane) afforded the product as colorless oil (200 mg, 1.10 mmol, 77%). Analytical data corresponded to those described in the literature.[100]

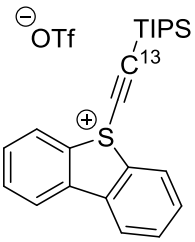
Synthesis of triisopropyl((trimethylsilyl)ethynyl-1-^{13}C)silane (**329**)



329

For the synthesis of **329** a slightly modified literature procedure was used.[100] To a solution of the alkyne **328** (390 mg, 2.14 mmol, 1.00 equiv.) in THF (5 ml) was added slowly at -78 °C *n*BuLi (2.5 M in hexane, 2.57 mmol, 1.20 equiv.) The reaction was stirred for 15 min at -78 °C and then warmed up to 0 °C. After stirring for another 5 min at 0 °C the solution was cooled back to -78 °C and TMSCl (0.35 mL, 2.78 mmol, 1.30 equiv.) was added to the reaction mixture. The reaction mixture was stirred for another 12 h, slowly warming up to rt. A saturated aqueous solution of NH_4Cl was added to the reaction mixture. The reaction mixture was extracted with diethylether (3 x 20 mL) and the combined organic phases were washed with brine and subsequently dried over Na_2SO_4. Column chromatography (pure pentane) offered the product as colorless oil (361 mg, 1.42 mmol, 66%). Analytical data corresponded to those described in the literature.[100]

Synthesis of compound labeled 5-((triisopropylsilyl)ethynyl)-5*H*-dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate (**238f***)



238f*

Using the general procedure GPC, compound 2**38f*** was prepared from **329** (280 mg, 1.42 mmol, 1.00 equiv.), Tf_2O (0.24 mL, 1.42 mmol, 1.00 equiv.) and labeled trimethyl[2-[tris(1-methylethyl)silyl]ethynyl]silane (361 mg, 1.42 mmol, 1.00 equiv.), obtaining after washing a white powder (607 mg, 1.21 mmol, 85%). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 8.32 (d, *J* = 8.5 Hz, 2 H), 8.19 (dd, *J* = 7.7, 1.3 Hz, 2 H), 7.94 (dt, *J* = 7.7, 1.0 Hz, 2 H), 7.79 (dt, *J* = 7.7, 1.2 HZ, 2 H), 1.21-1.07 (m, 3 H), 1.02-1.00 (m, 18 H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ = 139.5, 135.4, 132.6, 131.0, 128.3, 125.0, 118.6 (enriched, major), 78.8 (enriched, minor), 18.6, 11.5. ppm**. ^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -78.87 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2945, 2866, 1462, 1448, 1271, 1249, 1226, 1153, 1072, 1062, 1028, 997, 966, 921, 880, 821, 766, 757, 704. **HR-MS** calc. for $C_{20}H_{12}BrS$: 365.1754; found: 365.1747 $[M]^+$ (ESI-HRMS).

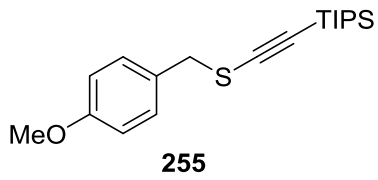
5.4 Electrophilic group transfer to nucleophiles

5.4.1 Reactions with benchmark nucleophiles

General procedure D (GPD)

To a suspension of a the desired nucleophile (1.00 equiv.) and Cs_2CO_3 (1.10 equiv.) in dry DCM/DCE (14 mL/mmol), was added the corresponding dibenzothiophenium salt (1.20-1.50 equiv.). The reaction was stirred for 12 h. at the specified temperature. After quenching with water (8 mL), the mixture was extracted using DCM (3 x 10 mL), the organic layers were combined, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude products were purified by column chromatography.

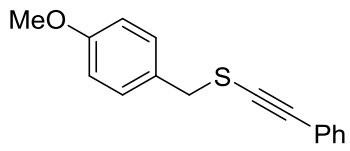
Synthesis of triisopropyl(((4-methoxybenzyl)thio)ethynyl)silane (**255**)



255

Using the general procedure GPD, compound **255** was prepared from (4-methoxyphenyl)methanethiol (30.9 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 20/1) compound **255** was obtained as a yellow oil (66.8 mg, 72%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.26 (td, *J* = 8.7, 3.1 Hz, 2 H), 6.84 (td, *J* = 8.7, 3.1 Hz, 2 H), 3.92 (s, 2 H), 3.80 (s, 3 H), 1.04 ppm (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 159.2, 130.3, 128.9, 114.1, 98.7, 95.7, 55.5, 40.4, 18.8, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2992, 2941, 2863, 2836, 2721, 2557, 2087, 1881, 1610, 1584, 1510, 1462, 1441, 1423, 1383, 1365, 1317, 1302, 1250, 1236, 1205, 1174, 1123, 1105, 1072, 1036, 1016, 995, 919, 881, 855, 828, 807, 745, 727, 674, 654. **HR-MS** calc. for $C_{19}H_{30}OSSi$: 334.1787; found: 334.1781 $[M]^+$ (EI-HRMS). Analytical data corresponded to those previously reported.[161]

Synthesis of (4-methoxybenzyl)(phenylethynyl)sulfane (**256**)

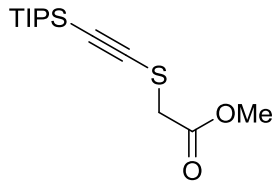


256

Using the general procedure GPD, compound **256** was prepared from (4-methoxyphenyl)methanethiol (34.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78 mg, 0.24 mmol, 1.10 equiv.) and **238a** (115 mg, 0.55 mmol, 1.50 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 5/1) compound **256** was obtained as a yellow oil (76.1 mg, 70 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.34 7.23 (m, 7 H), 6.85 (td, *J* = 8.6, 2.0 Hz, 2 H, 3.97 (s, 2 H), 3.78 ppm (s, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 159.4, 131.4, 130.4, 128.7, 128.9, 128.1, 123.6, 114.1, 94.6, 79.6, 55.4, 40.2 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061, 2953,2931, 2906, 2834, 2359, 2332, 2164, 1885, 1734, 1608, 1595, 1583, 1509, 1486, 1462, 1440, 1421, 1317, 1302, 1248, 1236, 1205, 1174, 1236, 1205, 1174, 1105, 1068,

1031, 913, 883, 829, 752, 689, 653, 544, 530, 514. **HR-MS** for $C_{16}H_{14}OS$: calc.: 255.0838; found: 255.0834 $[M+H]^+$ (ESI-HRMS).

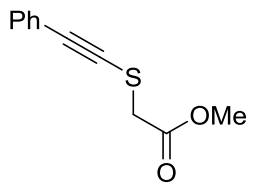
Synthesis of methyl 2-(((triisopropylsilyl)ethynyl)thio)acetate (**257**)



257

Using the general procedure GPD, compound **257** was prepared from the methyl 2-mercaptoacetate (71.6 mg, 0.29 mmol, 1.00 equiv.), Cs_2CO_3 (103 mg, 0.32 mmol, 1.10 equiv.) and **238f** (162 mg, 0.65 mmol, 1.20 equiv.) in dry DCM (4 mL). The reaction was carried out at RT for 12 h. After flash chromatography (hexane/EtOAc : 25/1) compound **257** was obtained as a yellow oil (71.6 mg, 87 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 3.77 (s, 3 H), 3.51 (s, 2 H), 1.06 ppm (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 168.7, 99.5, 93.5, 52.9, 38.0, 18.8, 11.5. ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2943, 2865, 2093, 1742, 1462, 1435, 1406, 1384, 1273, 1193, 1130, 1072, 1012, 996, 919, 881, 854, 675, 659. **HR-MS** calc. for $C_{14}H_{26}O_2SSi$: 287.1496; found: 287.1497 $[M+H]^+$ (ESI-HRMS).

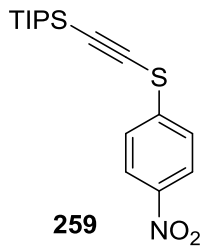
Synthesis of methyl 2-((phenylethynyl)thio)acetate (**258**)



258

Using the general procedure GPD, compound **258** was prepared from methyl 2-mercaptoacetate (45.6 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151.1 mg, 0.47 mmol, 1.10 equiv.) and **238a** (283 mg, 0.65 mmol, 1.50 equiv.) in dry DCM. The reaction was carried out at RT for 12 h. After flash chromatography (hexane/EtOAc : 20/1) compound **258** was obtained as a yellow oil (45.6 mg, 91 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.43-7.39 (m, 2 ppm **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 168.9, 131.8, 128.6, 128.4, 123.0, 100.2, 94.7, 53.0, 37.7 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3078, 3058, 3031, 3001, 2951, 2843, 2168, 1571, 1486, 1435, 1404, 1271, 1194, 1155, 1128, 1007, 900, 880, 842, 753, 689, 645, 622, 604. **HR-MS** calc. for $C_{11}H_{10}O_2S$: 207.0474; found: 207.0689 $[M+H]^+$ (ESI-HRMS).

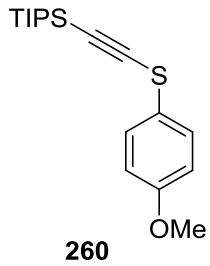
Synthesis of triisopropyl(((4-nitrophenyl)thio)ethynyl)silane (**259**)



259

Using the general procedure GPD, compound **259** was prepared from 4-nitrobenzenethiol (34.1 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (pure hexane) compound **259** was obtained as a yellow oil (56.6 mg, 76%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.20 (td, *J* = 8.6, 2.8 Hz, 2 H) , 7.57 (td, *J* = 8.6, 2.8 Hz, 2 H), 1.15 ppm (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 146.3, 142.9, 125.8, 124.3, 106.8, 88.2, 18.9, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2943, 2863, 2096, 1597, 1581, 1515, 1467, 1461, 1383, 1353, 1336, 1315,1254, 1233, 1107, 1081, 1016, 992, 917, 880, 851, 837, 738, 721, 676, 652, 627. **HR-MS** calc. for $C_{17}H_{25}NO_2SSiNa$: 358.1269; found: 358.1269 $[M+Na]^+$ (ESI-HRMS).

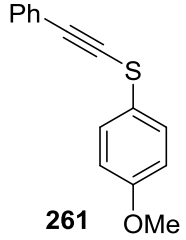
Synthesis of triisopropyl(((4-methoxyphenyl)thio)ethynyl)silane (**260**)



260

Using the general procedure GPD, compound **260** was prepared from the 4-methoxy-benzenethiol (30.8 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (pure hexane) compound **260** was obtained as a yellow oil (52.0 mg, 73%). **^{1}H NMR** (300 MHz, CDCl3) δ = 7.37 (td, *J* = 8.9, 2.2 Hz, 2 H),6.89 (td, *J* = 9.0, 2.2 Hz, 2 H), 3.80 (s, 3 H), 1.11 ppm (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 158.7, 128.2, 122.9, 114.9, 101.4, 92.7, 55. 4, 18.7, 11.5 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =2940, 2803, 2090, 1592, 1576, 1488, 1461, 1383, 1290, 1244, 1174, 1104, 1086, 1071, 1033, 1017, 995, 881, 857, 821, 802, 675, 658, 636, 622, 591, 573, 515. **HR-MS** for $C_{18}H_{28}OSSi$: calc.: 320.1630; found: 320.1632 $[M]^+$ (EI-HRMS).

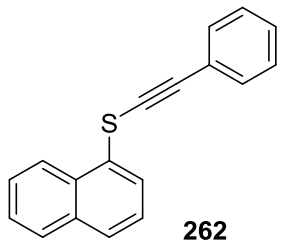
Synthesis of (4-methoxyphenyl)(phenylethynyl)sulfane (**261**)



261

Using the general procedure GPD, compound **261** was prepared from 4-methoxy-benzenethiol (60.0 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238a** (283 mg, 0.65 mmol, 1.50 equiv.) in dry DCM. The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 20/1) compound **261** was obtained as a yellow oil (66.5 mg, 64 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.52-7.44 (m, 4 H), 7.34 (m, 3 H), 6.92 (td, *J* = 9.0, 2.3 Hz, 2), 3.81 ppm (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 159, 132, 128, 123, 115, 96, 55 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3061, 3030, 3002, 2955, 2938, 2904, 2834, 2167, 1590, 1574, 1490, 1459, 1440, 1289, 1243, 1173, 1027, 1005, 914, 821, 797, 752, 718, 689, 655, 635, 621. **HR-MS** calc. for $C_{15}H_{12}OS$: 241.0682; found: 241.0689 $[M+H]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[162]

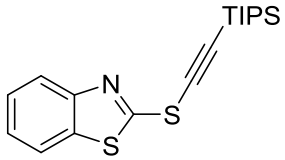
Synthesis of naphthalen-1-yl(phenylethynyl)sulfane (**262**)



262

Using the general procedure GPD, compound **262** was prepared from naphthalene-1-thiol (68.8 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238a** (283 mg, 0.65 mmol, 1.50 equiv.) in dry DCM. The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 50/1) compound **262** was obtained as a yellow oil (54.5 mg, 49 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.18 (qd, *J* = 7.7, 1.0 Hz, 1 H), 7.97 (dd, *J* = 7.42, 1.3 Hz, 1 H), 7.91 (m_C, 1 H), 7.79 (d, *J* = 8.5 Hz, 1 H), 7.64-7.49 (m, 5 H), 7.39-7.36 ppm (m, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 133.9, 131.8, 130.8, 129.8, 128.7, 128.7, 128.4, 127.6, 126.7, 126.6, 126.0, 125.66, 123.6, 123.1, 97.9, 75.8 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3852, 3054, 3031, 2987, 2954, 2941, 2888, 2863, 2163, 1738, 1697, 1684, 1591, 1563, 1503, 1487, 1456, 1442, 1414, 1369, 1336, 1166, 766. **MS** calc. for $C_{18}H_{12}S$: 260.1; found: 260.1 $[M]^+$ (EI-MS).

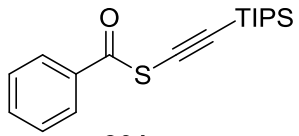
Synthesis of 2-(((triisopropylsilyl)ethynyl)thio)benzo[*d*]thiazole (**263**)



263

Using the general procedure GPD, compound **263** was prepared from benzo[*d*]thiazole-2-thiol (36.8 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1 to 10:1) compound **263** was obtained as a yellow oil (78.9 mg, 98%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.87 (ddd, *J* = 8.2, 1.4, 0.6 Hz, 1 H), 7.83 (ddd, *J* = 8.2, 1.4, 0.6 Hz, 1 H), 7.44 (ddd, *J* = 8.2, 7.8, 1.4, 1 H), 7.34 (ddd, *J* = 8.2, 7.8, 1.4 Hz, 1 H), 1.20-1.15 (m, 21) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 165.5, 154.4, 135.8, 126.4, 124.7, 122.1, 121.1, 108.8, 87.6, 18.84, 11.6.ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2941, 2889, 2863, 2097, 1464, 1425, 1284, 1365, 1309, 1275, 1258, 1237, 1124, 1073, 1020, 1009, 996, 933, 919, 881, 853, 846, 805, 753, 725, 704, 753, 725, 704, 676, 659. **HR-MS** calc. for $C_{18}H_{25}NS_2Si$: 348.1270; found: 348.1270 $[M+H]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[161]

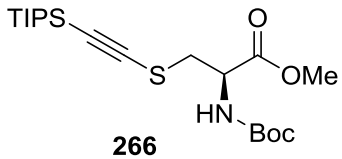
Synthesis of *S*-((triisopropylsilyl)ethynyl) benzothioate (264)



264

Using the general procedure GPD, compound **264** was prepared from the benzothioic *S*-acid (30.4 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238a** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 20/1) compound **264** was obtained as a yellow oil (46.0 mg, 66%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.87 (m_C, 2 H), 7.63 (tt, *J* = 7.5, 1.3 HZ, 1 H), , 7.48 (t, *J* = 7.7 Hz, 2 H), 1.15 ppm (m_C, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 187.5, 135.5, 134.3, 129.2, 127.5, 109.6, 86.0, 18.8, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 2864, 2104, 1703, 1462, 1448, 1201, 1176, 1072, 1017, 997, 919, 880, 856, 804, 767, 742, 673, 637. **HR-MS** calc. for $C_{18}H_{26}OSSiNa$: 341.1360; found: 341.1366 $[M+Na]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[104]

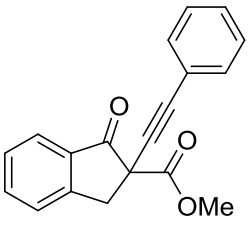
Synthesis of methyl *N*-(*tert*-butoxycarbonyl)-*S*-((triisopropylsilyl)ethynyl)-*L*-cysteinate (**266**)



266

Using the general procedure GPD, compound **266** was prepared from methyl-(tert-butoxycarbonyl)-*L*-cysteinate (51.8 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 10/1) compound **266** was obtained as a yellow oil (731 mg, 80%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 5.49 (d, *J* = 7.9 Hz, 1 H), 4.70 (s, 1 H), 3.26 (dd, *J* = 13.1, 4.4 Hz, 1 H), 3.13 (dd, *J* = 14.3, 5.1 Hz, 1 H), 1.46 (s, 9 H), 1.08 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 170.7, 155.2, 98.2, 94.5, 80.3, 53.9, 52.7, 38.4, 28.2, 18.6, 11.3 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3370, 2943, 2981, 2865, 2091, 1749, 1717, 1499, 1461, 1437, 1415, 1391, 1365, 1349, 1309, 1249, 1214, 1161, 1056, 1016, 995, 918, 881, 854, 800, 777, 759, 734, 676, 659. **HR-MS** calc. for $C_{20}H_{37}NOSSi$: 433.2551; found: 433.2549 $[M+NH_4]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[161]

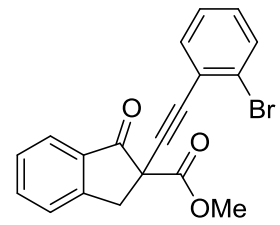
Synthesis of methyl 1-oxo-2-(phenylethynyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**232**)



232

Using the general procedure GPD, compound **232** was prepared from 2,3-dihydro-1-oxo-1*H*-Indene-2-carboxylic acid methyl ester (81 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238a** (284 mg, 0.65 mmol, 1.50 equiv.) in dry DCE (6 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **232** was obtained as a yellow oil (98.5 mg, 79 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.82 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.64 (ddd, *J* = 7.7, 7.2, 1.2 Hz, 1 H), 7.49 (dt, *J* = 7.7, 0.9 Hz, 1 H), 7.47 – 7.35 (m, 3 H), 7.31 – 7.19 (m, 4H), 4.00 (d, *J* = 17.1 Hz, 1 H), 3.80 (s, 3 H), 3.59 ppm (d, *J* = 17.2 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 196.0, 168.5, 152.0, 135.8, 133.2, 131.8, 128.3, 128.0, 128.0, 126.3, 125.6, 122.2, 85.2, 83.7, 55.9, 53.7, 41.0 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3054, 3034, 2953, 2842, 2150, 2059, 1997, 1956, 1718, 1605, 1589, 1573, 1490, 1476, 1463, 1432, 1326,1300, 1229, 1211, 1173, 1155, 1094, 1063, 990, 954, 917, 884, 807, 791, 753, 732, 689, 650. **HR-MS** calc. for $C_{19}H_{14}O_3$: 291.1016; found: 291.1018 $[M]^+$ (ESI-HRMS).

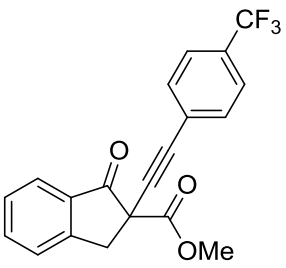
Synthesis of methyl 2-((2-bromophenyl)ethynyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**269**)



269

Using the general procedure GPD, compound **269** was prepared from 2,3-dihydro-1-oxo-1*H*-Indene-2-carboxylic acid methyl ester (81 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238e** (330 mg, 0.65 mmol, 1.50 equiv.) in dry DCE (6 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **269** was obtained as a yellow oil (125.0 mg, 79 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.87 – 7.79 (m, 1 H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.56 – 7.36 (m, 4 H), 7.27 – 7.06 (m, 2 H), 4.03 (d, *J* = 17.1 Hz, 1 H), 3.82 (s, 3 H), 3.67 ppm (d, *J* = 17.1 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 195.7, 168.3, 152.2, 136.0, 133.6, 133.2, 132.3, 129.7, 128.2, 126.9, 126.5, 125.9, 125.8, 124.5, 90.0, 82.5, 56.3, 53.9, 40.9 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3648, 3439, 3061, 2952, 2930, 2841, 1719, 1605, 1588, 1557, 1467, 1429, 1326, 1300, 1254, 1230, 1211, 1174, 1154, 1121, 1108, 1095, 1062, 1042, 1026, 987, 953, 920, 883, 863, 831, 811, 792, 752, 706, 689, 664, 652, 605. **HR-MS** calc. for $C_{19}H_{13}BrO_3$: 369.0121; found: 369.0118 $[M+H]^+$ (ESI-HRMS).

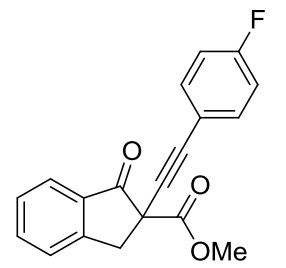
Synthesis of methyl 1-oxo-2-((4-(trifluoromethyl)phenyl)ethynyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**270**)



270

Using the general procedure GPD, compound **270** was prepared from 2,3-dihydro-1-oxo-1H-Indene-2-carboxylic acid methyl ester (81 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238c** (323 mg, 0.65 mmol, 1.50 equiv.) in dry DCE (6 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **270** was obtained as a yellow oil (109 mg, 74 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.88 – 7.82 (m, 1 H), 7.68 (ddd, *J* = 7.7, 7.2, 1.2 Hz, 1 H), 7.54 (s, 4 H), 7.52 – 7.50 (m, 1 H), 7.45 (ddd, *J* = 7.9, 7.2, 0.9 Hz, 1 H), 4.03 (d, *J* = 17.1 Hz, 1 H), 3.82 (s, 3 H), 3.62 ppm (d, *J* = 17.2 Hz, 1 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 195.8, 168.3, 152.2, 136.1, 133.2, 132.3, 130.3 (q, *J* = 32.5 Hz), 128.4, 126.5, 126.3, 125.9, 125.1 (q, *J* = 3.8 Hz), 122.8, 88.0, 82.6, 56.1, 54.0, 41.0 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -62.87 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2143, 1721, 1607, 1437, 1320, 1263, 1235, 1212, 1165, 1121, 1104, 1063, 1014, 919, 842, 751, 702, 689. **HR-MS** calc. for $C_{20}H_{13}O_{238f3}$: 358.0817; found: 358.0822 $[M]^+$ (EI-HRMS).

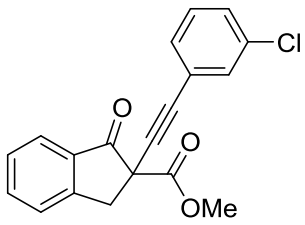
Synthesis of methyl 2-((4-fluorophenyl)ethynyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**271**)



271

Using the general procedure GPD, compound **271** was prepared from 2,3-dihydro-1-oxo-1*H*-Indene-2-carboxylic acid methyl ester (81 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238d** (291 mg, 0.65 mmol, 1.50 equiv.) in dry DCE (6 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **271** was obtained as a yellow oil (87.0 mg, 65 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.81 (qd, *J* = 7.7, 0.7 Hz, 1 H) , 7.66 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.50 (dt, *J* = 7.6, 0.9 Hz, 1 H), 7.46-7.39 (m, 3 H), 6.95 (tt, *J* = 8.7, 2.3, 2 H), 4.00 (d, *J* = 17.1 Hz, 1 H), 3.81 (s, 3 H), 3.60 ppm (d, *J* = 17.1 Hz, 1 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 196.2, 168.7, 164.3, 161.0, 152.3, 136.1, 134.0 (d, *J* = 8.3 Hz), 133.4, 128.3, 126.5, 125.9, 118.5 (d, *J* = 3.6 Hz), 115.5 (d, *J* = 22.5 Hz, 85.1 (d, *J* = 2.0 Hz), 82.9, 60.4, 56.0, 53.8, 41.1, 21.1, 14.3. ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3073, 2953, 1718, 1655, 1600, 1589, 1505, 1476, 1464, 1433, 1405, 1327, 1299, 1212, 1174, 1154, 1093, 1060, 1013, 990, 954, 919, 884, 863, 836, 818, 800, 790, 818, 800, 790, 750, 688, 636, 750, 688, 636. **HR-MS** calc. for $C_{19}H_{1238f}O_3$: 326.1187; found: 326.1183 $[M+NH_4]^+$ (ESI-HRMS).

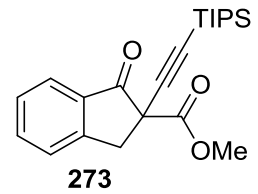
Synthesis of methyl 2-((3-chlorophenyl)ethynyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**272**)



272

Using the general procedure GPD, compound **23** was prepared from 2,3-dihydro-1-oxo-1*H*-Indene-2-carboxylic acid methyl ester (81 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238b** (302 mg, 0.65 mmol, 1.50 equiv.) in dry DCE. The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **272** was obtained as a yellow oil (113 mg, 81 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.88 – 7.83 (m, 1 H), 7.75 – 7.63 (m, 1 H), 7.53 (dt, *J* = 7.8, 0.9 Hz, 1 H), 7.48 – 7.42 (m, 2 H), 7.33 (dt, *J* = 7.4, 1.5 Hz, 1 H), 7.21 (ddd, *J* = 8.0, 7.4, 0.5 Hz, 1 H), 4.03 (d, *J* = 17.2 Hz, 1 H), 3.83 (s, 3 H), 3.61 ppm (d, *J* = 17.6 Hz, 1 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 195.9, 168.4, 152.1, 136.1, 134.0, 133.2, 131.9, 130.1, 129.4, 128.8, 128.3, 126.5, 125.8, 124.1, 86.7, 82.5, 56.0, 53.9, 41.0 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3646, 3562, 3439, 3066, 3035, 2953, 2927, 2847, 1719, 1605, 1590, 1560, 1474, 1463, 1431, 1409, 1328, 1294, 1262, 1231, 1211, 1174, 1155, 1095, 1074, 1062, 1018, 996, 954, 926, 883, 852, 820, 786, 767, 751, 717, 680, 602. **HR-MS** calc. for $C_{19}H_{13}ClO_3$: 325.0630; found: 325.0626 $[M]^+$ (ESI-HRMS).

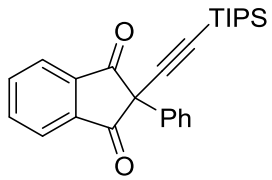
Synthesis of methyl 1-oxo-2-((triisopropylsilyl)ethynyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**273**)



273

Using the general procedure GPD, compound **273** was prepared from 2,3-dihydro-1-oxo-1H-Indene-2-carboxylic acid methyl ester (81.8 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238f** (267 mg, 0.52 mmol, 1.20 equiv.) in dry DCM (6 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **273** was obtained as a yellow oil (86.0 mg, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = δ 7.80 (qd, *J* = 7.6, 0.7 Hz, 1 H), 7.64 (dt, *J* = 7.6, 1.3 Hz, 1 H), , 7.47 (qd, *J* = 7.8, 0.9 Hz, 1 H), 7.40 (qt, *J* = 7.5, 9.0 Hz, 1 H), 3.91 (d, *J* = 17.4 Hz, 1 H), 3.75 (s, 3 H), 3.47 (d, *J* = 17.4 Hz, 1 H), 1.03 ppm (s, 21 H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ = 195.8, 168.7, 152.1, 135.8, 133.5, 128.2, 126.4, 125.8, 103.2, 85.7, 56.5, 53.7, 18.8, 11.4. ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 2809, 2168, 1754, 1725, 1607, 1590, 1463, 1433, 1249, 1210, 1176, 1134, 1093, 1070, 1017, 995, 966, 955, 921, 881, 827, 811, 774, 751, 713, 675, 661, 635. **HR-MS** calc. for $C_{22}H_{30}O_3Si$: 371.2037; found: 371.2034 $[M+H]^+$ (ESI-HRMS).

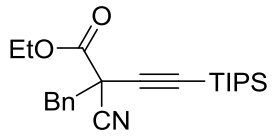
Synthesis of 2-phenyl-2-((triisopropylsilyl)ethynyl)-1*H*-indene-1,3(2*H*)-dione (**274**)



274

Using the general procedure GPD, compound **274** was prepared from 2-phenyl-1H-indene-1,3(2H)-dione (48.9 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **274** was obtained as a yellow oil (84.0 mg, 95%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 78.13 (dd, *J* = 5.9, 3.1 Hz, 2 H), 7.94 (dd, *J* = 5.9, 3.1 Hz, 2 H), 7.39-7.3 (m, 5 H), 1.06 ppm (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 194.9, 141.5, 136.4, 135.3, 128.9, 128.3, 127.4, 124.9, 101.0, 89.5, 59.9, 18.8, 11.5 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2931, 2881, 2360, 2348, 2170, 1755, 1735, 1709, 1585, 1498, 1460, 1337, 1249, 1160, 1037, 1019, 997, 919, 880, 855, 759, 727, 695, 678, 581. **HR-MS** calc. for $C_{26}H_{30}O_2SiNa$: 425.1902; found: 425.1632 $[M+Na]^+$ (EI-HRMS).

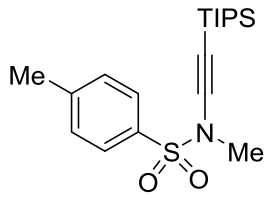
Synthesis of ethyl 2-benzyl-2-cyano-4-(triisopropylsilyl)but-3-ynoate (**275**)



275

Using the general procedure GPD, compound **275** was prepared from α-cyano-benzenepropanoic acid ethyl ester (29.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (*n*-Hexane/EtOAc 20/1) compound **275** was obtained as a yellow oil (38.0 mg, 70%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.38-7.30 (m, 5 H), 4.27 (dd, *J* = 14.3, 7.5 Hz, 2 H), 4.27 (dd, *J* = 17.8, 13.7 Hz, 2 H) , 3.40 ppm (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 164.7, 133.2, 128.4, 115.8, 97.3, 90.3, 64.0, 44.3, 18.6, 13.96, 11.2 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =2945, 2890, 2863, 1742, 1703, 1495, 1463, 1453, 1389, 1381, 1366, 1276, 1236, 1162, 1098, 1070, 1059, 1030, 1009, 997, 919, 906, 883, 853, 806, 772, 742, 706, 699, 678, 660, 627, 607. **HR-MS** calc. for $C_{23}H_{33}NOSiNa$: 406.2173; found: 406.2165 $[M+Na]^+$ (ESI-HRMS).

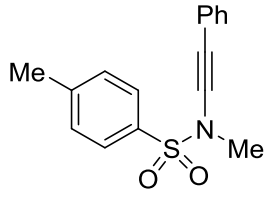
Synthesis of *N*,4-dimethyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide (**281**)



281

Using the general procedure GPD, compound **281** was prepared from *N*-methyl-4-(methylbenzene)sulfonamide (40.8 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM. The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 8/1) compound **281** was obtained as a yellow oil (53.8 mg, 67 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.80 (td, *J* = 8.3, 1.7 Hz, 2 H), 7.33 (d, *J* = 7.3 Hz, 2 H), 3.07 (s, 3 H), 2.45 (s, 3 H), 1.04 ppm (s, 21 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 144.8, 133.5, 129.8, 128.0, 98.2, 67.6, 39.5, 21.8, 18.7, 11.0 ppm. **HR-MS** calc. for $C_{24}H_{33}NO_2SSiNa$: 450.1893; found: 450.1444 $[M+Na]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[163]

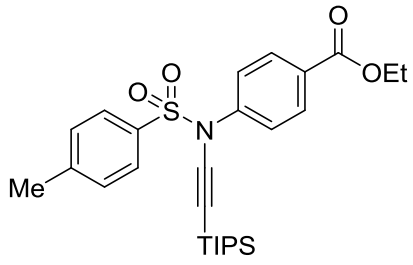
Synthesis of *N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide (**282**)



282

Using the general procedure GPD, compound **282** was prepared from *N*-methyl-4-(methylbenzene)sulfonamide (79.7 mg, 0.43 mmol, 1.00 equiv.), Cs_2CO_3 (151 mg, 0.47 mmol, 1.10 equiv.) and **238a** (283 mg, 0.65 mmol, 1.50 equiv.) in dry DCM. The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 8/1) compound **282** was obtained as a yellow oil (67.7 mg, 55 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.76 (td, *J* = 8.3, 1.5 Hz, 2 H), 7.30-7.17 (m, 7 H), 3.06 (s, 3 H), 2.37 ppm (s, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 144.9, 133.4, 131.5, 129.9, 128.4, 127.9, 122.8, 84.1, 77.2, 69.2, 39.4, 21.7 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =2940, 2890, 2964, 2172, 1747, 1710, 1695, 1589, 1456, 1383, 1362, 1348, 1332, 1310, 1277, 1255, 1245, 1232, 1224, 1200, 1189, 1142, 1126, 1105, 1061, 1051, 1020, 995, 937, 882, 840, 805, 784, 768, 747, 692, 676, 662, 640. **HR-MS** calc. for $C_{16}H_{15}NO_2S$: 286.0898; found: 286.0896 $[M+H]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[164]

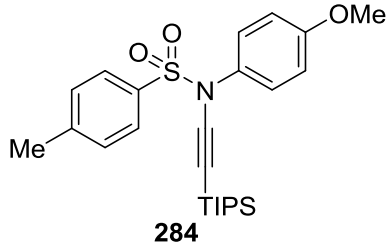
Synthesis of Ethyl 4-((4-methyl-*N*-((triisopropylsilyl)ethynyl)phenyl)sulfonamido)benzoate (**283**)



283

Using the general procedure GPD, compound **283** was prepared from ethyl 4-((4-methylphenyl)sulfonamido)benzoate (67.7 mg, 0.22 mmol, 1.00 eq.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 eq.) and the dibenzothiophenium salt **238f** (136 mg, 0.26 mmol, 1.20 eq.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1) compound **283** was obtained as a colorless oil (63.7 mg, 55%). **^{1}H NMR** (300 MHz,$CDCl_3$) δ = 8.00 (td, *J* = 8.7, 2.2 H, 2 H), 7.56 (td, *J* = 8.4, 2.1 Hz, 2 H), 7.41 (td, *J* = 8.7, 2.6 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 4.37 (q, *J* = 7.0 Hz, 2 H), 2.42 (s, 3 H), 1.38 (t, *J* = 7.1 Hz 3 H), 1.06 ppm (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 165.7, 145.3, 142.8, 139.9 130.4, 129.6, 128.2, 125.0, 95.6, 71.4, 61.4, 21.9, 18.8, 17.9, 14.5, 12.5, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2941, 2923, 2863, 2160, 2154, 1504, 1464, 1370, 1253, 1186, 1169, 1088, 1029, 1017, 995, 905, 881, 836, 807, 791, 733, 703, 791, 733, 703, 676, 664, 649, 574, 550, 524. **HR-MS** for $C_{27}H_{37}NO_4SSi$: calc.: 500.2285; found: 500.2281 $[M+H]^+$ (ESI-HRMS).

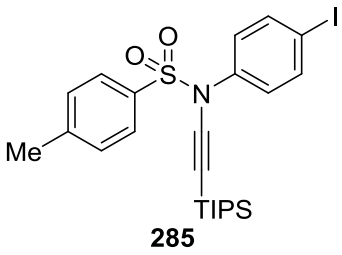
Synthesis of *N*-(4-methoxyphenyl)-4-methyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide (**284**)



284

Using the general procedure GPD, compound **284** was prepared from the *N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (64.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1 to 10:1) compound **284** was obtained as a colorless oil (50.0 mg, 50%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.56 (td, *J* = 8.2, 2.1 Hz, 2 H), 7.25 (qd, *J* = 8.0, 0.7 Hz, 2 H), 7.14 (td, *J* = 9.2, 2.3 Hz, 2 H), 6.82 3.80 (s, 3 H), 2.44 (s, 3 H), 1.05 ppm (s, 21 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 145.2, 138.8, 138.1, 132.6, 129.5, 128.3, 127.6, 95.9, 93.3, 70.4, 21.7, 18.6, 11.4 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958, 2941, 2922, 2890, 2863, 2157, 1597, 1585, 1505, 1464, 1444, 1420, 1399, 1370, 1356, 1302, 1254, 1209, 1186, 1169, 1138, 1118, 1106, 1087, 1072, 1029, 1018, 995, 970, 944, 905, 881, 836, 808, 790, 733, 703, 675, 665, 648, 603. **HR-MS** calc. for $C_{25}H_{35}NO_3SSiNa$: 458.2180; found: 458.2174 $[M+Na]^+$ (ESI-HRMS).

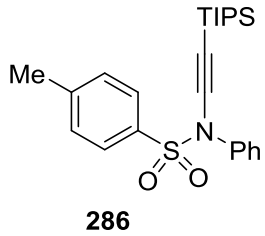
Synthesis of *N*-(4-iodophenyl)-4-methyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide (**285**)



285

Using the general procedure GPD, compound **285** was prepared from the *N*-(4-iodophenyl)-4-methylbenzenesulfonamide (122.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **285** was obtained as a white solid (73.0 mg, 62%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.64 (td, *J* = 8.5, 2.6 Hz, 2 H), 7.56 (td, *J* = 8.3, 2.3 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.03 (td, *J* = 8.5, 2.6 Hz, 2 H), 2.43 (s, 3 H), 1.05 ppm (m, 21 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 145.3, 138.9, 138.3, 132.7, 129.6, 128.4, 127.7, 96.0, 93.4, 70.5, 21.8, 18.7, 11.5 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =2958, 2941, 2921, 2889, 2863, 2157, 1597, 1585, 1505, 1464, 1444, 1370, 1356, 1302, 1254, 118, 1106, 1088, 1072, 1029, 1018, 995, 905, 881, 836, 808, 7890, 733, 703, 675, 665, 648, 603. **HR-MS** calc. for $C_{24}H_{32}NO_2SSiINa$: 576.0860; found: 576.0848 $[M+Na]^+$ (ESI-HRMS).

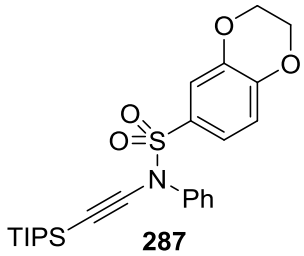
Synthesis of 4-methyl-*N*-phenyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide (**286**)



286

Using the general procedure GPD, compound **286** was prepared from *N*-phenyl- tolylsulfonamide (54.4 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **286** was obtained as a yellow oil (63.3 mg, 67 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.56 (td, *J* = 8.3, 2.0 Hz), 7.35-7.27 (m, 5 H), 7.26-7.22 (m, 2 H), 2.43 (s, 3 H), 1.05 ppm (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 144.9, 138.9, 133.1, 129.4, 129.0, 128.4, 128.0, 126.0, 96.7, 69.8, 21.9, 18.9, 11.7 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 2867, 2361, 2163, 1709, 1591, 1486, 1461, 1368, 1291, 1250, 1171, 1133, 1090, 1073, 1039, 1017, 996, 923, 896, 881, 812, 773, 713, 661, 643. **HR-MS** calc. for $C_{24}H_{33}O_2SSiNa$: 450.1893; found: 450.1883 $[M+Na]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[165]

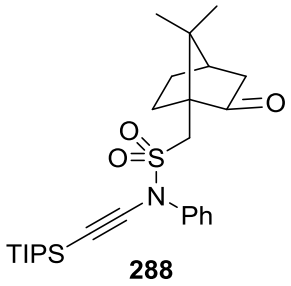
Synthesis of *N*-phenyl-*N*-((triisopropylsilyl)ethynyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (**287**)



287

Using the general procedure GPD, compound **287** was prepared from *N*-phenyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (64.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1 to 10:1) compound **287** was obtained as a white solid (64.0 mg, 62%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.36-7.26 (m, 6 H), 7.11 (dd, *J* = 8.9, 2.1 HZ), 6.87 (d, *J* = 8.9 Hz, 1 H), 4.33- 4.30 (m, 2 H), 4.27-4.25 (m, 2 H), 1.06 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) = 148.5, 143.3, 139.0, 129.0, 128.2, 128.0, 126.0, 122.1, 118.3, 117.5, 96.8, 69.9, 64.8, 64.2, 18.9, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2941, 2889, 2863, 2161, 1591, 1581, 1489, 1460, 1420, 1373, 1319, 1285, 1253, 1204, 1168, 1126, 1105, 1075, 1063, 1047, 1027, 1017, 995, 920, 900, 878, 814, 768, 711, 697, 687, 677, 662, 645, 627, 611. **HR-MS** calc. for $C_{25}H_{33}NO_4SSiNa$: 494.1780; found: 494.1792 $[M+Na]^+$ (ESI-HRMS).

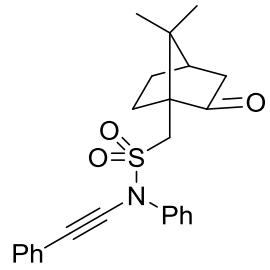
Synthesis of 1-((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-phenyl-*N*-((triisopropyl-silyl)ethynyl)methanesulfonamide (**288**)



288

Using the general procedure GPD, compound **288** was prepared from 1-((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-phenylmethane-sulfon-amide (68.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc 15/1 to 10:1) compound **288** was obtained as a white solid (64.0 mg, 60%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.58-7.55 (m, 2 H), 7.45-7.39 (m, 2 H), 7.32 (tt, *J* = 7.7, 1.3 Hz, 1 H), 3.79 (d, *J* = 13.6 Hz, 1 H) , 3.27 (d, *J* = 13.6 Hz, 1 H), 2.52 (dt, *J* = 13.6, 3.3 Hz, 1 H), 2.38 (td, *J* = 19.5, 4.4 Hz, 1 H), 2.11-1.95 (m, 2 H), 1.92 (d, *J* = 19.5 H, 1 H), 1.64-1.55 (m, 1 H), 1.44-1.36 (dt, *J* = 8.7, 3.9 Hz, 1 H), 1.18-1.05 (m, 24 H, 21 H), 0.87 (s,.3 H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 214.3, 138.8, 129.4, 128.0, 125.2, 96.2, 71.0, 58.5, 47.9, 46.6, 43.1, 42.5, 27.0, 25.5, 20.2, 20.0, 18.8, 11.5 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2941, 2888, 2823, 2162, 1739, 1591, 1489, 1456, 1414, 1397, 1369, 1296, 1281, 1260, 1245, 1208, 1167, 1130, 1106, 1070, 1051, 1028, 1011, 997, 972, 920, 893, 881, 855, 819, 772, 743, 704, 687, 678, 662, 688, 678, 662, 640, 625, 614. **HR-MS** calc. for $C_{27}H_{41}NO_3SSiNa$: 486.2504; found: 486.2486 $[M+Na]^+$ (ESI-HRMS).

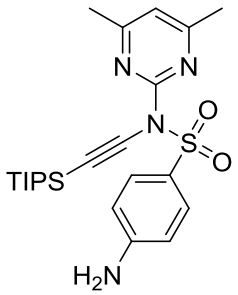
Synthesis of 1-((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-phenyl-*N*-(phenylethynyl)-methanesulfonamide (**289**)



289

Using the general procedure, compound **289** was prepared from 1-((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-phenylmethanesulfonamide (79.7 mg, 0.22 mmol, 1.00 eq.), Cs_2CO_3 (151 mg, 0.24 mmol, 1.10 eq.) and the dibenzothiophenium salt **3a** (115 mg, 0.26 mmol, 1.20 eq.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 12/1 to 10/1) compound **289** was obtained as a yellow oil (50.1 mg, 56 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.64-7.62 (m, 2 H), 7.47-7.43 (m, 4 H), 7.36 (tt, *J* = 7.34, 1.8 Hz, 1 H), 7.34-7.30 (m, 3 H), 3.85 (d, *J* = 15.3 Hz, 1 H), 3.38 (d, *J* = 15.3 Hz, 1 H), 2.52 (dt, *J* = 12.7, 4.2 Hz, 1 H), 2.40 (td, *J* = 18.4, 4.2 Hz, 1 H), 2.12-2.03 (m, 2 H), 1.94 (d, *J* = 17.4 Hz, 1 H), 1.66 (q, *J* = 4.4 Hz, 1 H), 1.42 (ddd, *J* = 9.8, 3.3, 3.3 Hz, 1 H), 1.16 (s, 3 H), 0.89 ppm (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ =214.4, 138.9, 131.6, 129.6, 128.4, 128.2, 125.5, 122.6, 82.4, 71.5, 58.6, 47.3, 43.2, 42.6, 27.0, 25.5, 20.3, 19.9 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2957, 2888, 2864, 2238, 2161, 1742, 1684, 1591, 1489, 1471, 1455, 1443, 1415, 1392, 1369, 1338, 1300, 1281, 1262, 1201, 1165, 1130, 1106, 1081, 1066, 1052, 1025, 998, 966, 920, 894, 854, 817, 784, 774, 754, 689, 641, 598, 571, 554, 533, 524, 518. **HR-MS** for $C_{24}H_{25}NO_3S$: calc.: 406.1482; found: 406.1482 $[M-H]^-$ (ESI-HRMS).

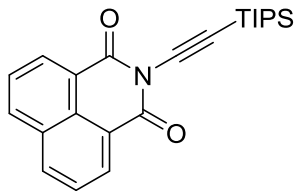
Synthesis of 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide (**290**)



290

Using the general procedure, compound **290** was prepared from Sulfadimidine (55.1 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and the dibenzothiophenium salt **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at rt for 12 h. A saturated aqueous solution of NH_4Cl was added. After flash chromatography using (DCM/methanol 25:1) compound **290** was obtained as a white solid (59.0 mg, 58%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.96 (td, *J* = 8.7, 2.7 Hz, 2 H), 6.67 (s, 1 H), 6.63 (td, *J* = 8.7, 2.7 Hz, 2 H), 4.20 (s, 2 H), 2.36 (s, 6 H), 1.12 (s, 21 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 168.1, 158.0, 151.7, 132.0, 126.7, 116.1, 113.2, 92.7, 74.7, 23.8, 18.9, 11.7 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2954, 2941, 2888, 2823, 2162, 1739, 1591, 1489, 1456, 1414, 1397, 1369, 1296, 1281, 1260, 1245, 1208, 1167, 1130, 1106, 1070, 1051, 1028, 1011, 997, 972, 920, 893, 881, 855, 819, 772, 743, 704, 687, 678, 662, 688, 678, 662, 640, 625, 614, 597, 625, 614, 597, 530, 521. **HR-MS** for $C_{23}H_{34}N_4Si_1$: calc.: 395.2626; found: 395.2626 $[M+H]^+$ (ESI-HRMS).

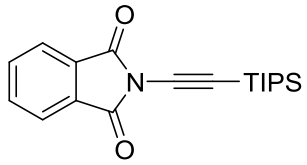
Synthesis of 2-((triisopropylsilyl)ethynyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**291**)



291

Using the general procedure GPD, compound **291** was prepared from 1H-benzoisoquinoline-1,3(2H)-dione (43.4 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (*n*-Hexane/EtOAc : 10/1) compound **291** was obtained as a white solid (50.0 mg, 60%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.66 (dd, *J* = 7.4, 1.1 Hz, 2 H), 8.26 (dd, *J* = 8.3, 1.1 Hz, 2 H), 7.79 (dd, *J* = 8.3, 7.4 HZ, 2 H), 1.20 ppm (m, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 162.8, 134.9, 132.0, 131.8, 127.1, 127.2, 121.6, 89.0, 80.5, 77.2, 18.9, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2955, 2940, 2924, 28889, 2862, 2722, 2364, 2353, 2333, 2209, 2192, 2170, 2162, 2148, 1726, 1692, 1635, 1625, 1583, 1559, 1540, 1512, 1489, 1459, 1512, 1489, 1459, 1434, 1409, 1370, 1351, 1335, 1254, 1231, 1223, 1173, 1142, 1104, 1081, 1047, 1015, 993, 940, 908, 892, 880, 839, 798, 767, 729, 697, 677, 646, 623, 614. **HR-MS** calc. for $C_{23}H_{27}NO_2Si$: 378.1884; found: 378.1893 $[M+H]^+$ (ESI-HRMS).

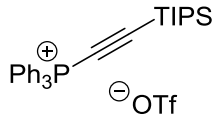
Synthesis of 2-((triisopropylsilyl)ethynyl)isoindoline-1,3-dione (**292**)



292

Using the general procedure GPD, compound **292** was prepared from the compound **238f** (33.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and the dibenzothiophenium salt **292** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1) compound **292** was obtained as a white solid (24.0 mg, 33%). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ = 7.93 (dd, *J* = 6.9, 2.9 Hz, 2 H), 7.82 (dd, *J* = 6.9, 2.9 Hz, 2 H), 1.16 (s_{br}, 21 H) ppm.^{13}C NMR (126 MHz, Chloroform-*d*) δ = 165.1, 135.1, 131.2, 124.2, 86.2, 76.6, 18.6, 11.2 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2940, 2890, 2864, 2172, 1747, 1710, 1695, 1589, 1456, 1332, 1309, 1277, 1255, 1245, 1232, 1224, 1200, 1189, 1132, 1126, 1105, 1061, 1051, 1020, 995, 937, 882, 840, 805, 784, 768, 747, 693, 676, 662, 640, 676, 662, 640, 597, 573, 528.

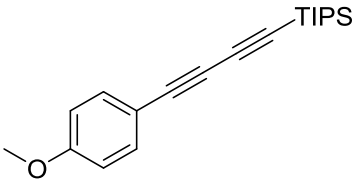
Synthesis of triphenyl((triisopropylsilyl)ethynyl)phosphonium trifluoromethanesulfonate (**303**)



303

To a solution of triphenylphospine (116 mg, 0.44 mmol, 1.00 equiv.) in DCM (6 ml) was added compound **238f** (237 mg, 0.46 mmol, 1.00 equiv.) and the resulting reaction mixture was stirred for 12 h at RT. Then the solvent was removed in *vacuo* and the residue washed with ether (3 x 10 mL) and pentane (2 x 10 ml). The remaining solid was dried in *vacuo* to afford the compound **303** as white solid (231 mg, 88%).**^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 7.96-7.89 (m_C 3 H), 7.80-7.74 (m, 9 H), 7.71-7.68 (m, 3 H) ppm. **^{13}C NMR** (101 MHz, CD_2Cl_2) δ = 136.3 (d, *J* = 3.1 Hz), 133.2 (d, *J* = 12.6 Hz), 130.9 (d, *J* = 14.2 Hz), 118.0 (*J* = 100.2 Hz), 86.0 (*J* = 159.9 Hz), 18.5, 11.3 ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = –76.97 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2953, 2868, 2125, 1460, 1439, 1264, 1223, 1179, 1146, 1109, 1067, 1030, 995, 882, 824, 764, 750, 726, 705, 689, 665, 635. **HR-MS** calc. for $C_{29}H_{36}PSi$: 443.2318; found: 443.2315 $[M+H]^+$ (ESI-HRMS).

Synthesis of triisopropyl((4-methoxyphenyl)buta-1,3-diyn-1-yl)silane (**304**)

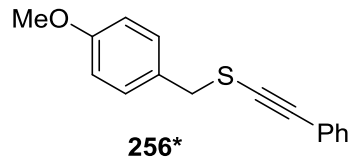


304

To a solution of the alkyne (29.0 mg, 0.22 mmol, 1.00 equiv.) in THF (3 mL) was added *n*BuLi (2.5 M, 0.1 mL, 0.23 mmol, 1.05 equiv.) at –78 °C. The solution was warmed up to 0 °C and stirred at this temperature for 5 min. Then the solution was cooled back to –78 °C and dibenzothiophenium salt **238f** (136 mg, 0.26 mmol, 1.20 equiv.) was added to the reaction mixture. The reaction mixture was warmed up slowly to rt and stirred for another 12 h at this temperature. The reaction mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were dried over $MgSO_4$. Column chromatography (pure hexane) afford the desired product **304** as yellow oil. (13.0 mg, 4.25 µmol, 19%).**^{1}H NMR** (300 MHz, Chloroform-*d*) δ = 7.46 (td, *J* = 8.9, 2.1 Hz, 2 H), 6.84 (td, *J* = 8.9 Hz, 2 H), 3.81 (s, 3 H), 1.11 (s, 21 H) ppm. **^{13}C NMR** (126 MHz, Chloroform-*d*) δ = 160.4, 134.4, 114.2, 113.5, 89.9, 87.2, 75.9, 73.7, 55.5, 18.8, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3003, 2942, 2891, 2865, 2363, 2200, 2097, 1716, 1603, 1567, 1508, 1462, 1442, 1416, 1384, 1365, 1295, 1250, 1172, 1105, 1097, 1071, 1028, 1017, 997, 919, 881, 829, 802, 673, 641, 590, 578, 533. **HR-MS** for $C_{20}H_{28}OSi$: calc.: 312.1909; found: 312.1908 $[M]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[166]

Synthesis of Labeled Compounds

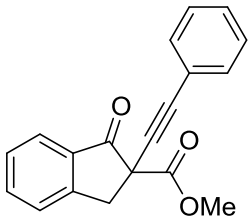
Synthesis of labeled (4-methoxybenzyl)(phenylethynyl)sulfane (**256***)



256*

Using the general procedure GPD, compound **256*** was prepared from (4-methoxyphenyl)methanethiol (34.0 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78 mg, 0.24 mmol, 1.10 equiv.) and **238a*** (115 mg, 0.65 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 5/1) compound **256*** was obtained as a yellow oil (31.2 mg, 56 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.36 7.28 (m, 7 H), 6.89 (td, *J* = 8.6, 3.3 Hz, 2 H) , 4.00 (s, 2 H), 3.81 ppm (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.4, 131.5, 130.4, 128.7, 128.4, 128.1, 123.6, 114.1 (enriched, 100%), 94.6, 79.6, 55.4, 40.2 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3059, 3030, 2997, 2954, 2930, 2906, 2833, 2164, 1608, 1595, 1583, 1572, 1509, 1486, 1462, 1440, 1421, 1317, 1201, 1248, 1236, 1205, 1174, 1126, 1105, 1068, 1030, 1000, 912, 882, 863, 828, 752, 727, 689, 653, 635. **HR-MS** calc. for $C_{16}H_{14}OS$: 255.0838; found: 255.0838 $[M+H]^+$ (ESI-HRMS).

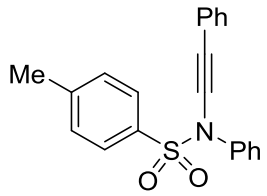
Synthesis of labeled methyl 1-oxo-2-(phenylethynyl)-2,3-dihydro-1H-indene-2-carboxylate (**232***)



232*

Using the general procedure GPD, compound **232*** was prepared from methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (38.0 mg, 0.20 mmol, 1.00 equiv.), Cs_2CO_3 (71.7 mg, 0.47 mmol, 1.10 equiv.) and the dibenzothiophenium salt **238a*** (130.5 mg, 0.65 mmol, 1.50 equiv.) in dry DCE (3 mL). The reaction was carried out at 60 °C for 12 h. After flash chromatography using (hexane/EtOAc 15/1) compound **232*** was obtained as a yellow oil (36.0 mg, 62 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 7.9 Hz, 1 H), 7.67 (dd, *J* = 8.0, 7.5 Hz, 1 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 7.46-7.41 (m, 3 H), 7.29-7.22 (m, 3 H).**^{13}C NMR** (75 MHz, $CDCl_3$) = 196.5, 168.8, 152.4, 136.1, 133.4, 132.1, 128.6, 128.35, 126.6, 126.0, 122.5, 85.4 (enriched, 57%), 84.0 (enriched, 43%), 56.1, 54.0, 41.2. ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3439, 3054, 3034, 3021, 2952, 2846, 1718, 1605, 1589, 1574, 1536, 1514, 1490. 1476, 1463, 1432, 1340, 1326, 1300, 1230, 1211, 1172, 1154, 1094, 1066, 1027, 1019, 990, 954, 918, 883, 863, 829, 809, 793, 752, 689, 623, 601; **HR-MS** calc. for $C_{19}H_{14}O_3$: 291.1016; found: 291.1012 $[M]^+$ (ESI-HRMS).

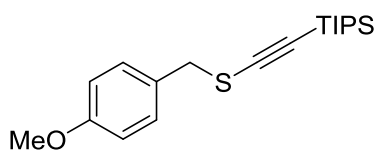
Synthesis of labeled 4-methyl-*N*-phenyl-*N*-(phenylethynyl)benzenesulfonamide (**286***)



238*

Using the general procedure GPD, compound **286*** was prepared from 4-methyl-*N*-phenylbenzenesulfonamide (54.4 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238a*** (114 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1) compound **286*** was obtained as a yellow solid (45.0 mg, 58 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.55 (td, *J* = 8.3, 2.1 Hz, 2 H), 7.33-7.18 (m, 12 H), 2.37 ppm (s, 3 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 145.1, 142.2, 139.1, 133.1, 131.6, 129.6, 129.2, 128.4, 128.4, 128.1, 126.4, 122.8, 83.1 (enriched, 100%), 77.2, 70.6, 21.9 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =3062, 3033, 2953, 2922, 2868, 2238, 2197, 1705, 1665, 1593, 1489, 1454, 1593, 1489, 1454, 1443, 1402, 1369, 1307, 1293, 1257, 1168, 1120, 1087, 1068, 1024, 1004, 972, 917, 886, 836, 812, 781, 754, 702, 689, 681, 652, 611. **HR-MS** calc. for $C_{21}H_{17}NOS$: 348.1053; found: 348.1056 $[M+H]^+$ (ESI-HRMS).

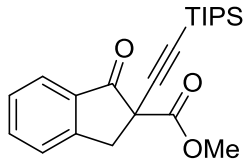
Synthesis of labeled triisopropyl(((4-methoxybenzyl)thio)ethynyl)silane (**255***)



255*

Using the general procedure, compound **255*** was prepared from (4-methoxyphenyl)methanethiol (30.9 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and the **238f*** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 20/1) compound **255*** was obtained as a yellow oil (51.0 mg, 70%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.29 (td, *J* = 8.6, 2.9 Hz, 2 H), 6.87 (td, *J* = 8.6, 2.9 Hz, 2 H), 3.94 (s, 2 H), 3.82 (s, 3 H), 1.07 (s, 21 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 159.0, 130.1, 128.6, 113.9, 98.5 (enriched, 76%), 95.5 (enriched, 24%), 55.3, 40.2, 18.6, 11.6 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 2891, 2864, 2087, 1610, 1512, 1463, 1441, 1302, 1251, 1237, 1175, 1037, 1017, 996, 882, 856, 830, 675, 657. **HR-MS** calc. for $C_{19}H_{30}OSSi$: 335.1852; found: 335.1859 $[M+H]^+$ (EI-HRMS).

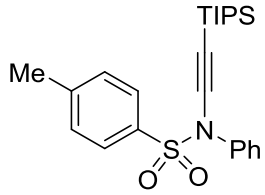
Synthesis of labeled methyl 1-oxo-2-((triisopropylsilyl)ethynyl)-2,3-dihydro-1*H*-indene-2-carboxylate (**273***)



273*

Using the general procedure GPD, compound **273*** was prepared from methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (41.8 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78 mg, 0.24 mmol, 1.10 equiv.) and **238f*** (136 mg, 0.24 mmol, 1.20 equiv.) in dry DCM (6 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc : 15/1) compound **273*** was obtained as a yellow oil (53.0 mg, 78 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 7.5 Hz, 1 H), 7.65 (dt, *J* = 8.3, 1.2 Hz, 1 H), 7.48 (d, *J* = 7.3 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 3.94 (d, *J* = 17.3 Hz, 1 H), 3.77 (s, 3 H), 3.50 (d, *J* = 17.3 Hz, 1 H), 1.04 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 195.9, 168.7, 152.1, 135.8, 133.4, 128.1, 126.4, 125.7, 103.2 (enriched, minor), 85.7 (enriched, major), 56.5, 53.7, 41.4, 18.8, 11.4 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2942, 2891, 2864, 2169, 1754, 1724, 1607, 1590, 1463, 1433, 1384, 1366, 1325, 1201, 1250, 1210, 1196, 1176, 1154, 1096, 1064, 1016, 995, 955, 920, 881, 826, 807, 792, 750, 676, 661, 637. **HR-MS** calc. for $C_{22}H_{30}O_3Si$: 335.1852; found: 335.1859 $[M+H]^+$ (ESI-HRMS).

Synthesis of labeled 4-methyl-*N*-phenyl-*N*-((triisopropylsilyl)ethynyl)benzenesulfonamide (**281***)



281*

Using the general procedure, compound **281*** was prepared from 4-methyl-N-phenylbenzenesulfonamide (54.4 mg, 0.22 mmol, 1.00 equiv.), Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and **238f*** (136 mg, 0.26 mmol, 1.20 equiv.) in dry DCM (3 mL). The reaction was carried out at RT for 12 h. After flash chromatography using (hexane/EtOAc 15/1) compound **281***was obtained as a yellow oil (30.0 mg, 32 %). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.55 (td, *J* = 8.1, 1.5 Hz, 2 H), 7.34-7.24 (m, 5 H), 7.23 (d, *J* = 9.4 Hz, 2 H), 2.41 (s, 3 H), 1.04 (s, 21 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 144.9, 138.9, 133.0, 129.4, 129.0, 128.4, 128.0, 126.0, 96.7 (enriched, minor), 69.8 (enriched, major), 21.9, 18.8, 11.7. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 2958, 2939, 2923, 2888, 2862, 2165, 2129, 1591, 1488, 1455, 1367, 1304, 1291, 1261, 1176, 1167, 1132, 1120, 1088, 1073, 1018, 996, 926, 891, 882, 812, 801. 771, 712, 702, 688, 680, 670, 654, 628, 583,. **HR-MS** calc. for $C_{24}H_{33}O_2SSi$: 428.2074; found: 428.2077 $[M+H]^+$ (ESI-HRMS).

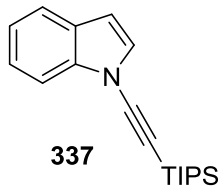
5.4.2 Attempts towards metal catalyzed reactions

Lewis acid catalysis

General procedure E (GPE):

To a solution of the indole (0.22 mmol, 1.00 equiv.) in the desired solvent (0.07 M) was added the catalyst system, the base (0.24 mmol, 1.10 equiv.) and the reagent (136 mg, 0.26 mmol, 1.20 equiv.). The reaction mixture was stirred at specified temperature for 12 h. Then the reaction mixture was filtered through a short pad of silica with ethyl acetate (around 100 mL) as eluent and subsequently the solvent was removed under reduced pressure. The residue was purified by flash chromatography and the resulting products were examined by NMR and mass spectroscopy.

Synthesis of 1-((triisopropylsilyl)ethynyl)-1*H*-indole (**337**)



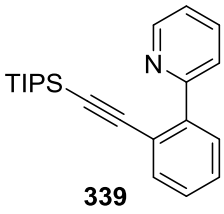
337

Following the general procedure GPE: Indole (25.0 mg, 0.22 mmol, 1.00 equiv.), the catalyst system chloro(triphenylphosphine)gold(I) (10.0 mg, 0.02 mmol, 0.10 equiv.) and silver hexafluoroantimonate(V) (7.0 mg, 0.02 mmol, 1.00 equiv.), the reagent, Cs_2CO_3 (78.0 mg, 0.24 mmol, 1.10 equiv.) and DCM (3 mL) were used. The reaction was stirred at rt and after flash chromatography the product **337** could be isolated as yellow oil (25.0 mg, 0.08 mmol, 38%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 7.9 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.38 (dt, *J* = 7.4, 0.9 Hz, 1 H), 7.30-7.23(m, 2 H), 6.59 (dd, *J* = 3.5, 0.9 Hz, 1 H), 1.22 (s, 21 H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 138.4, 129.1, 127.8, 123.7, 122.1, 121.3, 111.5, 105.3, 94.7, 68.9, 18.9, 11.5 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) =2941, 2890, 2863, 2179, 1612, 1524, 1457, 1383, 1352, 1340, 1324, 1295, 1221, 1201, 1122, 1088, 1072, 1041, 1011, 995, 919, 881, 777, 760, 740, 713, 674, 658, 623, 589, 562, 517, 503. **HR-MS** calc. for $C_{19}H_{27}NSi$: 298.1986; found: 298.1982 $[M+H]^+$ (EI-HRMS). Analytical data corresponded to those previously reported.[167]

Entry	Catalyst	Additive	Base	Solvent	Yield (%)	Comments
1	$AuClPPh_3$	$AgSbF_6$	Cs_2CO_3	DCM	**38**	*N*-alkynylated product **337**
2	$AuClPPh_3$	$AgSbF_6$	K_3PO_4	DCM	0	Isolated starting material **333**
3	$AuClPPh_3$	$AgSbF_6$	TBAOAC	DCM	0	Isolated starting material **333**
4	$AuClPPh_3$	$AgSbF_6$	KOAC	DCM	0	Isolated starting material **333**
5	$AuClPPh_3$	$AgSbF_6$	Cs_2CO_3	DCE	23	Reaction at 60 °C
6	$AuClPPh_3$	$AgSbF_6$	Cs_2CO_3	DCM	0	*N*-Methylindole **334** as a substrate; re-isolated
7	AgCl	–	Cs_2CO_3	DCM	23	*N*-alkynylated product **337**
8	AgCl	–	Cs_2CO_3	Et_2O	25	*N*-alkynylated product **337**
9	AgCl	–	K_2CO_3	THF	23	*N*-alkynylated product **337**
10	AgCl	–	–	DCM	0	Isolated starting material **333**
11	$PtCl_2$	–	Cs_2CO_3	DCM	0	No reaction
12	$PtCl_2$	–	DIPEA	DCM	0	Reaction at 60°C, Isolated starting material **333**
13	$PtCl_2$	–	–	DCE	0	Reaction at 80 °C, Isolated starting material **333**
14	$AuCl_3$	–	Cs_2CO_3	DCM	0	No reaction
15	$AuCl_3$	–	–	DCM	0	*N*-Methylindole as a substrate

C-H alkynylation experiments

Synthesis of 2-(2-((triisopropylsilyl)ethynyl)phenyl)pyridine (**339**)



339

General procedure: To a solution of the 2-phenylpyridine (34.1 mg, 0.22 mmol, 1.00 equiv.) in DCE/DCM (0.1 M) was added the catalyst and the corresponding base. The reagent (136 mg, 0.26 mmol, 1.20 equiv.) was added and the reaction mixture was stirred for 12 h at the elaborated temperature. The reaction mixture was filtrated over a short pad of silica and the solvent was removed by evaporation. The residue was purified by column chromatography (hexane: EtOAc = 95:5) to afford the product **339** as colorless oil. Analytical data corresponded to those described in the literature.

Entry	Catalyst	Additive	Base	Solvent	T (°C)	Yield (%)
1	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	–	DCM	rt	Traces of the product **339**
2	$[RhCp^*Cl_2]_2$ (2%)	$Zn(OTf)_2$ (10%)	–	DCE	rt	SM* + traces of the product **339**
3	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	–	DCE	80	34
4	$[RhCp^*Cl_2]_2$ (2%)	$Zn(OTf)_2$ (10%)	–	DCE	80	32
5	$[IrCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (10%)	–	DCM	rt	0 (SM)
6	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	–	MeCN	80	4
7	$MnBr(CO)_5$	$HNCy_2$ (20%)	–	DCE	80	Traces of the product **339**
8	$[RhCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (10%)	–	DCE	80	Mixture of SM and product
9	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	–	DCE (twice diluted)	80	24
10	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (20%)	–	DCE	80	Mixture of SM and product
11	$[RhCp^*Cl_2]_2$ (8%)	$AgSbF_6$ (10%)	–	DCE	80	Mixture of SM and product
12	$[RhCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (5%)	–	DCE	80	Mixture of SM and product
13	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Cs_2CO_3	DCM	rt	0 (SM*)
14	$[IrCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (10%)	Cs_2CO_3	DCM	rt	0 (SM)
15	$[RhCp^*Cl_2]_2$ (4%)	$AgSbF_6$ (5%)	Cs_2CO_3 (2.00 equiv.)	DCE	80	Traces of the product **339**
16	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	TBAOAc	DCM	rt	0 (SM)
17	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Cesium pivalate	DCE	80	Decomposition of **238f**

18	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	K_3PO_4	DCE	rt	Traces of the product **339**
19	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	H_2O	DCE	80	Traces of the product **339**
20	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	$K_4P_2O_7$	DCE	rt	SM
21	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Pyridine	DCE	80	SM
22	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Lutidine	DCE	80	SM
23	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	2,6-Di-*tert*-butylpyridine	DCE	80	Product **339** (4%)
24	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	2,6-Di-*tert*-butylpyridine	DCE	rt	Traces of the product **339**
25	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	2,6-Di-*tert*-butylpyridine (0.50 eq)	DCE	rt	Traces of the product **339**
26	$MnBr(CO)_5$	–	$HNCy_2$	DCE	80	Traces of the product **339**
27	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DMAP	DCE	80	Traces of the product **339**
28	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DIPEA	DCE	80	Traces of the product **339**
29	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	Proton sponge	DCE	rt	0 (SM)
30	$[RhCp^*Cl_2]_2$ (2%)	$AgSbF_6$ (10%)	DBU	DCE	80	Decomposition of **238f**

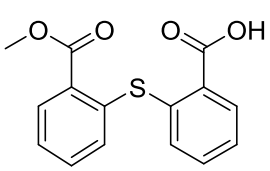
*SM = Starting material **338**.

5.5 Synthesis attemps towards a system with internal base

Synthesis of methyl 2-mercaptobenzoate (**341**)

To a solution of thiosalicylic acid (**340**, 2.50 g, 16.2 mmol, 1.00 equiv.) in methanol (13 mL) was added sulfuric acid (0.43 mL, 8.10 mmol, 0.50 equiv.) at 0 °C and the reaction mixture was stirred under reflux for 18 h. The solvent was removed under reduced pressure and sat $NaHCO_3$-solution was added to the residue. The aqueous phase was extracted with DCM (3 x 15 mL). The combined organic phases were washed by brine. After removal of the solvent under reduced pressure the product **341** could be isolated as yellow oil (2.55 g, 15.2 mmol, 94%). . **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.95-8.00 (m, 1H), 7.26-7.29 (m, 2 H), 7.08-7.15 (m, 1 H), 4.67 (s, 1 H), 3.89 (s, 3 H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 166.9, 138.0, 132.2, 131.5, 130.7, 125.6, 124.3, 52.0 ppm. **HR-MS** calc. for $C_8H_8O_2S$: 167.0172; found: 167.0172 $[M+H]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[168]

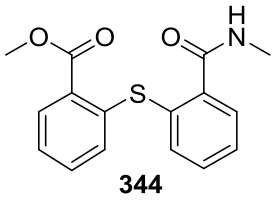
Synthesis of 2-((2-(methoxycarbonyl)phenyl)thio)benzoic acid (**343**)



343

To a solution of the ester **341** (1.00 g, 5.94 mmol, 1.00 equiv.) and 2-iodobenzoic acid (**342**, 1.47 g, 5.94 mmol, 1.00 equiv.) in pyridine (7 mL) was added copper(I) oxide (0.43 g, 2.97 mmol, 0.05 equiv.) and the reaction mixture was stirred for 22 h at 114 °C. Afterwards the reaction mixture poured to a solution of hydrochloric acid (1 M, 100 mL). The aqueous solution was extracted by ethyl acetate (3 x 50 mL). The combined organic phases were washed by diluted hydrochloric acid (1 M, 3x 100 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was washed with hexane and chloroform to afford the desired compound **343** (1.16 g, 4.02 mmol, 68%) as yellow solid. **^{1}H-NMR** (300 MHz, CD_3CN): δ [ppm] = 7.94-7.90 (m, 1 H), 7.86-7.84 (m, 1 H), 7.49-7.31 (m, 5 H), 7.26-7.26 (m, 1H), 7.14-7.10 (m, 1 H), 3.78 (s, 3 H) ppm. **^{13}C-NMR** (126 MHz, CD_3CN): δ [ppm] = 168.0, 167.9, 134.2, 133.7, 133.6, 133.3, 133.2, 133.0, 132.3, 131.6, 131.3, 128.4, 128.0, 127.7, 52.9 ppm. **IR** (ATR): $\tilde{\nu}$ [cm^{-1}] = 557, 694, 720, 743, 932, 1039, 1057, 1111, 1253, 1270, 1666, 1728, 2643, 2817, 2951. **HR-MS** calc. for $C_{15}H_{12}O_4S$: 287.0384; found: 287.0385 $[M+H]^+$ (ESI-HRMS).). Analytical data corresponded to those previously reported.[136b]

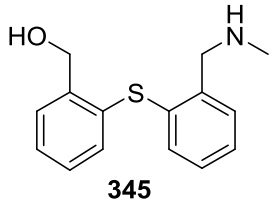
Synthesis of methyl 2-((2-(methylcarbamoyl)phenyl)thio)benzoate (**344**)



344

For the synthesis of **344** a slightly modified literature procedure was used.[136b] To a solution of the acid **343** (798 mg, 2.77 mmol, 1.00 equiv.) was added thionyl chloride (6.30 mL, 87.0 mmol, 31.4 equiv.) and the resulting solution was stirred for 3 h at 70 °C. The excess of thionyl chloride was removed under reduced pressure and residue was dissolved in THF (40 mL). The solution was cooled to 0 °C, methylamine was added dropwise to the reaction mixture and the solution was stirred for 12 h at rt. The reaction mixture was poured to water and extracted by DCM (3 x 100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc + 1 % Net_3 , 1:5) to afford the desired compound **344** as white solid (586 mg, 1.94 mmol, 70%). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 7.98-7.95 (m, 1H), 7.89-7.86 (m, 1 H), 7.39- 7.55 (m, 3 H), 7.30 (ddd, J = 8.1 Hz, 7.3 Hz, 1.7 Hz, 1 H), 7.19 (dd, J = 7.4 Hz, 1.3 Hz, 1 H), 6.89 (dd, J = 7.9 Hz, 1.7 Hz, 1 H),), 3.92 (s, 3 H), 2.83 (d, J = 4.9 Hz, 3 H) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$): δ [ppm] = 168.2, 167.9, 140.7, 139.9, 136.5, 132.8, 131.2, 130.7, 130.2, 130.1, 129.6, 128.9, 125.5, 52.5, 26.9 ppm. **IR** (ATR): $\tilde{\nu}$ [cm^{-1}] = 526, 688, 705, 740, 1252, 1434, 1561, 1634, 1709, 2955, 3099, 3261. **HR-MS** calc. for $C_{16}H_{15}NO_3S$: 300.0700; found: 300.0695 $[M+H]^+$ (ESI-HRMS).). Analytical data corresponded to those previously reported.[136b]

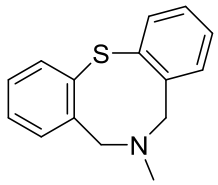
Synthesis of (2-((2-((methylamino)methyl)phenyl)thio)phenyl)methanol (**345**)



345

For the synthesis of **345** a slightly modified literature procedure was used.[136b] To a solution of the amide **344** (1.20 g, 3.99 mmol, 1.00 equiv.) in benzene was added phosphorus pentachloride (0.83 g, 3.99 mmol, 1.00 equiv.) and the reaction mixture was heated under reflux for 2 and subsequently the solvent was removed by reduced pressure. The residue was taken up by THF (15 mL) and a suspension of lithium aluminium hydride was added to the reaction mixture at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and afterwards for another 30 h at rt. *Iso*-propanol was added at -78 °C to the reaction mixture. The suspension was filtrated over celite and the solvent removed under reduced pressure. The water (50 mL) was added to the reaction mixture and aqueous phase was extracted by DCM (3 x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure to afford the desired product **345** as colorless oil (698 mg, 2.70 mmol, 68%). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 7.44 (ddt, J = 7.5 Hz, 1.3 Hz, 0.7 Hz, 1 H), 7.35-7.18 (m, 5 H), 7.12 (m_C, 2 H) 7.07 (td, J = 8.0 Hz, 7.5 Hz, 1.7 Hz, 1 H), 4.64 (s, 2 H), 3.84 (s, 2 H), 2.43 (s, 5 H) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$): δ [ppm] = 142.1, 139.4, 135.0, 133.4, 133.3, 131.6, 130.0, 129.2, 128.5, 128.3, 128.2, 127.1, 63.3, 54.0, 35.9 ppm. **HR-MS** calc. for $C_8H_8O_2S$: 282.0923; found: 282.0922 $[M+Na]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[136b]

Synthesis of 6-methyl-6,7-dihydro-5*H*-dibenzo[*b*,*g*][1,5]thiazocine (**346**)



346

For the synthesis of **345** a slightly modified literature procedure was used.[136b] To a solution of the alcohol **345** (673 mg, 2.59 mmol, 1.00 equiv.) in benzene (11 mL) was added thionyl chloride (6.70 mL, 92.2 mmol, 35.5 equiv.) and the solution was stirred for 3 h at 70 °C. Afterwards the solvent was removed under reduced pressure and the residue was taken up by ethanol (5.6 mL). A solution of sodium hydroxide (1.45 g, 25.8 mmol, 9.95 equiv.) in ethanol (5.6 mL) was added to the residue and the reaction mixture was stirred at 70 °C overnight. Afterwards the solvent was removed under reduced pressure and water (50 mL) was added. The aqueous phase was extracted by ethyl acetate (50 mL) and the solvent was removed under reduced pressure. After purification by column chromatography (hexane/EtOAc + 1 % NEt_3 , 2:1) the desired compound **346** could be isolated as white solid (452 mg, 1.87 mmol, 72%). **^{1}H-NMR** (300 MHz, CD_3CN): δ [ppm] = 2.09 (s, 3 H), 3.79 (d, J = 1.4 Hz, 2 H), 7.01-7.07 (m, 3 H), 7.12-7.18 (m, 2 H), 7.19-7.24 (m, 1 H), 7.30-7.35 (m, 1 H), 7.42-7.46 (m, 1 H). **IR** (ATR): $\tilde{\nu}$ [cm^{-1}] = 2876, 2360, 1467, 1435, 1427, 1416, 1357, 1326, 1276, 1261, 1185, 1174, 1152, 1117, 1056, 1032, 985, 954, 926, 824, 767, 756, 726, 678, 607, 547, 517. **HR-MS** calc. for **$C_{15}H_{15}NS$**: 242.0996; found: 242.0998 $[M+H]^+$ (ESI-HRMS). Analytical data corresponded to those previously reported.[136b]

5.6 Synthesis of potential fluorine containing transfer-reagents

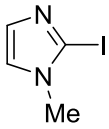
5.6.1 Synthesis of a trifluoromethyl-reagent

Synthesis of silver(I) trifluoromethanethiolate (**350**)


350

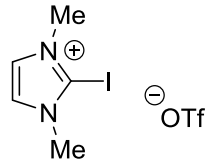
Following a slightly modified literature procedure,[137] to a solution of silver fluoride (2.15 g, 17.0 mmol, 1.00 equiv.) in MeCN (15 mL) was added carbon disulfide (2.04 mL, 33.9 mmol. 2.00 equiv.). The reaction mixture was stirred for 18 °C under reflux. Then the solvent was removed in vacuo and the residue was dissolved in Et_2O (300 mL).The mixture led rest at 0 °C. After approximately 7 d the product could be isolated as white crystals (1.90 g, 9.08 mmol, 54%). Analytical data corresponded to those described in the literature.[137]

Synthesis of 2-iodo-1-methyl-1H-imidazole (**352**)


352

Following a slightly modified literature procedure,[138] *n*BuLi (1.6 M, 13.7 mL, 21.9 mmol, 1.20 equiv.) was added slowly to a solution of *N*-methyl imidazol (1.50 g, 18.3 mmol, 1.00 equiv.) in THF (250 mL) at -78 °C. The reaction mixture was stirred for 1 h at this temperature before a solution of iodine (5.80 g, 22.8 mmol, 1.25 equiv.) in THF (50 mL) was added at -78 °C. The solution was warmed up to rt and stirred at this temperature for 3 d. Then the solvent was removed by evaporation. The residue was taken up by DCM, washed with water, sat. $Na_2S_2O_4$ solution, brine and dried over Na_2SO_4. After removal of the solvent the product **352** could be isolated as white solid (3.20 g, 15.4 mmol, 84%). Analytical data corresponded to those described in the literature.[138]

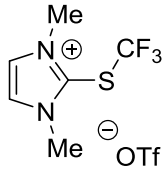
Synthesis of 2-iodo-1,3-dimethyl-1*H*-imidazol-3-ium trifluoromethanesulfonate (**354**)



354

Following a slightly modified literature procedure,[138] to a solution of compound **352** (4.08 g, 19.6 mmol, 1.00 equiv.) in DCM (100 mL) was added MeOTf (6.44 g, 39.2 mmol, 2.00 equiv.) at rt. The Solution was stirred for 16 h at rt. After removal of the solvent by filtration the product **354** could be obtained as white solid (5.35 g, 14.4 mmol, 73%). Analytical data corresponded to those described in the literature.[138]

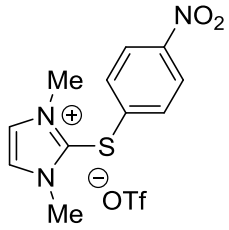
Synthesis of 1,3-dimethyl-2-((trifluoromethyl)thio)-1*H*-imidazol-3-ium trifluoromethanesulfonate (**355**)



355

A solution of the imidazolium salt **354** (1.00 g, 2.69 mmol, 1.00 equiv.) and the silver thiolate **350** (561 mg, 2.69 mmol, 1.00 equiv.) in dry MeCN (10 mL) was stirred at 100 °C for 12 h in the microwave. The solution was separated from the AgI via filtration and the solvent was evaporated *in vacuo*. The remaining solid was washed with DCM (2 x 4 ml) to afford the product **355** as white solid (651 mg, 1.88 mmol, 76%). **^{1}H-NMR** (300 MHz, CD_3CN): δ [ppm] = 7.76 (s, 2 H), 3.98 (s, 6 H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ = 130.8, 128.5 127.9 (q, J = 315.3 Hz), 122.0 (q, J = 317.9 Hz), 38.0 ppm. **^{19}F NMR** (282 MHz, CD_3CN) = -39.97, -79.32 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3121, 2360, 2342, 1509, 1280, 1242, 1226, 1182, 1147, 1109, 1095, 1026, 800, 759, 739, 637, 630, 571, 541, 516. **HR-MS** calc. for $C_6H_8F_3N_2S$: 197.0355; found: 197.0358 $[M]^+$ (ESI-HRMS).

Synthesis of 1,3-dimethyl-2-((4-nitrophenyl)thio)-1*H*-imidazol-3-ium trifluoromethanesulfonate (**368**)

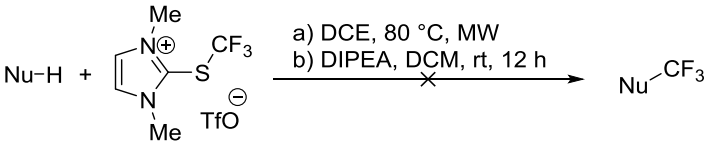


368

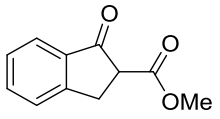
To a solution of the imidazolium salt **355** (50.0 mg, and the thiol in MeCN (1.5 mL) was added DIPEA (55.9 mg, 0.43 mmol, 3.00 equiv.). The solution was stirred for 12 h at rt. Afterwards the solvent was removed under reduced pressure and the residue was washed with mixture of THF/ether (3:7, 8 x 15 mL) to afford the product **368** as yellow solid **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 8.24 (td, J = 9.0, 2.6 Hz, 2 H), 7.81 (s, 2 H), 7.33 (td, J = 9.0, 2.6 Hz, 2 H), 3.98 (s, 6 H). **^{19}F NMR** (282 MHz, CD_2Cl_2) = -79.32 ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3158, 3130, 3114, 3090, 3068, 1598, 1571, 1513, 1478, 1340, 1258, 1227, 1185, 1169, 1151, 1010, 853, 825, 785, 757, 739, 724, 687, 678, 636, 574, 528, 517. **HR-MS** calc. for $C_{11}H_{12}N_3O_2S$: 250.064474; found: 250.064390 $[M]^+$ (ESI-HRMS).

General procedure for the "transfer"-reaction of compound 355

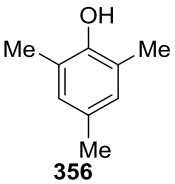
To a solution of the nucleophile (1.00 equiv.) was added the compound **355** (1.20 equiv.) and the base (1.10 equiv.) and the reaction was stirred for 12 h at the elaborated temperature in the chosen solvent (0.14 M). Afterwards a saturated, aqueous solution of NH_4Cl was added to the reaction mixture and the aqueous solution was extracted with DCM (3 x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed by evaporation. The residues were analyzed by NMR, GC-MS and TLC.



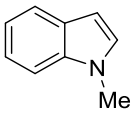
355



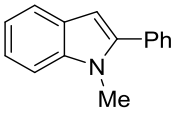
202



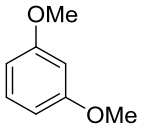
356



357



358



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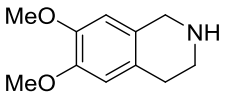
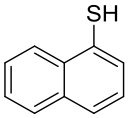
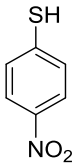


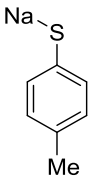
360



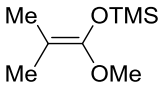
361



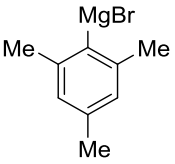
362



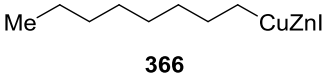
363



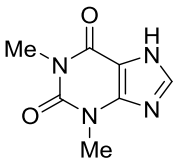
364



365



366

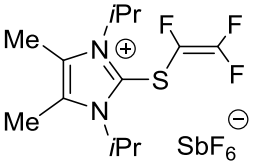


367

Entry	Nucleophile	Base	Solvent	temperature	comment
1	naphthalene-1-thiol	DIPEA	MeCN	rt	dimer formation
2	*beta*-keto ester	K_2CO_3	MeCN	rt	Starting material
3	thiolate	-	MeCN	rt	Protonated starting material
4	*beta*-keto ester	DIPEA	MeCN	rt	Starting material
5	1,3-dimethoxybenzene	-	DCE	80 °C	mw, starting material
6	1,3-dimethoxybenzene	-	MeCN	80 °C	mw, starting material
7	Nitro-thiol	DIPEA	MeCN	rt	Dimer + trithiocarbonate
8	Nitro-thiol	DIPEA	DMF	-78 °C to rt	Dimer + trithiocarbonate
9	Nitro-thiol	DIPEA	DMF	-50 °C to rt	Dimer + trithiocarbonate
10	2,4,6-trimethylphenol	DIPEA	MeCN	rt	decomposition
11	mesitylmagnesium bromide	-	THF	0°C to rt	decomposition
12	1-methyl-2-phenyl-1H-indole	/	DCE	80 °C	mw, starting material
13	1-methyl-2-phenyl-1H-indole	/	DCE	80 °C	$AgSbF_6$, mw, starting material
14	6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline	DIPEA	toluene	rt	starting material
15	Nitro-thiol	-	MeCN	rt	+ Bortrifluorid-etherat, starting material
16	1-Methoxy-2-methyl-1-trimethylsiloxy-propen	-	MeCN	rt	Starting material
17	theophylline	-	DCM/ water	rt	+ 1.00 equiv. of H_2O_2, starting material
18	$ZnCuIC_8H_{17}$	-	THF	rt	decomposition

5.6.2 Preparation of the trifluoroethylene-compound

Synthesis of 1,3-diisopropyl-4,5-dimethyl-2-((1,2,2-trifluorovinyl)thio)-1H-imidazol-3-ium hexafluorostibate(V) (**385**)

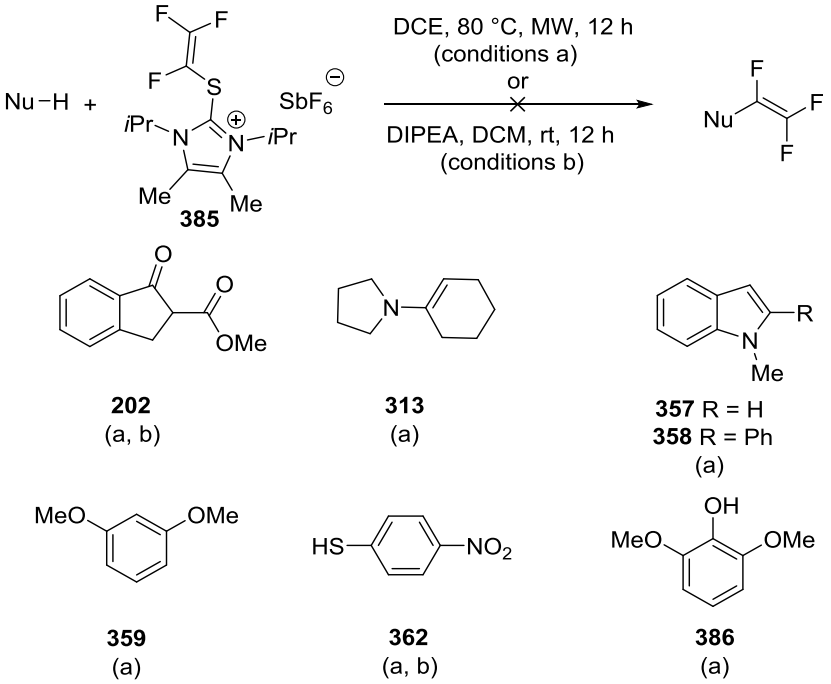


385

Step 1: The zinc solution was prepared by a slightly modified literature procedure.[146] A solution of $ZnCl_2$ (1.72 g, 12.5 mmol, 1.00 equiv.) in THF (7.5 mL) in a flame dried three-neck flask equipped with a dry ice reflux condenser was cooled to 15 °C. Condensed 1,1,1,2-tetrafluoroethane (1.50 mL, 18.0 mmol, 1.50 mmol) was added to the reaction mixture. Then freshly prepared LDA (in hexane, 13.5 mL, 25 mmol, 2.00 equiv.), was added to the reaction mixture. The reaction mixture was stirred for 1 h at 15 °C and subsequently warmed up to rt. The concentration of the zinc solution (22.5 mL, 0.3 M/L) was determined by the *Knochel*-titration method.[147]

Step 2: To a solution of the dibromide **185** (2.42 g, 6.5 mmol, 1.00 equiv.) in THF (15 mL) was added at -78 °C the formerly prepared zincate solution. The solution was stirred for 1 h at -78°C and then slowly warmed up to rt. The solvent was removed and the residue was washed twice with diethylether (2 x 50 mL). The resulting grey solid was solved in DCM and filtrate over a short pad of celite. Then the solution was washed three times with a saturated solution of $NaSbF_6$ and the combined organic phases were dried over Na_2SO_4. After removing the solvent under reduced pressure the product could be obtained as yellow solid. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ = 5.43 (hept, J = 7.3 Hz, 2 H), 2.45 (s, 6 H), 1.63 (d, 7.3 Hz, 12 H) ppm. **^{13}C NMR** (101 MHz, CD_2Cl_2) δ = 157.3 (ddd, *J* = 302.3, 283.2, 47.1 Hz), 132.6, 130.0, 121.4 (ddd, *J* = 302.1, 26.0, 26.0 Hz), 54.8, 21.2, 11.0 ppm. **^{19}F NMR** (282 MHz, CD_2Cl_2) δ = -82.2 2 (dd, 41.7, 35.2 Hz), -102.24 (dd, *J* = 121.3, 35.2 Hz), -116.55 (s), -153.36 (dd, *J* = 121.3, 41.3 Hz) ppm. **IR** (ATR): $\tilde{\nu}$ (cm^{-1}) = 3647, 2999, 1747, 1614, 1459, 1334, 1220, 1131, 1051, 937, 663, 628, 592. **HR-MS** calc. for $C_{13}H_{20}F_3N_2S$: 293.1294; found: 293.1293 $[M]^+$ (ESI-HRMS).

General procedure for the "transfer"-reaction of compound 385



Method A: To a solution of the nucleophile (0.13 mmol, 1.00 equiv.) was added the transfer reagent (0.15 mmol, 1.20 equiv.) and the reaction was stirred for the elaborated time in the DCE (0.14 M) at 80 °C. Afterwards a saturated, aqueous solution of NH_4Cl was added to the reaction mixture and the aqueous solution was extracted with DCM (3 x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed by evaporation. The residues were analyzed by NMR, GC-MS and TLC.

Method B: To a solution of the nucleophile (0.13 mmol, 1.00 equiv.) was added the transfer reagent (0.15 mmol, 1.20 equiv.) and the reaction was stirred for the elaborated time in DCM (0.14 M). Afterwards a saturated, aqueous solution of NH_4Cl was added to the reaction mixture and the aqueous solution was extracted with DCM (3 x 15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed by evaporation. The residues were analyzed by NMR, GC-MS and TLC.

Method A

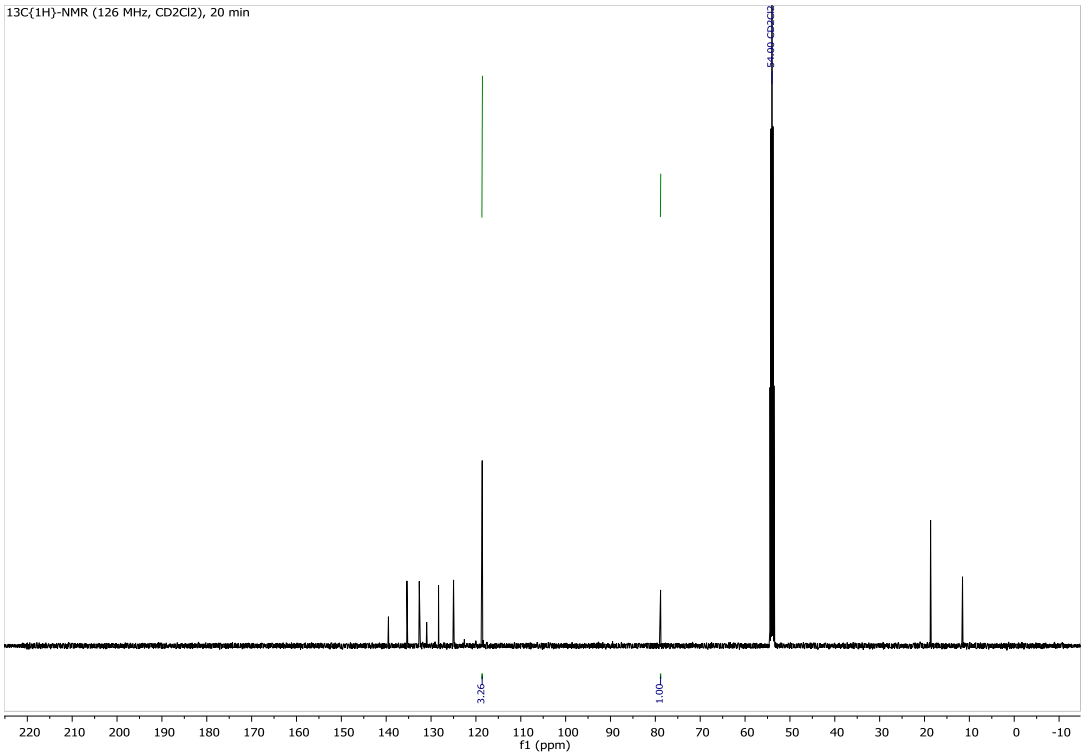
Entry	Nucleophile	comment
1	Nitro-thiol	starting material (nucleophile)
2	*β*-keto ester	decomposition
3	2,6-dimethoxyphenol	starting material (nucleophile)
4	1,3-dimethoxybenzene	starting material (nucleophile)
5	1-(cyclohex-1-en-1-yl)pyrrolidine	starting material (nucleophile)
6	1-methyl-2-phenyl-1H-indole	starting material (nucleophile)
7	1-methyl-2-phenyl-1H-indole	starting material (nucleophile)

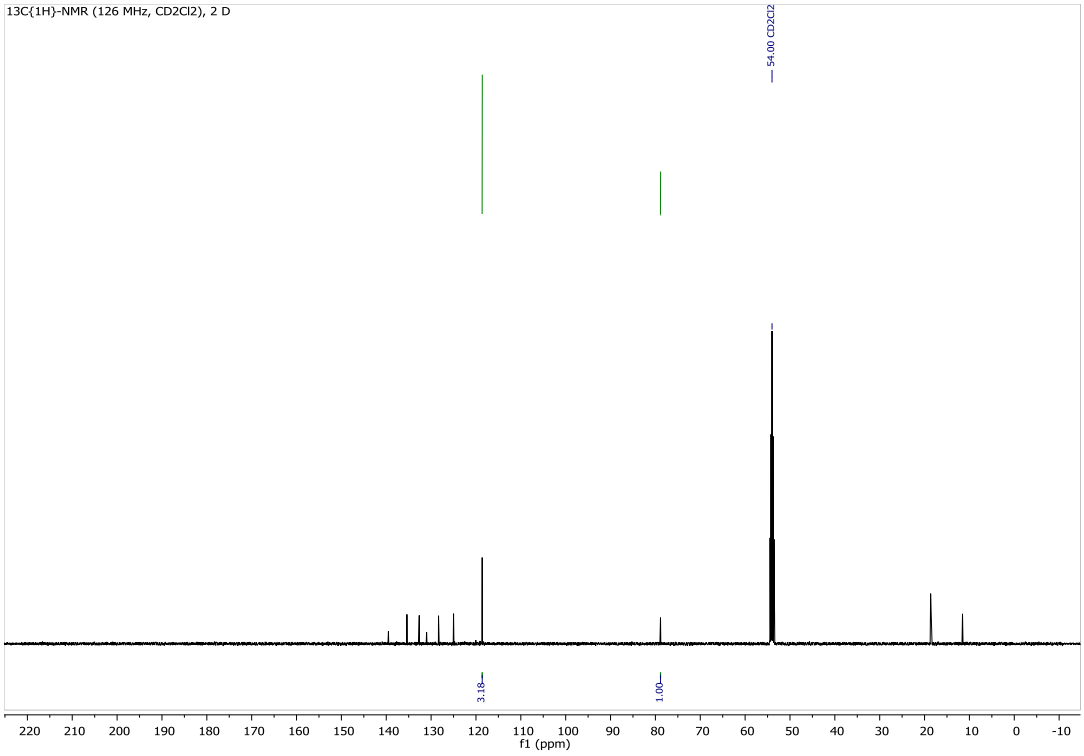
Method B

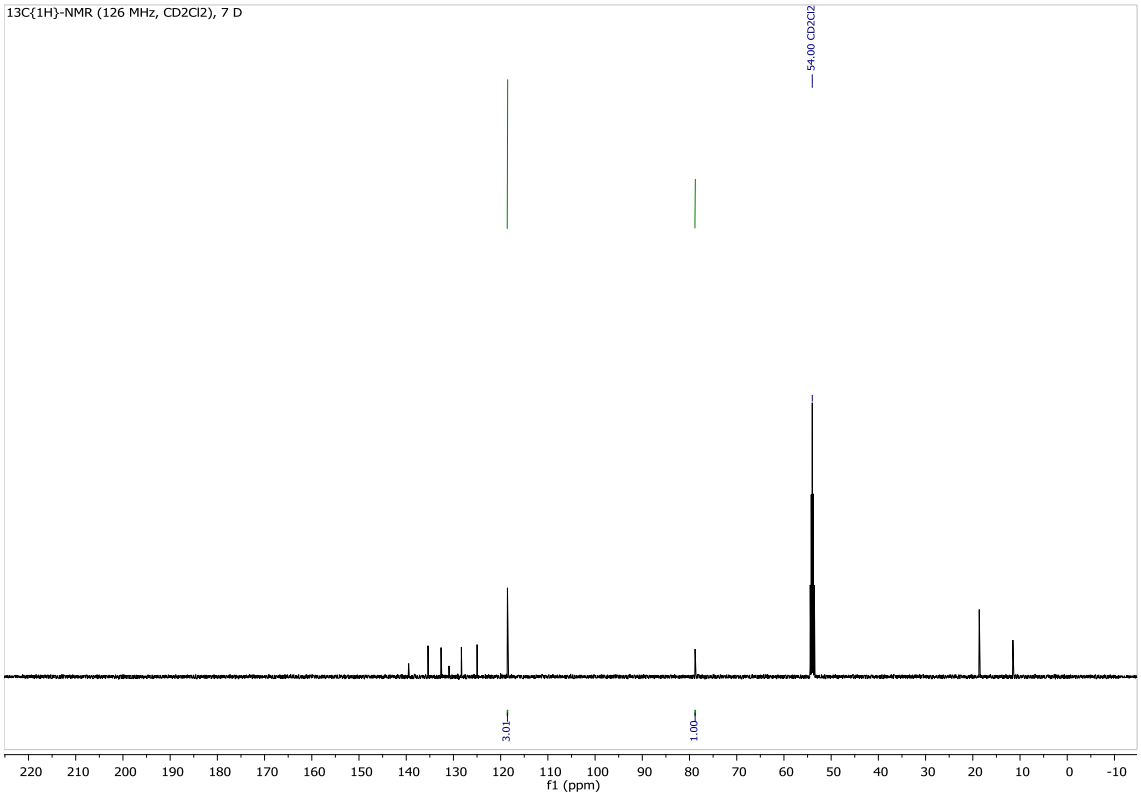
Entry	Nucleophile	comment
1	Nitro-thiol	starting material(nucleophile)
2	β-keto ester	decomposition

5.7 Investigations towards the Isomerisation of compound 238f*

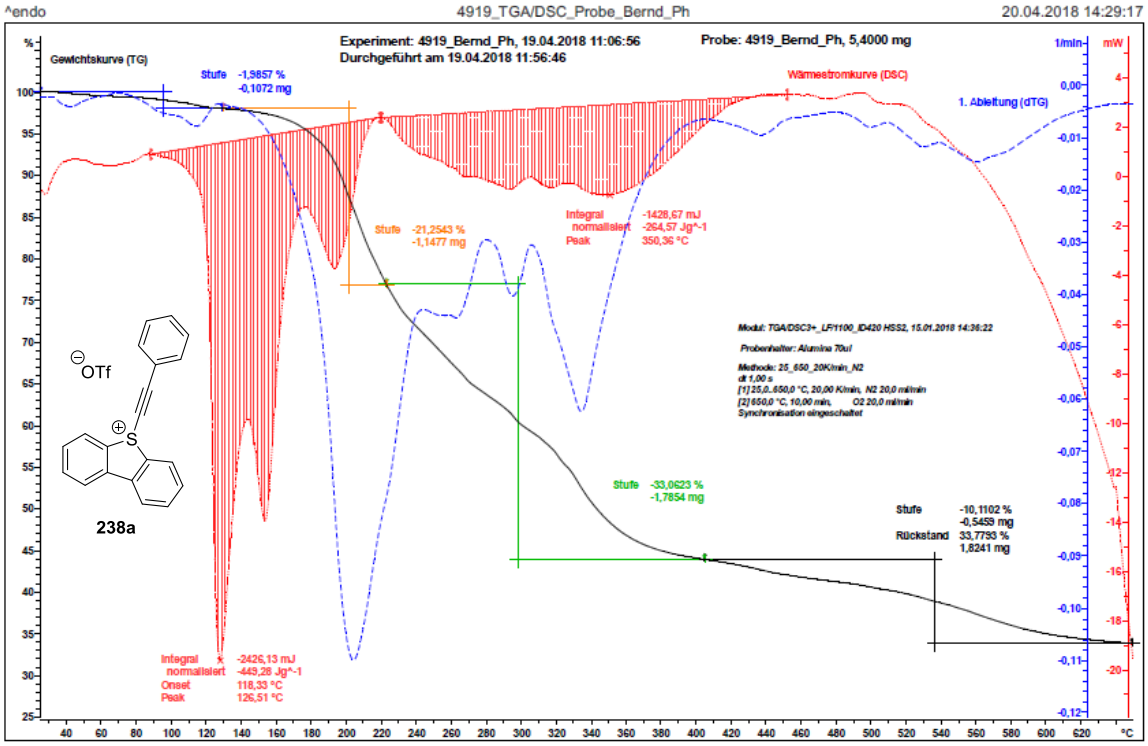
A NMR solution of the reagent **238f*** in Methylene chloride-d^2 was measured directly after synthesis (20 min in solution), after 2 d in solution and after 7 d, showing no further Isomerisation of the compound **238f***.

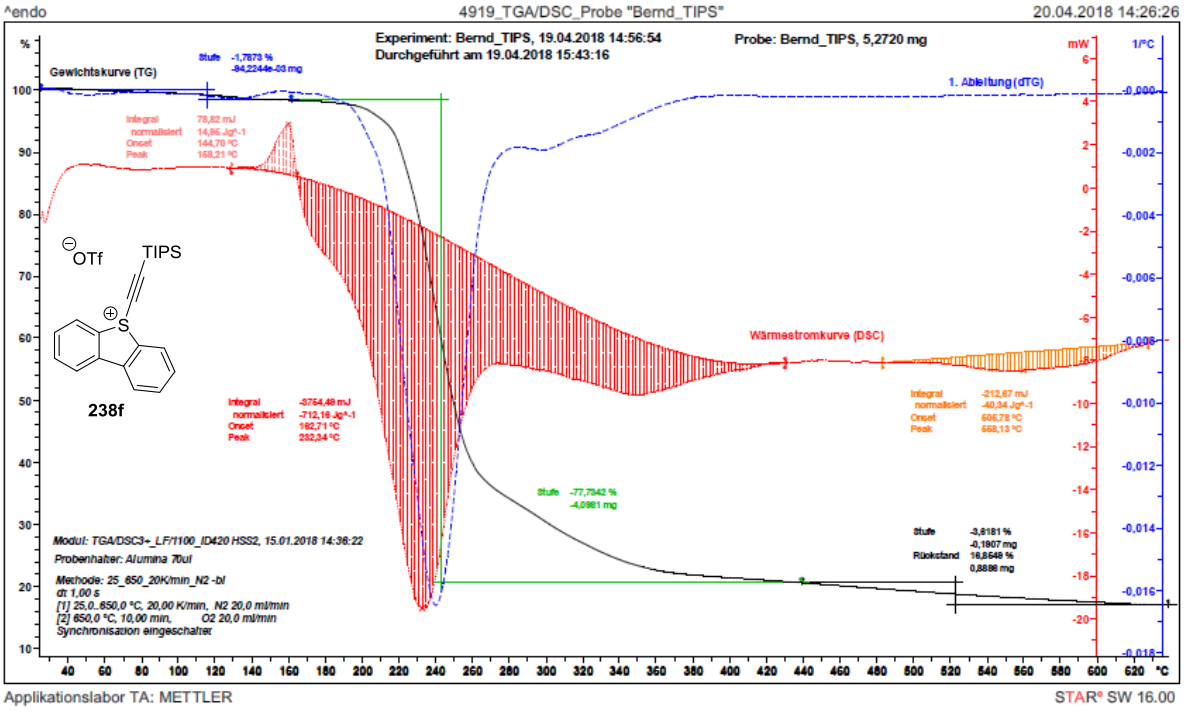





13C{1H}-NMR (126 MHz, CD2Cl2), 7 D
54.00 CD2Cl2
3.01
1.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

5.8 Differential scanning calorimetry (DSC)





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