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Traditio et Innovatio

Alkyne-Carbonyl Metathesis Reaction in Polycyclic Synthesis

Cumulative Dissertation

by

Maryam Sobhani

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Reviewer:
I. Prof. Dr. Dr. h.c. mult. Peter Langer, Universität Rostock, Institut für Chemie
II. Prof. Dr. Jens Christoffers, Universität Oldenburg, Institut für Chemie

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Summary of the Project

The aim of this dissertation is to develop an efficient methodology for the design of several new carbo- and heterocycles containing enones, such as benzotropones, naphthothiophenes and benzoazepines. The focus is on using Alkyne-Carbonyl Metathesis (ACM) reaction due to its high atom economy and efficiency. In this regard, a metal free, Brønsted acid mediated intramolecular ACM reaction has been developed to form new seven- and six-membered carbocycles. In general, regio- and chemoselective palladium-catalyzed cross-coupling reactions with various boronic acids and alkynes were applied in all studies to synthesize the precursors for the ring closing ACM reaction.

Zusammenfassung des Projekts

Ziel dieser Dissertation ist die Entwicklung einer effizienten Methodik zur Entwicklung mehrerer, neuer Carbo- und Heterocyclen, die Enone enthalten, wie Benzotropone, Naphthothiophene und Benzoazepine. Der Schwerpunkt liegt dabei auf der Alkin-Carbonyl-Metathese (ACM)-Reaktion, da diese sehr atomsparend und -effizient ist. In diesem Zusammenhang wurde eine metallfreie, Brønsted-Säure-vermittelte intramolekulare ACM-Reaktion zur Bildung neuer sieben- und sechsgliedriger Carbocyclen entwickelt. Für alle Studien wurden regio- und chemoselektive Palladium-katalysierte Kreuzkupplungsreaktionen mit verschiedenen Boronsäuren und Alkinen eingesetzt um die Vorstufen für die Ringschluss-Alkin-Carbonyl-Metathese zu synthetisieren.

List of Abbre*via*tion

AcOH	Acetic acid	**m**	Multiplet
Ac_2O	Acetic anhydride	***m***	meta
Anal. calcd.	Elemental Analysis	**mp**	Melting point
Ar	Aryl	**MS**	Mass Spectrometry
ATR	Attenuated total reflection	**MsOH**	Methanesulfonic acid
br	broad	***nBu***	*n*-Butyl
calcd	Calculated	**NEt_3**	Triethylamine
d	Doublet	**NMR**	Nuclear magnetic resonance
dd	Double doublet	***o***	ortho
ddd	Doublet of doublets of doublets	**OAc**	Acetate
DCM	Dichloromethane	**OCHO**	Formyl
DCE	1,2-Dichloroethane	**OMe**	Methoxy
DEPT	Distortionless Enhancement by Polarisation Transfer	***p***	para
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	**Ph**	Phenyl
DMF	Dimethyl formamide	**ppm**	Parts per million
DMSO	Dimethyl sulfoxide	**pt**	Pseudo triplet
ε	Extinction coefficient	**[Pd]**	Palladium complex
EI	Electron Ionization	**PPh_3**	Triphenylphosphine
ESI	Electronspray Ionization	***p*-TsOH**	*para*-Toluensulfonic acid
Et	Ethyl	**R**	Organic moiety
EtOAc	Ethyl acetate	**R_f**	Retention factor
EtOH	Ethanol	**rt**	Room temperature
Equiv	Equivalent	**s**	Singlet
Hex	Hexyl	**t**	Triplet
h	Hour	**TFA**	Trifluoroacetic acid
HRMS	High Resolution Mass Spectroscopy	**TFAA**	Trifluoroacetic anhydride
Hz	Hertz	**THF**	Tetrahydrofuran
IR	Infrared Spectroscopy	**TLC**	Thin Layer Chromatography
J	Coupling constant	**UV/Vis**	Ultraviolet and visible absorption spectroscopy
Me	Methyl	**XPhos**	2-Dicyclohexyl phosphino-2',4',6'-triisopropylbiphenyl
MeOH	Methanol	**λ**	wavelength

I. Introduction

In organic synthesis, carbon–carbon (C-C) bond formation through numerous chemical reactions enables chemists to synthesize novel organic structures in an efficient way.[1] In the chemical, medical, and materials science industries, C-C bond formation plays a critical role to construct previously inaccessible structures and to develop new frameworks of organic molecules.[2-13] Several new, efficient and sustainable methods have been developed and employed to build C-C bonds over the last two decades. Among these, metathesis reactions have become a powerful tool and one of the most widely used transformations for C-C bond formation in modern organic synthesis.[14]

Metathesis Reactions

The name metathesis comes from the Greek μΕταψΕσιζ that means transpose, "change the position of". (meta: change, tithemi: place).[15a] Metathesis reactions are kind of chemical reaction in which two hydrocarbons are converted to two new hydrocarbons by exchanging their electronic patterns of bonding.

Therefore, metathesis reactions involve the exchange of atoms or functional groups between substrates, leading to the rearrangement of matching partners and the formation of new compounds. [15b,c] This formation has emerged as a powerful synthetic method for the construction of complex molecules that are difficult or impossible to synthesize by conventional approaches. One of the advantageous of this transformation is the fewer formation of undesired by-products and hazardous waste. of undesirable by-products and hazardous waste.

There are many interesting examples of the use of metathesis in the synthesis of natural products,[196,14e] pharmaceuticals,[17] nanostructured materials,[18] heterocyclic and macrocyclic compounds,[19] specialty polymers[20] and many more.[21]

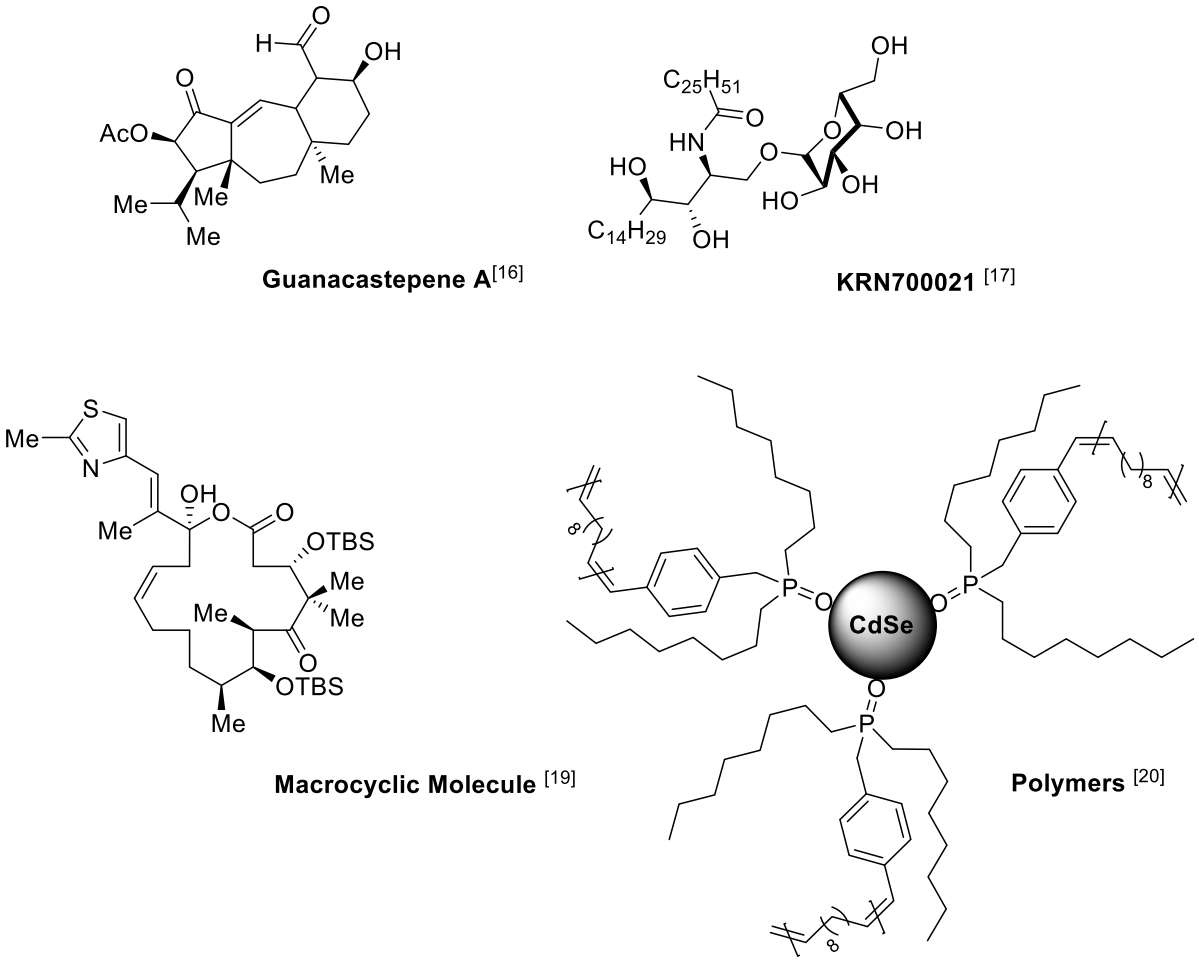
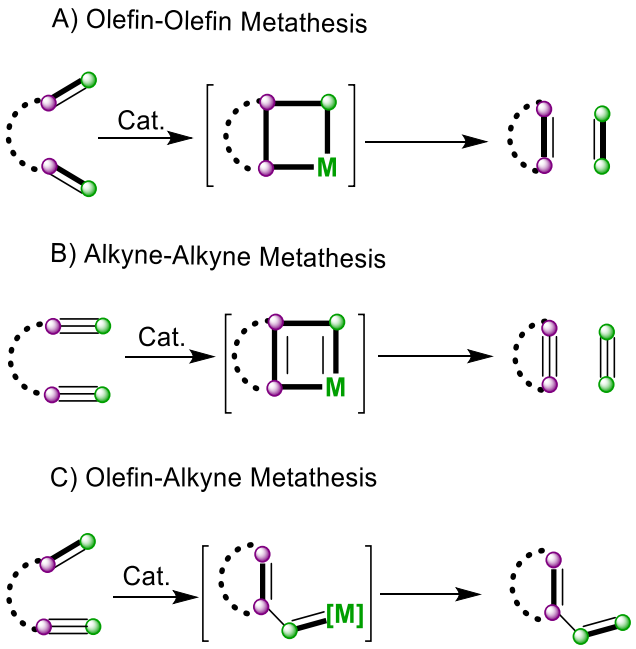


Figure 1. Synthesis examples using metathesis.

There are several types of metathesis reactions that can be classified in different ways depending on reaction condition.[15] Among this classification the main types of metathesis reactions between olefins and/or alkynes. are summarized in scheme 1. This includes olefin-olefin metathesis reaction, which is the most widely applied metathesis reaction, plus the metathesis between two alkynes as an analog of the olefin-olefin metathesis reaction, and olefin-alkyne, resulting in the formation of 1,3-diene containing products.[22]



Scheme 1. Different types of metathesis reactions between olefins and/or alkynes.

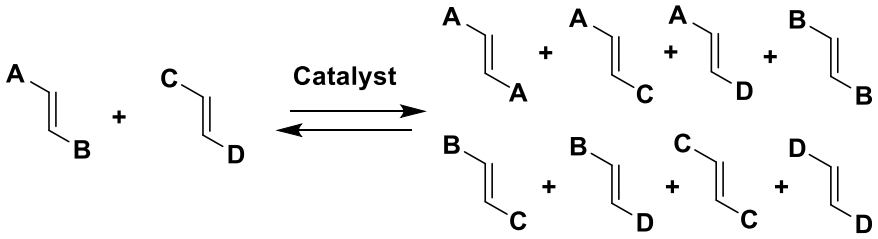
1. Olefin (Alkene) Metathesis

Alkene metathesis was discovered accidentally during studies on Ziegler-Natta polymerizations by industrial chemists.[23] Since that time, this method has been demonstrated to be extremely valuable in preparing compounds relevant to a wide range of research areas, including polymer chemistry, synthetic organic chemistry, bioorganic chemistry,[16,24] and Fine-chemical production.[25]

Olefin metathesis is a well-known transformation which comprises the redistribution of the carbon double bonds of two olefins. The C-C double bonds of two olefins are broken to form two new different double bonds. In this metathesis reaction, the catalyst establishes equilibrium between the starting alkenes, the (E)- and (Z)-stereoisomers of all possible substituent combinations, and ethylene. Thus, alkene metathesis reactions can generally lead to a wide range of products (Scheme 2), which would initially indicate limited selectivity. However, it has been shown that alkene metathesis reactions are both selective and practical in many synthetic routes.[24,25] In this regard, there are various conditions that can enhance the selectivity

while the reaction is undergoing equilibrium. In this regard, there are several factors which can enhance the selectivity during the reaction equilibrium.

(i) When one of the reaction products are much more stable than the others.
(ii) When the catalyst reacts selectively with one species and generates only one product.
(iii) When one or more products, such as ethylene gas, can be removed from the system, so that the equilibrium will be shifted according to Le Chatelier's principle.

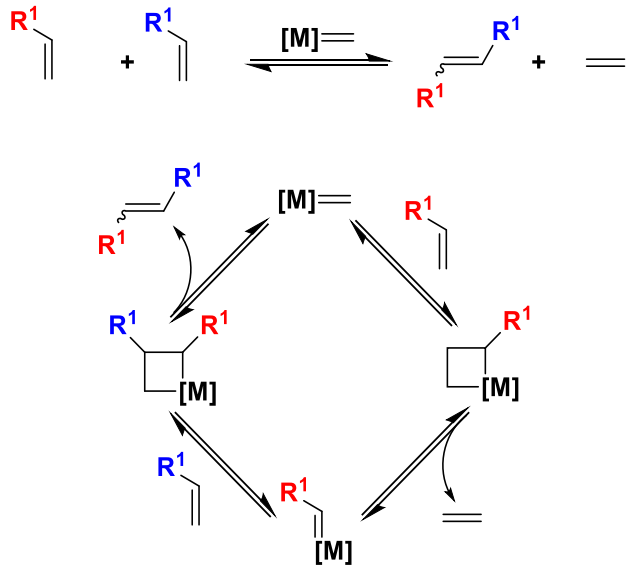


Scheme 2. General equation for the alkene metathesis reaction.

Almost all metathesis reactions take advantage of at least one of these features. Among them the stability of the build π-conjugated system plays a critical role and is considered to be a critical driving force for the transformation.[26] However, the driving force of the reaction can be varied in a different type of olefin metathesis reaction.

1.1. Mechanism

This olefin metathesis, characterized by a sequence of [2+2] cycloadditions and subsequent [2+2] cycloreversions between the reactive partners, can be driven by various catalysts. Illustrated in Scheme 3, the catalyst becomes part of a four-membered species, with [2+2] cycloreversion ultimately leading to product formation and catalyst turnover.[27] Despite the reversible nature of these steps, the reaction ultimately leads to thermodynamically stable product(s), which is crucial in many applications.



Scheme 3. Mechanism of the olefin metathesis reaction.

1.2. History and Catalyst development

The development of well-defined metathesis catalysts that are tolerant to a wide range of functional groups, lead metathesis reactions become one of the most powerful methods in organic synthesis. A great number of stable and reactive catalysts have been designed in the last 70 years enabling chemists to carry out this transformation easily. Figure 2 summarizes major milestones in the history of the olefin metathesis reaction.[28] Indeed, synthetic organic chemistry has progressed rapidly through metathesis reactions since Schrock and Grubbs discovered molybdenum and ruthenium carbene complexes in 1990 and 1992, respectively.[29]

In 2005, Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock were awarded the Nobel Prize in Chemistry for their work that led to the elucidation of the reaction mechanism and the discovery of a variety of highly active ruthenium-based catalysts.[30]

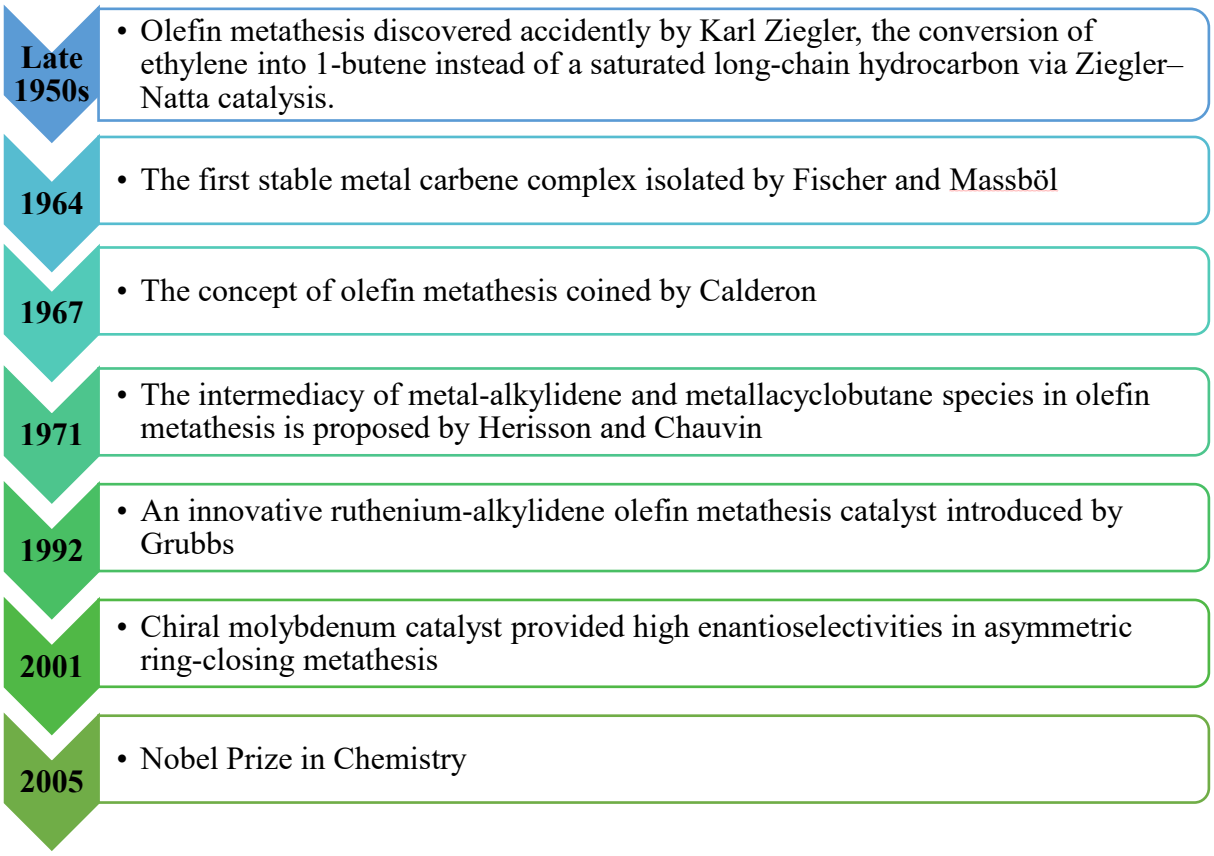


Figure 2. A brief history of olefin metathesis.[29-31]

The most popular and commercially available transition metal complexes for metathesis reactions are presented in Figure 3. The molybdenum carbene complex **1** was found to be effective in the metathesis of olefins by Schrock *et al*.[28a] Later, Grubbs applied this catalyst for the synthesis of unsaturated oxygen heterocycles *via* ring-closing olefin metathesis.[28b] Several studies of olefin metathesis using the synthetic ruthenium carbene complex **5** followed. In addition to **5**, Grubbs discovered that ruthenium carbene complex **2**, which is now commercially available and has the same chemical reactivity.[29] A new series of ruthenium catalysts comprising heterocyclic carbene ligands, **3** and **4**, were developed simultaneously by Herrmann[28d], Nolan[28e], and Grubbs[28f] in 1999. This generation of catalyst are more efficient than the first-generation ruthenium catalysts **2** and **5**.[29,31] A significant development in catalyst activity was the development of Grubbs-type initiators with ruthenium alkylidenes containing chelating ligand **6**.[32] These catalysts are generally referred to as Grubbs–Hoveyda catalysts and exhibit a remarkable degree of stability in metathesis reactions.

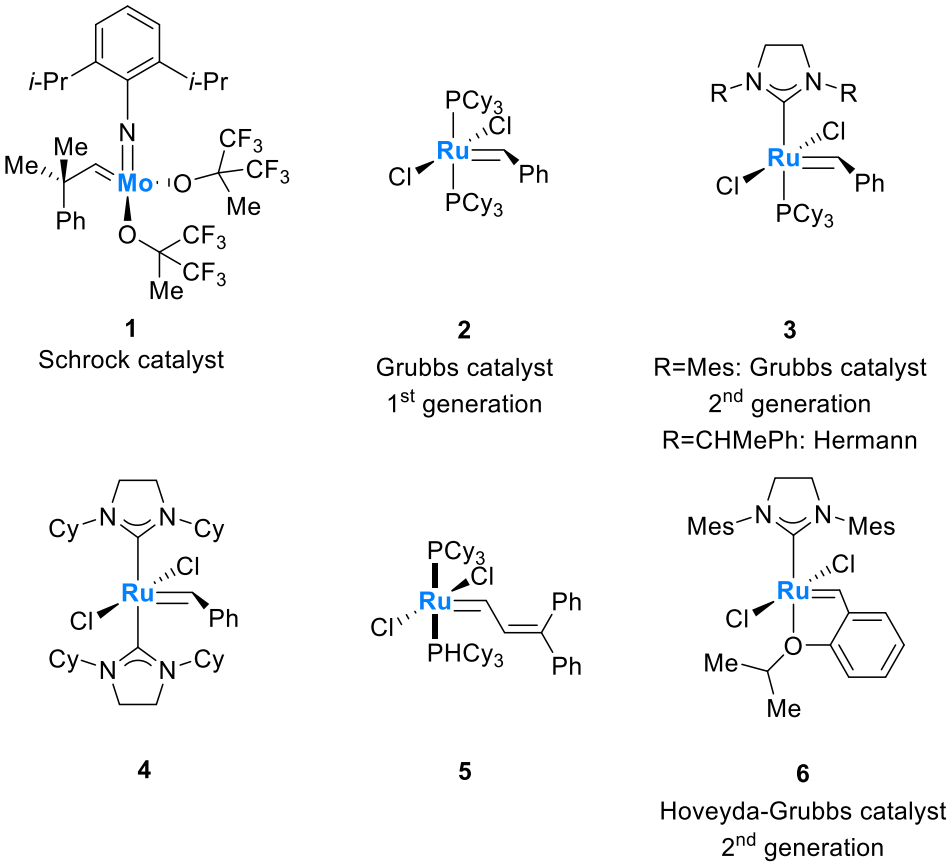
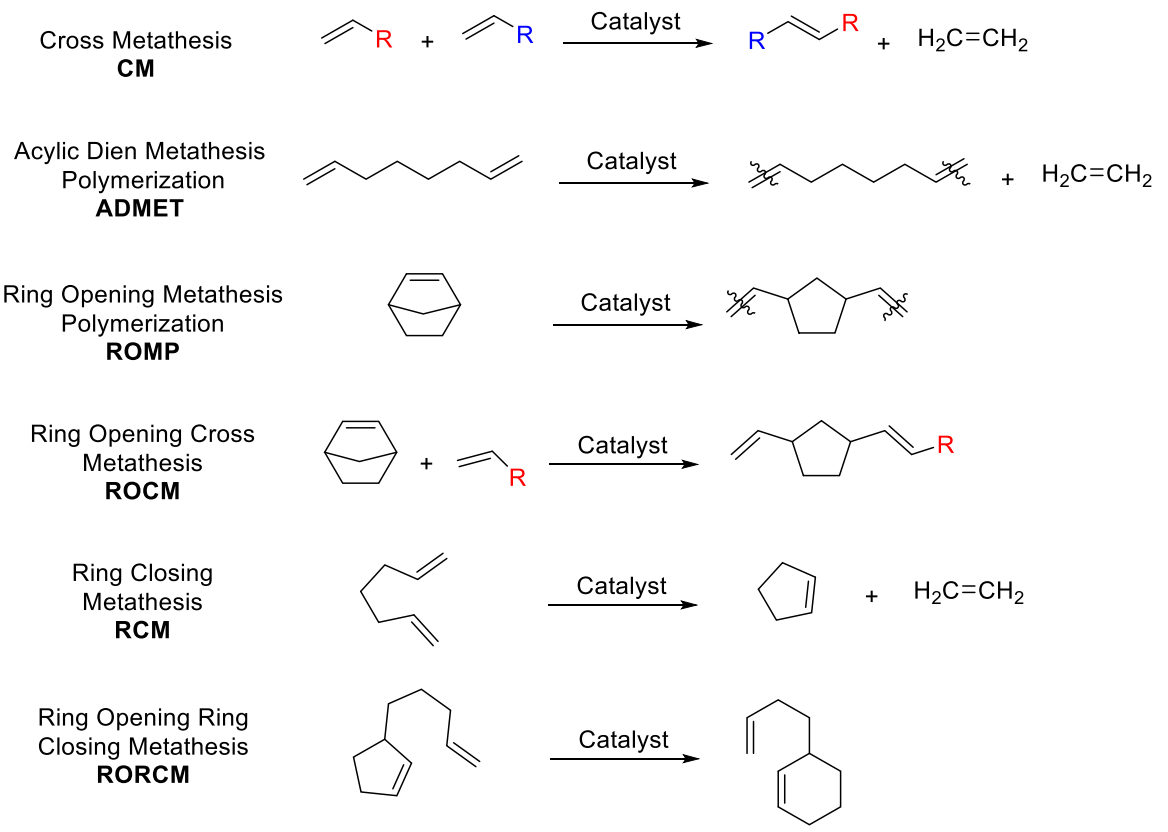


Figure 3. Common catalysts used in metathesis transformation reactions.

1.3. Classifications of Olefin Metathesis

The olefin metathesis reaction has experienced tremendous growth due to significant advances in catalyst design. This has led to an impressive range of applications for organic chemists. As shown in Scheme 4, a variety of selective olefin metathesis reactions can be conducted in the presence of a catalyst.



Scheme 4. Main classification of olefin metathesis reaction.

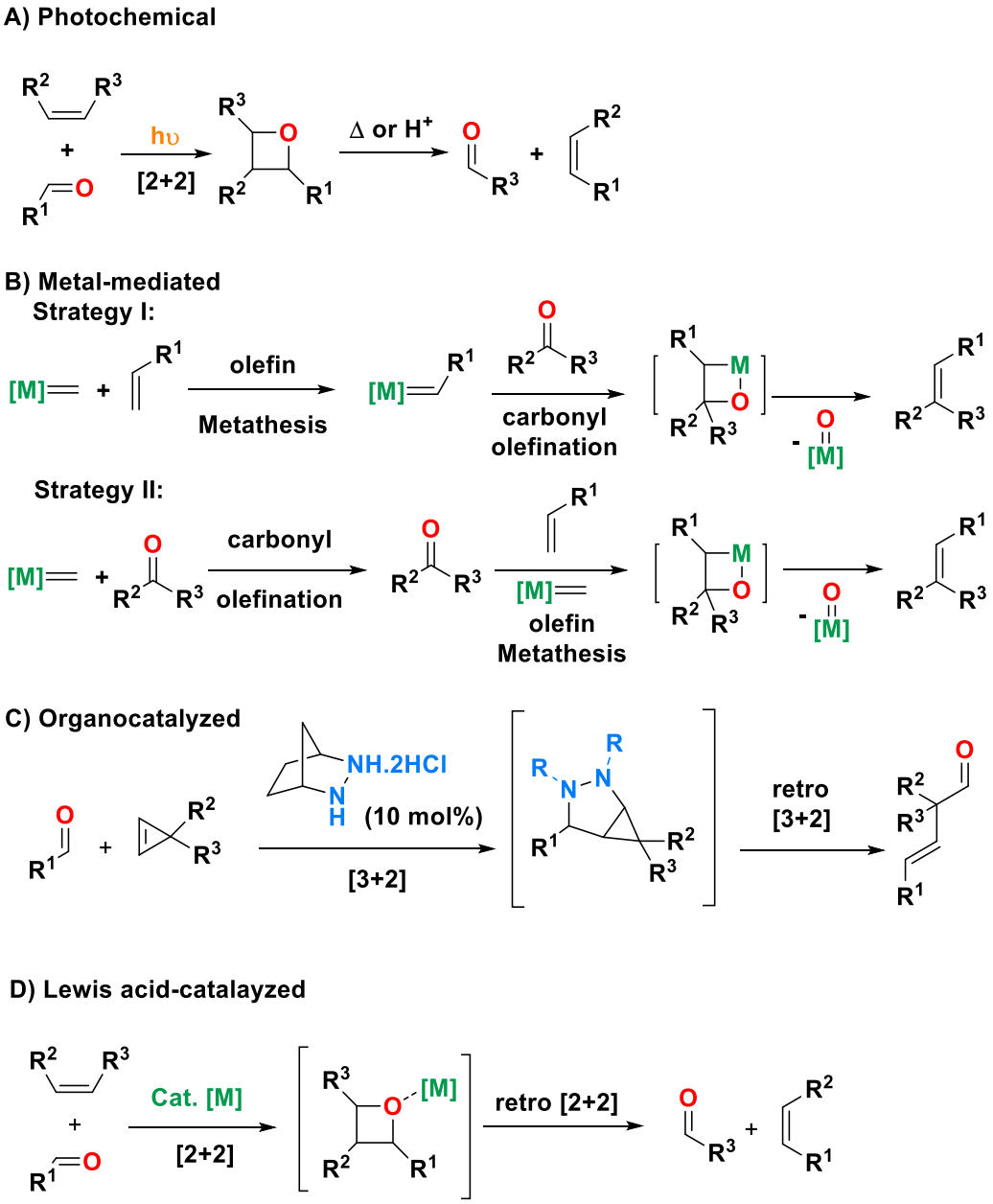
2. Carbonyl–Olefin Metathesis

By modifying metathesis reactions, it has become possible to replace an olefin substrate with another functional group through certain reactions. Like olefin metathesis, a carbonyl-olefin metathesis reaction between an olefin and a carbonyl compound produces new C-C double bond.

2.1.Mechanistic Studies

The first approach for the carbonyl-olefin metathesis involved a two-step sequence including a photoinduced [2+2] cycloaddition, followed by a subsequent acidic and/or thermal fragmentation step to induce cycloreversion and generate the corresponding metathesis

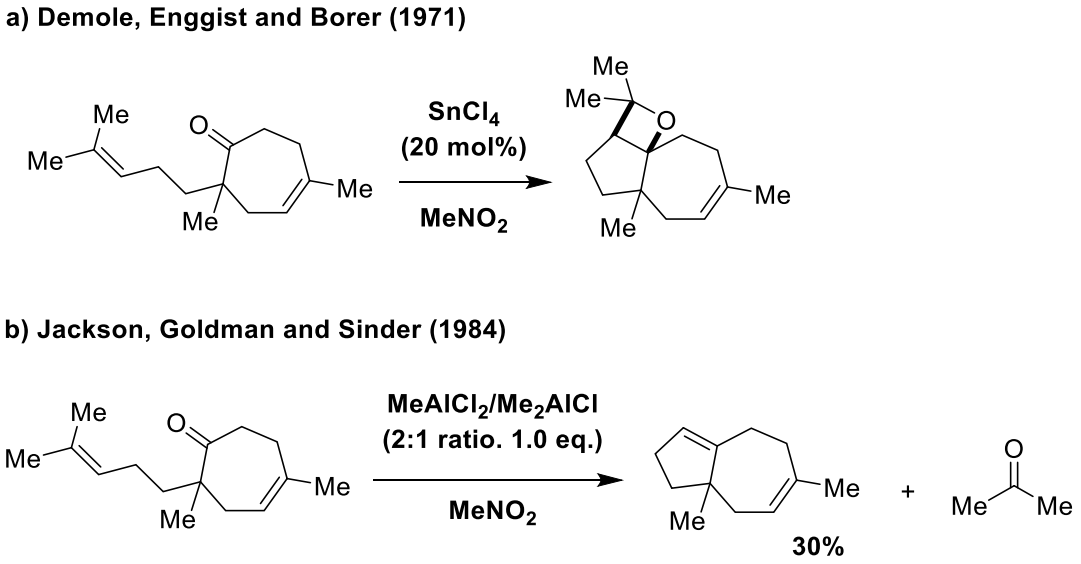
products (Scheme 5, A).[33] Nowadays, instead of this traditional photochemical method, transition metal catalyst systems are typically used to promote the carbonyl-olefin metathesis reaction. The metal-mediated mechanism can typically proceed in two different sequences, including olefin-olefin and carbonyl-olefin metathesis (Scheme 5, B). Depending on the type of metal reagent, these transformations may occur in a different order, forming oxametallacyclobutane and later the desired alkene and metal-oxo species. This process can only occur if stoichiometric or supra-stoichiometric amounts of metal are present.[34] The Lambert group reported the first catalytic strategy for the carbonyl-olefin metathesis based on a [3+2]-cycloaddition reaction in presence of hydrazine 2HCl as an organocatalyst (Scheme 5, C). A detailed description regarding recent developments of the hydrazine-mediated carbonyl-olefin metathesis reaction has been published by Lambert in 2019.[35] Moreover, Lewis acid catalysts have been recently employed to promote the carbonyl-olefin metathesis. In this transformation the Lewis acid activates carbonyls for a [2+2]-cycloaddition with alkenes in order to form an oxetane intermediate, which is subsequently activated with the Lewis acid for the reverse cycloaddition to produce novel alkenes and carbonyls as the metathesis products (Scheme 5, D).[36]



Scheme 5. Overview of metathesis reactions between olefins and carbonyls.

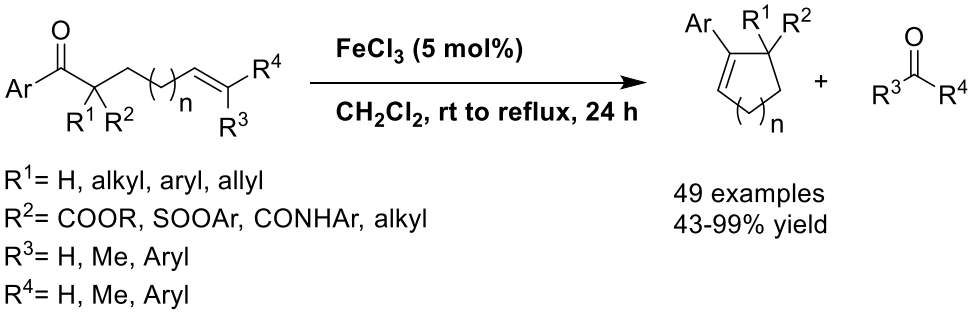
In 1971, Demole, Enggist, and Borer reported the reaction of cycloheptanone using 20 mol% $SnCl_4$ to form oxetane in 58% yield.[37] According to the proposed mechanism, *cis* - oxetane is formed exclusively through an intramolecular [2+2] cycloaddition mechanism (Scheme 6). Later in 1984, Snider and coworkers disclosed that treatment of cycloheptanone with stoichiometric amounts of $MeAlCl_2$/Me_2AlCl (in a 2:1 ratio) in dichloromethane for 10 hours

provides diene in 30% yield as a metathesis product. The authors demonstrated the apparent involvement of the Lewis acid, as evidenced by the absence of any reaction when cycloheptanone was treated with $Me_{1.5}AlCl_{1.5}$. In contrast, the addition of stoichiometric amounts of $MeAlCl_2$ resulted in the formation of a complex mixture.[38]



Scheme 6. First examples of Lewis acid mediated carbonyl-olefin metathesis.

Subsequently, more efficient methods have been investigated for this type of metathesis using different types of Lewis acids. In this regard, a variety of cyclopentenes, cyclohexenes, polyaromatic hydrocarbons, and functionalized pyrrolines were synthesized using various Lewis acids, including $FeCl_3$, $GaCl_3$, I_2, trityl- and tropylium tetrafluoroborate salts. An important breakthrough in carbonyl-olefin metathesis was made in 2017 by the Schindler group using $FeCl_3$ as a catalyst. They present almost 50 examples in moderate to excellent yields under mild reaction conditions (Scheme 7).[36]

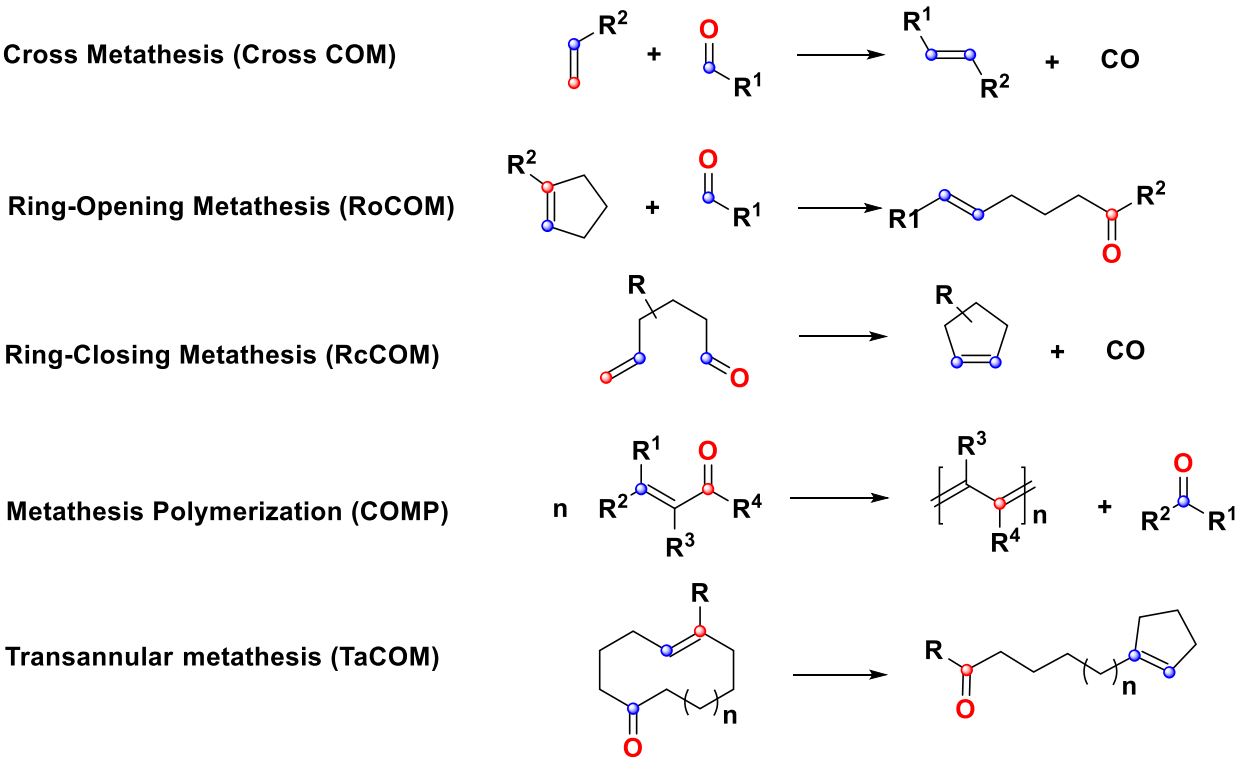


Scheme 7. Carbonyl-olefin metathesis reported by Schindler.

An overview of achievements in the field of Lewis acid mediated and Lewis acid catalyzed carbonyl–olefin metathesis reactions was published by the groups of Schindler and Ravider in 2017 and 2018, respectively.[39]

2.2. Classifications of Carbonyl -Olefin Metathesis

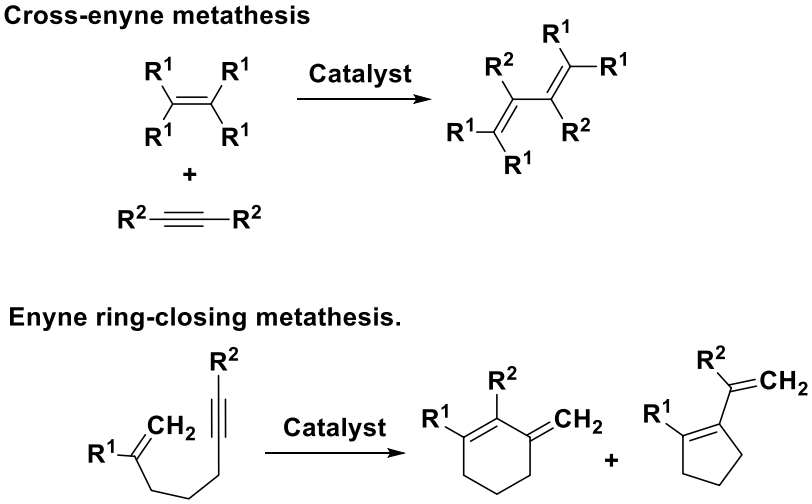
Similar to the olefin-olefin metathesis, the carbonyl-olefin metathesis reactions are categorized into five main classes which are summarized in Scheme 8. A major advantage of carbonyl-olefin metathesis reactions over olefin-olefin metathesis is that they are usually irreversible, making them a better choice for reaction design and for achieving high yields and conversions.[40]



Scheme 8. Classification of carbonyl-olefin metathesis.

3. Olefin-Alkyne Metathesis

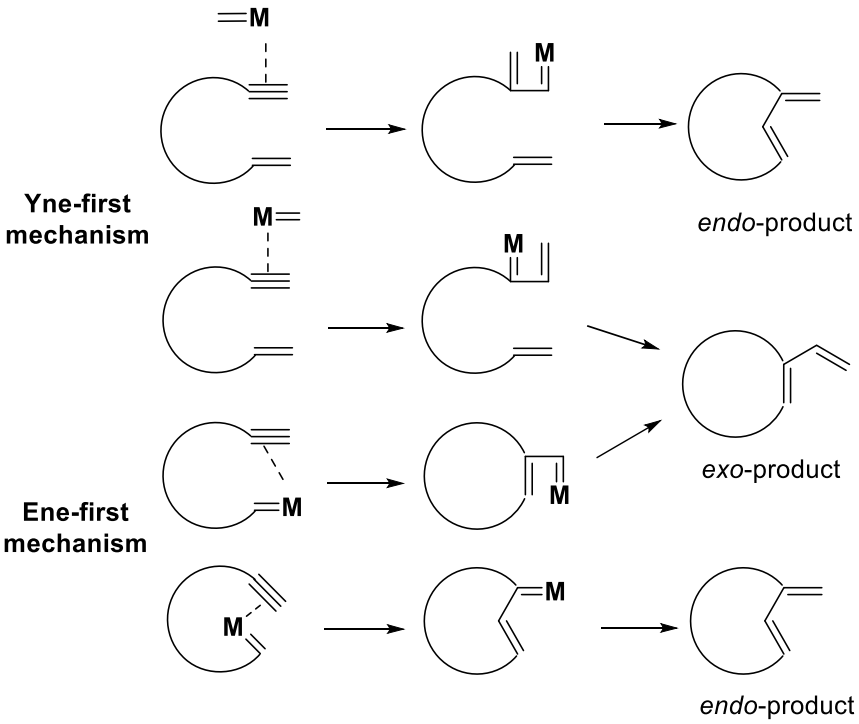
Olefin-alkyne metathesis (Ene-Yne Metathesis) involves the reaction and conversion of an alkene and an alkyne into a conjugated 1,3-diene using a carbene complex. The intermolecular metathesis reaction occuring between an alkene and an alkyne is known as a cross-enyne metathesis (CEYM), while the intramolecular metathesis reaction of an enyne molecule is called ring-closing enyne metathesis reaction (RCEM) (Scheme 9).[41]



Scheme 9. Different types of olefin-alkyne metathesis.

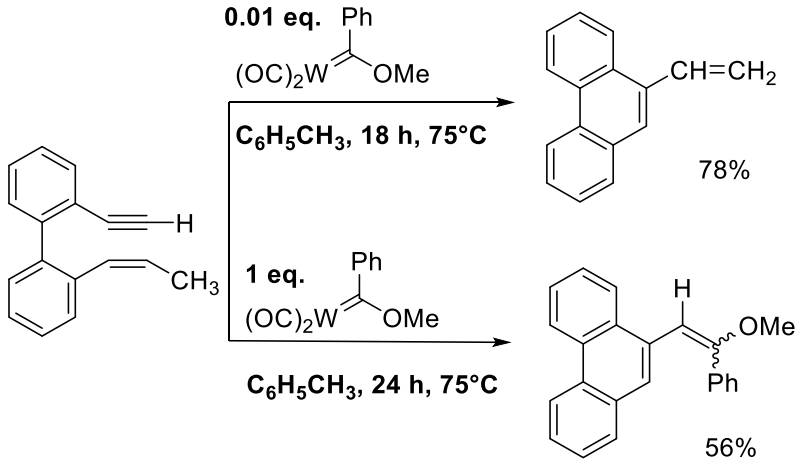
3.1. Mechanistic Studies and Furthers investigation

Enyne RCM has a significant potential for building complex carbo- or heterocycles, but its selectivity is limited by the two possible mechanisms involved in the enyne metathesis. As a result of both "ene-first" and "yne-first" mechanisms, two different initiation modes can occur, leading to two different products (Scheme 10). There are some cases in which endo-product formation is favored, whereas generally, exo-product formation is preferred. In general, a conjugated 1,3-diene is produced as a consequence of the formation of a thermodynamically-stable product.[42]



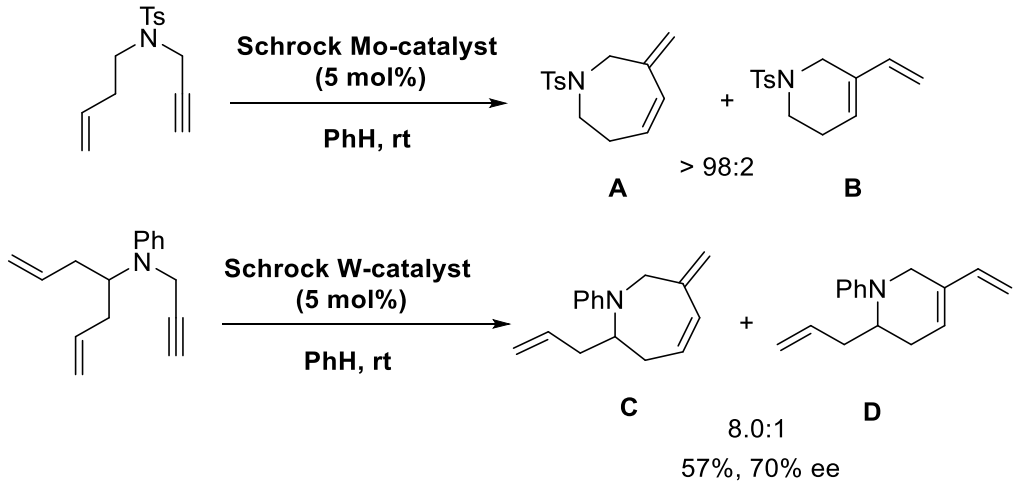
Scheme 10. Endo/exo mechanism in enyne RCM.

In 1985, Katz and Sivavec reported the first enyne metathesis by converting biphenyl into phenanthrene using tungsten carbene complexes. As shown in Scheme 11, different products are obtained based on the amount of tungsten carbene used in the reaction. This reaction displays high stereoselectivity when the metal atom is added exclusively to one of the alkyne carbon atoms.[43]



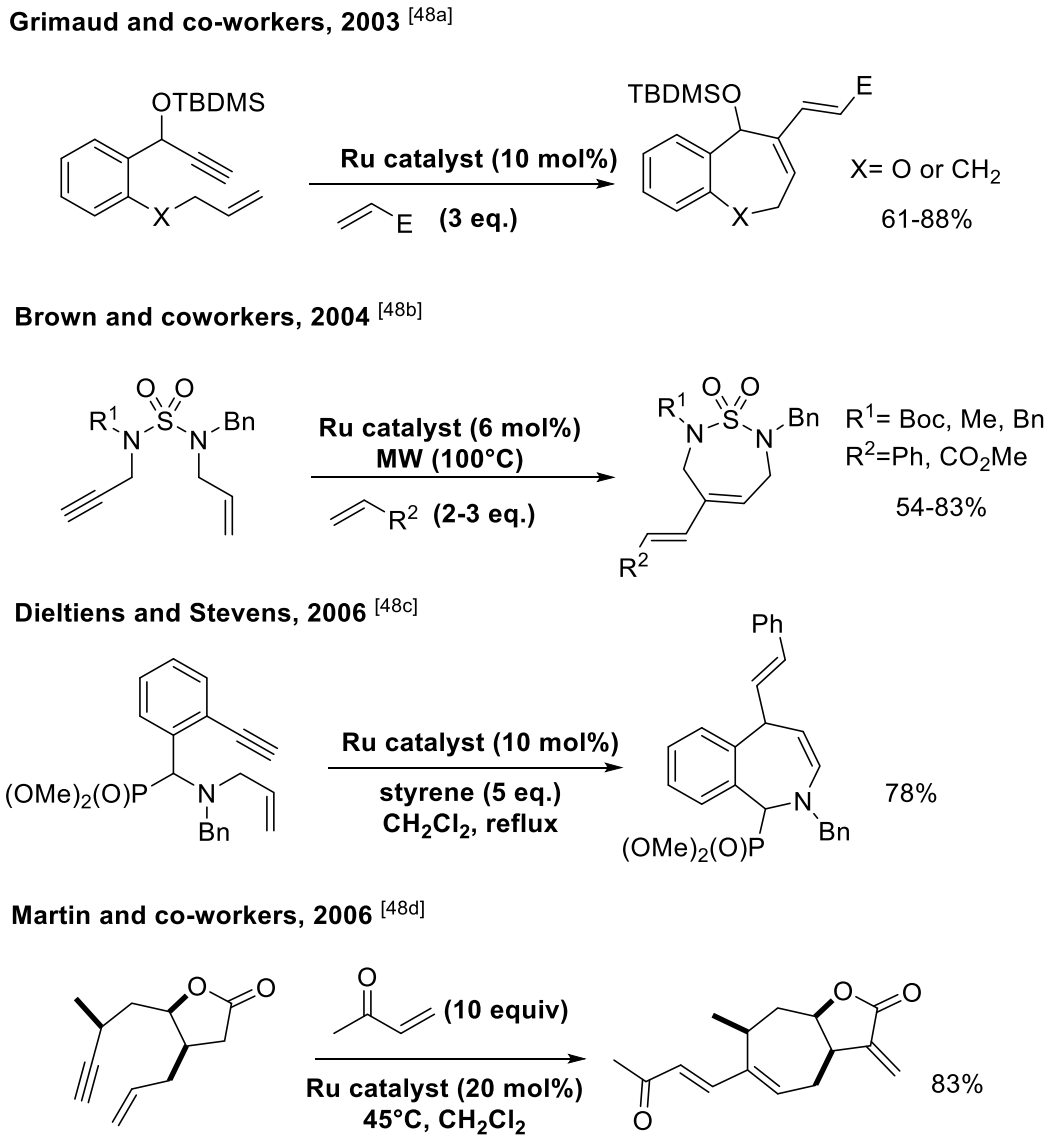
Scheme 11. The first reported enyne metathesis reaction involving the Fischer tungsten-carbene complex.

A literature review indicates that a number of enyne metathesis processes have been developed using metal catalysts including tungsten, molybdenum, and ruthenium-carbene-based Grubbs-type complexes.[41] In a study by the Hoveyda group, the molybdenum- and tungsten-alkylidene complexes were applied to produce highly selective endo products **A** and **C**, respectively, *via* enyne ring-closing metathesis of enynes (Scheme 12). Using a chiral complex, an enantioselective RCM was obtained with a 70% ee of the product.[44]



Scheme 12. Endo-mode selectivity in enyne metathesis.

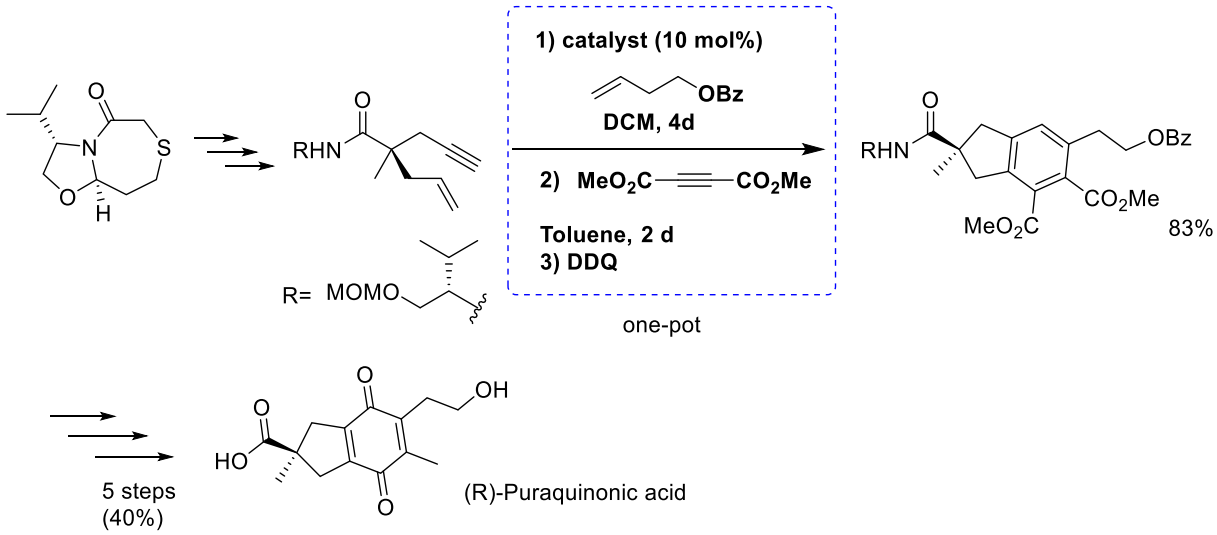
Further investigation has been performed into the possibility of transforming the 1,3-diene, resulting from the ene-yne cross-metathesis, in tandem procedure to various cyclic compounds. Further studies were carried out to examine the possibility of converting the 1,3-diene resulting from the ene-yne cross metathesis into various cyclic compounds by the tandem method. Scheme 13 depicts a few examples of a selective tandem ring-closing metathesis (RCM)-cross-metathesis (CM) process between enynes and electron-deficient alkenes.[45]



Scheme 13. Examples of tandem enyne RCM/CM between enynes and electron deficient alkenes.

Moreover, it is ideal to combine enyne metathesis with the Dies-Alder reaction in a tandem process, since the 1,3-dienes obtained from the metathesis reaction are suitable substrates for the Dies-Alder reaction. The cycloaddition reaction can, however, be accelerated by high temperature or Lewis acid in some cases.[46] Recently this methodology has been widely employed to acquire rather complex molecules, mainly in pharmaceutical chemistry.

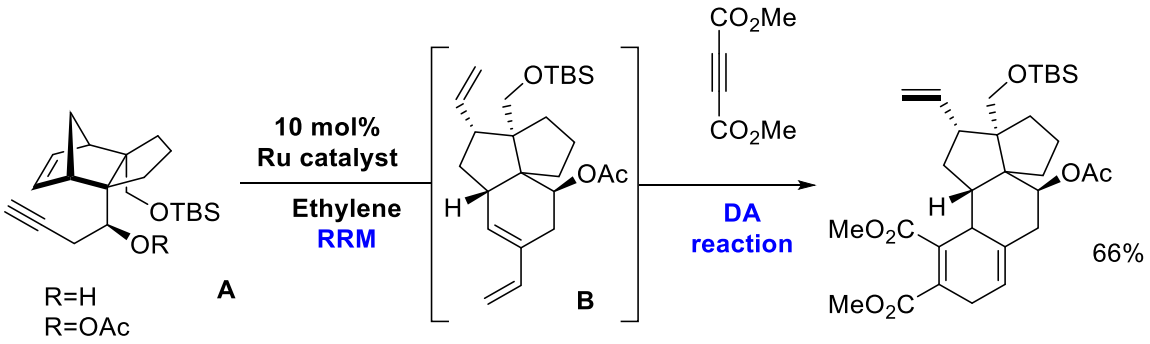
The Gleason group reported the stereoselective synthesis of (*R*)-puraquinonic acid, a metabolite with anticancer properties, using an enyne metathesis/Dies-Alder/aromatization sequence (Scheme 14). The quaternary stereocenter of the enyne has been achieved from readily available bicyclic thioglycolate lactam. As a next step, an effective one-pot protocol has been developed involving RCEYM/diene-ene CM while using O-protected 3-buten-1-ol, an intermolecular Diels–Alder reaction, and final oxidation that promoted aromatization. A relatively long reaction period (6 days) resulted in a very good 83% overall yield and easy conversion into enantiopure (*R*)-puraquinonic acid.[47]



Scheme 14. Synthesis of (R)-puraquinonic acid by RCEYM/DA/aromatization.

In more recent work, a tandem enyne metathesis Diels-Alder process of norbornene derivatives for the construction of condensed polycarbocycle, showing effective antibacterial properties, was reported by Ghosh and Datta in 2018 (Scheme 15). First, diol **A** underwent a ring-rearrangement process involving a domino ROM, followed by a RCEYM to give tricyclic

intermediate **B**. Next, the *in-situ* Diels–Alder reaction took place between the metathesis product and dimethyl acetylenedicarboxylate (DMAD) to form the target polycarbocycle.[48]



Scheme 15. Formation of polycarbocycles *via* ring-rearrangement/Diels-Alder reaction in a one pot reaction.

In addition to the above examples, further literature review indicates the integration of atom-economical enyne metathesis reaction with various chemical transformations *via* one-pot principles, which can be performed in a cascade reaction, leading to a variety of complex and cyclic molecules.[49]

4. Alkyne-Carbonyl Metathesis

4.1. Overview and History

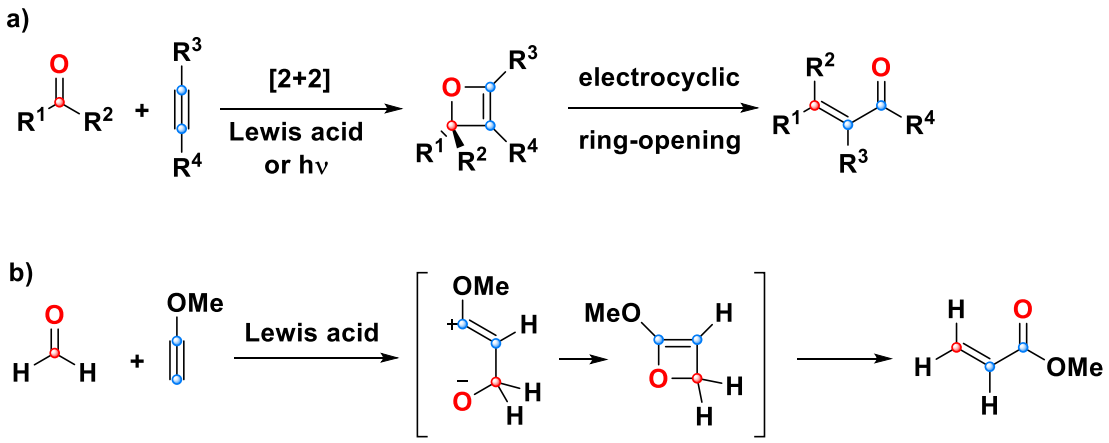
Metathesis reaction involving a carbonyl group and alkyne is referred to alkyne-carbonyl metathesis (ACM) or yne-carbonyl metathesis. This metathesis reaction provides a remarkable strategy to construct unsaturated carbonyl compounds. [14f] The carbonyl-alkyne metathesis reaction differs from the carbonyl–olefin metathesis reaction in that no by-products are formed. Therefore, this reaction is considered to be completely atom-efficient.

As an alternative to the traditional olefinations, including the Horner–Wadsworth–Emmons and Wittig reactions, ACM has been used to synthesize a variety of carbocycles, heterocycles,

and polycyclic aromatic frameworks using Lewis acid such as $Yb(OTf)_3$, BF_3•OEt_2, $AgSbF_6$, $AuCl_3$-$AgSbF_6$, Fe(III) halides and other (Brønsted) acids.[50]

In 1965, Büchi discovered this reaction during the cycloaddition of carbonyls and alkyne for the synthesis of oxetenes.[51] Following the UV-light irradiation of carbonyls and alkynes, alkyne-carbonyl metathesis was observed. Three years later, Vieregge described a Lewis acid-catalyzed variation of the described transformation, resulting in higher yields, regio- and stereoselectivity than the photochemical method.[52]

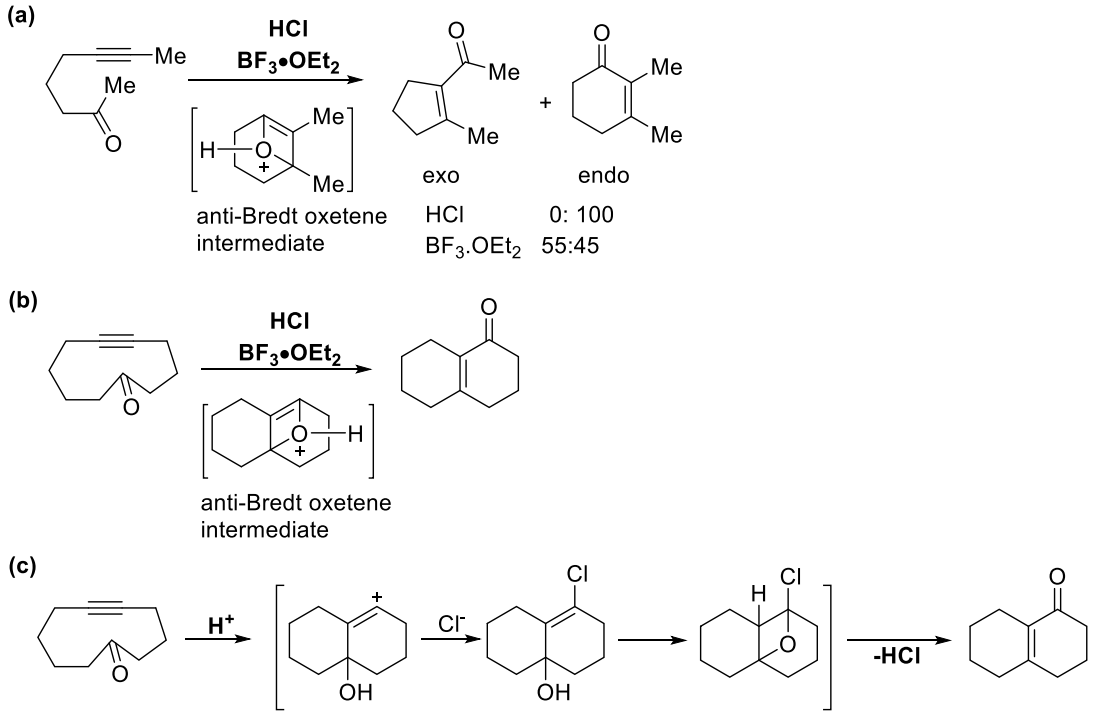
As shown in Scheme 16, the first proposed mechanism starts with a [2+2] cycloaddition between a carbonyl and an alkyne. Then, an electrocyclic ring-opening of the resulting unstable oxetene intermediate generates an α,β–unsaturated carbonyl product.[53] The proposed mechanism has been proven in some cases by the isolation of oxetene intermediates.[47,48,53] Another study conducted by Pons *et al.* suggested that the use of a Lewis acid provokes asynchronous oxetene intermediate formation and further electrocyclic ring-opening to methyl acrylate (Scheme 16 b).[54]



Scheme 16. The first proposed mechanism for alkyne-carbonyl metathesis.

Bos and Arens used boron trifluoride as a Lewis acid catalyst in the ACM reaction to construct α,β-unsaturated ketones with higher yields and selectivity compared to the photochemical approach.

The formation of cyclic enones promoted by both Lewis and Brønsted acids was reported in earlier studies of intramolecular ACM reactions by Hanack, Weiler, and others (Scheme 17 a, b). Using O-18 labeling, Harding showed that the carbonyl oxygen of the starting compounds was completely incorporated into the final product.[56] Previous mechanisms for the formation of endocyclic enones assumed that a highly stretched intermediate such as an anti-Bredt oxetene is involved in the process. Although previous mechanisms for the endo-cyclic enone formation have been considered to involve a highly stretched intermediate like an anti-Bredt oxetene. (Scheme 17a and b). Based on NMR experiments, Wempe suggested a novel mechanism that incorporates tricyclic oxetane intermediates (Scheme 17 c).[56]

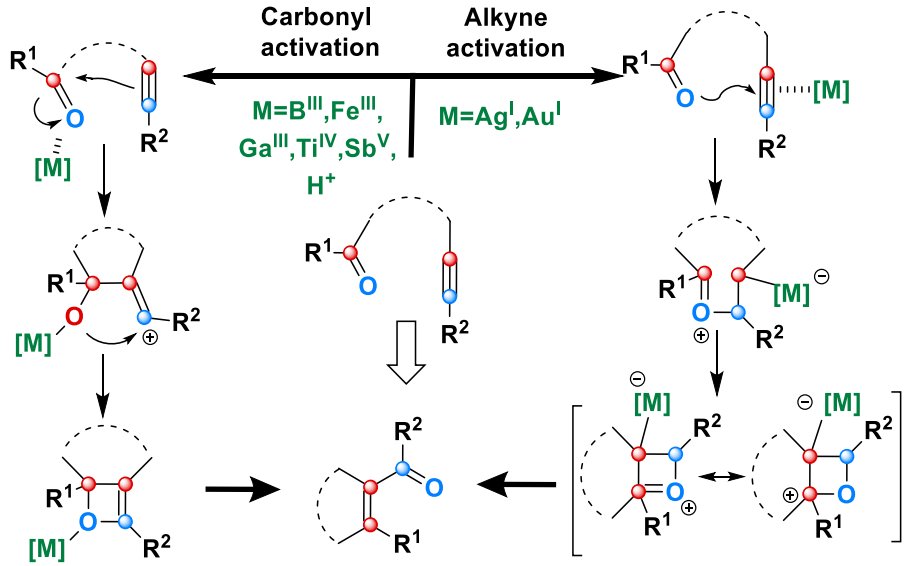


Scheme 17. Intramolecular ACM reaction promoted by Lewis and Brønsted acids.

In the following decades, Lewis and Brønsted acids were shown to have significant effects on the metathesis of heteroatom-substituted alkynes with carbonyl compounds, including acetals and esters as well.

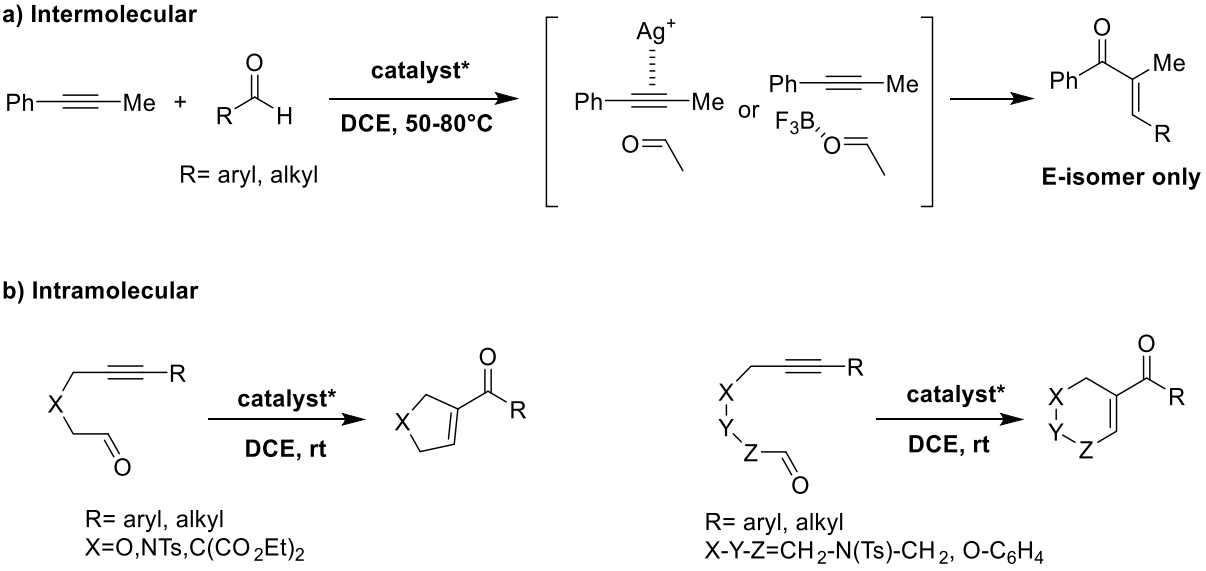
4.2.Mechanistic Studies

The type of catalyst has a remarkable impact on the mechanism of this transformation. Oxophilic Lewis acids, like BF_3, $FeCl_3$ or $InCl_3$, as well as Brønsted acids, activate the carbonyl group for the nucleophilic attack by the alkyne to form their corresponding vinylic cation, which construct an oxetene intermediate through a ring-closing reaction. As a final step, electrocyclic ring-opening results in the carbonyl-alkyne metathesis products. Contrary to this, Lewis-acids that are π-electrophilic, like Ag(I) and Au(I), can preferentially coordinate to the alkyne moiety to activate the triple bond, which provides a nucleophilic attack of carbonyl oxygen. Next, the alkyne-carbonyl metathesis product is eventually generated *via* electrocyclization which is proposed to proceed through the formation of an oxetenium intermediate.[57]



Scheme 18. Different mechanisms involved in the ACM reaction.

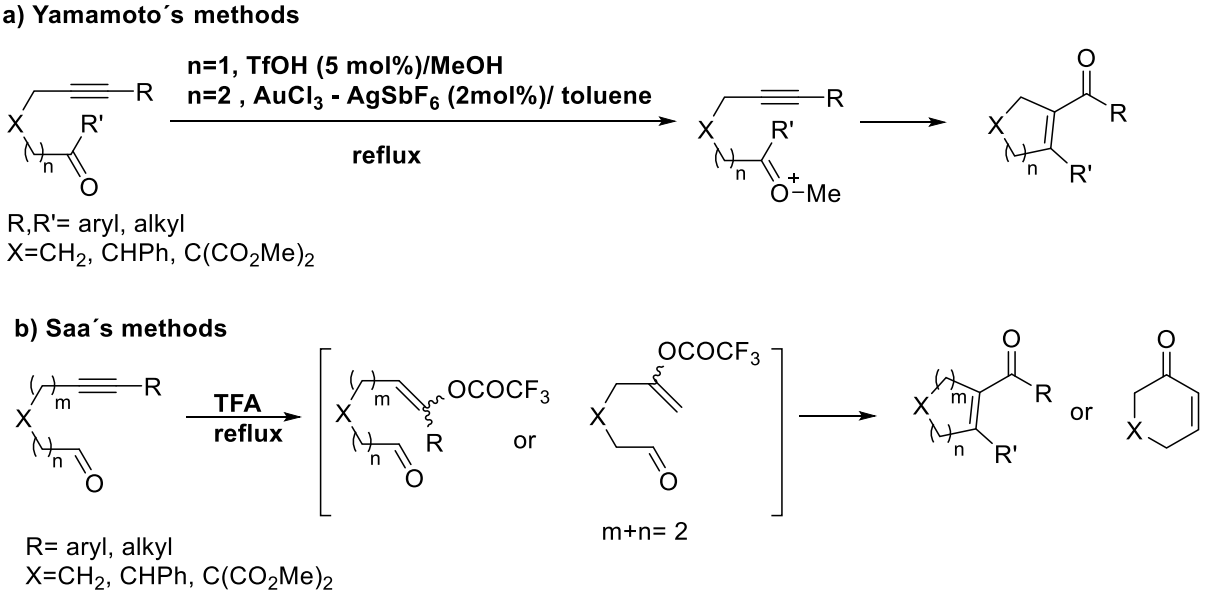
In this regard, Krische *et al.* used ^{13}C-NMR spectroscopy to show that $AgSbF_6$ activates the C-C triple bonds in an intermolecular/intramolecular reaction of aromatic/aliphatic alkynes and aldehydes unlike $AgSbF_6$, SbF_5-alcohol or $In(OTf)_3$-alcohol catalytic systems activate the carbonyl group of aldehydes in alkyne-aldehyde reactions. So, both π and σ acids can catalyze alkyne-carbonyl metathesis (Scheme 19 a). In another study, intramolecular ACM reactions were shown to be effective for synthesizing heterocyclic structures (Scheme 19b).[58]



Scheme 19. Krische's method for alkyne-carbonyl metathesis.

The intramolecular reaction of carbon-tethered 6-alkynyl ketones catalyzed by Au(III) and that of 5-alkynyl ketones catalyzed by TfOH (Scheme 20 a) has been reported by Jin and Yamamoto. In MeOH, the TfOH catalyst worked well, which can be attributed to the formation of reactive oxonium intermediates.[57a, 59]

Using trifluoroacetic acid (TFA) media, Saa's group has reported a similar formation of carboxylic enones from 5- ,6- ,7-alkynals. It is interesting to note that terminal 5-alkynals were found to generate 6-membered ring products, while internal ones generate 5-membered rings. Based on the authors' proposal, the difference between these two cyclization modes suggests the formation of vinyl trifluoroacetate intermediates, which is a consequence of the aldol mechanism (Scheme 20b).[60]

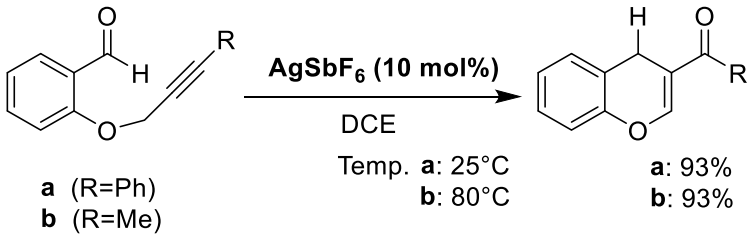


Scheme 20. Yamamoto and Saa's methods.

Metathesis of alkyne-carbonyl is a crucial method used for the synthesis of heterocyclic and fused polycyclic compounds under environmentally friendly conditions. In the following, a brief description of important approaches of the past few decades is presented.

4.3. Ring Closing Metathesis of Aldehyde

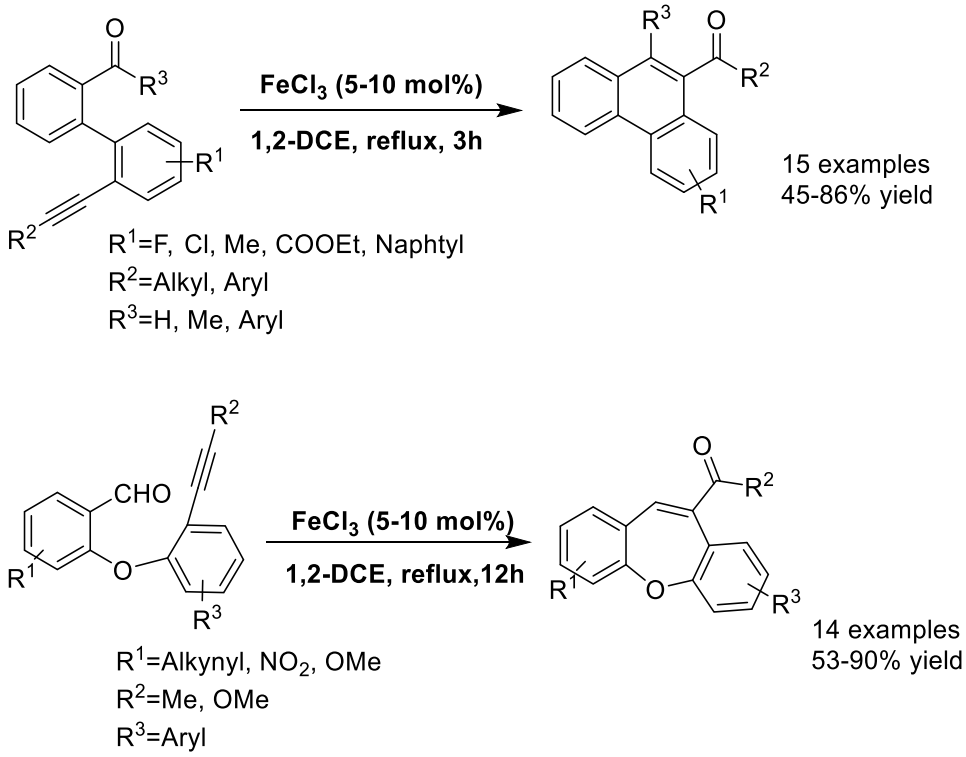
There has been considerable interest in the use of O-alkynyl salicylaldehyde derivatives to form medium-sized heterocyclic structures through alkyne-carbonyl metathesis. The first ring-closing ACM reaction involving O-propargyl salicylaldehydes was introduced by Krische in the presence of $AgSbF_6$ as an efficient catalyst (Scheme 21).[58a]



Scheme 21. First example of catalytic ring-closing ACM reaction for heterocyclic synthesis.

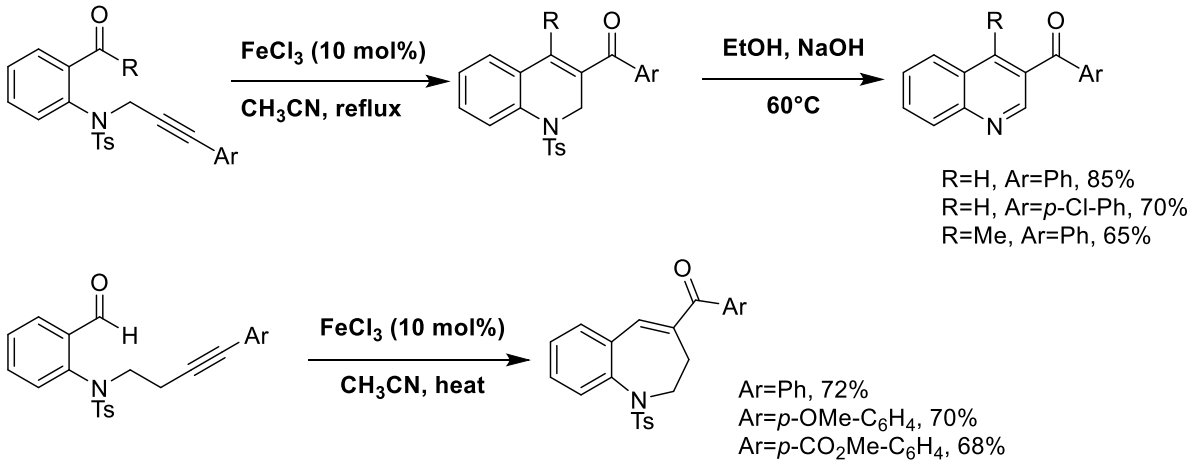
Similar reports describe the application of Au- and Ru-based catalysts to synthesize 2*H*-chromene derivatives using O-propargyl salicylaldehyde as a precursor.[61]

In 2012, Jana's group used $FeCl_3$ as an inexpensive and environmentally friendly catalyst for the intramolecular metathesis reaction to synthesize various functionalized 2*H*-chromenes.[62] Three years later a similar approach was used to synthesize dibenzo[*b,f*]oxepine and benzo[*b*]oxepine core structures. These structures have important applications in medicinal chemistry and show interesting biological role like anticancer, antitumor or inhibitor. This report was the first example of the synthesis of seven-membered heterocycles using ACM in literature (Scheme 22).[63]



Scheme 22. Iron(III) catalyzed synthesis of phenanthrenes and dibenzooxepines.

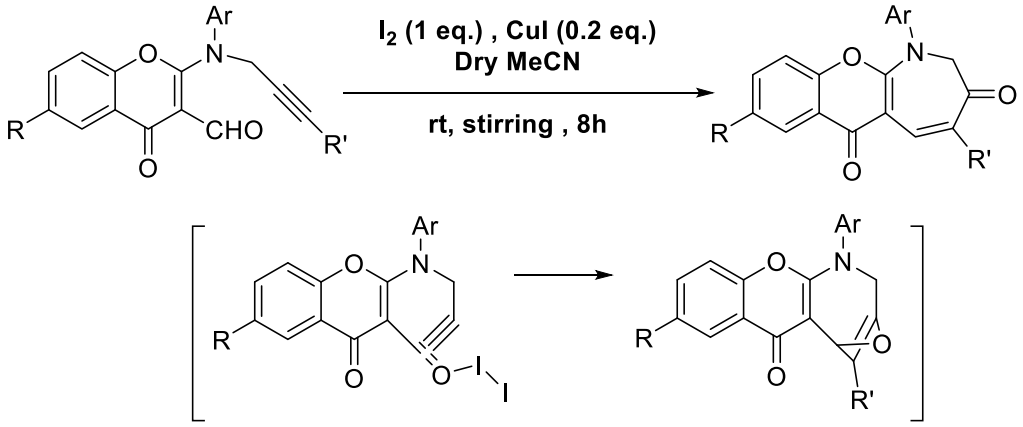
This method has been further developed by substituting oxygen with nitrogen and varying alkyne chain lengths to form six- or seven-membered nitrogen-containing heterocycles (Scheme 23).[64]



Scheme 23. Iron catalyzed synthesis of dihydroquinolines and dihydrobenzo[*b*]azepines.

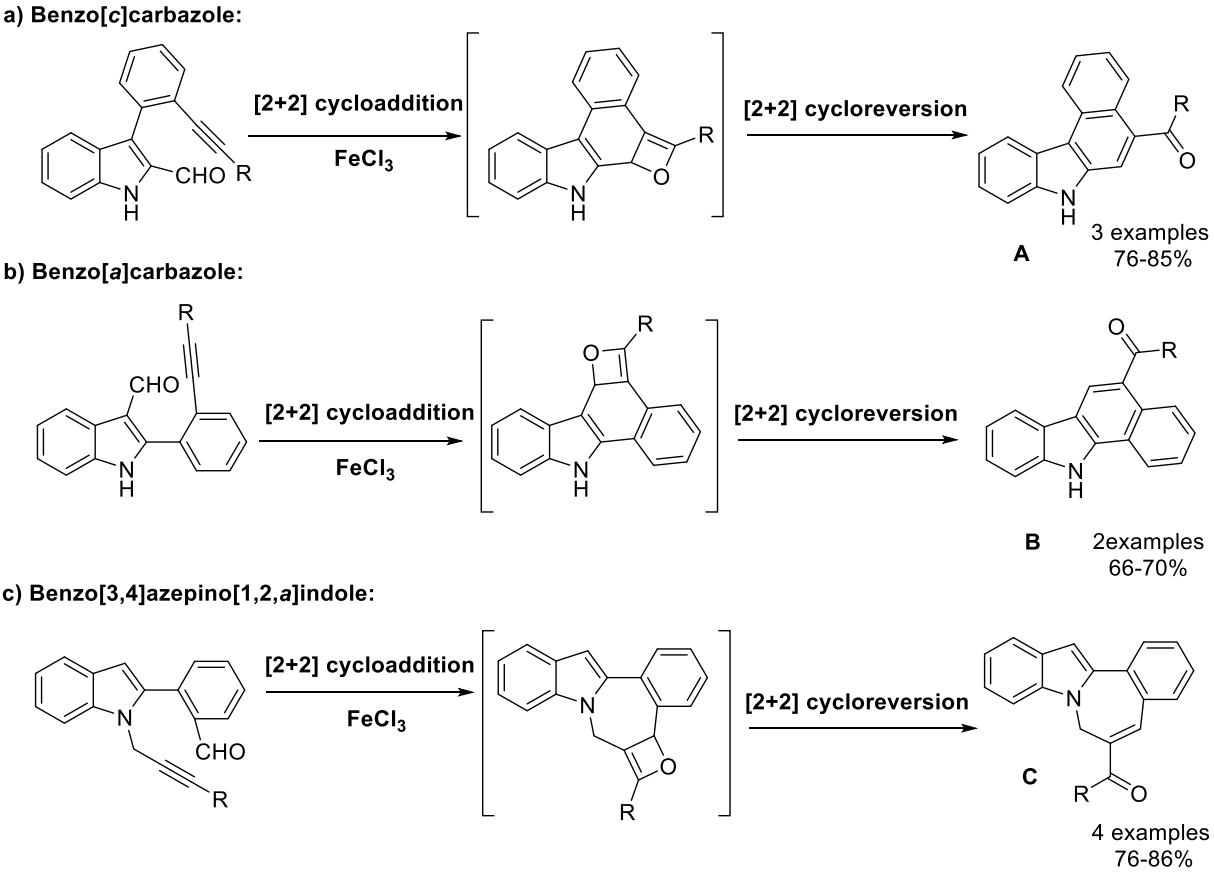
A highly effective alkyne-carbonyl metathesis was described by Bandyopadhyay *et al*. (Scheme 24). In this study, I_2/CuI was used for the first time to initiate intramolecular alkyne-carbonyl metathesis by activating carbonyl and alkyne components, respectively. As a result, a synthetic route for previously unreported 1-aryl-1,2-dihydrochromeno[2,3-*b*]azepine-3,6-dionenes was developed.

The authors proposed a mechanism for the alkyne-carbonyl metathesis mediated by iodine/CuI. As a Lewis acid, iodine coordinates to the oxygen of the aldehyde, while CuI activates the triple bond of the alkyne to facilitate the alkyne-carbonyl interaction. An alkyne and a carbonyl moiety approaching orthogonally form oxetene, which undergoes cycloreversion to form azepinedione.[65]



Scheme 24. Alkyne-carbonyl metathesis mediated by I_2/CuI.

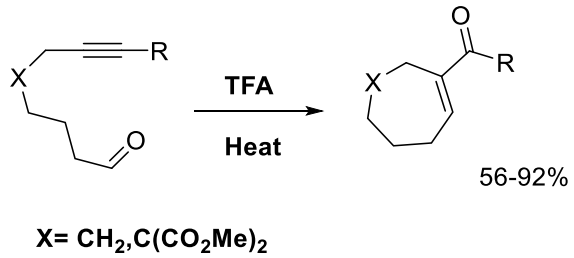
Recently, Jana *et al.*[66] developed a considerable method to prepare diverse benzo[*c*]carbazoles **A**, benzo[*a*]carbazoles **B**, and benzo[3,4]azepino[1,2-*a*]indoles **C** through an intramolecular alkyne-carbonyl metathesis catalyzed by inexpensive and environmentally friendly $FeCl_3$ (Scheme 25). This method displays an efficient, straightforward and atom economic strategy which exhibits a broad substrate scope leading to good yields with high regio- and chemoselectivity.



Scheme 25. Examples of alkyne-carbonyl metathesis on indole derivatives.

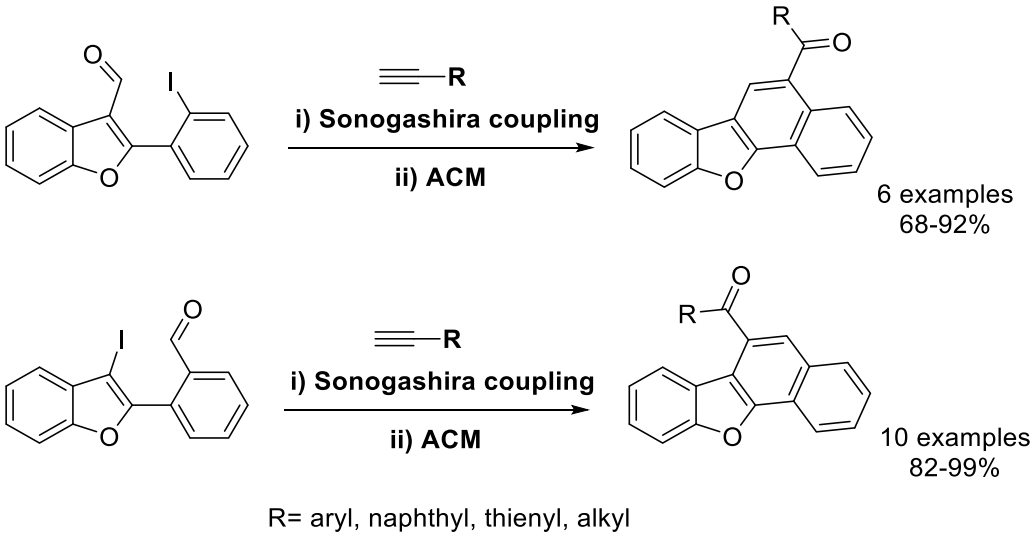
More approaches have been investigated to synthesize different types of complex molecules and polycyclic compounds through ACM reactions. However, recent progress in the use of Brønsted acids as environmentally friendly reagents have led to new ideas on how the application of this strategy can benefit future chemical syntheses.

The seven-membered *exo*-cycloalkenone is an important structure that is found in natural products with unique pharmacological properties. Saa *et al*. reported the first TFA-mediated (exo-)carbocyclization of non-terminal 5-, 6- and 7-alkynals to produce cyclic enones in good to excellent yields. The reaction proceeds through the formation of oxetene intermediates in the presence of TFA (Scheme 26).[60]



Scheme 26. Exo-carbocyclization of non-terminal 5-, 6- and 7-alkynals.

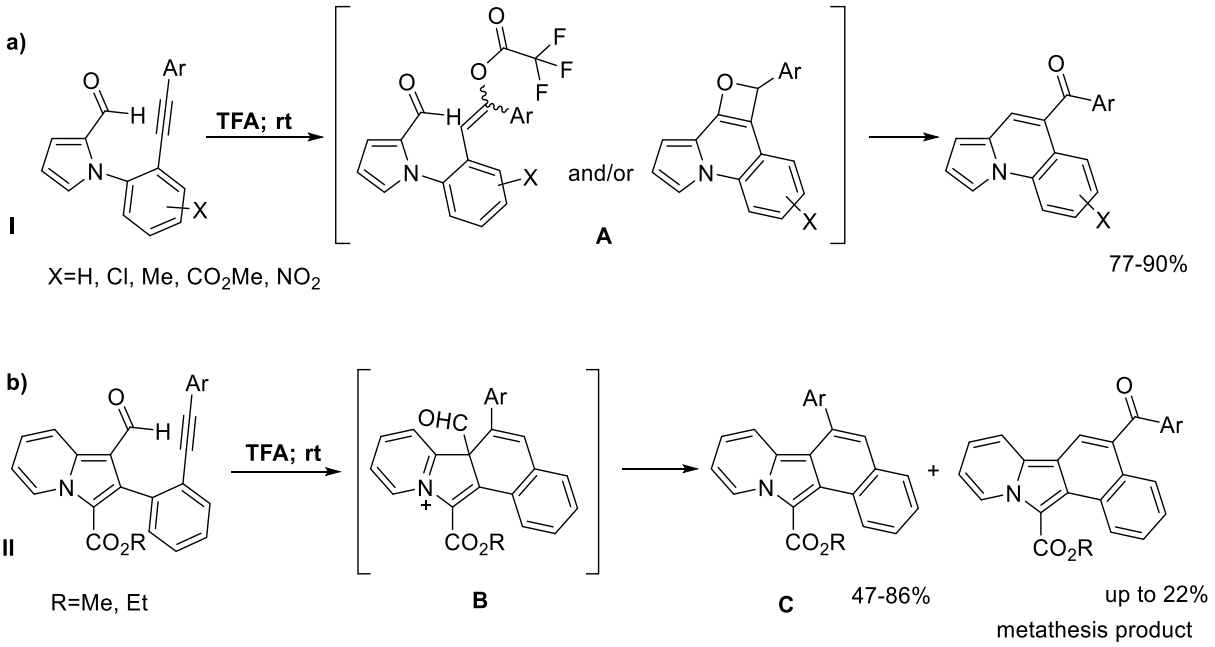
A new synthetic route to achieve a wide range of 5- and 6-acylated naphtho[1,2-*b*]benzofurans was published by Kim in 2017 and 2018 (Scheme 27). The reaction proceeds *via* Sonogashira coupling followed by TFA catalyzed intramolecular alkyne carbonyl metathesis. The excellent functional group tolerance made it possible to synthesize a wide range of heterocyclic aromatic compounds.[67]



Scheme 27. Synthesis of 5-and 6-acylated naphto[1,2-*b*]benzofurans.

According to Kim's achievement, TFA can mediate the metathesis between the triple bond and carbonyl group of indolizines to produce pyrroloquinolines. It has been noted by the author that the reaction can take place through the aldol reaction, as previously proposed by Saa's group, or *via* a [2+2] cycloaddition (Scheme 20b). The method allowed the synthesis of new pyrrolo[1,2-*a*]quinolines with carbonyl substituents at the C5 position, which are not accessible

by any other method (Scheme 28a).[68] Nevertheless, starting from indolizine **II**, benzopyridoindole **C** was obtained in front of the metathesis product in a good yield (Scheme 28b). The process involves hydroarylation of the indolizine ring at the C3 position, followed by deformylation and aromatization of intermediate **B**.[68b]



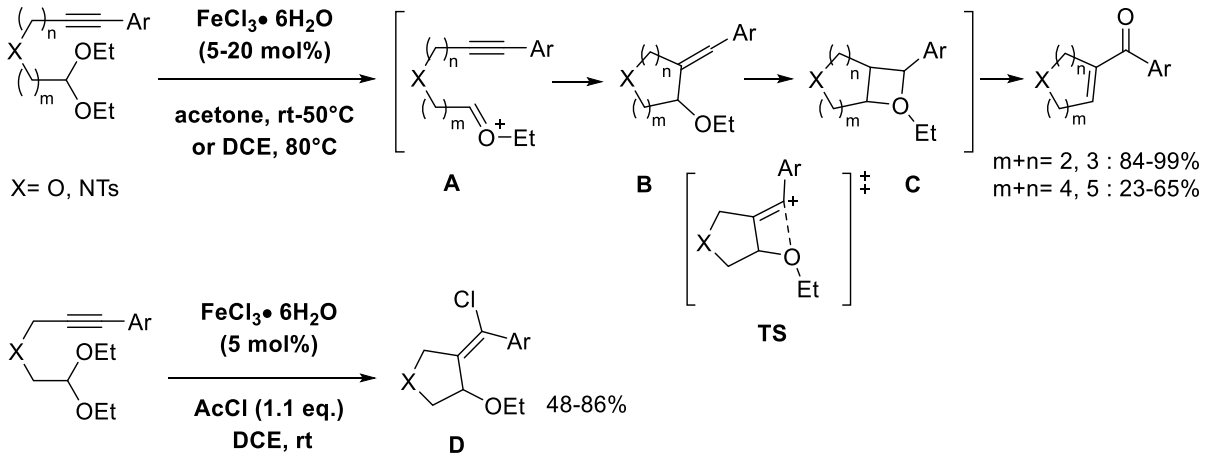
Scheme 28. TFA-mediated formation of cyclic enones.

4.4. Ring Closing Metathesis of alkyne-acetals

Considering that alkyne-carbonyl metathesis reactions are generally accomplished in acidic environments, the use of acetals or ketals instead of carbonyl groups is another strategy to construct polycyclic or medium-sized ring structures.

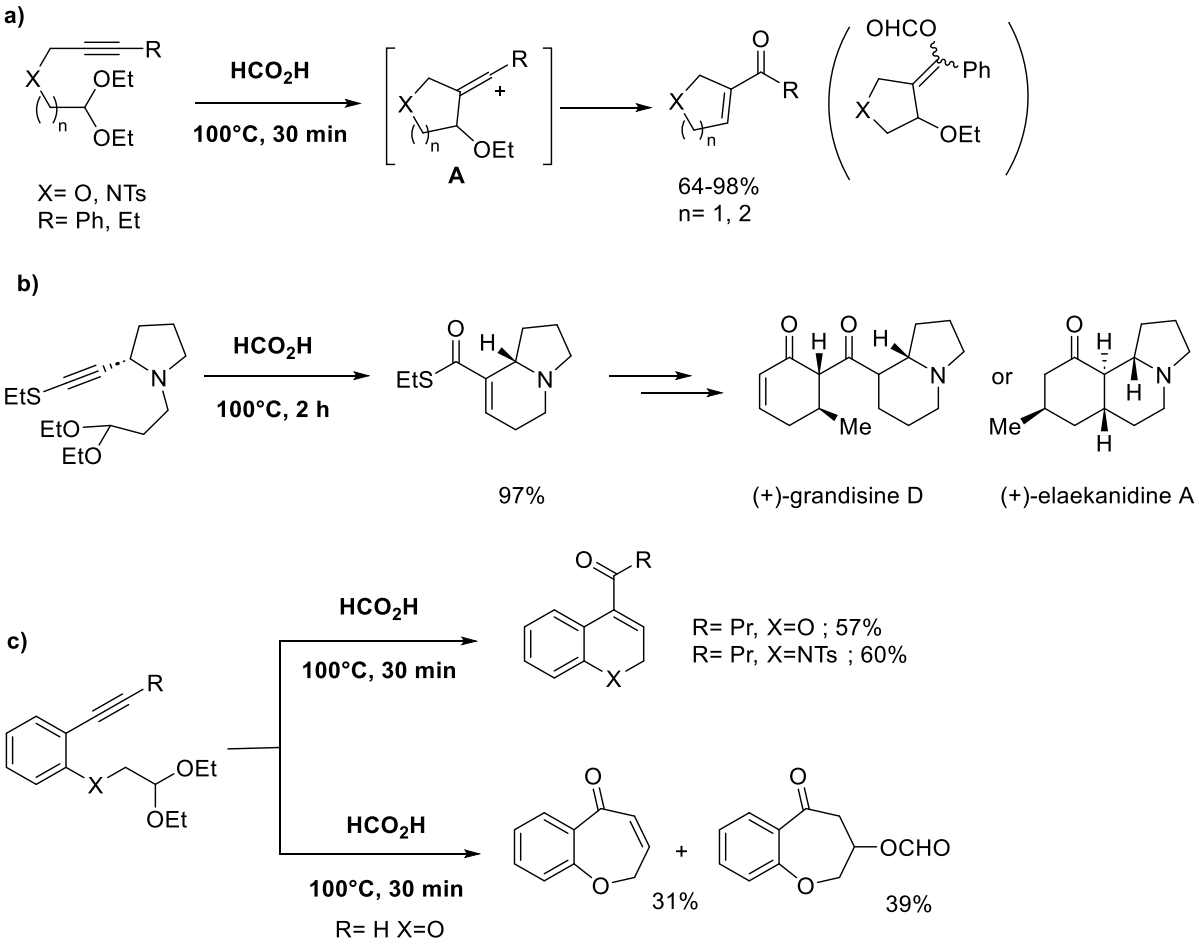
Yu and Li used ring-closing metathesis of alkyne- acetal to synthesis five- to eight-membered heterocycles in the presence of $FeCl_3$. In accordance with the experimental results, the reaction mechanism includes [2+2] cycloaddition of oxocarbenium **TS** and cycloreversion of intermediate **C** (Scheme 29).[69] It has been shown by computational studies that the formation of **C** requires the crossing of an energy barrier of 17.2 kcal/mol from **B** to reach the transition

state **TS**. As a result, the chloride anion efficiently traps **B** at relatively low temperatures resulting in product **D**.



Scheme 29. $FeCl_3$ catalyzed ring-closing reaction of alkynyl acetals.

The Taylor group has done extensive research on the use of formic acid in alkyne-acetal cyclization. In a reaction with formic acid at 100 °C, alkynyl acetals were converted to five- or six-members cyclic enones in good to excellent yields (Scheme 30a).[70] The reaction proceeded through intermediate **A**, which was isolated after 30 minutes at room temperature. Scheme 30b shows that the same method could be applied to the synthesis of nitrogen heterocycles, resulting in an excellent yield of indolizine, which was then efficiently converted to enantiopure indolizidine (5 steps, overall yield 14%).[71] Interestingly, as a result of the ring-closing reaction, the internal alkyne was converted to a chromene and dihydroquinoline moiety, while the terminal alkyne led to benzoxepinone derivatives in 31 and 39% yield. (Scheme 30 c).[72]



Scheme 30. Formic acid-mediated ring-closing reaction of alkyne-acetal.

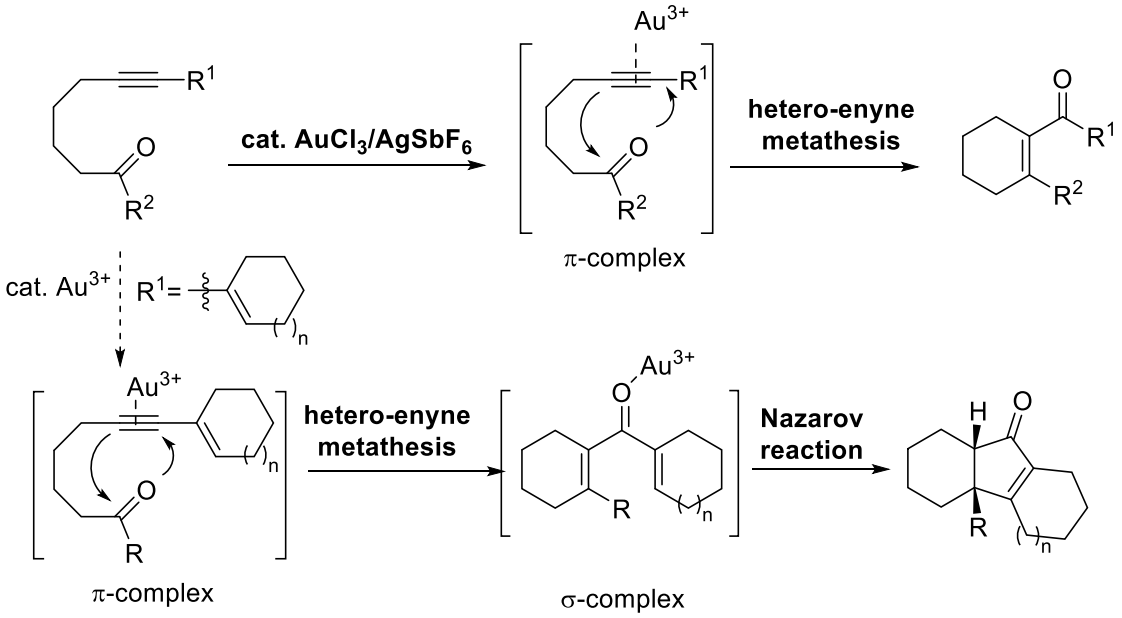
4.5. Alkyne-Carbonyl Metathesis in Domino Reactions

As mentioned above, the alkyne-carbonyl metathesis is an effective method for the construction of α,β-unsaturated carbonyl structures. Either the carbon atom of the carbonyl group or the β-carbon of α,β-unsaturated enones, which are both electrophilic carbons, can react with nucleophiles depending on the conditions. Consequently, these functional groups are widely used as precursors in consecutive reactions catalyzed by Lewis or Brønsted acids.

The development of domino reactions with cyclization of metathesis products provides an advanced synthetic route for other cyclic compounds.[73] To extend the intermolecular alkyne-

carbonyl metathesis to cyclic compounds, a domino reaction can be performed with cyclization of the metathesis product.

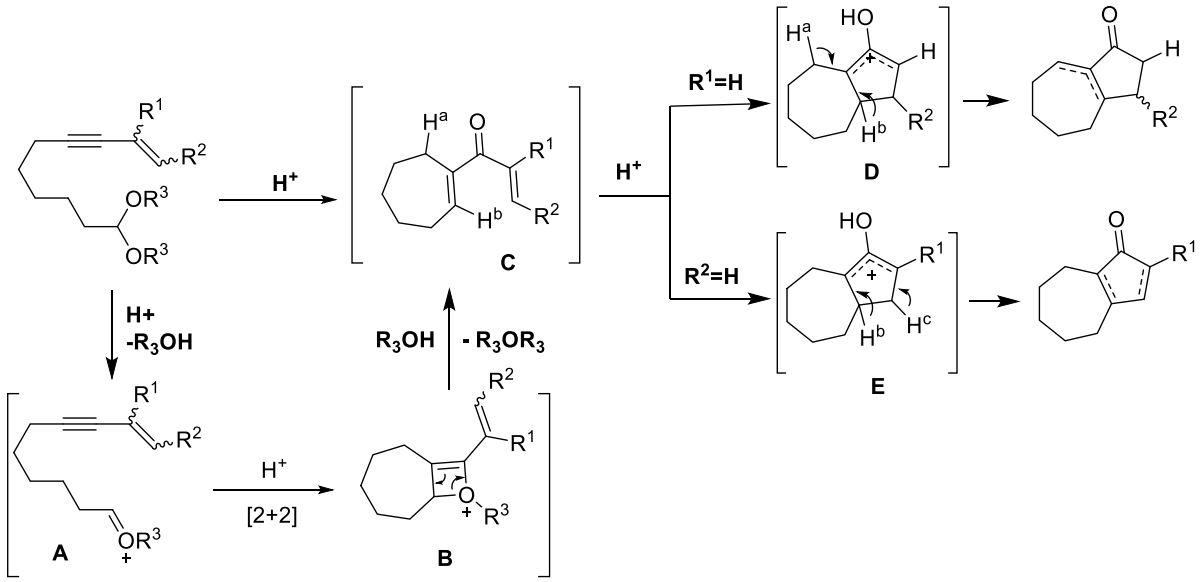
An interesting domino heteroenyne metathesis and Nazarov reaction of 6-alkynyl ketones has been published by Jim and Yamamoto in 2008. As shown in Scheme 31, an Gold(III) catalyst has been employed to achieve various fused tri- and tetracyclic enones from 1,3-enynyl ketones with very high diastereoselectivity. It was found that Au(III) plays a dual role in activating both the triple in the metathesis reaction and the carbonyl oxygen to facilitate the Nazarov reaction. Nevertheless, catalytic Nazarov reaction in this system has been occurred extremely smoothly.[74]



Scheme 31. Role of Au(III) in domino ACM reaction.

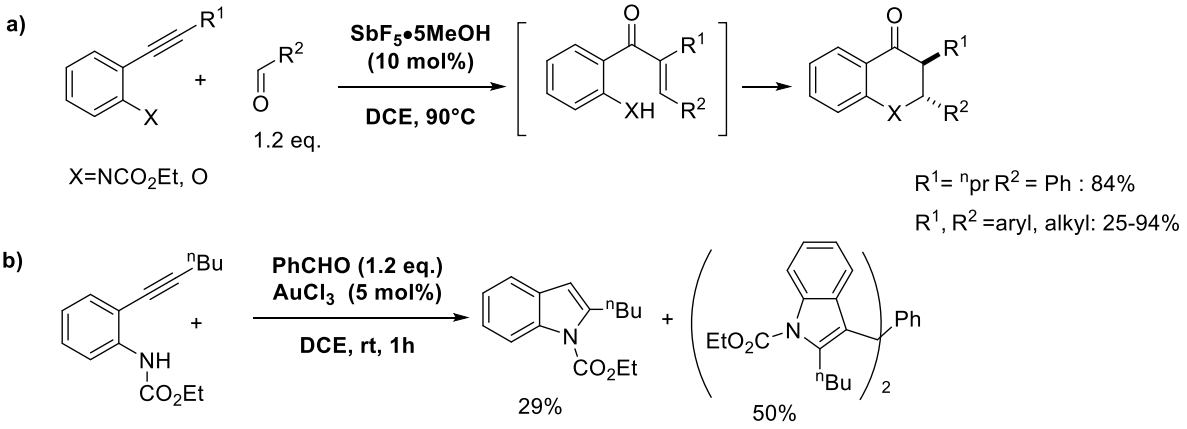
Decahydroazulene structures have also been formed by Sea's group using the same domino reaction. In this study, the metal-free catalyst HBF_4 catalyzed a standard heteroalkyne metathesis to provide the oxetene intermediate through [2+2] cycloaddition, which was then converted to the α-β unsaturated carbonyl compound **C**. In the presence of a Brønsted acid, the azulene-one structure was formed through a stereospecific Nazarov reaction. As shown in

Scheme 32, depending on which proton is eliminated in the Nazarov intermediate **D** (H^a or H^b) or **E** (H^b or H^c), it is possible to obtain different isomers.[75]



Scheme 32. Synthesis of azulene-1-one motifs using the ACM/Nazarov cyclization sequence.

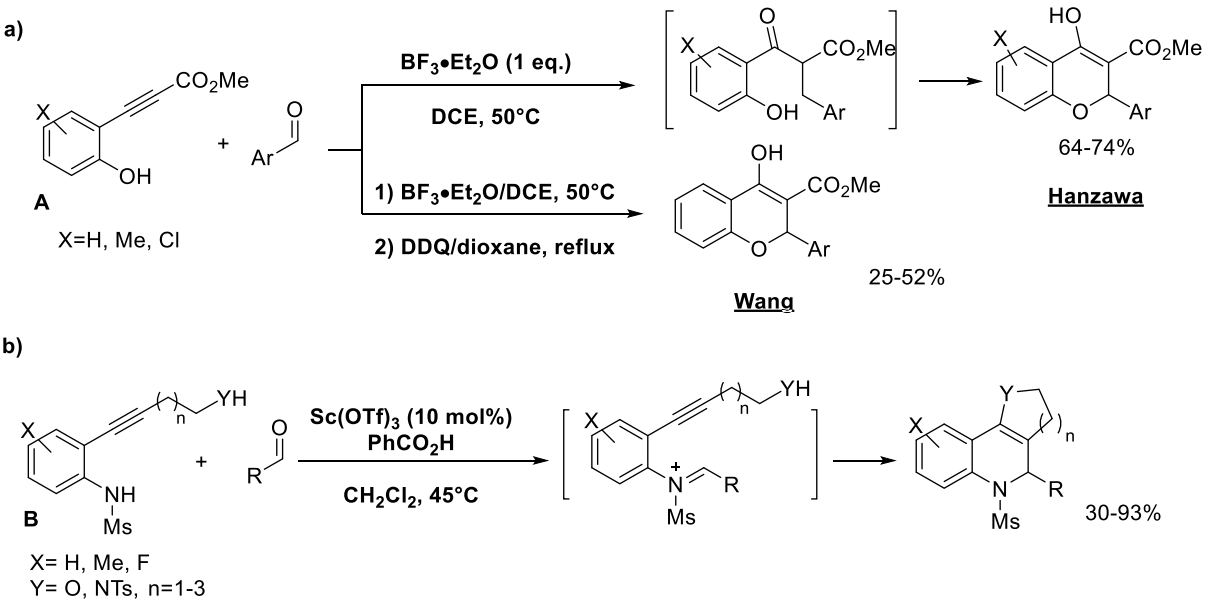
In 2008 Hanzawa group reported a highly stereoselective synthesis of trans-2,3-disubistituted indanoes through the intermolecular metathesis of phenylalkynes and aldehydes, in which SbF_5-alcohol complex activates the aldehydes and intermediate as a sigma acid catalyst. The authors applied the domino reaction to the synthesis of heterocycles from *o*-alkynylaniline.[73a,b, 76] In the synthesis of dihydroquinolinones, SbF_5•MeOH efficiently catalyzed the intermolecular metathesis of *o*-alkynylanilines with aldehydes and subsequent cyclization of enone intermediates. The intermediate can be isolated under similar conditions at lower temperature. It has been shown that the catalyst must be sigma acidic, as π–acid catalysts, such as $AuCl_3$, promote the cyclization of starting material before the intermolecular reaction occurs (Scheme 33 b).



Scheme 33. ACM/cyclization sequence of domino reactions.

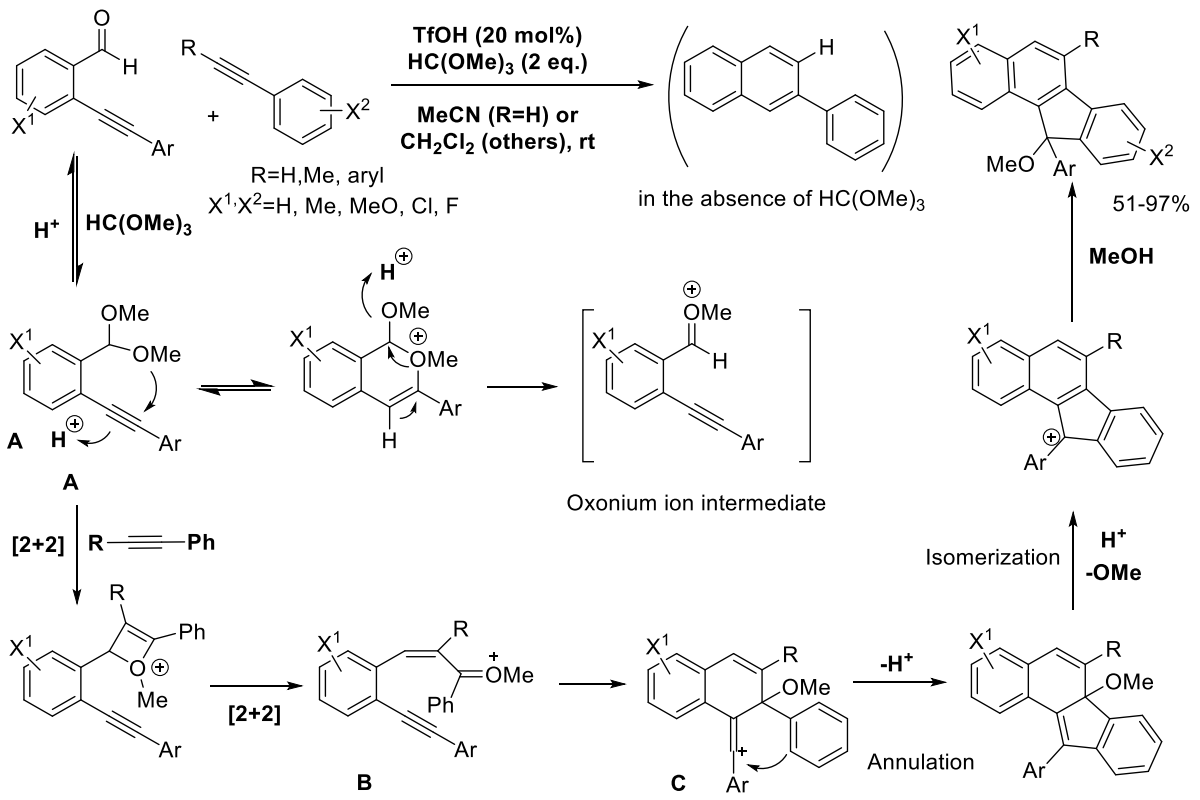
Another group independently published domino reactions of *o*-alkynylphenols and anilines with aldehydes.[77] In the analogue manner to Hanzawa's group, the group of Wang developed the BF_3-mediated synthesis of 4-chromanone from *o*-alkynylphenols having the electron-withdrawing group. In this report the domino reaction has been extended to the one pot synthesis of 4-chromenone with the use of DDQ as oxidant. (Scheme 34 a)

On the other hand, the synthesis of fused dihydroquinolines by Ma *et al*. was considered to proceed through a prins-type cyclization of iminium intermediates derived from **B** and aldehydes, which can be regarded as an alternative reaction pathway from *o*-alkynylanilines and aldehydes.[77b] For these reactions, $Sc(OTf)_3$ catalytic system were effective and particularly the dual catalyst of $Sc(OTf)_3$ and $PhCO_2H$ showed good yields of products from electron-deficient aldehydes (R=4-NCC_6H_4, 4-$MeOCOC_6H_4$, etc.) (Scheme 34b).



Scheme 34. ACM-domino approach to heterocyclic structures.

Balamurugan found that TfOH catalyzed alkyne-carbonyl metathesis and cyclization to form benzofluorenes from 2-(arylethynyl)benzaldehydes with aromatic alkynes. To achieve the desired product, the use of orthoformate along with TfOH is needed, as the use of neat TfOH, naphthalene is obtained. For a better understanding of the reaction, the author treated acetal **A** with TfOH in the absence of orthoformates to produce end products. According to the author, the desired product is obtained through consecutive electrophilic cyclization reactions from intermediate **B**.[78] Scheme 35 provides more details about the plausible mechanism suggested by the author. To construct the benzo[*a*]fluorene framework, [2+2] cycloaddition/alkyne acetal coupling of *in situ* generated acetals is followed by double bond isomerization.

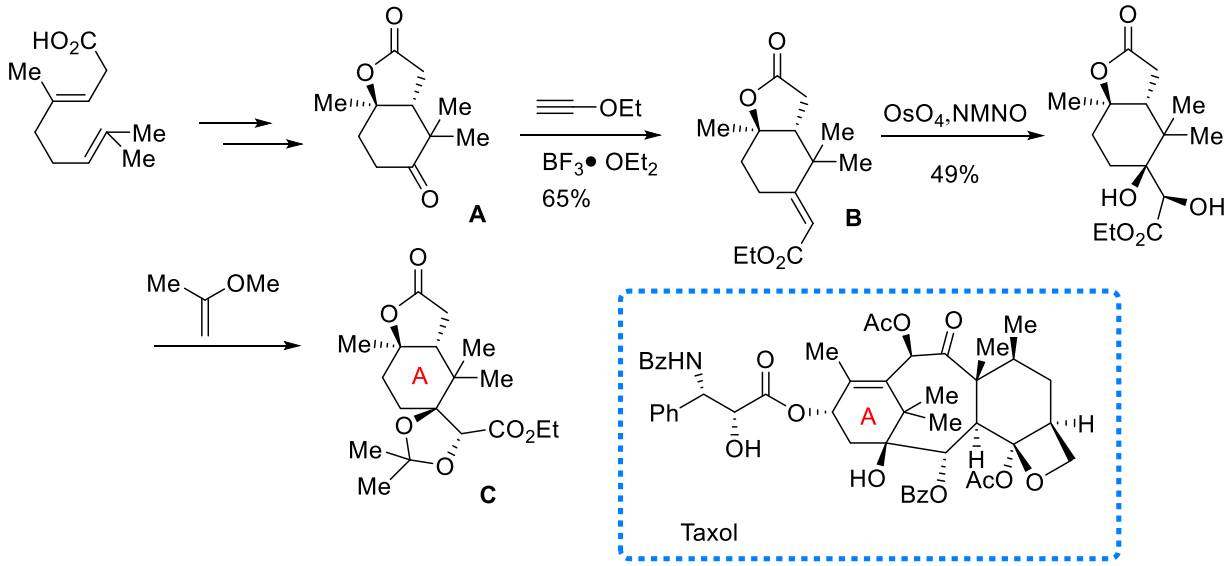


Scheme 35. Domino approach for the synthesis of benzo[*a*]fluorenes.

4.6. Alkyne-Carbonyl Metathesis in Natural Product Synthesis

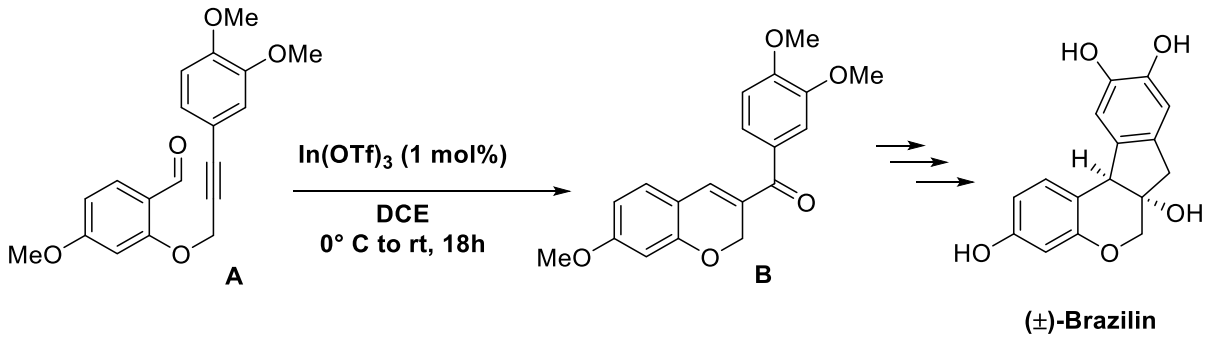
It has already been shown that alkyne-carbonyl metathesis produces structural motifs, such as α,β-unsaturated ketones, esters, and amide which are common structural motifs in natural products.

Crich pioneered the use of the alkyne-carbonyl metathesis reaction in the synthesis of the Taxol A-ring synthon.[79] According to the authors, a classical olefination reaction, such as Wittig, Horner-Wadsworth-Emmons or Julia reaction, did not produce product **B** from ketone **A**. Nevertheless, **B** could be isolated in 65% yield as a single isomer when **A** was treated with ethoxyacetylene and BF_3•OEt_2. Using two steps, including dihydroxylation and diol protection, the product was further converted into the desired Taxol A-ring synthon **C**.



Scheme 36. Synthesis of Taxol A-ring synthon.

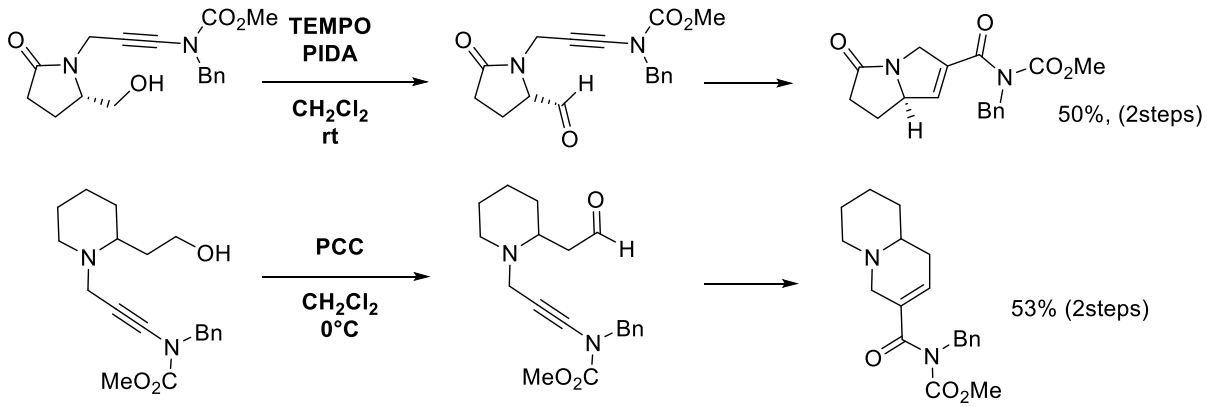
According to Kim, a ring-closing alkyne-carbonyl metathesis can lead to the rapid formation of molecular structures for tetracyclic homoisoflavonoids such as Brazilin. Using catalytic amounts of $In(OTf)_3$, the authors produced exocyclic enone **B** from aldehyde **A**, which was used to construct the Brazilin core. After a series of subsequent steps, (±)-Brazilin was synthesized in nine steps with an overall yield of 70%.[60b]



Scheme 37. Total synthesis of (±) brazilin.

In the past decade, bicyclic alkaloids have attracted the attention of the synthetic community due to their structural diversity and biological activity (Fig. 2).

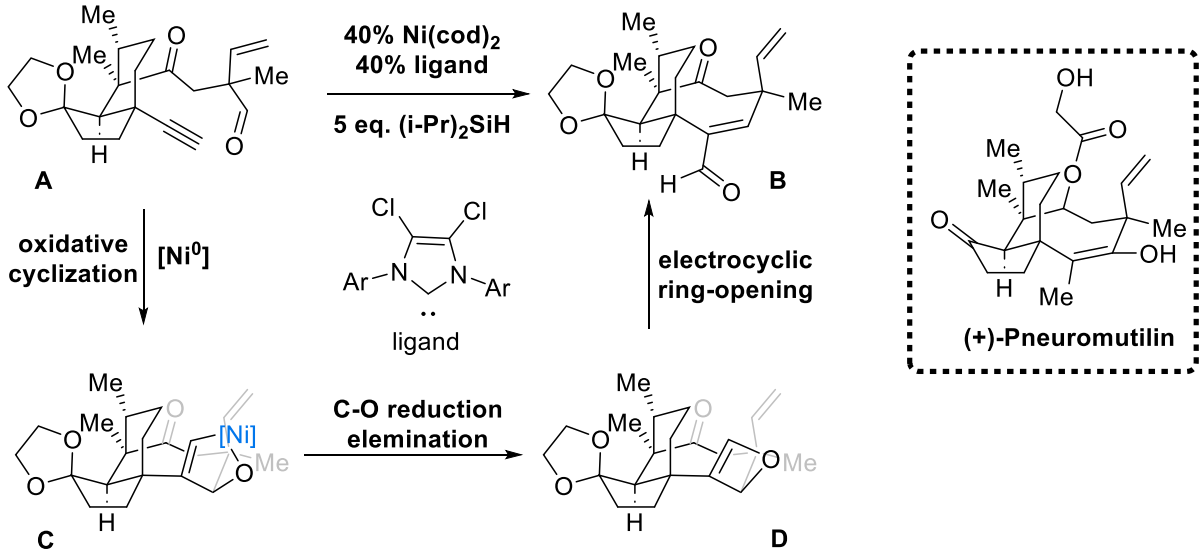
Using a ring-closing alkyne-carbonyl metathesis reaction, Hsung demonstrated the possibility of obtaining pyrrolizidine and quinolizidine cores. According to their report, ynamides as alkynyl components underwent BF_3-mediated metathesis reaction and provided nitrogen-containing heterocycles. Under optimized oxidative conditions, hetero RC-ACM occurred in situ to give pyrrolizidinone in 50% yield. By further developing this tandem oxidation–ACM sequence, 53% of quinolizidine could be effectively accessed. Hence, a new synthetic approach was provided to develop such alkaloid core structures.[80]



Scheme 38. Synthesis of pyrrolizidine and quinolizidine cores.

Pneuromutilin is an antibacterial drug that inhibits protein synthesis by binding to the peptidyl transferase component of the 50S subunit of ribosomes. A modular synthetic route for this compound has been reported by Herzon in 2017.[81]

To access the eight-membered carbocycle, the reductive coupling of nickel was used as the key disconnection. First precursor **A** was generated in four steps with a total yield of 45%. Then, in the present of nickel catalyst and tri-*iso*-propylsilane as a reductant, the enone **B** was isolated in 55%. It has been proposed that the product results from the oxidative cyclization of Nickel(0) to form the metallacycle **C**. Rather than reacting with bulky $(i\text{-Pr})_3SiH$, reductive elimination of nickel(II) center **C** produced oxetene **D**. Subsequently, an electrocyclic ring-opening resulted in **B** as the formal metathesis product.

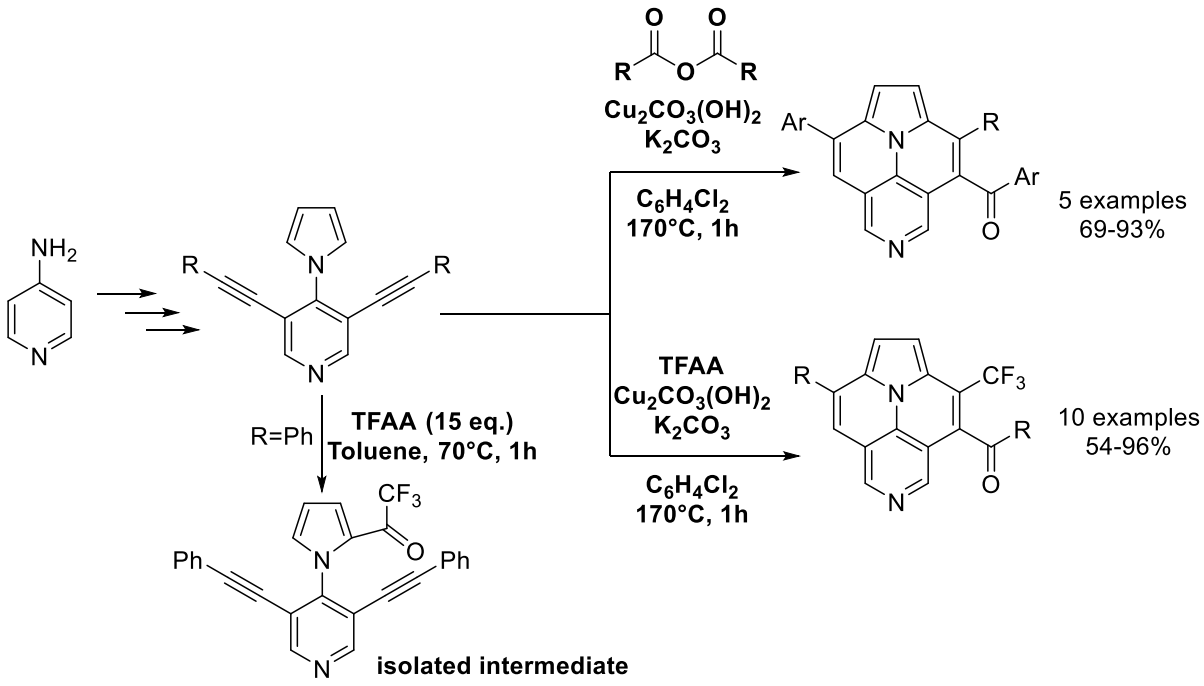


Scheme 39. Ni-catalyzed ACM reaction of Pneuromutilin.

The most important reactions for the synthesis of various-sized rings and heterocycles are described. Indeed, a literature survey reveals that the ACM reaction has been used to synthesize a variety of natural products and complex molecules over the past 10 years by using metal-free catalysts, photochemical promotion, and transition metal reagents.[82] There is still a room for improvement in the various aspects of this methodology.

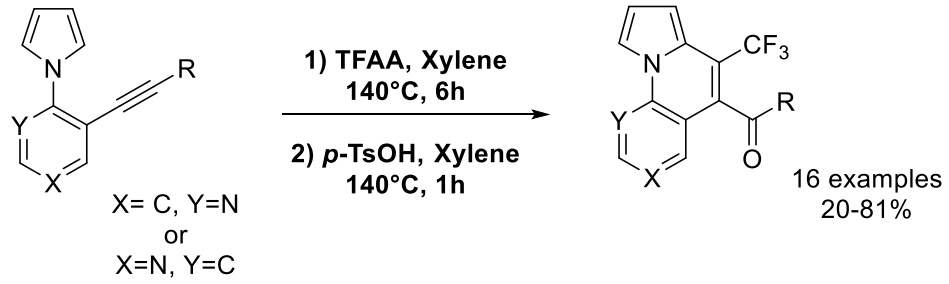
5. ACM Reaction Study Conducted by Prof. Langer's Group

In 2018, through acylation followed by intramolecular alkynyl carbonyl metathesis, a range of aza-ullazines was prepared from easily accessible 3,5-diakynyl-4-pyrrolopyridines in Prof. Langer´s group.[83] Initially, 4-amino pyridine was used as the starting material, which was then converted into 3,5-dialkynyl-4-pyrrolopyridine. Later in the presence of Cu-catalyst, it was treated with various acyl derivatives to form the fused ring structure. Optimizing the reaction conditions led to the preparation of different derivatives of the aza-ullazine product.



Scheme 40. Synthesis of aza-ullazines by intramolecular ACM.

Using this methodology, it was possible to synthesize a greater number of polycyclic heteroaromatic core structures. For example, in 2020, Langer's group published a two-step one-pot synthesis of pyrrolo[1,2-*a*][1,6]- and [1,8]naphthyridines by electrophilic acylation followed by alkyne-carbonyl metathesis (Scheme 41).[84]



Scheme 41. Synthesis of pyrrolo[1,2-*a*][1,6]- or [1,8]naphthyridines *via* ACM.

In light of these previous studies in Prof. Langer's group, the present work investigates the synthesis of polycyclic heteroaromatic compounds *via* the ACM reaction. The motivation for using this methodology based on the interesting properties of polycyclic compounds as well as the limited number of existing synthetic routes for obtaining six- and seven-membered ring structures. The current work provides new insights into the synthesis of polycyclic compounds *via* Brønsted-acid-mediated ACM reactions.

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II. Contribution to Manuscripts

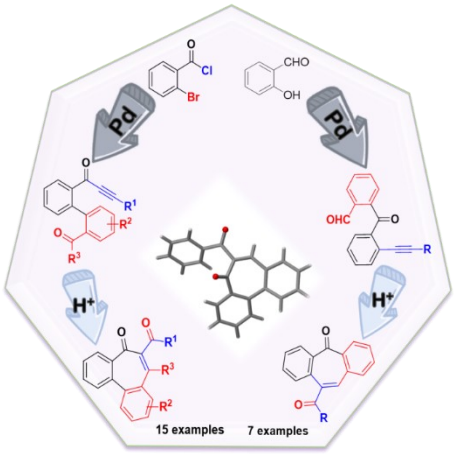
Original publications are presented in the next chapter. A summary of my contributions to each publication is given in the subchapter.

Publication I

Synthesis of Dibenzotropones by Alkyne-Carbonyl Metathesis

Maryam Sobhani, Anna Frey, Andre Rettmann, Richard Thom, Alexander Villinger, Peter Ehlers,*and Peter Langer*

DOI: 10.1021/acs.joc.1c01132
Full paper*: J. Org. Chem*. **2021**, 86, 14420−14432



Abstract: Dibenzocycloheptanones (dibenzotropones) were prepared by Brønsted acid mediated intramolecular alkyne-carbonyl metathesis (ACM) reactions. The cyclization precursors are readily available by Sonogashira reaction of 2-bromobenzoyl chloride with terminal alkynes, followed by Suzuki reactions with benzaldehydes. The ACM reactions are highly modular and atom economic and allow for the construction of two regioisomeric series of dibenzotropones.

Keywords: alkyne-carbonyl metathesis; catalysis; cross-coupling; carbacycles; cyclization

Contribution to this work: 70%

In this paper, two series of regioisomeric products were synthesized. The first serious including 15 examples was investigated by Maryam Sobhani and Richard Thom during his bachelor thesis.
I optimized the reaction condition of all three steps. The substrate scope as well isolation and evaluation of analytical data were performed with help of R. Thom. Furthermore, I wrote all version of manuscript, as well as the supporting information. Dr. Villinger performed single crystal structure measurement and refinement. Conception, supervision and manuscript revision by Dr. Peter Ehlers and Prof. Dr. Peter Langer.

Maryam Sobhani Prof. Dr. Peter Langer

Publication II

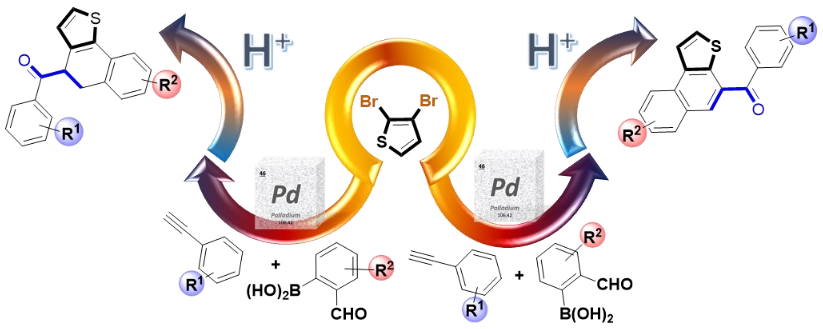
Regioselective Synthesis of Naphthothiophenes by Pd Catalyzed Cross-Coupling Reactions and Alkyne-Carbonyl Metathesis

Maryam Sobhani, Alexander Villinger, Peter Ehlers*, Peter Langer*

DOI: 10.1021/acs.joc.1c02838
Full paper: *J. Org. Chem.* **2022**, 87, 4560−4568

Abstract: Naphthothiophenes were prepared from commercially available 2,3-dibromothiophenes in two steps by one-pot Suzuki/Sonogashira or Sonogashira/Suzuki coupling reactions, followed by intramolecular alkyne-carbonyl-metathesis reactions. The cyclization reaction proceeds without any metal catalyst in the presence of *p*-toluenesulfonic acid and provides a rapid access to two series of isomeric naphthothiophenes. The optical properties of the products (fluorescence) were studied.

Keywords: cyclizations, cross-coupling, heterocycles, palladium, regioselectivity



Contribution to this work: 90%

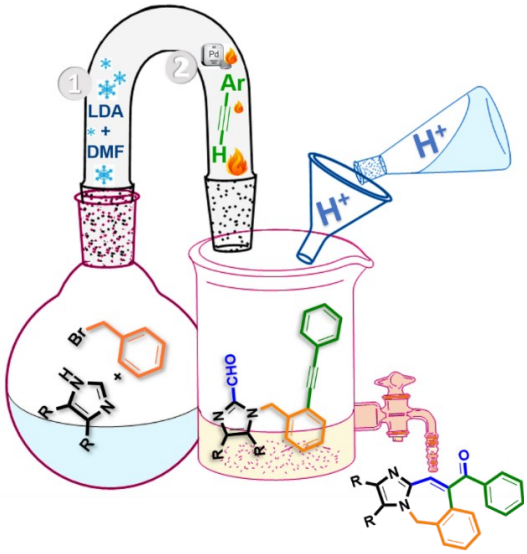
In this paper, I performed all experiments regarding the optimization, substrate scope, and analytical measurements including UV-Vis. In addition, I evaluated the analytical data and wrote all version of manuscript, as well as the supporting information. Dr. Villinger performed single crystal structure measurement and refinement. Conception, supervision and manuscript revision by Dr. Peter Ehlers and Prof. Dr. Peter Langer.

Maryam Sobhani Prof. Dr. Peter Langer

Publication III

Synthesis of Imidazo[1,2-a]benzoazepines by Alkyne-Carbonyl-Metathesis

Maryam Sobhani[a], Rúben Manuel Figueira de Abreu[a], Alexander Villinger[a], Peter Ehlers[a]*, Peter Langer[a,b]*



DOI: 10.1039/D2OB01320G
Full paper: *Org. Biomol. Chem.*, **2022**,20, 9207-9216

Abstract: Imidazo[1,2-*a*]benzoazepines were prepared by Brønsted acid-mediated intramolecular alkyne-carbonyl metathesis (ACM). The starting materials, imidazole and benzimidazole derivatives, were prepared by *N*-alkylation, formylation and Sonogashira cross-coupling reaction. The final intramolecular ACM delivered the final products in good to excellent yields and with a wide tolerance towards functional groups.

Keywords: alkyne-carbonyl metathesis; cyclizations; heterocycles; palladium; cross-coupling.

Contribution to this work: 65%

I optimized all the reaction condition. In addition, 7 examples of substrate scope were synthesized and isolated by Maryam Sobhani. Rúben Manuel Figueira de Abreu synthesized and isolated 14 examples of the reaction scope. Furthermore, after evaluation of analytical data, I wrote all version of manuscript, as well as the supporting information. Dr. Villinger performed single crystal structure measurement and refinement. Conception, supervision and manuscript revision by Dr. Peter Ehlers and Prof. Dr. Peter Langer.

Maryam Sobhani Prof. Dr. Peter Langer

Curriculum vita

Date and place of the birth: 27.03.1988 – Tehran /Iran

Sep 2018– Sep 2022	PhD (Chemistry) University of Rostock • The Alkyne-Carbonyl Metathesis Reaction in Polycyclic Synthesis
Sep 2011– Feb 2013	Master (Organic Chemistry) Sharif University of Technology, Tehran (Iran), working group Prof. Dr. Matloubi Moghadam • The stereoselective synthesis of the tetrahydrothiopyrano[2,3-*b*]indole Skeletones *via* tandem reaction of indoline-2-thiones to Baylis-Hillman adduct acetates • Silica-Supported DABCO-tribromide, versatile and Recyclable Catalyst for the Chemoselective Oxidation of Sulfides to Sulfoxides and Oxidative Coupling of Thiols into Disulfides.
Sep 2006– Mar 2011	Bachelor (applied Chemistry) Department of science, Alzahra University, Tehran (Iran), Grade16.27 out of 20 (good)

Publications

- "Synthesis of Imidazo[1,2-a]benzoazepines by Alkyne-Carbonyl-Metathesis". (*Org. Biomol. Chem*., **2022**,20, 9207-9216)

- "Regioselective Synthesis of Naphthothiophenes by Pd Catalyzed Cross-Coupling Reactions and Alkyne-Carbonyl Metathesis". (J. Org. Chem**. 2022**, 87, 7, 4560-4568)

- "Synthesis of Dibenzotropones by Alkyne-Carbonyl Metathesis" (J. Org. Chem. **2021**, 86, 21, 14420–14432)

- "The stereo selective synthesis of the tetrahydrothiopyranonn [2,3-b] indole skeletons *via* tandem reaction of indoline-2-thiones to Baylis-Hillman adduct acetates". (Tetrahedron. **2013**. 69, 38, 23)

Conference participations

- Oral presentation: "Design, Synthesis and Characterizing of novel Naphtothiophenes as organic dyes to absorb light" 3nd Rohan DAAD SDG Summer school, 9-21 September 2019, Hanoi University of Science, Vietnam.

- Poster: "DABCO-tribromide supported on magnetic iron oxide nanoparticles: magnetically recoverable catalyst for oxidative coupling of thiols to disulfides" 4th International Congress on Nano science& Nanotechnology, 8-10 September 2012, Kashan University, Kashan, Iran.

- Poster: "Synthesising tetrahydrothiopyranonn [2,3-*b*] indole skeletons *via* tandem reaction which can show biological activities" 20th International Congress on Organic Chemistry, 3-5 July 2013, Bu-Ali Sina University, Hamedan, Iran.

III. Appendix

I. Publication

II. Publication

III. Publication

I. Publication

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Synthesis of Dibenzotropones by Alkyne-Carbonyl Metathesis

Maryam Sobhani, Anna Frey, Andre Rettmann, Richard Thom, Alexander Villinger, Peter Ehlers,* and Peter Langer*

Cite This: J. Org. Chem. 2021, 86, 14420−14432 Read Online

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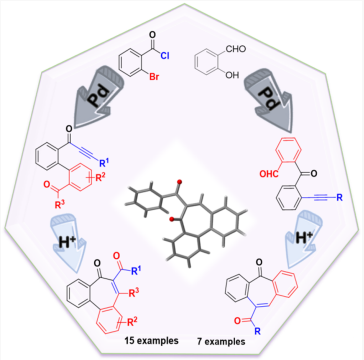
ABSTRACT: Dibenzocycloheptanones (dibenzotropones) were prepared by Brønsted acid mediated intramolecular alkyne-carbonyl metathesis (ACM) reactions. The cyclization precursors are readily available by Sonogashira reaction of 2-bromobenzoyl chloride with terminal alkynes, followed by Suzuki reactions with benzaldehydes. The ACM reactions are highly modular and atom economic and allow for the construction of two regioisomeric series of dibenzotropones.



INTRODUCTION

The assembly of seven-membered carbocycles is a challenging topic as compared to the synthesis of five- and six-membered rings,[1] because of ring strain and entropic reasons. However, seven-membered carbocycles are present in several natural products and synthetic bioactive compounds. This includes, for example, tropane alkaloids, scabronine, cortistatin, liphagal, and frondosins.[2] The biological potential of such structures for drug discovery, such as the development of novel anticholinergic agents similar to spiriva, benzatropine, and hyoscyamine,[3] has fostered the interest in the development of new synthetic methods to access seven-membered carbocycles (Figure 1).[4] Classical synthetic strategies toward such carbocycles include intramolecular cyclization reactions of carbonyl compounds,[5] cycloaddition reactions,[6] ring closing metathesis,[7] and ring expansion (Scheme 1).

While olefin metathesis reactions have been widely reported in the literature, alkyne-carbonyl metathesis (ACM) reactions are more rare and have in recent years emerged as a versatile synthetic tool for the construction of α,β-unsaturated carbonyl compounds with 100% atom economy.[9] The ACM reaction has been reported to be catalyzed by various Lewis and Brønsted acids such as $AgSbF_6$,[10] $FeCl_3$,[11] $Yb(OTf)_3$,[12] $In(OTf)_3$,[13] CuI/I_2, TfOH,[14] and many others.[15] The intramolecular (ring-closing) ACM allows the formation of various carbo- and heterocycles that are not easily available by traditional procedures. The formation of conjugated enones via ACM reaction is dependent on the type of catalyst (Scheme 2). Brønsted and Lewis acids can catalyze or mediate intra- and intermolecular metathesis of alkyne-carbonyl involving a [2 + 2] cycloaddition followed by cycloreversion. Depending on the employed acid, the substrates can be activated either on the carbonyl moiety (oxophilic Lewis acids or Brønsted acids) or on the triple bond (π-electrophilic Lewis acids).

It is noteworthy that the carbonyl group formed in the product represents a valuable handle for subsequent functionalization and derivatization reactions.[15] Recently, the synthesis of cycloalkenones, indolizines, and chromenones have been reported using ACM reactions.[17] Despite recent achievements in the field of ACM reactions, some critical drawbacks still remain unsolved such as limited substrate scope, formation of side-products, requirement of chlorinated solvents, or the need of toxic transition metal catalyst.[18] Therefore, the design of new and sustainable ACM protocols, using highly active catalysts with high selectivity and improved functional group tolerance, is of ongoing interest in current research.[19] Herein, we report a metal-free, Brønsted acid mediated synthesis of dibenzocycloheptanones (dibenzotropones) by intramolecular ACM reactions. This methodology is highly modular and allows selective access to regioisomeric products. The transformations show a very good functional group tolerance, and starting mnaterials are readily available.

RESULTS AND DISCUSSION

Intermediates **4** were prepared by Sonogashira and Suzuki coupling reactions. According to a published procedure,[20]

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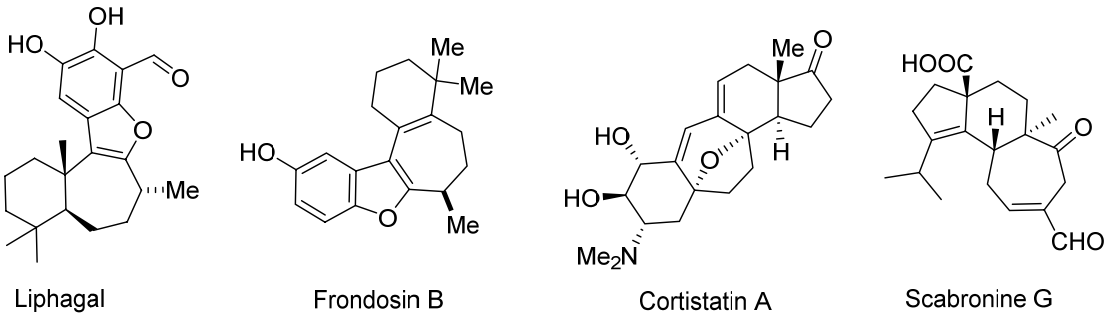
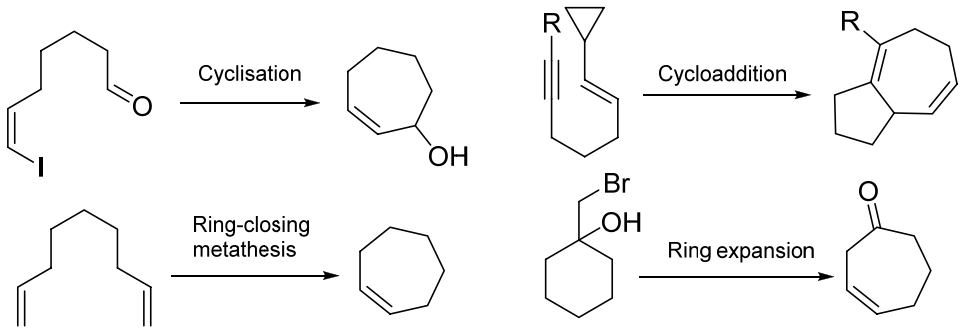
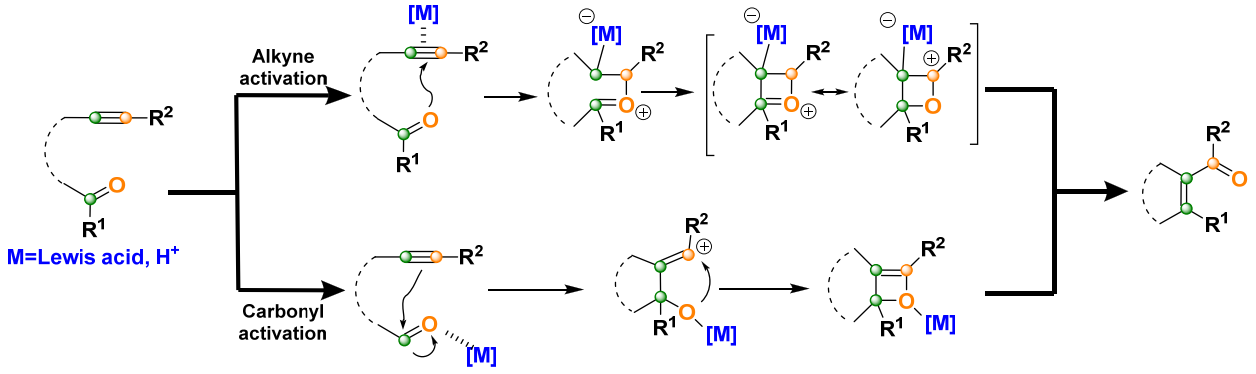


Figure 1. Natural and bioactive compounds containing a cycloheptane moiety.

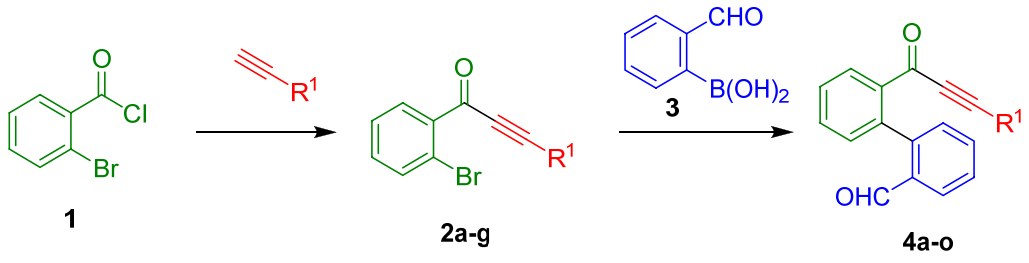
Scheme 1. Strategies for the Synthesis of Seven-Membered Carbocycles



Scheme 2. Proposed Mechanism for Alkyne-Carbonyl Metathesis by Lewis and Brønsted Acids



Scheme 3. Synthesis of Starting Materials 4a−o



intermediates **2a−g** were synthesized by reaction of 2-bromobenzoyl chloride with arylacetylenes (Scheme 3, Table S1).

The Suzuki coupling reaction of **2a−g** with 2-formylarylboronic acids **3**, in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$, using K_2CO_3 as the base in 1,4-dioxane at 65 °C, gave the desired cyclization precursors **4a−o** in high yields (Table S2). It is important to note that the employed conditions proved to be applicable also for ketone-based arylboronic acids which was exemplarily shown for the synthesis of compound **4f** in satisfactory yield. The ACM reaction was studied next. In this context, we screened three Brønsted acids, trifluoroacetic acid (TFA), methanesulfonic acid (MsOH), and *p*-toluenesulfonic acid (*p*-TsOH) to examine their efficiency. For this purpose, cyclization precursor **4a** was chosen as a model substrate. Treatment of **4a** with 15

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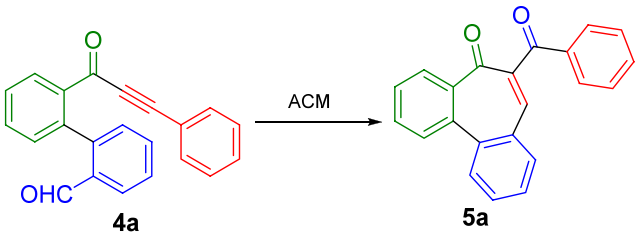
equiv of *p*-TsOH in toluene gave the desired product **5a** in 68% yield after 4 h (Table 1, entry 1). Different solvents were

Table 1. Optimization of the Synthesis of 5a



Entry	Catalyst (equiv)	Solvent	Time (h)	Temp (°C)	Yield (%)
1	*p*-TsOH (15)	Toluene	4	85	68
2	TFA (15)	Toluene	4	85	35
3	MsOH (15)	Toluene	4	65	0
4	*p*-TsOH (20)	Toluene	4	85	63
5	*p*-TsOH (15)	Toluene	3	100	10
6	*p*-TsOH (15)	THF	3	60	20
7	***p*-TsOH (15)**	**HFIP**	**3**	**60**	**73**
8	*p*-TsOH (15)	Hexane	3	60	62
9	*p*-TsOH (10)	Toluene	4	85	51
10	*p*-TsOH (5)	HFIP	4	60	47

examined next. When hexafluoroisopropanol (HFIP) was used, product **5a** was obtained in 70% yield (15 equiv of *p*-TsOH, 60 °C, 3 h, Table 1, entry 7).

Subsequently, the scope of the ACM reaction was explored using starting materials **4a−o** (Table 2). Various substrates containing electron-donating or electron-withdrawing groups provided the desired products **5a−o** in moderate to excellent yields (31−98%).

Product **5e**, containing a 4-*t*Bu group, was isolated in the best yield among all synthesized products. In contrast, ketone derived product **5f** gave the lowest yield, which might be a result of the reduced electrophilicity of ketones as compared to aldehydes and by steric repulsion of the methyl and the benzoyl group. A steric effect of substituent R^1 or R^2 on the yield was not observed. Moreover, different functional groups R^2 did not significantly change the yield. For compound **5g**, containing a fluorine substituent *ortho* to the formyl group, a drop of the yield to 40% was observed. However, for closely related products **5k** and **5m** no decrease of the yield was observed.

Suitable crystals for single crystal X-ray diffraction analysis have been obtained by slow evaporation of ethanolic solutions of compounds **5a**, **5c**, **5n**, and **5o**. The crystal structure analyses independently confirmed the structure of the products.

All molecules crystallized in similar conformations with the same orientation of the attached benzoyl groups relative to the tropone moiety with dihedral angles in the range 24.9°−32.6°. No deviation from the boat conformation was observed for the 7-membered ring.

The synthesis of isomeric dibenzotropones was studied next. The reaction of salicyl aldehyde with 2-bromobenzohydrazide and subsequent oxidation afforded product **6** (Scheme 4).[21] The Sonogashira reaction of **6** afforded cyclization precursors **7a−g** (Table S4).

The ACM reaction was next studied using **7a** as a model compound. An assay with various Brønsted and Lewis acids, solvents, reaction times, and temperatures was carried out (Table 3). Dibenzotropone **8a** could be isolated in up to 64% yield using 5 equiv of *p*-TsOH in toluene at 80 °C (entry 10). In general, similarly to the synthesis of tropones **5a−o**, employment of Brønsted acids was superior to Lewis acids. The amount of *p*-TsOH could be reduced from 15 to 5 equiv as compared to the synthesis of **5a−o**.

The preparative scope was studied (Table 4). The presence of electron-donating groups, like Me or OMe, resulted in higher yields (64% and 62%) as compared to electron-withdrawing substituents (CF_3 and F). The ACM reaction of compound **7f**, bearing an aliphatic side chain located directly at the triple bond, afforded the desired compound **8f**, albeit, in only 19% yield.

CONCLUSION

Several diarylcycloheptanones (dibenzotropones) were prepared by ring-closing alkyne-carbonyl metathesis reactions mediated by *p*-TsOH. The cyclization precursors are readily available by Pd catalyzed cross-coupling reactions. The synthetic strategy is highly modular and could be used to access two series of regioisomeric products.

EXPERIMENTAL SECTION

General Experimental Information. The nuclear magnetic resonance spectra ($^1H/^{13}C/^{19}F$ NMR) were recorded on a Bruker AVANCE 300 III, 250 II, or 500. Analyzed chemical shifts δ are referenced to residual solvent signals of the deuterated solvents $CDCl_3$ (δ = 7.26 ppm/77.0 ppm). Multiplicities due to spin−spin correlation are reported as follows: s = singlet, d = doublet, dd = double doublet, t = triplet, pt = pseudo triplet, m = multiple and further described through their coupling constants *J*. Infrared spectra (IR) were measured as attenuated total reflection (ATR) experiments with a Nicolet 380 FT-IR spectrometer. The signals have been characterized through their wave numbers $\tilde{\nu}$, and their corresponding absorption has been characterized as very strong (vs), strong (s), medium (m), weak (w), or very weak (vw). Basic and high-resolution mass spectra (MS/HRMS) were measured on instruments which are paired with a preceding gas chromatograph (GC) or liquid chromatograph (LC). The samples have been ionized through electron impact ionization (EI) on an Agilent 6890/5973 or Agilent 7890/5977 GC-MS equipped with an HP-5 capillary column using helium carrier gas or by applying electron spray ionization (ESI) on an Agilent 1200/6210 Time-of-Flight (TOF) LC-MS. Melting points (mp) were determined by a Micro-Hot-Stage GalenTM III Cambridge Instruments and are not corrected.

Materials. The applied solvents toluene, hexane, acetonitrile, 1,4-dioxane, xylene, and dichloromethane were obtained as dry solvents through commercial sources and employed without further purification. Solvents for extraction and column chromatography were available after previous distillation. Reagents, catalysts, ligands, acids, and bases have been utilized as received. Column chromatography was performed using Merck Silica gel 60 (particle size 63−200 μm).

General Method for the Preparation of Starting Materials. *General Procedure (A) for the Synthesis of 2-Bromophenyl Ethynyl Ketones* ***2.*** To a mixture of a 1-alkyne (1.2 mmol) and 2-bromobenzoyl chloride (**1**) (1 equiv) in Et_3N (3 mL) and toluene (1 mL) were added $PdCl_2(PPh_3)_2$ (3 mol %) and CuI (3 mol %). The mixture was stirred at room temperature under an argon atmosphere for 12−15 h. After addition of water, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Finally, the crude was purified by column chromatography (heptane/ethyl acetate, 10:1).

*1-(2-Bromophenyl)-3-phenylprop-2-yn-1-one (**2a**).* The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as a brown oil (65%, 402 mg). IR (ATR): $\tilde{\nu}$ = 2193 (vs), 1646 (vs), 1583 (s), 1430 (m), 1294 (s), 1271 (s), 993

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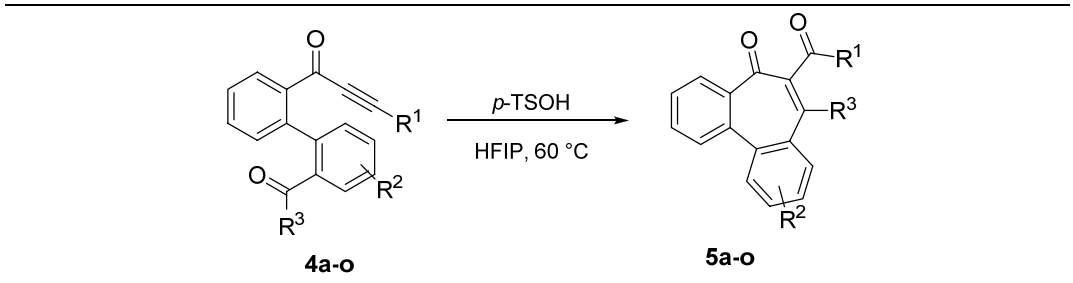
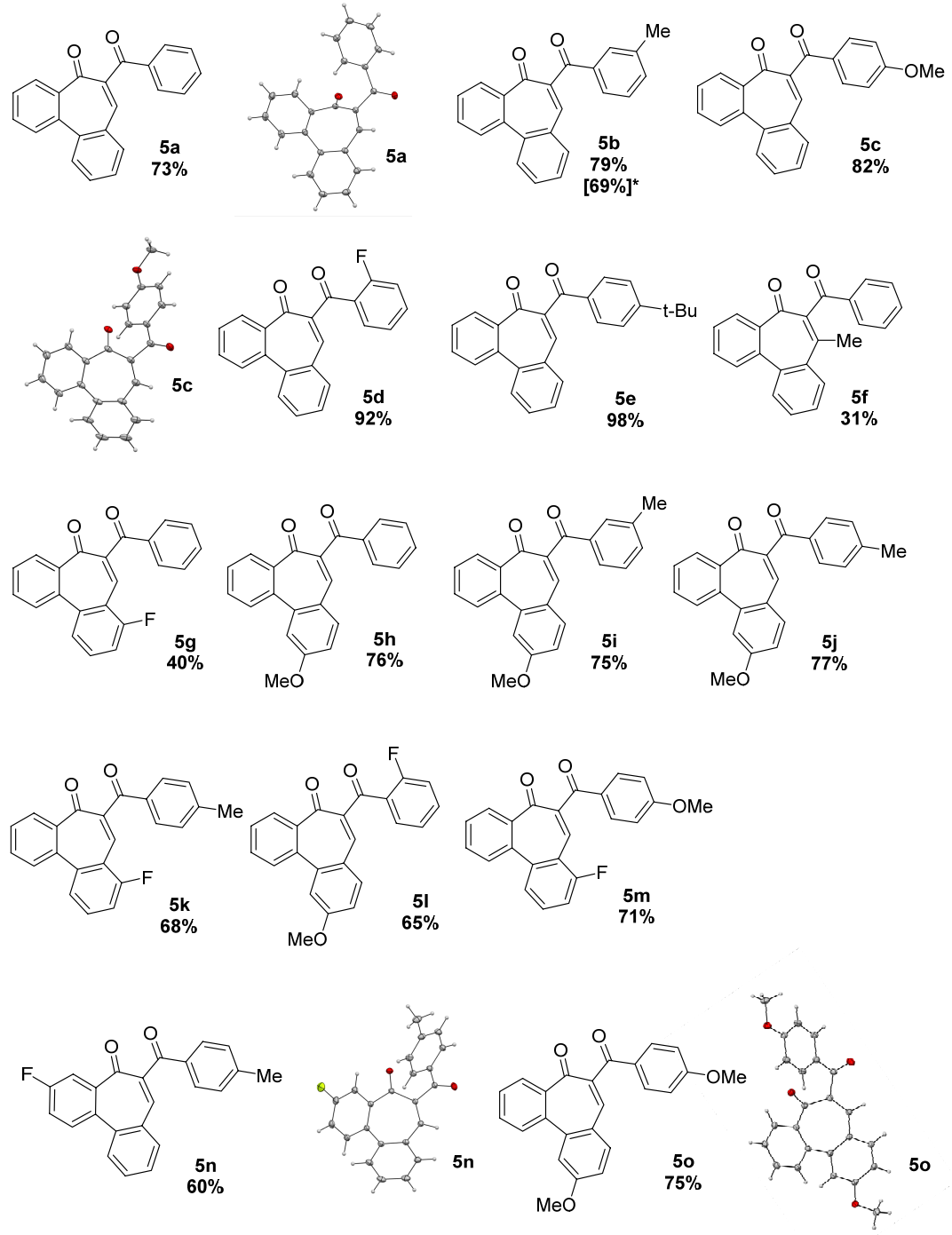
Table 2. Synthesis of Products 5a−o (Yields Refer to Isolated Yields)[a]





[a]* denotes reaction was carried out by using 2 mmol (650 mg) of 4b.

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Scheme 4. Synthesis of Precursors 7a−g

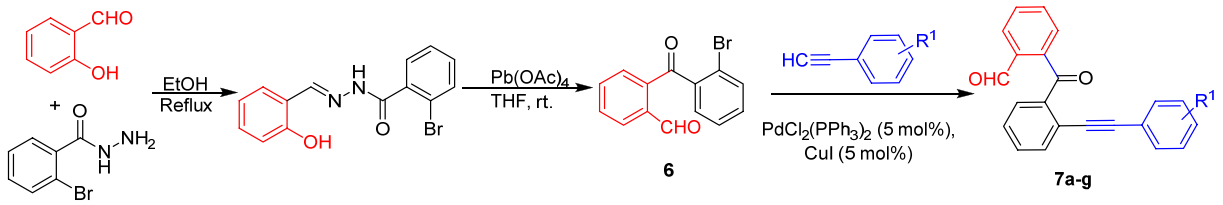
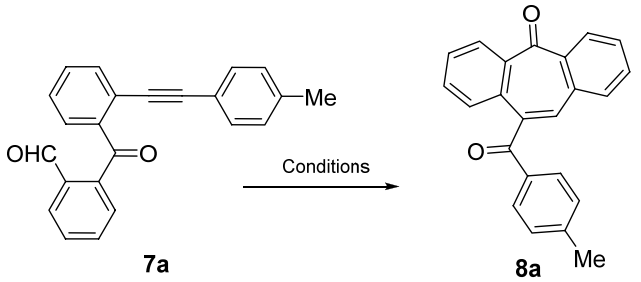


Table 3. Optimization of the Synthesis of 8a



Entry	Catalyst (equiv)	Solvent	Time (h)	Temp (°C)	Yield (%)
1	*p*-TsOH (15)	HFIP	20	60	40
2	*p*-TsOH (15)	Toluene	20	80	36
3	*p*-TsOH (15)	Toluene	20	100	47
4	*p*-TsOH (15)	Hexane	20	70	36
5	*p*-TsOH (15)	Xylene	6	140	traces
6	*p*-TsOH (15)	Octafluoro-pentanol	6	140	18
7	*p*-TsOH (30)	Toluene	6	80	traces
8	MSOH (10)	Toluene	20	60	16
9	*p*-TsOH (10)	Toluene	6	80	60
10	***p*-TsOH (5)**	**Toluene**	**6**	**80**	**64**
11	TFA (10)	Toluene	6	80	22
12	$In(OTf)_3$ (2)	Toluene	6	80	30
13	$FeCl_3$ (15 mol %)	Toluene	6	80	20

(vs), 1061 (m), 1006 (vs), 754 (vs), 1201 (s), 736 (vs), 686 (vs), 618 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96−8.03 (m, 1H), 7.54−7.65 (m, 3H), 7.29−7.42 (m, 5H).^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 178.5, 149.6, 137.5, 133.9, 133.5, 133.1, 132.4, 131.6, 130.9, 129.1, 128.6, 127.8, 119.7, 94.2, 88.1. HRMS (ESI): calcd for $C_{16}H_{11}{}^{79}BrO$ $[M]^+$ 297.9987, found 297.9984; calcd for $C_{16}H_{11}{}^{81}BrO$ $[M]^+$ 299.9967, found 299.9967.

1-(2-Bromophenyl)-3-(m-tolyl)prop-2-yn-1-one (**2b**). The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as a yellow oil (40%, 120 mg) IR (ATR): $\tilde{\nu}$ = 2184 (vs), 1644 (s), 1583 (vs), 1298 (s), 1218 (vs), 1061 (m), 1014 (vs), 989 (s), 900 (vs), 781 (vs), 734 (s), 686 (m), 622 (vs) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.70 (dd, J = 7.9 Hz, J = 1.2 Hz, 1H), 7.38 (s, 1H), 7.44−7.48 (m, 3H), 7.30 (dd, J = 15.3 Hz, J = 1.2 Hz, 2H), 2.37 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 177.9, 142.7, 137.9, 135.1, 133.9, 133.4, 132.8, 131.2, 130.1, 127.5, 126.1, 121.2, 119.9, 93.4, 91.7, 20.4. MS (EI, 70 eV): m/z (%) = 300 (41), 298 (42), 272 (56), 271 (12), 270 (56), 190 (12), 189 (37), 1143 (100), 115 (7). HRMS (ESI): calcd for $C_{16}H_{11}{}^{79}BrO$ $[M]+$ 297.9987, found 297.9984; calcd for $C_{16}H_{11}{}^{81}BrO$ $[M]^+$ 299.9967, found 299.9967.

1-(2-Bromophenyl)-3-(2-fluorophenyl)prop-2-yn-1-one (**2c**). The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as a yellow solid (62%, 374 mg). Mp: 57 °C. IR (ATR): $\tilde{\nu}$ = 2199 (s),1634 (s), 1488 (vs), 1304 (s), 1261 (s), 1218 (s), 1208 (s), 999 (vs), 781 (vs), 756 (vs), 734 (vs), 699 (s), 622 (s), 579 (vs), 480 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01−8.05 (m, 1H), 7.52−7.57 (m, 1H), 7.43−7.50 (m, 1H), 7.29−7.38 (m, 2H), 7.21−7.28 (m, 1H), 7.06 (dd, J = 7.6 Hz, J = 1.1 Hz, 1H), 6.96−7.04 (m, 1H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 177.0, 163.8 (d, J = 256.0 Hz), 136.9, 135.1, 134.8, 133.6, 133.4, 133.0 (d, J = 8.3 Hz), 124.4 (d, J = 3.7 Hz), 121.4, 116.0 (d, J = 20.4 Hz), 109.0 (d, J = 15.3 Hz), 127.5, 92.1, 87.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −110.48. MS (EI, 70 eV): m/z (%) = 304 (26), 302 (27), 276 (65), 274 (66), 194 (36), 175 (16), 168 (12), 147 (100), 119 (16), 99 (36), 98 (11), 93 (12), 76 (16), 75 (23). HRMS (EI): calcd for $C_{15}H_8BrOF[M]^+$ 301.9737, found 301.9741; calcd or $C_{15}H_8{}^{81}BrOF[M]^+$ 303.9716, found 303.9723.

1-(2-Bromophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (**2d**). The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as a yellow solid (45%, 283 mg). Mp: 52 °C. IR (ATR): $\tilde{\nu}$ = 2180 (vs), 1642 (s), 1597 (s), 1506 (vs), 1290 (vs), 1251 (vs), 1205 (vs), 1168 (vs), 1059 (vs), 1024 (s), 997 (s), 830 (s), 734 (vs), 680 (vs), 608 (s), 538 (vs) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.00−8.08 (m, 1H), 7.66−7.72 (m, 1H), 7.56−7.65 (m, 2H), 7.32−7.49 (m, 2H), 6.88−6.96 (m, 2H), 3.83−3.87 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 177.6, 161.9, 137.9, 135.2, 134.8, 133.1, 132.5, 127.3, 121.1, 114.4, 111.8, 95.6, 88.1, 55.4. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 316 (M^+ 31), 315 (5), 314 (31), 288 (22), 286 (20), 273 (16), 271 (17), 164 (46), 159 (100), 144 (17), 116 (24), 88 (26), 62 (16), 50 (13). HRMS (EI): calcd for $C_{16}H_{11}{}^{79}BrO_2F[M]^+$ 313.9936, found 313.9936; calcd for $C_{16}H_{11}{}^{81}BrO_2$ $[M]^+$ 315.9916, found 315.9916; calcd for $C_{16}H_{11}{}^{83}BrO_2$ $[M]^+$ 315.9918, found 313.9918.

1-(2-Bromophenyl)-3-(4-(tert-butyl)phenyl)prop-2-yn-1-one (**2e**). The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as an orange oil (63%, 428 mg). IR (ATR): $\tilde{\nu}$ = 2190 (vs), 1649 (s), 1601 (s), 1585 (vs), 1463 (vs), 1296 (s), 1265 (vs), 1205 (s), 1187 (s), 1059 (vs), 1016 (m), 1001 (m), 835 (m), 814 (m), 777 (s), 736 (m), 668 (m), 637 (s), 563 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.97−8.01 (dd, J = 7.7, J = 1.8, 1H), 7.61−7.65 (dd, J = 8.0, J = 1.2, 1H), 7.50−7.54 (d, J = 8.5, 2H), 7.28−7.41 (m, 4H), 1.25−1.27 (s, 9H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 177.7, 154.8, 137.8, 134.9, 133.2, 133.1, 132.7, 127.4, 125.8, 121.2, 116.9, 95.0, 87.9, 35.1, 31.1. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 342 (M^+, 36), 340 (36), 328 (19), 327 (99), 326 (20), 325 (100), 297 (13), 269 (13), 203 (16), 202 (33), 189 (19), 185 (36),155 (44), 115 (20). HRMS (EI): calcd for $C_{19}H_{17}{}^{79}BrOF[M+1]^+$ 340.0457, found 340.0452, calcd for $C_{19}H_{17}{}^{81}BrOF$ $[M+1]^+$ 342.0438, found 340.0434.

1-(2-Bromophenyl)-3-(p-tolyl)prop-2-yn-1-one (**2f**). The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as a brown solid (79%, 473 mg). Mp: 93−95 °C. IR (ATR): $\tilde{\nu}$ = 2190 (vs), 1642 (s), 1583 (s), 1298 (s), 1199 (vs), 1170 (vs), 999 (vs), 822 (m), 729 (s), 684 (s), 674 (s), 647 (s), 538 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.67−7.74 (m, 1H), 8.03−8.09 (m, 1H), 7.33−7.49 (m, 2H), 7.51−7.58 (m, 2H), 7.18−7.25 (m, 2H), 2.40 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 177.6, 141.8, 137.8, 134.9, 133.2, 132.6, 129.5, 127.3, 121.2, 116.9, 95.0, 87.9, 21.8. (Signal of three quaternary carbon is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 300 (44), 299 (11), 298 (47), 272 (50), 271 (14), 270 (50), 191 (11), 190 (15), 189 (38), 144 (11), 143 (100), 115 (11), 95 (13). HRMS (EI):

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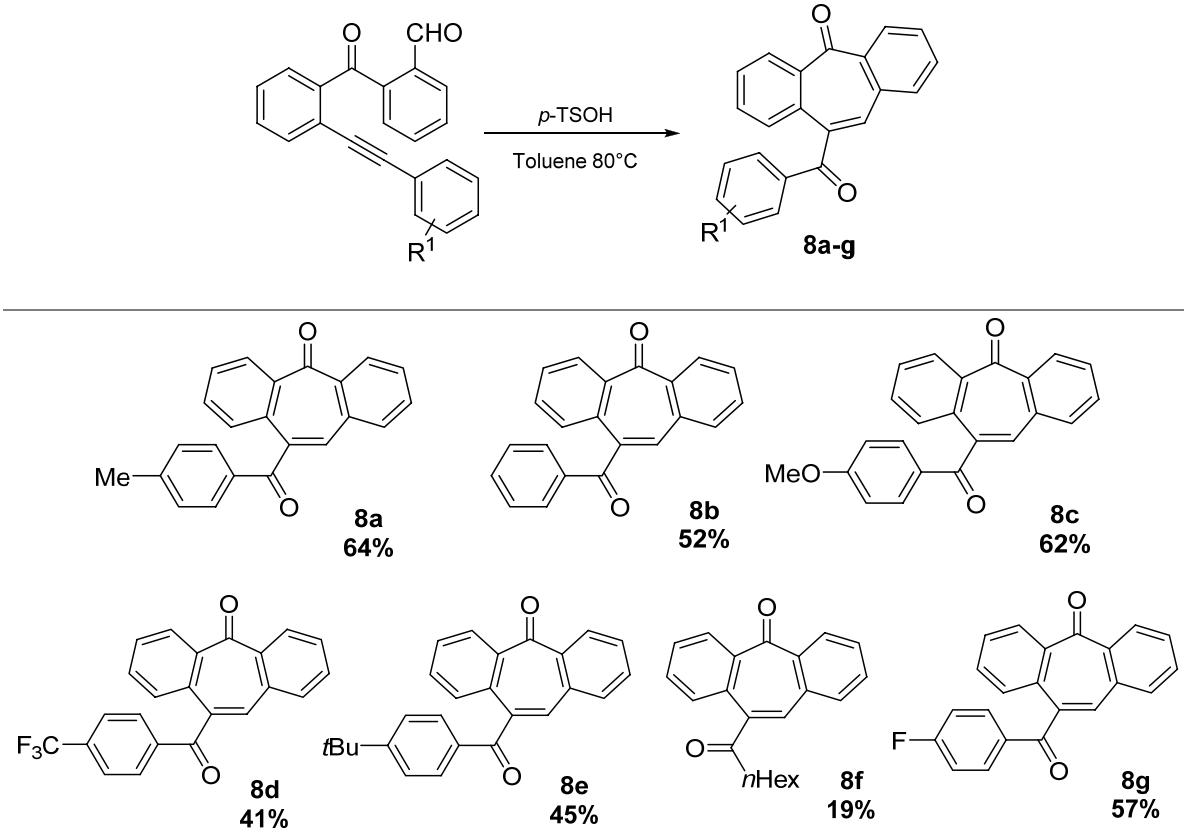
Table 4. Synthesis of 8a−g



calcd for $C_{16}H_{11}{}^{79}BrO$ [M]+ 297.9987, found 297.9990; calcd for $C_{16}H_{11}{}^{81}BrO$ $[M]^+$ 299.9967, found 299.9976.

*1-(2-Bromo-5-fluorophenyl)-3-(p-tolyl)prop-2-yn-1-one (**2g**).* The title compound was obtained after column chromatography (heptane/ethyl acetate, 10:1) as an orange solid (72%, 454 mg). Mp: 48−51 °C. IR (ATR): $\tilde{\nu}$ = 2176 (s), 1651 (s), 1570 (s), 1461 (s), 1294 (s), 1255 (s), 1226 (s), 1154 (s), 1008 (s), 884 (s), 808 (s), 744 (s), 587 (m), 540 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (dd, J = 8.7, J = 3.1 Hz, 1H), 7.53 (dd, J = 8.8 J = 5.0 Hz, 1H), 7.40−7.45 (m, 2H), 7.07−7.12 (m, 2H), 6.99 (ddd, J = 8.8, J = 7.5, J = 3.1 Hz, 1H), 2.27 (s, 3H). ^{13}C $\{^1H\}$ NMR (63 MHz, $CDCl_3$): δ = 176.0, 161.4 (d, J = 249.5 Hz), 142.1, 138.9 (d, J = 6.2 Hz), 136.3 (d, J = 7.3 Hz), 133.2, 129.6, 120.5 (d, J = 22.3 Hz), 119.3 (d, J = 24.3 Hz), 116.5, 115.3 (d, J = 3.4 Hz), 95.8, 87.6, 21.8. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.20. MS (EI, 70 eV): m/z (%) = 318 (20), 316 (22), 290 (22), 288 (22), 207 (30), 144 (13), 143 (100), 115 (14), 94 (22), 89 (16). HRMS (EI): calcd for $C_{16}H_{10}{}^{79}BrFO$ ($[M]^+$) 315.9893, found 315.9899; calcd For $C_{16}H_{10}{}^{81}BrFO$ ($[M]^+$) 317.9873, found 317.9882.

*General Procedure (B) for the Synthesis of Compounds **4a−o**.* To a reaction vial containing a solution of 2-bromophenyl ethynyl ketones **2a−g** (1 mmol) in 2 mL of 1,4-dioxane were added 2-formylarylboronic acid (1.2 equiv) and 3 mol % of $Pd(PPh_3)_4$. Then, 2 equiv of K_2CO_3 and 1 mL water were added to the reaction mixture. The vial was flushed with argon and sealed. The reaction mixture was stirred under heating in an oil bath (65 °C) until TLC revealed complete conversion of the starting material. The reaction mixture was allowed to cool to room temperature, diluted with H_2O, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by column chromatography (heptane/ethyl acetate, 10:1) to afford the corresponding product.

*2-(2-(3-Phenylprop-2-ynoyl)phenyl)thiophene-3-carbaldehyde (**4a**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange solid was obtained in 61% (201 mg) yield. Mp: 76−78 °C. IR (ATR): $\tilde{\nu}$ = 2190 (s), 1690 (vs), 1638 (vs), 1593 (s), 1488 (s), 1442 (s), 1294 (m), 1284 (s), 1201 (m), 1008 (m), 993 (s), 752 (s), 686 (s), 643 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.63−9.64 (d, J = 1.3 Hz, 1H), 8.09−8.14 (m, 1H), 7.60−7.64 (dd, J = 5.0, J = 1.3 Hz, 1H), 7.53−7.59 (m, 2H), 7.24−7.41 (m, 6H), 7.03−7.06 (d, J = 5.0 Hz, 1H). ^{13}C $\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 191.5, 178.6, 144.3, 138.9, 137.2, 134.1, 133.4, 132.9, 132.4, 132.2, 131.4, 130.9, 130.8, 128.6, 128.5, 128.2, 128.1, 119.8, 93.9, 88.2. MS (EI, 70 eV): m/z (%) = 311 (M^+, 0), 282 (23), 281 (100), 253 (13), 252 (25), 250 (13), 181 (32), 152 (24), 151 (11), 129 (20). HRMS (EI): calcd for $C_{20}H_{13}O_2$ F ($[M+1]^+$) 328.0900, found 329.0978.

*2′-(3-(m-Tolyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4b**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 53% (170 mg) yield. IR (ATR): $\tilde{\nu}$ = 2184 (vs),1690 (vs), 1636 (vs), 1593 (vs), 1300 (s), 1222 (s), 1195 (s), 1024 (s), 754 (s), 686 (vs), 643 (m), 626 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14−8.18 (m, 1H), 9.80 (s, 1H), 7.88−7.93 (m, 1H), 7.46−7.53 (m, 3H), 7.35−7.41 (m, 1H), 7.19−7.22 (m, 2H), 7.11−7.18 (m, 5H), 2.23 (s, 3H). ^{13}C $\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 191.5, 178.6, 144.3, 138.8, 138.4, 137.3, 134.1, 133.5, 133.4, 132.3, 132.2, 131.7, 131.4, 130.9, 130.1, 128.4, 128.4, 128.1, 128.0, 119.6, 94.3, 88.0, 21.2. MS (EI, 70 eV): m/z (%) = 325 (M^+, 2), 324 (7), 323 (9), 296 (24), 295 (100), 282 (8), 281 (37), 265 (8), 252 (24), 181 (36), 153 (7), 152 (31), 151 (13), 143 (21). HRMS (EI): calcd for $C_{23}H_{16}O_2$ ($[M+1]^+$) 324.1144, found 324.1136

*2′-(3-(3-Methoxyphenyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4c**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 44% (148 mg) yield. IR (ATR): $\tilde{\nu}$ = 2182 (m), 1690 (s), 1634 (vs), 1597 (vs), 1506 (s), 1257 (m), 1168 (vs), 1088 (m), 1004 (m), 793 (w), 754 (w), 694 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 8.11−8.16 (m, 1H), 7.88−7.93 (m, 1H), 7.47−7.56 (m, 3H),

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7.34−7.41 (m, 1H), 7.25−7.30 (m, 2H), 7.16−7.23 (m, 2H), 6.72−6.78 (m, 2H), 3.72 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 190.6, 177.6, 160.7, 143.4, 137.6, 136.5, 134.0, 133.0, 132.3, 131.1, 131.0, 130.1, 129.9, 127.4, 127.0, 126.8, 113.3, 110.5, 94.2, 87.3, 54.4. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 341 (M^+, 10), 340 (41), 339 (23), 312 (29), 311 (100), 297 (11), 281 (20), 268 (18), 239 (23), 181 (14), 152 (13), 135 (18). HRMS (EI): calcd for $C_{23}H_{16}O_3$ ([M+1]$^+$) 340.1094, found 340.1088.

*2′-(3-(2-Fluorophenyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4d**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 57% (185 mg) yield. IR (ATR): $\tilde{\nu}$ = 2193 (s), 1690 (vs), 1638 (vs), 1595 (vs), 1504 (s), 1222 (vs), 1197 (vs), 1156 (vs), 1001 (vs), 837 (s), 752 (s), 694 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12−8.17 (m, 1H), 9.83 (s, 1H), 7.92 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.50−7.59 (m, 3H), 7.39−7.43 (m, 1H), 7.32−7.36 (m, 2H), 7.20−7.26 (m, 2H), 6.94−6.99 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 191.6, 178.5, 164.0 (d, J = 254.0 Hz), 144.2, 138.9, 137.2, 135.3, 135.2, 134.1, 133.4, 132.4, 132.2, 131.3, 130.9, 128.5, 128.2, 128.1, 116.2, 116.0, 116.0 (d, J = 22.3 Hz), 92.8, 88.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −108.08. MS (EI, 70 eV): m/z (%) = 329 (M^+, 2), 328 (7), 327 (8), 300 (26), 299 (100), 271 (12), 270 (19), 268 (18), 181 (22), 152 (11), 147 (9). HRMS (EI): calcd for $C_{22}H_{13}O_2$ F ([M+1]$^+$) 328.0841, found 328.0853.

*2′-(3-(4-(tert-Butyl)phenyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4e**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 38% (139 mg) yield. IR (ATR): $\tilde{\nu}$ = 2184 (vs), 1644 (vs), 1583 (vs), 1430 (s), 1298 (vs), 1218 (vs), 1061 (m), 1014 (m), 900 (s), 781 (m), 734 (m), 686 (vs), 622 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 8.12−8.21 (m, 1H), 7.91−7.95 (m, 1H), 7.45−7.60 (m, 3H), 7.37−7.43 (m, 1H), 7.28 (s, 4H), 7.22−7.24 (m, 1H), 7.18−7.22 (m, 1H), 1.22 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 191.6, 178.7, 154.6, 144.3, 138.8, 137.4, 134.1, 133.4, 132.9, 132.2, 131.3, 130.9, 128.4, 128.1, 128.0, 125.6, 116.7, 94.6, 88.1, 35.1, 31.0. (Signal of three quaternary carbon is absent, which may relate to signal overlap). MS (EI, 70 eV): m/z (%) = 367 (M^+, 8), 366 (31), 365 (25), 338 (31), 337 (100), 323 (12), 21 (14), 309 (15), 307 (17), 282 (20),281 (88), 181 (34), 152 (18), 147 (11). HRMS (EI): calcd for $C_{26}H_{22}O$ ([M+1]$^+$) 366.1614, found 366.1604.

*1-(2′-Acetyl-[1,1′-biphenyl]-2-yl)-3-phenylprop-2-yn-1-one (**4f**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), a yellow oil was obtained in 67% (217 mg) yield. IR (ATR): $\tilde{\nu}$ = 2193 (s), 1247 (s), 1282 (s), 1591 (m), 1488 (m), 688 (vs), 1684 (s), 1203 (s), 1008 (s), 993 (s), 754 (vs), 1638 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.13−8.18 (m, 1H), 7.64−7.69 (m, 1H), 7.49 (dd, J = 7.2 Hz, J = 1.9 Hz, 1H), 7.40−7.46 (m, 1H), 7.33−7.39 (m, 4H), 7.22−7.33 (m, 3H), 7.12−7.17 (m, 2H), 2.19 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 201.5, 178.9, 144.8, 142.4, 140.2, 138.9, 136.0, 132.8, 132.5, 131.5, 131.3, 131.0, 130.9, 130.6, 128.8, 128.5, 128.3, 127.7, 127.6, 120.1, 93.1, 88.2, 29.1. MS (GC-MS, EI, 70 eV): m/z (%) = 324 ([M]+, 1), 309 (5), 282 (24), 281 (100), 253 (6), 252 (19), 251 (5), 250 (15), 195(46), 152 (9), 151 (5), 129 (29), 101 (6). HRMS (EI): calcd for $C_{23}H_{16}O_2$ 324.1144, found 324.1142.

*3-Fluoro-2′-(3-phenylpropioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4g**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), a dark green oil was obtained in 45% (146 mg) yield. IR (ATR): $\tilde{\nu}$ = 1675 (s), 1659 (s), 1593 (s), 1442 (vs), 1261 (vs), 1228 (s), 1214 (s), 985 (s), 804 (s), 756 (vs), 729 (s), 699 (s), 688 (vs), 655 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.09 (s, 1H), 8.20−8.25(m, 1H), 7.50−7.55 (m, 2H), 7.42−7.49 (m, 3H), 7.24−7.38 (m, 3H), 7.12−7.17 (m, 1H), 7.07 (dd, J = 70.6 Hz, J = 8.4 Hz, 1H), 6.91−6.96 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 188.0 (d, J = 6.3 Hz), 178.3, 164.0 (d, J = 260.1 Hz), 144.7, 139.5, 136.1, 134.7, 134.6, 132.9, 132.7, 131.9, 131.1, 130.8, 128.6, 128.3, 126.5, 122.6 (d, J = 7.0 Hz), 120.0, 115.9 (d, J = 21.4 Hz), 93.3, 87.9. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −119.3.MS (EI, 70 eV): m/z(%) = 328(4), 237 (12), 300 (26), 299 (100), 272 (6), 270 (21), 268 (7), 250 (5), 200 (6), 199 (40), 170 (10), 129 (11). HRMS (EI): calcd for $C_{22}H_{13}O_2$ F ([M+1] $^+$) 328.0900, found 329.0978

*4-Methoxy-2′-(3-phenylpropioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4h**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 71% (241 mg) yield. IR (ATR): $\tilde{\nu}$ = 2199 (m), 1677 (s), 1642 (s), 1591 (s), 1562 (s), 1488 (s), 1300 (s), 1251 (s), 1208 (s), 1102 (s), 1004 (s), 756 (s), 696 (m), 614 (m) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 8.11−8.17 (m, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.47−7.59 (m, 2H), 7.21−7.39 (m, 6H), 6.85−6.91 (m, 1H), 6.68 (d, J = 2.5 Hz, 1H), 3.76 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 190.1, 178.5, 163.4, 146.6, 138.7, 137.3, 132.9, 132.2, 131.8, 131.1, 130.7, 130.6, 128.5, 128.4, 127.9, 119.9, 115.8, 113.9, 93.8, 88.2, 55.6. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 341 (13), 340 (40), 312 (100), 311 (66), 284 (20), 282 (33), 281 (24), 268 (16), 235 (62), 207 (28), 193 (15), 164 (24), 163 (36), 105 (18), 77 (26). HRMS (EI): calcd for $C_{23}H_{16}O_3$ ([M+1]$^+$) 340.1100, found 341.1178

*5-Methoxy-2-(2-(3-(3-methylphenyl)prop-2-ynoyl)phenyl)-benzaldehyde (**4i**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 63% (223 mg) yield. IR (ATR): $\tilde{\nu}$ = 1634 (vs), 1585 (vs), 1543 (vs), 1278 (vs), 1226 (vs), 1168 (vs), 806 (s), 773 (s), 744 (s), 732 (vs) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 8.11−8.16 (m, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.48−7.57 (m, 2H), 7.22−7.26 (m, 1H), 7.14−7.19 (m, 4H), 6.88 (m, 1H), 6.68 (d, J = 2.5 Hz, 1H), 3.76 (s, 3H), 2.25 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 190.1, 178.5, 163.4, 146.7, 138.7, 138.3, 137.4, 133.4, 132.2, 131.8, 131.6, 131.1, 130.5, 130.0, 128.4, 128.4, 127.9, 119.7, 115.8, 113.9, 94.2, 88.0, 55.6, 21.1. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%): 354 (18), 353 (12), 326 (28), 325 (100), 311 (81), 282 (15), 253 (13), 252 (13), 239 (21), 211 (39), 168 (11), 143 (13), 139 (14). HRMS (EI): calcd for $C_{24}H_{18}O$ S ([M+1]$^+$) 354.12505, found 354.1416.

*5-Methoxy-2′-(3-(p-tolyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4j**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 56% (198 mg) yield. IR (ATR): $\tilde{\nu}$ = 2188 (s), 1638 (s), 1591 (s), 1562 (s), 1436 (s), 1298 (s), 1251 (s), 1216 (s), 1098 (s), 1004 (s), 814 (s), 692 (s), 519 (s) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 3.74 (s, 3H), 6.67 (d, J = 2.6 Hz, 1H), 6.86 (dd, J = 9.1 Hz, J = 2.9 Hz, 1H), 7.01−7.08 (m, 2H), 7.20−7.26 (m, 3H), 7.43−7.56 (m, 2H), 7.87 (d, J = 8.7 Hz, 1H), 8.09−8.14 (m, 1H), 9.64 (d, J = 0.7 Hz, 1H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 190.1, 178.6, 163.4, 146.7, 141.5, 138.6, 137.5, 133.0, 132.1, 131.8, 131.1, 130.5, 129.6, 129.3, 128.4, 127.9, 116.8, 115.8, 113.9, 94.5, 88.1, 55.6, 21.7. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 354 ([M]$^+$, 18), 353 (17), 326 (29), 325 (100), 312 (22), 311 (88), 282 (21), 253 (14), 232 (20), 239 (36), 168 (19), 152 (12), 143 (25), 139 (34), 115 (15). HRMS (EI): calcd for $C_{24}H_{18}O_3$ 354.1250, found 354.1240.

*3-Fluoro-2′-(3-(p-tolyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4k**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 30% (102 mg) yield. IR (ATR): $\tilde{\nu}$ = 2188 (s), 1696 (s), 1636 (s), 1603 (s), 1566 (s), 1461 (m), 1294 (s), 1236 (s), 1201 (s), 1004 (s), 797 (s), 756 (s), 692 (s), 536 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.08 (s, 1H), 8.19−8.23 (m, 1H), 7.48−7.54 (m, 2H), 7.41−7.48 (m, 1H), 7.30−7.35 (m, 2H), 7.12−7.16 (m, 1H), 7.03−7.11 (m, 3H), 6.93 (d, J = 7.6 Hz, J = 1.1 Hz, 1H), 2.30 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 188.01 (d, J = 6.1 Hz), 178.31, 163.9 (d, J = 260.2 Hz), 144.8, 141.5, 139.3, 136.2, 134.7, 134.5, 133.0, 132.5, 131.8, 131.1, 129.4, 128.3, 126.5, 122.6, 116.9, 115.8 (d, J = 21.5 Hz), 94.0, 87.8, 21.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −119.22. MS (EI, 70 eV): m/z (%) = 342 ([M]$^+$, 11), 341 (18), 314 (28), 313 (100), 299 (31), 271 (9), 270 (24), 200 (6), 199 (37), 170

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(13), 143 (13). HRMS (EI): calcd. for $C_{23}H_{15}FO_2$ ([M]$^+$) 342.1050, found 342.1045.

*2′-(3-(2-Fluorophenyl)propioloyl)-5-methoxy-[1,1′-biphenyl]-2-carbaldehyde (**4l***).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 63% (198 mg) yield. IR (ATR): $\tilde{\nu}$ = 2199 (m), 1677 (s), 1642 (s), 1591 (s), 1562 (s), 1488 (s), 1300 (s), 1251 (s), 1208 (s), 1102 (s), 1004 (s), 756 (s), 696 (m), 614 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, J = 0.7 Hz, 1H), 8.21−8.25 (m, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.52−7.58 (m, 2H), 7.33−7.39 (m, 2H), 7.22−7.27 (m, 1H), 7.02−7.11 (m, 2H), 6.87−6.91 (m, 1H), 6.67 (d, J = 2.5 Hz, 1H), 3.77 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 190.1, 178.1, 163.5 (d, J = 255.7 Hz), 163.4, 146.6, 138.9, 136.8, 134.6, 132.7 (d, J = 8.2 Hz), 132.5, 131.9, 130.6, 128.5, 128.0 (d, J = 6.8 Hz), 127.8, 124.3 (d, J = 3.8 Hz), 115.9, 115.6, 113.9, 108.9 (d, J = 15.3 Hz), 92.3, 86.5, 55.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = 106.72. MS (EI, 70 eV): m/z (%) = 358 ([M]$^+$, 3), 330 (34), 329 (100), 311 (21), 286 (11), 270 (11), 257 (39), 211 (44), 168 (18), 152 (11), 147 (28), 139 (29), 99 (14). HRMS (ESI-TOF): cacld. for $C_{23}H_{16}FO_3$ ([M + H]$^+$) 359.1083, found 359.1091. *The NMR shows impurity which can not be purified by column chromatography.

*3-Fluoro-2′-(3-(4-methoxyphenyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4m**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange solid was obtained in 43% (153 mg) yield. Mp: 124−126 °C. IR (ATR): $\tilde{\nu}$ = 2188 (s), 1694 (s), 1632 (s), 1599 (s), 1562 (s), 1508 (s), 1255 (s), 1166 (s), 1020 (s), 826 (s), 752 (s), 684 (s), 542 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.05 (s, 1H), 8.16−8.21 (m, 1H), 7.46−7.51 (m, 2H), 7.39−7.45 (m, 1H), 7.33−7.39 (m, 2H), 7.09−7.14 (m, 1H), 7.04 (ddd, J = 10.7, J = 8.4, J = 1.1 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.77 (d, J = 8.9 Hz, 2H), 3.71 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 188.1 (d, J = 6.0 Hz), 178.3, 163.9 (d, J = 260.2 Hz), 161.7, 144.9, 139.2, 135.0, 134.6 (d, J = 10.4 Hz), 132.4, 131.7, 131.1, 128.2, 126.5 (d, J = 3.6 Hz), 122.6 (d, J = 7.1 Hz), 115.8 (d, J = 21.5 Hz), 114.4, 111.8, 94.6, 88.0, 55.4. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −119.10. MS (EI, 70 eV): m/z (%) = 358 ([M]$^+$, 8), 357 (11), 330 (25), 329 (100), 299 (9), 286 (20), 258 (11), 257 (32), 199 (25), 170 (27), 159 (19), 144 (13), 135 (12), 116 (14). HRMS (ESI-TOF): cacld. for $C_{23}H_{16}FO_3$ ([M + H]$^+$) 359.1083, found 359.1081.

*4′-Fluoro-2′-(3-(p-tolyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4n**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 17% (59 mg) yield. IR (ATR): $\tilde{\nu}$ = 2180 (s), 1692 (s), 1642 (s), 1597 (s), 1471 (m), 1304 (s), 1263 (s), 1156 (s), 1018 (s), 1004 (m), 816 (s), 762 (s), 536 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.81 (d, J = 0.7 Hz, 1H), 7.90 (dd, J = 7.7, J = 1.5 Hz, 1H), 7.83 (dd, J = 9.0, J = 2.5 Hz, 1H), 7.47−7.54 (m, 1H), 7.37−7.44 (m, 1H), 7.16−7.26 (m, 5H), 7.04−7.10 (m, 2H), 2.28 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 191.4, 177.2 (d, J = 2.2 Hz), 162.2 (d, J = 250.0 Hz), 143.0, 141.8, 138.9 (d, J = 6.4 Hz), 134.8 (d, J = 3.6 Hz), 134.2, 133.8 (d, J = 7.5 Hz), 133.5, 133.1, 131.1, 129.4, 128.6, 128.4, 119.2 (d, J = 21.4 Hz), 117.8 (d, J = 23.3 Hz), 116.4, 95.5, 87.8, 21.8. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.22. MS (EI, 70 eV): m/z (%) = 342 ([M]$^+$, 16), 341 (17), 314 (22), 313 (100), 300 (9), 299 (46), 270 (17), 199 (20), 170 (12), 143 (13). HRMS (EI): calcd for $C_{23}H_{15}FO_2$ ([M]$^+$) 342.1050; found 342.1047.

*5-Methoxy-2′-(3-(4-methoxyphenyl)propioloyl)-[1,1′-biphenyl]-2-carbaldehyde (**4o**).* Following general procedure B, after column chromatography (heptane/ethyl acetate, 10:1), an orange oil was obtained in 56% (208 mg) yield. IR (ATR): $\tilde{\nu}$ = 2182 (s), 1679 (m), 1591 (s), 1508 (s), 1292 (s), 1249 (s), 1205 (s), 1170 (s), 1111 (m), 1001 (s), 830 (s), 732 (s), 696 (m), 540 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, J = 0.7 Hz, 1H), 8.08 (m, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.46−7.50 (m, 2H), 7.24−7.29 (m, 2H), 7.16−7.22 (m, 2H), 6.81−6.87 (m, 1H), 6.73−6.76 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 194.8, 190.2, 178.6, 163.4, 146.8, 145.4, 138.5, 135.0, 132.1, 131.4, 131.0, 130.4, 130.1, 128.4, 127.9, 127.0, 123.8, 115.8, 114.3, 111.6, 95.1, 88.3, 55.6, 55.4. MS (EI, 70 eV): m/z (%) = 371 ([M+1]$^+$, 6), 370 ([M]$^+$, 25), 369 (16), 342 (35), 341 (100), 327 (16), 311 (21), 298 (13), 239 (9), 226 (13), 211 (19), 139 (10). HRMS (ESI-TOF): cacld. for $C_{24}H_{19}O_4$ ([M + H]$^+$) 371.1283, found [M + H]$^+$) 371.1289.

*General Procedure for the Synthesis of Compounds **5a**−**o**.* A mixture of the respective carbaldehyde **4a**−**o** (0.3 mmol), 15 equiv of *p*-TsOH in hexafluoroisopropanol (HFIP) (2 mL) was stirred at 60 °C in an oil bath for 3 h. After completion of the reaction, a solution of $NaHCO_3$ was added to quench the reaction. Then, the aqueous layer was extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4. The final product (**5**) was purified by column chromatography (10:1, heptane/ethyl acetate).

*6-Benzoyl-5H-dibenzo[a,c][7]annulen-5-one (**5a**).* The reaction of **4a** (0.32 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), an orange was solid obtained in 73% (73 mg) yield. Mp: 198−200 °C. IR (ATR): $\tilde{\nu}$ = 2201 (m),1657 (s), 1609 (m), 1490 (m), 1449 (m), 1418 (m), 1306 (m), 1265 (vs), 1224 (m), 1208 (s), 1006 (m), 758 (m), 668 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82−7.89 (m, 2H), 7.82 (m, 1H), 7.65−7.73 (m, 4H), 7.57−7.64 (m, 2H), 7.52−7.57 (m, 1H), 7.44−7.52 (m, 2H), 7.32−7.39 (m, 2H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 194.6, 192.4, 142.8, 142.5, 141.5, 138.7, 137.1, 136.6, 133.0, 133.0, 132.0, 131.7, 131.0, 130.7, 130.0, 129.2, 129.0, 128.7, 128.5. MS (EI, 70 eV): m/z (%) = 311 (M$^+$ 5), 310 (19), 283 (16), 42), 282 (81), 281 (87), 254 (26), 253 (29), 252 (20), 205 (56),177 (57), 176 (83), 151 (29), 150 (26), 105 (48). HRMS (ESI): calcd for $C_{22}H_{14}O_2$ ([M+1]$^+$) 310.0988, found 310.0982.

*6-(3-Methylbenzoyl)-5H-dibenzo[a,c][7]annulen-5-one (**5b**).* The reaction of **4b** (0.30 mmol, 100 mg, and 2 mmol, 650 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a yellow solid was obtained in 79% (79 mg) and 69% (449 mg) yield respectively. Mp: 198−200 °C. IR (ATR): $\tilde{\nu}$ = 1646 (m), 1585 (m), 1383 (vs), 1276 (vs), 1183 (m), 987 (m), 754 (s), 736 (m), 690 (m), 670 (vs) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, 2H), 7.82 (s, 1H), 7.69 (m, 2H), 7.61−7.65 (m, 1H), 7.58 (m, 1H), 7.51−7.55 (m, 2H), 7.43−7.50 (m, 2H), 7.20−7.32 (m, 2H), 2.29 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 194.7, 192.6, 143.0, 142.6, 141.3, 138.7, 138.3, 137.1, 136.6, 133.8, 133.0, 132.0, 131.7, 131.0, 130.6, 129.9, 129.7, 128.8, 128.7, 128.5, 128.4, 126.4, 21.3. MS (EI, 70 eV): m/z (%) = 325 (M$^+$15), 324 (60), 297 (22), 296 (100), 295 (86), 282 (21), 281 (89), 268 (20), 253 (16), 252 (21), 205 (62), 177 (45), 176 (54), 151 (17), 119 (3), 91 (43). HRMS (ESI-TOF): calcd for $C_{23}H_{16}O_2$ ([M+1]$^+$) 325.1150, found 325.1228.

*6-(4-Methoxybenzoyl)-5H-dibenzo[a,c][7]annulen-5-one (**5c**).* The reaction of **4c** (0.3 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a yellow solid was obtained in 82% (82 mg) yield. Mp: 155−157 °C. IR (ATR): $\tilde{\nu}$ = 1636 (vs), 1591 (vs), 1508 (vs), 1313 (s), 1255 (s), 1162 (m), 1026 (s), 985 (vs), 843 (m), 754 (m), 734 (vs), 604 (vs) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.79−7.94 (m, 2H), 7.69−7.81 (m, 3H), 7.65−7.74 (m, 2H), 7.52−7.67 (m, 2H), 7.42−7.58 (m, 2H), 6.78−6.91 (m, 2H), 3.79 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 193.2, 192.3, 163.6, 143.4, 142.4, 140.6, 138.5, 136.6, 132.8, 132.1, 131.7, 131.6, 131.0, 130.4, 129.9, 129.7, 128.9, 128.7, 128.4, 113.8, 55.5. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 341 (23),340 (93), 312 (45), 311 (72), 295 (12), 284 (24), 281 (47), 239 (13), 205 (17), 177 (22), 176 (32), 135 (100), 92 (18), 77 (24). HRMS (ESI-TOF): calcd for $C_{23}H_{16}O_3$ ([M+1]$^+$) 340.1100, found 341.1169.

*6-(2-Fluorobenzoyl)-5H-dibenzo[a,c][7]annulen-5-one (**5d**).* The reaction of **4d** (0.3 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a brown solid was obtained in 92% (92 mg) yield. IR (ATR): $\tilde{\nu}$ = 1642 (vs), 1593 (vs), 1504 (s), 1294 (s), 1259 (s), 1228 (vs), 1154 (s), 985 (m), 845 (m), 752 (vs), 732 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82−7.91 (m, 2H), 7.80 (d,

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J = 1.8 Hz, 1H), 7.69−7.76 (m, 3H), 7.46−7.68 (m, 5H), 7.03 (m, 2H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 193.1, 192.2, 142.4 (d, J = 20.4 Hz), 141.6, 137.7 (d, J = 155.9 Hz), 133.5, 133.4, 133.1, 131.9, 131.9, 131.8, 131.7, 131.1, 130.8, 130.0, 129.0, 128.7, 128.6, 128.5, 115.8, 115.5. (Signal of one quaternary carbon is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −105.04. MS (EI, 70 eV): m/z (%) = 329 (7), 328 (29), 301 (20), 300 (100), 299 (99), 283 (12), 272 (20), 271 (23), 205 (41), 177 (36), 176 (137), 151 (14), 123 (34), 95 (31). HRMS (ESI-TOF): calcd for $C_{22}H_{13}O_2F$ ($[M+1]^+$) 328.0900, found 329.0978.

*6-(4-(tert-Butyl)benzoyl)-5H-dibenzo[a,c][7]annulen-5-one (**5e**).* The reaction of **4e** (0.27 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a yellow solid was obtained in 98% (98 mg) yield. Mp: 143−145 °C. IR (ATR): $\tilde{\nu}$ = 1651 (s), 1601 (vs), 1292 (vs), 1265 (m), 1189 (m), 985 (s), 847 (s), 793 (s), 758 (m), 740 (s), 715 (vs) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (dd, J = 7.7 Hz, J = 1.3 Hz, 2H), 7.88 (s, 1H), 7.86 (dd, J = 0.4 Hz, J = 0.4 Hz, 1H), 7.73−7.81 (m, 4H), 7.71 (dd, J = 2.1 Hz, J = 1.5 Hz, 1H), 7.63−7.70 (m, 1H), 7.54−7.63 (m, 1H), 7.45−7.51 (m, 2H), 1.38 (s, 9H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 194.2, 192.5, 156.9, 143.2, 142.5, 141.0, 138.6, 136.6, 134.2, 132.9, 132.1, 131.7, 131.0, 130.5, 129.9, 129.3, 128.9, 128.7, 128.4, 125.5, 35.2, 31.1. MS (EI, 70 eV): m/z (%) = 367 (12), 66 (45), 351 (27), 339 (18), 338 (74), 337 (24), 323 (42), 310 (20), 309 (58), 295 (19), 282 (24), 281 (100), 233 (13), 205 (24), 177 (33), 176 (34), 161 (36), 118 (13). HRMS (ESI-TOF): calcd for $C_{22}H_{13}O_2F$ ($[M+1]^+$) 366.1620, found 367.1698.

*6-Benzoyl-7-methyl-5H-dibenzo[a,c][7]annulen-5-one (**5f**).* The reaction of **4f** (0.3 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), an orange oil was obtained in 31% (31 mg) yield. IR (ATR): $\tilde{\nu}$ = 1686 (vs),1595 (m), 1562 (m), 1463 (s), 1354 (s), 1267 (s), 1245 (m), 1218 (s), 1039 (s), 954 (s), 752 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85−7.87 (m, 1H), 7.75 (dd, J = 7.7, J = 1.5 Hz, 1H), 7.64−7.67 (m, 2H), 7.45−7.57 (m, 5H), 7.40 (dd, J = 8.4, J = 7.1 Hz, 2H), 7.33 (dd, J = 7.6, ^3J = 1.4 Hz, 1H), 7.26−7.29 (m, 1H), 2.28 (s, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 202.0, 188.7, 184.0, 140.5, 140.3, 139.5, 136.0, 135.0, 132.4, 131.0, 130.9, 128.8, 128.6, 128.4, 127.9, 127.7, 127.0, 98.2, 29.5. MS (EI, 70 eV): m/z (%) = 300 (9), 299 (42), 196 (10), 195 (64), 181 (10), 165 (17), 152 (17), 151 (7), 106 (7), 105 (100), 77 (40). HRMS (EI): calcd for $C_{23}H_{16}O_2$ ([M+]) 324.1144, found 324.1140.

*6-Benzoyl-8-fluoro-5H-dibenzo[a,c][7]annulen-5-one (**5g**).* The reaction of **4g** (0.3 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), an orange oil was obtained in 40% yield. IR (ATR): $\tilde{\nu}$ = 1659 (s), 1593 (s), 1556 (s), 1442 (vs), 1383 (vs), 1261 (m), 1228 (m), 1214 (m), 985 (s), 929 (s), 894 (s), 804 (vs), 756 (m), 729 (s), 699 (m), 688 (s), 655 (vs) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (dd, J = 1.2 Hz, J = 0.5 Hz, 1H), 7.93 (s, 1H), 7.76−7.83 (m, 3H), 7.71−7.75 (m, 1H), 7.66−7.69 (m, 1H), 7.53−7.64 (m, 2H), 7.43−7.49 (m, 2H), 7.24−7.31 (m, 2H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 194.1, 192.5, 161.0 (d, J = 253.4 Hz), 143.6 (d, J = 1.5 Hz), 142.8, 140.4, 136.8, 135.6 (d, J = 2.8 Hz), 133.1, 131.8, 131.4, 131.3, 130.0, 129.4, 128.5, 128.5, 126.6 (d, J = 3.5 Hz), 120.7 (d, J = 10.8 Hz), 114.8 (d, J = 22.9 Hz, CH). (Signal of three quaternary carbon is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −111.98. MS (EI, 70 eV): m/z (%) = , 329 (7), 328 (27), 301 (21), 300 (10), 299 (99), 272 (25), 271 (25), 270 (15), 223 (54), 195 (133), 194 (33), 175 (14), 105 (33), 77 (36). HRMS (ESI-TOF): calcd for $C_{22}H_{13}O_2F$ ($[M+1]^+$) 328.0900, found 329.0975.

*6-Benzoyl-9-methoxy-5H-dibenzo[a,c][7]annulen-5-one (**5h**).* The reaction of **4h** (0.3 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), an orange oil was obtained in 76% (76 mg) yield. IR (ATR): $\tilde{\nu}$ = 1663 (vs), 1642 (vs), 1593 (vs), 1548 (s), 1263 (vs), 1216 (vs), 1203 (vs), 1016 (vs), 983 (vs), 800 (s), 769 (vs), 729 (s), 692 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83−7.88 (m, 2H), 7.70−7.75 (m, 1H), 7.62−7.69 (m, 3H), 7.53−7.60 (m, 2H), 7.43−7.49 (m, 1H), 7.31−7.39 (m, 3H), 7.01 (dd, J = 8.6 Hz, J = 2.6 Hz, 1H), 3.87 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 194.9, 192.5, 161.3, 142.4, 142.0, 140.8, 140.0, 137.5, 136.2, 135.5, 132.7, 131.6, 129.9, 129.2, 129.0, 128.9, 128.8, 128.4, 128.3, 125.4, 116.2, 114.4, 55.7. MS (EI, 70 eV): m/z (%) = 341 (21), 340 (82), 313 (21), 312 (100), 311 (78), 284 (12), 239 (16), 236 (13), 235 (73), 164 (24), 163 (35), 105 (15), 77 (30). HRMS (ESI-TOF): calcd for $C_{23}H_{16}O_3$ ($[M+1]^+$) 340.1100, found 341.1178.

*10-Methoxy-6-(3-methylbenzoyl)-5H- dibenzo[a,c][7] annulen-5-one(**5i**).* The reaction of **4i** (0.28 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane: ethyl acetate), a yellow solid was obtained in 75% (75 mg) yield. Mp: 166−168 °C. IR (ATR): $\tilde{\nu}$ = 1646 (s), 1603 (s), 1587 (s), 1541 (s), 1273 (s), 1220 (s), 1173 (s), 989 (s), 868 (m), 818 (s), 771 (s), 752 (s), 727 (s), 530 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82−7.86 (m, 2H). 7.70 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.64 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.53−7.59 (m, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 7.5 Hz, J = 1.6 Hz, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.19−7.28 (m, 2H), 7.00 (dd, J = 8.6 Hz, J = 2.6 Hz, 1H), 3.85 (s, 3H), 2.28 (s, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 195.0, 192.7, 161.2, 142.5, 141.8, 140.8, 140.2, 138.2, 137.4, 136.2, 135.5, 133.6, 131.6, 129.9, 129.6, 129.1, 128.8, 128.3, 126.2, 125.4, 116.2, 114.4, 55.7, 21.3. MS (EI, 70 eV): m/z (%) = 355 ($[M+1]^+$, 22), 354 ($[M]^+$, 89), 327 (24), 326 (100), 311 (46), 298 (12), 283 (18), 239 (12), 236 (13), 235 (75), 207(18), 177 (19), 164 (23), 163 (36), 119 (57), 91 (98). HRMS (EI): calcd for $C_{24}H_{18}O_3$ ($[M]^+$) 354.1250, found 354.1241.

*10-Methoxy-6-(4-methylbenzoyl)-5H-dibenzo[a,c][7]annulen-5-one: (**5j**).* The reaction of **4j** (0.28 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a yellow solid was obtained in 77% (77 mg) yield. Mp: 166−168 °C. IR (ATR): $\tilde{\nu}$ = 1646 (s), 1603 (s), 1587 (s), 1541 (s), 1273 (s), 1220 (s), 1173 (s), 989 (s), 868 (m), 818 (s), 771 (s), 752 (s), 727 (s), 530 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.82−7.88 (m, 1H), 7.79 (d, J = 0.6 Hz, 1H), 7.71−7.76 (m, 1H), 7.51−7.68 (m, 5H), 7.32 (d, J = 2.6 Hz, 1H), 7.10−7.18 (m, 2H), 7.00 (dd, J = 8.6 Hz, J = 2.6 Hz, 1H), 3.85 (s, 3H), 2.32 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 194.5,192.5, 161.2, 143.6, 142.4, 141.6, 140.7, 140.3, 136.2, 135.4, 134.7, 131.6, 129.8, 129.2, 129.1, 128.8, 125.5, 116.1, 114.4, 55.6, 21.7 (Signal of three quaternary carbon is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 355 ($[M+1]^+$, 14), 354 ($[M]^+$, 53), 326 (100), 325 (51), 311 (38), 298 (20), 283 (18), 239 (20), 235 (73), 207 (21), 176 (19), 164 (51), 163 (80), 119 (57). HRMS (EI): calcd for $C_{24}H_{18}O_3$ ($[M]^+$) 354.1250, found 354.1245.

*8-Fluor-6-(4-methylbenzoyl)-5H-dibenzo[a,c][7]annulen-5-on (**5k**).* The reaction of **4k** (0.28 mmol,100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a yellow oil was obtained in 68% (68 mg) yield. IR (ATR): $\tilde{\nu}$ = 1665 (s), 1634 (s), 1593 (s), 1442 (s), 1395 (m), 1257 (s), 1119 (m), 890 (s), 835 (m), 756 (s), 674 (m), 567 (m), 532 (m). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, J = 0.7 Hz, 1H), 7.82−7.86 (m, 1H), 7.67−7.73 (m, 1H), 7.61−7.66 (m, 3H), 7.54−7.60 (m, 2H), 7.43−7.51 (m, 1H), 7.14−7.21 (m, 3H), 2.34 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 193.8, 192.6, 161.0 (d, J = 253.3 Hz), 144.1, 144.0, 142.9, 140.4, 135.6 (d, J = 2.9 Hz), 134.2, 131.7, 131.2 (d, J = 10.0 Hz), 130.9 (d, J = 10.5 Hz), 130.0, 129.6, 129.4, 129.3, 128.5, 126.6 (d, J = 3.4 Hz), 120.9 (d, J = 10.9 Hz), 114.8 (d, J = 23.0 Hz), 21.7 (Signal of two quaternary carbons is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.13. MS (EI, 70 eV): m/z (%) = 342 ($[M]^+$, 24), 314 (57), 313 (46), 299 (60), 286 (24), 271 (15), 270 (16), 223 (33), 195 (34), 194 (53), 175 (22), 168 (14), 119 (98), 91 (100). HRMS (ESI-TOF): calcd for $C_{23}H_{16}FO_2$ ($[M + H]^+$) 343.1134, found ($[M + H]^+$) 343.1140.

*6-(2-Fluorobenzoyl)-10-methoxy-5H-dibenzo[a,c][7]annulen-5-one (**5l**).* The reaction of **4l** (0.27 mmol, 100 mg) was carried out through the general procedure. After extraction and column

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chromatography (7:7:1, heptane/ethyl acetate/dichloromethane), an orange solid was obtained in 65% (65 mg) yield. IR (ATR): $\tilde{\nu}$ = 1644 (s), 1591 (s), 1545 (s), 1482 (s), 1453 (s), 1282 (s), 1201 (s), 1016 (s), 985 (s), 754 (s), 729 (s), 639 (m), 511 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.78−7.83 (m, 1H), 7.70−7.76 (m, 1H), 7.57−7.65 (m, 3H), 7.51−7.55 (m, 1H), 7.36−7.43 (m, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.14−7.20 (m, 1H), 6.96−7.03 (m, 2H), 3.85 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 192.4, 190.4, 161.7, 160.2 (d, J = 252.3 Hz), 143.1, 142.4, 141.3, 139.5, 136.3, 135.9, 133.5 (d, J = 8.7 Hz), 131.5, 130.9 (d, J = 2.7 Hz), 129.6, 129.0, 127.0 (d, J = 13.2 Hz), 125.2, 124.6 (d, J = 3.5 Hz), 116.2, 115.8 (d, J = 22.2 Hz), 114.3, 55.7 (Signal of one quaternary carbon is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −110.94. MS (EI, 70 eV): m/z (%) = 359 ([M+1]$^+$, 14), 358 ([M]$^+$, 55), 331 (22), 330 (100), 329 (41), 302 (15), 257 (22), 235 (90), 207 (32), 192 (18), 178 (18), 164 (50), 163 (82), 123 (62), 95 (59). HRMS (EI): calcd for $C_{23}H_{15}FO_3$ ([M]$^+$) 358.0999, found 358.1001.

*8-Fluoro-6-(4-methoxybenzoyl)-5H-dibenzo[a,c][7] annulen-5-one (**5m**).* The reaction of **4m** (0.28 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), a yellow oil was obtained in 71% (71 mg) yield. IR (ATR): $\tilde{\nu}$ = 1657 (s), 1593 (s), 1508 (m), 1442 (s), 1253 (s), 1164 (s), 1119 (m), 1024 (m), 983 (m), 894 (m), 839 (s), 756 (s), 614 (m) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.99 (d, J = 0.8 Hz, 1H), 7.82−7.89 (m, 1H), 7.71−7.80 (m, 3H), 7.57−7.70 (m, 3H), 7.43−7.56 (m, 1H), 7.14−7.24 (m, 2H), 6.83−6.91 (m, 2H), 3.81 (s, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 192.8, 192.6, 163.8, 161.0 (d, J = 253.0 Hz), 144.3, 142.8, 140.3, 135.7 (d, J = 2.8 Hz), 132.0, 131.7, 131.1 (d, J = 10.0 Hz), 130.4 (d, J = 10.4 Hz), 130.0, 129.5, 129.4, 128.6, 126.6 (d, J = 3.5 Hz), 120.9 (d, J = 10.9 Hz), 114.8 (d, J = 22.8 Hz), 113.9, 55.6. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.34. MS (EI, 70 eV): m/z (%) = 359 ([M+1]$^+$, 7), 358 ([M]$^+$, 28), 330 (15), 329 (26), 302 (15), 299 (25), 195 (16), 194 (27), 175 (11), 135 (100), 107 (13), 92 (27). HRMS (EI): cacld For $C_{23}H_{15}FO_3$ ([M]$^+$) 358.0999, found 358.0994.

*3-Fluoro-6-(4-methylbenzoyl)-5H-dibenzo[a,c][7] annulen-5-one (**5n**).* The reaction of **4n** (0.29 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), an orange solid was obtained in 60% (60 mg) yield. Mp: 192−193 °C. IR (ATR): $\tilde{\nu}$ = 1655 (s), 1603 (s), 1576 (m), 1407 (m), 1273 (m), 1199 (m), 940 (m), 849 (m), 758 (s), 744 (s), 604 (m), 538 (m), 476 (m). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (dd, J = 8.8 Hz, J = 5.1 Hz, 1H), 7.77−7.82 (m, 2H), 7.60 (ddd, J = 7.6 Hz, J = 5.6 Hz, J = 1.5 Hz, 3H), 7.48−7.55 (m, 1H), 7.41−7.47 (m, 2H), 7.36 (ddd, J = 8.8 Hz, J = 7.5 Hz, J = 2.9 Hz, 1H), 7.15−7.20 (m, 2H), 2.35 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 194.0, 191.0, 162.8 (d, J = 251.8 Hz), 144.10, 144.0, 142.4, 141.6, 137.8, 134.25, 133.17, 132.4 (d, J = 7.7 Hz), 131.8, 130.8 (d, J = 8.5 Hz), 129.3, 129.3, 128.5, 119.28 (d, J = 21.8 Hz), 114.9 (d, J = 23.0 Hz), 21.7. (Signal of three quaternary carbon is absent, which may relate to signal overlap.) ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.09. MS (EI, 70 eV): m/z (%) = 343 ([M+1]$^+$, 24), 342 ([M]$^+$, 98), 327 (17), 314 (57), 313 (64), 299 (66), 286 (35), 270 (17), 223 (37), 195 (28), 194 (37), 175 (13), 119 (100), 91 (67). HRMS (EI): calcd for $C_{23}H_{15}FO_2$ ([M]$^+$) 342.1050, found 342.1059.

*10-Methoxy-6-(4-methoxybenzoyl)-5H-dibenzo[a,c][7] annulen-5-one (**5o**).* The reaction of **4o** (0.27 mmol, 100 mg) was carried out through the general procedure. After extraction and column chromatography (10:1, heptane/ethyl acetate), an orange solid was obtained in 75% (75 mg) yield. Mp: 190−192 °C. IR (ATR): $\tilde{\nu}$ = 1649 (s), 1589 (s), 1541 (s), 1282 (s), 1253 (s), 1218 (s), 1160 (s), 1016 (s), 983 (s), 822 (s), 773 (s), 729 (s), 602 (m), 528 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (dd, J = 8.1, J = 1.2 Hz, 1H, CH), 7.83−7.87 (m, 2H), 7.75−7.79 (m, 2H), 7.73 (dd, J = 8.0, J = 1.2 Hz, 1H), 7.63−7.68 (m, 2H), 7.42 (d, J = 2.6 Hz, 1H), 7.10 (dd, J = 8.6, J = 2.6 Hz, 1H), 6.89−6.93 (m, 2H, CH), 3.96 (s, 3H), 3.87 (s, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 193.5, 192.4, 163.4, 161.1, 142.4, 141.2, 140.7, 140.6, 136.3, 135.3, 131.6, 131.6, 130.0, 129.9, 129.2, 128.9, 125.6, 116.1, 114.4, 113.7, 55.7, 55.5. (Signal of two quaternary carbons is absent, which may relate to signal overlap.) MS (EI, 70 eV): m/z (%) = 371 ([M+1]$^+$, 15), 370 ([M]$^+$, 53), 343 (17), 342 (70), 341 (56), 314 (15), 311 (27), 299 (17), 235 (33), 176 (14), 164 (34), 163 (54), 135 (100), 107 (18), 92 (38). HRMS (EI): cacld. For $C_{24}H_{18}O_4$ ([M]$^+$) 370.1199, found 370.1191.

*General Procedure for the Synthesis of Compounds **6**.* $Pb(OAc)_4$ (7.5 mmol, 3.3 g) was added slowly in several portions to the stirring solution of (*E*)-2-bromo-*N*′-(2-hydroxybenzylidene)benzohydrazide (6.73 mmol, 2.15 g) in THF (30 mL). The mixture turned immediately orange with a mild evolution of N_2 gas. The mixture was stirred at room temperature for 3 h (TLC control). The solid was filtered through a pad of Celite and washed with pure ethyl acetate. The filtrate was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. Product **9** was isolated by column chromatography (heptane/ethyl acetate, 2:1) as a yellow oil (1.94 g, 6.7 mmol, 89%).

*2-(2-Bromobenzoyl)benzaldehyde (**6**).* The product **6** was isolated after purification by column chromatography (heptane/EtOAc = 2:1) as a yellow oil (1.94 g, 6.7 mmol, 89%). IR (ATR): $\tilde{\nu}$ = 3064 (w), 2851 (w), 2748 (w), 1749 (m), 1639 (s), 1662 (s), 1586 (m), 1572 (m), 1463 (w), 1428 (m); ^1H NMR (300 MHz, $CDCl_3$) δ = 10.43−10.31 (s, 1H), 8.12−7.96 (ddd, J = 7.6, J = 1.5, J = 0.5 Hz, 1H), 7.72−7.69 (m, 1H), 7.69−7.65 (m, 1H), 7.6−7.57 (dd, J = 7.5, J = 1.4 Hz, 1H), 7.52−7.48 (m, 1H), 7.48−7.46 (m, 1H), 7.46−7.42 (m, 1H), 7.43−7.36 (m, 1H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ = 196.2, 191.4, 139.9, 139.5, 137.0, 133.8, 132.7, 132.5, 132.3, 130.7, 130.6, 129.0, 127.4, 120.6. MS (EI, 70 eV): m/z (%) = 289 (M+, 1), 210 (16), 209 (100), 153 (18), 152 (38), 151 (16), 77 (19), 76 (23), 75 (14), 74 (10), 51 (11), 50 (13); HRMS (ESI): calcd for $C_{14}H_9O_2{}^{79}Br$ ([M]$^+$) 287.9760, found 287.9780 and calcd for $C_{14}H_9O_2{}^{81}Br$ ([M]$^+$) 289.9760, found 289.9757.

*General Procedure for the Synthesis of Sonogashira Cross-Coupling Products **7a−g**.* **6**, $PdCl_2(PPh_3)_2$ (5 mol %), PPh_3 (10 mol %), and CuI (5 mol %) were dissolved in triethylamine (8 mL) under an argon atmosphere. Afterward, the corresponding 1-alkyne (1.2 equiv) was added via syringe. The solution was stirred for 24 h in an oil bath at 70 °C. Water was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the crude product was purified by column chromatography (heptane/CH_2Cl_2 = 5:1).

*2-(2-(p-Tolylethynyl)benzoyl)benzaldehyde (**7a**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 99% (573 mg) yield. IR (ATR): $\tilde{\nu}$ = 2920 (w), 2213 (w), 1776 (m), 1696 (s), 1656 (s), 1590 (m), 1572 (w), 1510 (m); ^1H NMR (300 MHz, $CDCl_3$) δ = 10.29 (s, 1H), 8.03−7.95 (m, 1H), 7.70 (ddd, J = 7.7, J = 1.5, J = 0.6 Hz, 1H), 7.64−7.61 (m, 1H), 7.60−7.58 (m, 1H), 7.58−7.56 (m, 1H), 7.56−7.53 (m, 1H), 7.49 (dd, J = 14.1, J = 1.5 Hz, 1H), 7.43 (dd, J = 7.5, J = 1.4 Hz, 1H), 7.06−7.01 (m, 2H), 7.01−6.95 (m, 2H), 2.30 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 196.6, 191.1, 141.6, 139.6, 138.8, 136.4, 133.4, 132.7, 131.7, 131.4, 131.2, 130.2, 130.0, 128.8, 128.7, 128.0, 123.0, 119.1, 96.6, 86.7, 21.3. MS (EI, 70 eV): m/z (%) = 324 (M+, 25), 296, (39), 295 (100), 253 (36), 252 (69), 250 (16), 193 (41), 189 (35), 176 (17), 126 (12), 77 (24), 51 (13); HRMS (ESI): calcd for $C_{23}H_{16}O_2$ ([M]$^+$) 324.1144, found 324.1142.

*2-(2-(Phenylethynyl)benzoyl)benzaldehyde (**7b**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 40% (231 mg) yield. IR (ATR): $\tilde{\nu}$ = 3962 (w), 2851 (w), 1780 (s), 1743 (w), 1695 (s), 1662 (s), 1558 (m), 1572 (w); ^1H NMR (300 MHz, $CDCl_3$) δ = 10.37 (s, 1H), 8.06−7.97 (m, 2H), 7.72−7.68 (m, 3H), 7.67−7.65 (m, 1H), 7.67−7.49 (m, 3H), 7.55−7.37 (m, 4H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ = 196.2,191.4, 141.6, 139.9, 139.4, 136.9, 133.8 132.7, 132.4, 132.3, 131.4, 130.7, 130.6, 129.0, 128.8, 128.1, 127.4, 101.2, 96.3, 87.3. MS (EI, 70 eV): m/z (%) = 310 (M$^+$, 20), 282 (36), 281

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(100), 265 (10), 254 (13), 253 (41), 252 (57), 250 (19), 176 (28); HRMS (ESI): calcd for $C_{22}H_{14}O_2$ ([M]$^+$) 310.0988, found 310.0988.

*2-(2-((4-Methoxyphenyl)ethynyl)benzoyl)benzaldehyde (**7c**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 93% (538 mg) yield. IR (ATR): $\tilde{\nu}$ = 3062 (w), 2919 (w), 2837 (w), 2213 (w), 1770 (w), 1693 (s), 1656 (s), 1590 (s), 1572 (m); ^{1}H NMR (250 MHz, $CDCl_3$) δ = 10.32 (s, 1H), 8.03−7.98 (m, 1H), 7.81−7.69 (m, 2H), 7.61−7.51 (m, 4H), 7.46 (dd, J = 7.5, J = 1.5, 1H), 7.33−7.17 (m, 1H), 6.97 (dd, J = 7.8, J = 1.8, 1H), 6.86−6.67 (m, 2H), 3.79 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 196.8, 191.5, 159.9, 141.8, 139.9, 136.6, 133.6, 133.3, 132.6, 131.7, 131.5, 130.4, 130.2, 129.9, 128.5, 128.1, 123.3, 120.2, 111.5, 110.5, 93.1, 91.2, 55.6. MS (EI, 70 eV): m/z (%) = 340 (M+, 13), 311 (33), 253 (31), 252 (58), 239 (85), 194 (65), 193 (69), 178 (36), 165 (65), 119 (57). HRMS (ESI): calcd for $C_{23}H_{16}O_3$ ([M]$^+$) 340.1094, found 340.1086.

*2-(2-((4-(Trifluoromethyl)phenyl)ethynyl)benzoyl)benzaldehyde (**7d**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 71% (411 mg) yield. IR (ATR): $\tilde{\nu}$ = 3064 (w), 2853 (w), 1697 (s), 1660 (s), 1613 (m), 1590 (m), 1572 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.27 (s, 1H), 8.06−7.98 (m, 1H), 7.69 (ddd, J = 12.4, J = 7.8, J = 1.3 Hz, 2H), 7.66−7.63 (m, 2H), 7.63−7.56 (m, 3H), 7.54−7.46 (m, 3H), 7.29−7.25 (m, 1H); ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ = 196.3, 191.1, 141.5, 139.8, 136.4, 133.9, 133.0, 132.0, 131.7, 131.6, 130.3, 130.3 (q, J = 17.2 Hz), 129.2, 128.8, 126.2, 125.1 (q, J = 3.8 Hz), 123.8 (q, J = 272.2 Hz), 94.3, 89.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −62.9. MS (EI, 70 eV): m/z (%) = 378 (M$^+$, 23), 350 (41), 349 (100), 281 (25), 253 (30), 252 (60), 193 (30), 176 (28), 76 (25); HRMS (ESI): calcd for $C_{23}H_{13}O_2F_3$ ([M]$^+$) 378.0862, found 378.0854.

*2-(2-((4-(tert-Butyl)phenyl)ethynyl)benzoyl)benzaldehyde: (**7e**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 66% (382 mg) yield. IR (ATR): $\tilde{\nu}$ = 3064 (m), 2961 (m), 2866 (w), 2213 (w), 1784 (m), 1695 (s), 1658 (s), 1590 (m), 1508 (m); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.20 (s, 1H), 7.97−7.88 (m, 1H), 7.60 (ddd, J = 7.6, J = 1.5, J = 0.6 Hz, 1H), 7.59−7.58 (m, 1H), 7.58−7.51 (m, 2H), 7.48−7.41 (m, 1H), 7.43 (dd, J = 7.7, J = 1.5 Hz, 1H), 7.34 (dd, J = 7.4, J = 1.5 Hz, 1H), 7.15 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 1.18 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ = 196.7, 191.2, 152.0, 141.6, 139.7, 136.5, 133.4, 132.8, 131.7, 131.5, 131.1, 130.4, 130.0, 128.7, 128.0, 125.1, 123.0, 119.1, 96.7, 86.7, 34.7, 31.0. MS (EI, 70 eV): m/z (%) = 367 (12), 366 (M$^+$, 44), 352 (27), 351 (100), 338 (20), 337 (40), 323 (27), 281 (49), 265 (12), 252 (27), 233 (24), 193 (41); HRMS (ESI): calcd for $C_{26}H_{22}O_2$ ([M]$^+$) 366.1614, found 366.1607.

*2-(2-(Oct-1-yn-1-yl)benzoyl)benzaldehyde (**7f**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 89% (515 mg) yield. IR (ATR): $\tilde{\nu}$ = 3062 (w), 2926 (s), 2856 (m), 1778 (s), 1697 (s), 1660 (s), 1582 (m), 1572 (w); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.28 (s, 1H), 8.08−7.95 (m, 2H), 7.70−7.63 (m, 2H), 7.53−7.46 (m, 2H), 7.44−7.38 (m, 2H), 2.11−1.96 (m, 2H), 1.33−1.16 (m, 8H), 0.87 (q, J = 7.1, J = 5.6 Hz, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ = 197.1, 191.2, 142.0, 140.0, 136.3, 132.6, 131.6, 131.3, 130.7, 130.2, 129.6, 128.4, 127.5, 123.6, 101.2, 78.6, 31.1, 28.4, 28.1, 22.4, 19.3, 13.9. MS (EI, 70 eV): m/z (%) = 318 (M$^+$, 28), 248 (38), 247 (17), 234 (19), 233 (100), 206 (19), 205 (86), 177 (54), 176 (92), 151 (31); HRMS (ESI): calcd for $C_{22}H_{22}O_2$ ([M]$^+$) 318.1614, found 318.1611.

*2-(2-((4-Fluorophenyl)ethynyl)benzoyl)benzaldehyde (**7g**).* The reaction of **6** (2 mmol, 578.3 mg) was carried out through the general procedure (E). After extraction and column chromatography (heptane/CH_2Cl_2 = 5:1), a yellow brownish oil was obtained in 79% (457 mg) yield. IR (ATR): $\tilde{\nu}$ = 3064 (w), 2963 (w), 2864 (w), 2215 (m), 1788 (m), 1659 (s), 1656 (s), 1590 (s), 1572 (m), 1508 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.26 (s, 1H), 7.94−7.83 (m, 1H), 7.71−7.58 (m; 1H), 7.51 (s, 1H), 7.50−7.47 (m, 2H), 7.47−7.41 (m, 2H), 7.41−7.28 (m, 1H), 7.18−7.10 (m, 1H), 7.08−6.98 (m, 1H), 6.78−6.94 (m, 2H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ = 196.4, 191.0, 162.5 (d, J = 250.5 Hz), 139.5, 136.3, 133.7, 133.4, 133.2, 132.8, 131.8, 131.4, 131.0, 128.7 (d, J = 12.6 Hz), 128.1 (d, J = 14.8 Hz), 125.0, 122.6, 118.3 (d, J = 3.6 Hz), 115.2 (d, J = 22.1 Hz), 96.6, 86.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −109.8. MS (EI, 70 eV): m/z (%) = 328 (M$^+$, 20), 300 (37), 299 (100), 271 (43), 270 (60), 194 (29), 193 (35), 77 (18); HRMS (ESI): calcd for $C_{22}H_{13}O_2F$ ([M]$^+$) 328.0894, found 328.0887.

*General Procedure for the Synthesis of **8a**−**g**.* Compound **7** (0.5 mmol) was dissolved in toluene in a Schlenk tube argon atmosphere. Afterward *p*-TsOH (5 equiv) was added. The solution was stirred for 6 h at 80 °C in an oil bath. A saturated $NaHCO_3$ solution was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, and the crude product was purified by column chromatography (heptane/ethyl acetate = 5:1).

*10-(4-Methylbenzoyl)-5H-dibenzo[a,d][7]annulen-5-one (**8a**).* The reaction of **8a** (0.48 mmol, 156.2 mg) was carried out through the general procedure. After extraction and column chromatography (*n*-heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 64% (100 mg) yield. IR (ATR): $\tilde{\nu}$ = 3060 (w), 2919 (w), 2853 (w), 2250 (w), 1786 (w), 1735 (w), 1648 (s), 1601 (s), 1568 (m); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05−8.03 (m, 1H), 8.02−8.00 (m, 1H), 7.74−7.71 (m, 1H), 7.71−7.68 (m, 1H), 7.62−7.59 (m, 1H), 7.57−7.54 (m, 2H), 7.45−7.43 (m, 3H), 7.01−6.99 (m, 2H), 6.87 (s, 1H), 2.34 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ = 197.1, 194.4, 144.5, 141.1, 140.4, 139.7, 134.1, 132.9, 132.7, 132.4, 131.9, 131.2, 130.4, 129.8, 129.6, 129.3, 129.3, 129.1, 128.8, 21.6. HRMS (ESI): calcd for $C_{23}H_{16}O_2$ ([M]$^+$) 324.11448, found 324.11430.

*10-Benzoyl-5H-dibenzo[a,d][7]annulen-5-one (**8b**).* The reaction of **8b** (1.41 mmol, 435.6 mg) was carried out through the general procedure. After extraction and column chromatography (heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 52% (226 mg) yield. IR (ATR): $\tilde{\nu}$ = 2135 (m), 2115 (m), 2105 (s), 2093 (s), 1870 (m), 1840 (s), 1827 (s), 1862 (m), 1668 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00 (dd, J = 8.0, J = 1.6 Hz, 2H), 7.79 (d, J = 1.3 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.51 (ddd, J = 13.8, J = 7.3, J = 1.7 Hz, 2H), 7.49−7.41 (m, 3H), 7.37−7.29 (m, 3H), 7.26−7.19 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = δ 197.3, 194.2, 140.7, 140.4, 139.6, 136.6, 133.4, 133.1, 132.7, 132.2, 131.8, 131.2, 131.1, 130.1, 129.9, 129.6, 129.5, 129.3, 129.2, 128.9, 128.7, 128.5. MS (EI, 70 eV): m/z (%) = 311 (24), 310 (M+, 100), 281 (43), 205 (14), 176 (25), 105 (55), 77 (32). HRMS (ESI): calcd for $C_{22}H_{14}O_2$ ([M]$^+$) 310.0988, found 310.0987.

*10-(4-Methoxybenzoyl)-5H-dibenzo[a,d][7]annulen-5-one (**8c**).* The reaction of **8c** (0.69 mmol, 236.2 mg) was carried out through the general procedure. After extraction and column chromatography (heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 62% (146 mg) yield. IR (ATR): $\tilde{\nu}$ = 2140 (m), 2084 (s), 1876 (s), 1839 (s), 1831 (s), 1804 (m), 1677 (m), 1668 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.06 (t, J = 1.5 Hz, 1H), 8.04 (dd, J = 2.1, J = 0.9 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.57−7.54 (m, 1H), 7.53 (d, J = 1.3 Hz, 1H), 7.52−7.38 (m, 2H), 7.33−7.24 (m, 3H), 6.86 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 3.79 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ = 195.9, 194.2, 163.8, 141.0, 140.2, 139.5, 132.9, 132.6, 132.4, 132.2, 131.8, 131.2, 131.1, 129.7, 129.6, 129.4, 129.2, 128.9, 128.6, 113.8, 55.4. MS (EI, 70 eV): m/z (%) = 341 (19), 340 (M$^+$, 75), 311 (13), 176 (14), 135 (100), 92 (10), 77 (14); HRMS (ESI): calcd for $C_{23}H_{16}O_3$ ([M]$^+$) 340.1094, found 340.1093.

*10-(4-(Trifluoromethyl)benzoyl)-5H-dibenzo[a,d][7]annulen-5-one (**8d**).* The reaction of **8d** (0.75 mmol, 287.1 mg) was carried out through the general procedure. After extraction and column chromatography (heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 41% (118 mg) yield. IR (ATR): $\tilde{\nu}$ = 2102 (m), 2081 (s), 2073 (s), 2064 (s), 1923 (s), 1894 (s), 1827 (m), 1799 (s), 1639 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99−7.80 (m, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.55 (dd, J = 4.8, J = 1.5 Hz,

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1H), 7.52−7.47 (m, 1H), 7.48−7.43 (m, 1H), 7.37 (dd, J = 7.6, J = 1.5 Hz, 1H), 7.18−7.14 (m, 2H), 7.33 (s, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 196.3, 194.3, 140.6, 140.1, 140.0, 139.7, 134.3, 132.5, 132.1, 131.8 (q, J = 29.4 Hz), 131.5, 131.3, 130.4, 129.8, 129.7, 129.2, 128.7, 125.7 (q, J = 3.7 Hz), 124.6 (d, J = 272.9 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ = −63.16. MS (EI, 70 eV): m/z (%) = 379 (25), 378 (M^+, 100), 349 (38), 205 (24), 177 (20), 176 (30), 173 (32), 145 (32); HRMS (ESI): calcd for $C_{23}H_{13}O_2F_3$ ([M]$^+$) 378.0862, found 378.0860.

*10-(4-(tert-Butyl)benzoyl)-5H-dibenzo[a,d][7]annulen-5-one (**8e**).* The reaction of **8e** (0.38 mmol, 141.8 mg) was carried out through the general procedure. After extraction and column chromatography (heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 45% (64 mg) yield. IR (ATR): $\tilde{\nu}$ = 2103 (m), 2070 (s), 1840 (m), 1826 (s), 1804 (m), 1664 (m), 1638 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (dd, J = 1.5, J = 0.5 Hz, 1H), 7.94−7.92 (m, 1H), 7.73−7.70 (m, 1H), 7.70−7.68 (m, 1H), 7.47−7.38 (m, 3H), 7.38−7.26 (m, 4H), 7.24−7.19 (m, 1H), 7.17 (s, 1H), 1.18 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ = 196.9, 194.1, 157.3, 140.9, 140.3, 139.6, 133.9, 132.9, 132.4, 132.4, 131.8, 131.2, 131.1, 130.2, 129.7, 129.6, 129.2, 129.0, 128.7, 125.5, 35.0, 30.9. MS (EI, 70 eV): m/z (%) = 367 (27), 366 (M^+, 96), 281 (19), 176 (22), 161 (100), 118 (13); HRMS (ESI): calcd for $C_{26}H_{22}O_2$ ([M]$^+$) 366.16143, found 366.1612.

*10-Heptanoyl-5H-dibenzo[a,d][7]annulen-5-one (**8f**).* The reaction of **8f** (0.81 mmol, 259.2 mg) was carried out through the general procedure. After extraction and column chromatography (heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 19% (49 mg) yield. IR (ATR): $\tilde{\nu}$ = 2143 (m), 2025 (s), 1889 (m), 1812 (s), 1804 (m), 1684 (m), 1632 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 (dd, J = 6.5, J = 2.7 Hz, 2H), 7.54−7.35 (m, 5H), 7.27 (s, 1H), 7.25−7.10 (m, 1H), 2.62 (t, J = 7.5 Hz, 2H), 1.54 (t, J = 7.5 Hz, 2H), 1.15 (m, 6H), 0.72 (t, J = 6.8 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 205.8, 194.8, 142.4, 141.5, 140.2, 132.7, 132.1, 131.2, 131.1, 130.8, 131.8, 130.0, 129.3, 129.1, 128.7, 128.3, 41.6, 31.4, 28.7, 24.7, 22.4, 13.9. MS (EI, 70 eV): m/z (%) = 318 (M^+, 32), 248 (40), 247 (17), 234 (19), 233 (100), 231 (11), 206 (15), 205 (76), 177 (38), 176 (59), 151 (18); HRMS (ESI): calcd for $C_{22}H_{22}O_2$ ([M]$^+$) 318.1614, found 318.1615.

*10-(4-Fluorobenzoyl)-5H-dibenzo[a,d][7]annulen-5-one (**8g**).* The reaction of **8g** (0.74 mmol, 328.34 mg) was carried out through the general procedure. After extraction and column chromatography (heptane/ethyl acetate = 5:1), a pale yellow oil was obtained in 57% (187 mg) yield. IR (ATR): $\tilde{\nu}$ = 2087 (s), 2065 (m), 2031 (m), 2000 (m), 1881 (s), 1842 (s), 1827 (m), 1803 (m), 1756 (w) 1710 (m), 1667 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (dd, J = 1.6, J = 0.6 Hz, 1H), 8.07 (dd, J = 1.7, J = 0.6 Hz, 1H), 7.91−7.85 (m, 2H), 7.66−7.63 (m, 1H), 7.62−7.56 (m, 2H), 7.55−7.42 (m, 2H, 1H), 7.36 (d, J = 0.6 Hz, 1H), 7.28 (ddd, J = 7.8, J = 1.4, J = 0.5 Hz, 1H), 7.12−7.04 (m, 2H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ = 195.8, 194.3, 165.8 (d, J = 256.3 Hz), 140.5, 140.4,139.8, 133.2, 133.0 (d, J = 3.0 Hz), 132.9 (d, J = 9.5 Hz), 132.7, 132.1, 131.9, 131.3, 130.1, 129.7, 129.5, 129.1, 128.7, 115.8 (d, J = 22.0 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ = −103.77. MS (EI, 70 eV): m/z (%) = 329 (24), 328 (M^+, 100), 300 (14), 299 (50), 176 (24), 123 (68), 95 (29). HRMS (ESI): calcd for $C_{22}H_{13}O_2F$ ([M]$^+$) 328.0894, found 328.0895.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01132.

Synthetic procedures and spectroscopic characterization of all compounds, copies of the NMR spectra of all products and X-ray crystallography data. (PDF)

Accession Codes

CCDC 2080999−2081002 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Peter Ehlers − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany; Leibniz Institut für Katalyse an der Universität Rostock, 18059 Rostock, Germany;* orcid.org/0000-0001-6444-7563; Phone: +49 381 498 6410; Email: peter.ehlers@uni-rostock.de; Fax: +49 381 498 6412

Peter Langer − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany; Leibniz Institut für Katalyse an der Universität Rostock, 18059 Rostock, Germany;* orcid.org/0000-0002-7665-8912; Phone: +49 381 498 6410; Email: peter.langer@uni-rostock.de; Fax: +49 381 498 6412

Authors

Maryam Sobhani − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany*

Anna Frey − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany*

Andre Rettmann − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany*

Richard Thom − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany*

Alexander Villinger − *Universität Rostock, Institut für Chemie, 18059 Rostock, Germany;* orcid.org/0000-0002-0868-9987

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01132

Notes

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II. Publication

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Regioselective Synthesis of Naphthothiophenes by Pd Catalyzed Cross-Coupling Reactions and Alkyne-Carbonyl Metathesis

Maryam Sobhani, Alexander Villinger, Peter Ehlers,* and Peter Langer*

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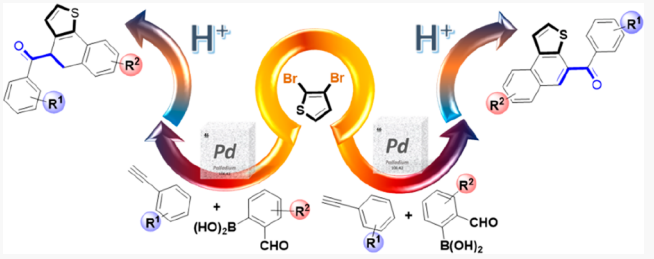
ABSTRACT: Naphthothiophenes were prepared from commercially available 2,3-dibromothiophenes in two steps by one-pot Suzuki/Sonogashira or Sonogashira/Suzuki coupling reactions, followed by intramolecular alkyne-carbonyl-metathesis reactions. The final cyclization reaction proceeds in the presence of *p*-toluenesulfonic acid and provides a rapid access to two series of isomeric naphthothiophenes.

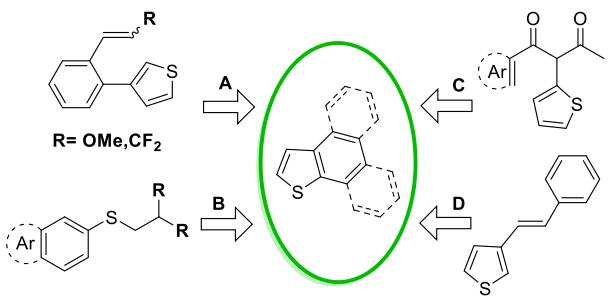


INTRODUCTION

The synthesis of polycyclic aromatic compounds plays a fundamental role in organic synthesis, as the products have important applications in various fields such as natural product chemistry,[1] synthesis of pharmaceuticals,[2] and development of organic materials. In this regard, thiophene-fused π-conjugated systems, such as naphthothiophenes, show promising optoelectronic properties and photochemical stability[3,4] and can, thus, be regarded as a new generation of materials in electronic devices.[5] Moreover, naphthothiophenes have been reported as promising anticancerogenic compounds.[6]

Accordingly, several attempts have been addressed toward the development of novel synthetic routes to these scaffolds. Methods for the synthesis of naphthothiopenes include, for instance, the cyclization of functionalized thiophenes or aryl sulfides in the presence of transition metals[7] or acids[8] (Scheme 1A,B) or the photocyclization of substituted thiophenes (Scheme 1C,D).[9,10] However, such methodologies are limited due to restrictions with regard to the substitution patterns of the starting materials.

Scheme 1. Known Strategies for the Synthesis of Naphthothiophenes[7−10]



Given the importance of these structures and our ongoing interest in the synthesis of polycyclic heteroaromatic structures from polyhalogenated compounds,[11] we describe herein a practical and convenient two-step synthetic route for the synthesis of naphthothiophene derivatives starting from commercially available 2,3-dibromothiophene and 2,3-dibromobenzothiophene, respectively. The developed methodology includes a one-pot Suzuki/Sonogashira or Sonogashira-/Suzuki cross-coupling protocol, followed by a Brønsted acid mediated intramolecular alkyne-carbonyl-metathesis (ACM) reaction as a key step (Scheme 2). ACM reactions reported so far are mostly mediated by Lewis acids which are in many cases expensive, toxic, or not readily available.[12] Our synthetic strategy takes advantage of the site-selectivity of Palladium catalyzed cross-coupling reactions and hence allows the preparation of two regioisomeric naphthothiophene derivatives in a step-economic manner from readily available 2,3-dibromothiophene **1** as starting material.

RESULTS AND DISCUSSION

Initially, starting materials **3** and **6** were obtained by sequential Sonogashira and Suzuki reaction, and the respective synthetic procedures were optimized. However, while the Suzuki reaction of 2,3-dibromothiophene **1** with 2-formylphenylboronic acid worked selectively with good yield using standard conditions, the subsequent Sonogashira reaction failed to proceed efficiently. Hence, a known one-pot Suzuki-Sonoga-

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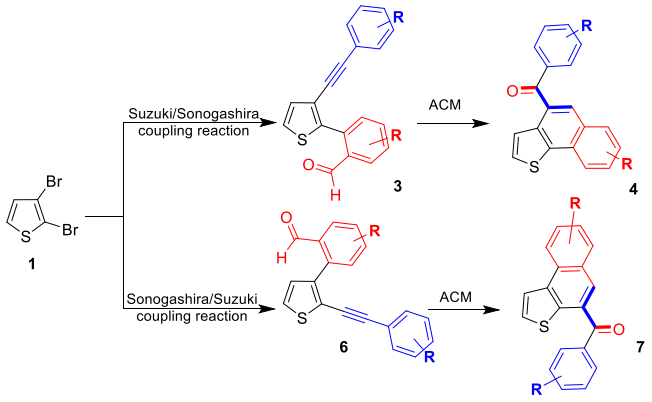
Scheme 2. Synthetic Strategy toward Naphthothiophene Derivatives (This Paper)

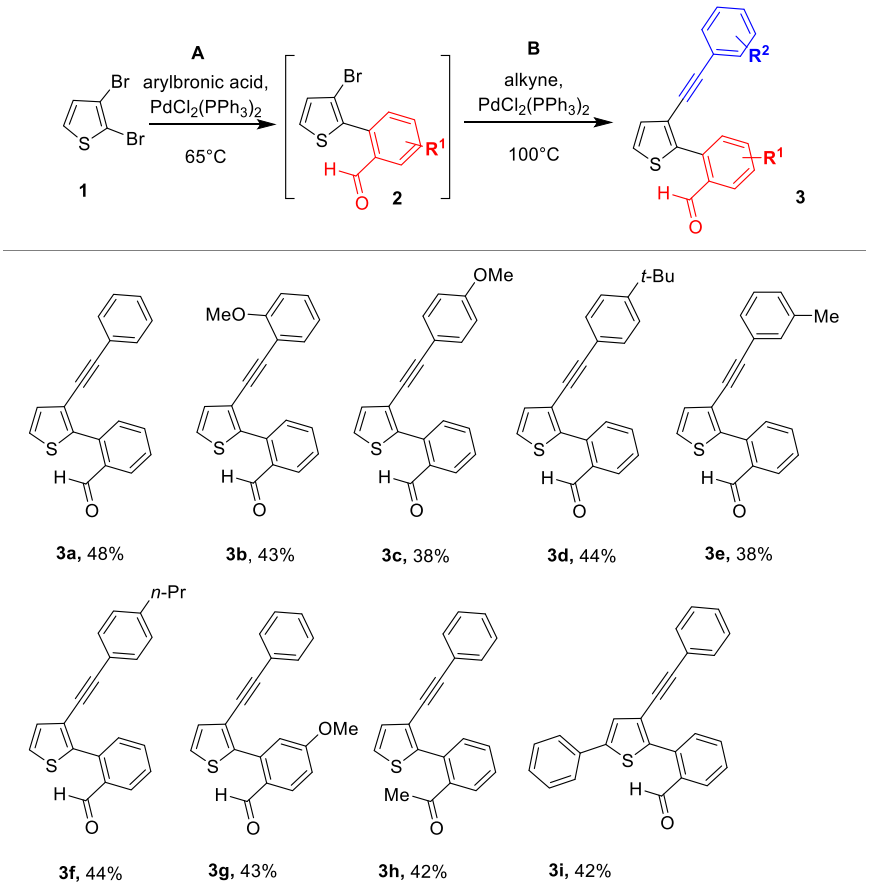


shira reaction procedure, developed by Verma and co-workers on tetrabromothiophene, was considered, delivering the desired starting material **3a** in moderate yield. Further elaborate optimization efforts to improve the yield remained unsuccessful (see Table S1 in the SI). It is important to note that the Sonogashira reaction requires the addition Cs_2CO_3, while initial Suzuki reaction worked best using K_2CO_3. Moreover, another portion of Pd catalyst is required for the second step to obtain improved yields. However, the different roles of base counterions in these reactions and potential deactivation pathways of the Pd catalyst are still unclear.

Subsequently, the scope of the reaction was studied using a variety of arylboronic acids and terminal alkynes. Compounds **3a–j** were obtained by one-pot sequential Suzuki-Sonogashira coupling reactions in 38–48% overall yields (over two steps). In general, the isolated yields are in the same range, independently from the substitution pattern of the employed arylalkynes and 2-formyl- or 2-acetylphenylboronic acids (Table 1). Hence, the outcome of the reaction is not affected by the choice of the 2-carbonylphenylboronic acid as well as the substitution pattern of the employed arylalkynes. Moreover, an additional phenyl ring on the thiophene does not affect the isolated yield.

Subsequently, the ACM cyclization of **3a** was screened using various Brønsted acids (for a comprehensive overview of all optimization reaction see SI, Table S2). The investigation was started by employment of 15 equiv of *p*-toluenesulfonic acid monohydrate (*p*-TsOH) in toluene and was monitored by TLC. To our delight, naphthothiophene **4a** could be isolated in 74% yield after 1 h. When the reaction was carried out in toluene using 15 eq. of trifluoroacetic acid (TFA, 2 h), the desired product was obtained in slightly improved yield (79%), while methanesulfonic acid (MsOH) delivered the product in lower yield (59%). It is noteworthy that, while TFA gave slightly improved yields for the synthesis of derivative **4a** as

Table 1. Synthesis of 3a–j[a]



[a]Yields refer to isolated products. Product **3i** was obtained from 2,3-dibromo-5-phenylthiophene. Conditions: A: 2-formylphenylboronic acid (1.2 equiv), $PdCl_2(PPh_3)_2$ (7 mol %), K_2CO_3 (2.5 equiv), DMF/EtOH (4:1), 65 °C, 8–10 h; B: phenylacetylene (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (5 mol %), L-Proline (15 mol %), Cs_2CO_3 (1.5 equiv), 100 °C, 12–14 h.

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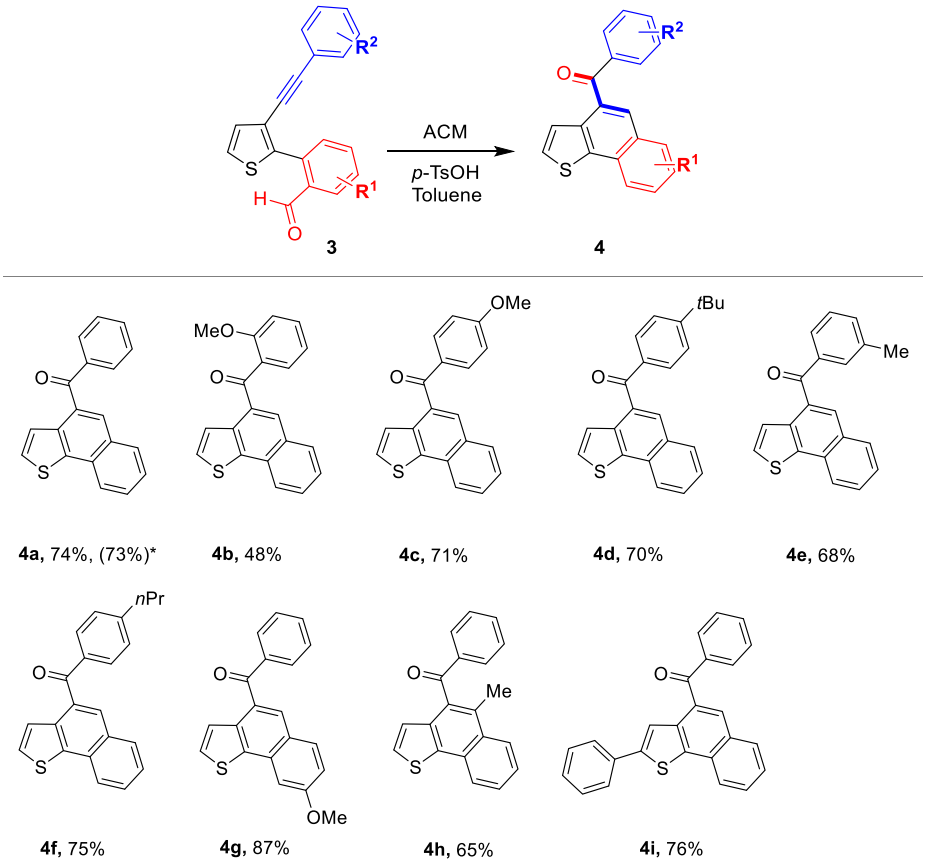
Table 2. ACM Reaction of 3a−j[a]



[a]Isolated yields. *Yield in parentheses: performing the reaction using 1 mmol (288 mg) of **3a**.

compared to *p*-TsOH (entry 2), it gave inferior results in the case of other derivatives. Thus, all further ACM reactions were performed in toluene with 15 eq. of *p*-TsOH.

The scope of the ACM cyclization was studied next using our optimized conditions. The cyclization of **3a−j** in the presence of *p*-TsOH afforded the desired products **4a−j** (Table 2). All products were isolated in good to very good yields. However, the presence of a methoxy group located in *ortho*-position of the arylalkynyl moiety resulted in a decrease of the yield **4b** (48%), most likely due to steric hindrance. In contrast, the presence of a methoxy group located at the 2-carbonylaryl moiety gave product **4g** in excellent yield (87%), which can be explained by the ability of the methoxy group to stabilize positive charges during the cyclization. The ACM reaction of **3h**, containing an acetyl- instead of a formyl-group, furnished the target compound **4h** in only slightly decreased yield (65%) as compared to the corresponding formyl derivative. Moreover, substitution of the thiophene moiety (**3i**) had no impact on the yield.

The synthesis of regioisomeric naphtho[2,1-*b*]thiophenes was next studied. The respective starting materials **6a−j** were prepared by changing the order of the coupling reactions starting with the Sonogashira reaction and otherwise using the same type of one-pot two-step procedure (see Table S3 in the SI).

Subsequent cyclization to naphtho[2,1-*b*]thiophenes **7** was carried out under the optimized ACM conditions described above. Cyclization of **6a−j** using *p*-TsOH in toluene afforded products **7a−j** in good to excellent yields (Table 3). The obtained yields only slightly differ from each other, which is mainly due to the required purification process by column chromatography. As was already mentioned above, employment of acetyl instead of formyl derivatives had no significant impact on the reaction outcome (products **7d**,**e**). Interestingly, when the alkyne moiety was functionalized by electron-withdrawing fluorine atoms located in *meta* or *ortho* position, the cyclization worked again very well and products **7f** and **7g** could be isolated in good and excellent yields (78 and 90%, respectively). Next, we checked the applicability of this reaction to synthesize benzo-annulated naphtho[2,1-*b*]-thiophenes using benzo[*b*]naphthothiophenes as a starting material. The ACM reaction of **6h** gave the desired product **7h** in excellent yield (91%). Likewise, **6i** and **6j** were successfully transformed to products **7i** and **7j** in 45% and 65% yields, respectively.

Single crystals of **4c** and **7c**, **7g**, and **7h** suitable for X-ray crystal structure analysis were obtained by slow evaporation from ethanol at room temperature (see Figures S1 and S2 and Table S4 in the SI). Compounds **4c**, **7c**, and **7h** crystallize in monoclinic space group $P2_1/c$ and **7g** in *Cc*.[13] Molecules of **4c**, **7c**, and **7h** are columnar packed in the crystal lattice dominated by poor S−S interaction, along *b*-axis and *a*-axis, respectively, whereas a herringbone pattern along the *a*-axis is observed for **7h** (Figure 1). A large noncoplanar dihedral angle between naphtothiophene and benzoyl moieties is determined for all compounds (see Figures S1 and S2 in the SI). Considering the maximum centroid−centroid distance (as a $\pi-\pi$ interaction criterion),[14] a week face-to-face π-stacking

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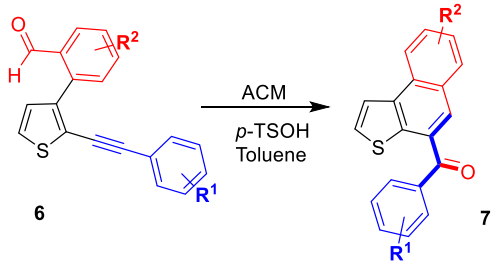
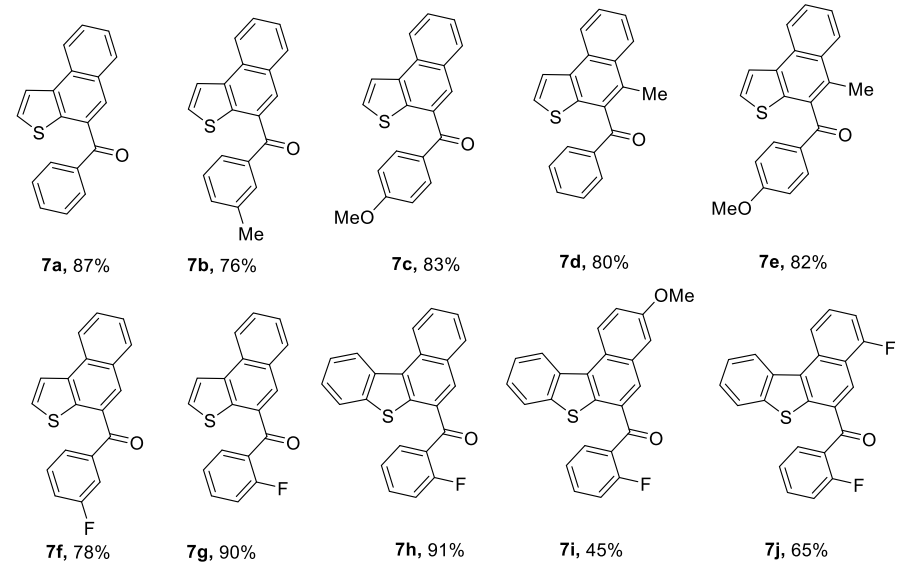
Table 3. Synthesis of 7a–j by ACM Reaction[a]





[a]Isolated yields.

interaction larger than 3.8 Å can be observed for **4c**, **7c**, and **7g**, while two neighboring benzonaphthothiophene molecules show close C–H···π interaction (face to edge) in the crystal lattice of **7h**. Shortest distances between two neighboring molecules fall within the range of 2.47–3.47 Å (Figure 1). Additional intermolecular hydrogen bond (C–H···O) is indicated for all structures as well as C–H···F for **7g** (see Figure S1 in the SI).

CONCLUSIONS

In summary, we reported a convenient and efficient synthetic route to naphtho[2,1-*b*]thiophenes and naphtho[1,2-*b*]-thiophenes as structural isomers. The strategy is based on site-selective Suzuki and Sonogashira coupling reactions, followed by ring-closing ACM reactions. The optimized reaction conditions allow for the synthesis of the products in good to excellent yields under mild reaction conditions.

EXPERIMENTAL SECTION

General Information. The nuclear magnetic resonance spectra (^{1}H/^{13}C/^{19}F NMR) were recorded on a Bruker AVANCE 300 III, 250 II, or 500. The analyzed chemical shifts δ are referenced to residual solvents signals of the deuterated solvent $CDCl_3$ (δ = 7.26 ppm/77.0 ppm). Multiplicities due to spin–spin correlation are reported as follows: s = singlet, d = doublet, dd = double doublet, t = triplet, pt = pseudo triplet, m = multiple, and further described through their coupling constants *J*. Infrared spectra (IR) were measured as attenuated total reflection (ATR) experiments with a Nicolet 380 FT-IR spectrometer. The signals have been characterized through their wave numbers $\tilde{\nu}$ and their corresponding absorption as very strong (vs), strong (s), medium (m), weak (w), or very weak (vw). UV–vis spectra were recorded on a Cary 60 UV–vis spectrophotometer and emission spectra with an Agilent Cary Eclipse fluorescence spectrophotometer. Basic and high-resolution mass spectra (MS/HRMS) were measured on instruments, which were paired with a preceding gas chromatograph (GC) or liquid chromatograph (LC). The samples have been ionized through electron impact ionization (EI) on an Agilent 6890/5973 or Agilent 7890/5977 GC–MS equipped with a HP-5 capillary column using helium carrier gas or by applying electron spray ionization (ESI) on an Agilent 1200/6210 Time-of-Flight (TOF) LC–MS. Melting points (mp) were determined by a Micro-Hot-Stage Galen TM III Cambridge Instruments and are not corrected.

Materials. The applied solvents toluene, hexane, acetonitrile, 1,4-dioxane, and dichloromethane were obtained as dry solvents through commercial sources and employed without further purification. Solvents for extraction and column chromatography were available after previous distillation. Other reagents, catalysts, ligands, acids, and bases have been utilized in purchased purity. Column chromatography was performed using Merck Silica gel 60 (particle size 63–200 μm).

*Procedure A: General Experimental Procedure for Pd-Catalyzed One-Pot Sequential Suzuki/Sonogashira Reactions (Synthesis of **3a–i**).* A solution of dibromothiophene **1** (1 mmol, 239 mg, 112 μL) in 2 mL of DMF/EtOH (4:1) in an argon flushed reaction vial was charged with 7 mol % of $Pd(PPh_3)_2Cl_2$ (0.049 g), 3.5 eq. of K_2CO_3 (0.482 g), and 1.2 mmol of boronic acid **2**. The reaction mixture was then stirred in a stainless-steel heating block at 65 °C. After completion of the first coupling reaction (monitored by TLC), 5 mol % of $Pd(PPh_3)_2Cl_2$ (0.049 g), 1.5 mmol of alkyne, 1.5 eq. of Cs_2CO_3 (0.488 g), CuI (5 mol %, 0.019 g), and L-proline (15 mol %, 0.065 g) were added. The reaction mixture was then stirred at 100 °C until

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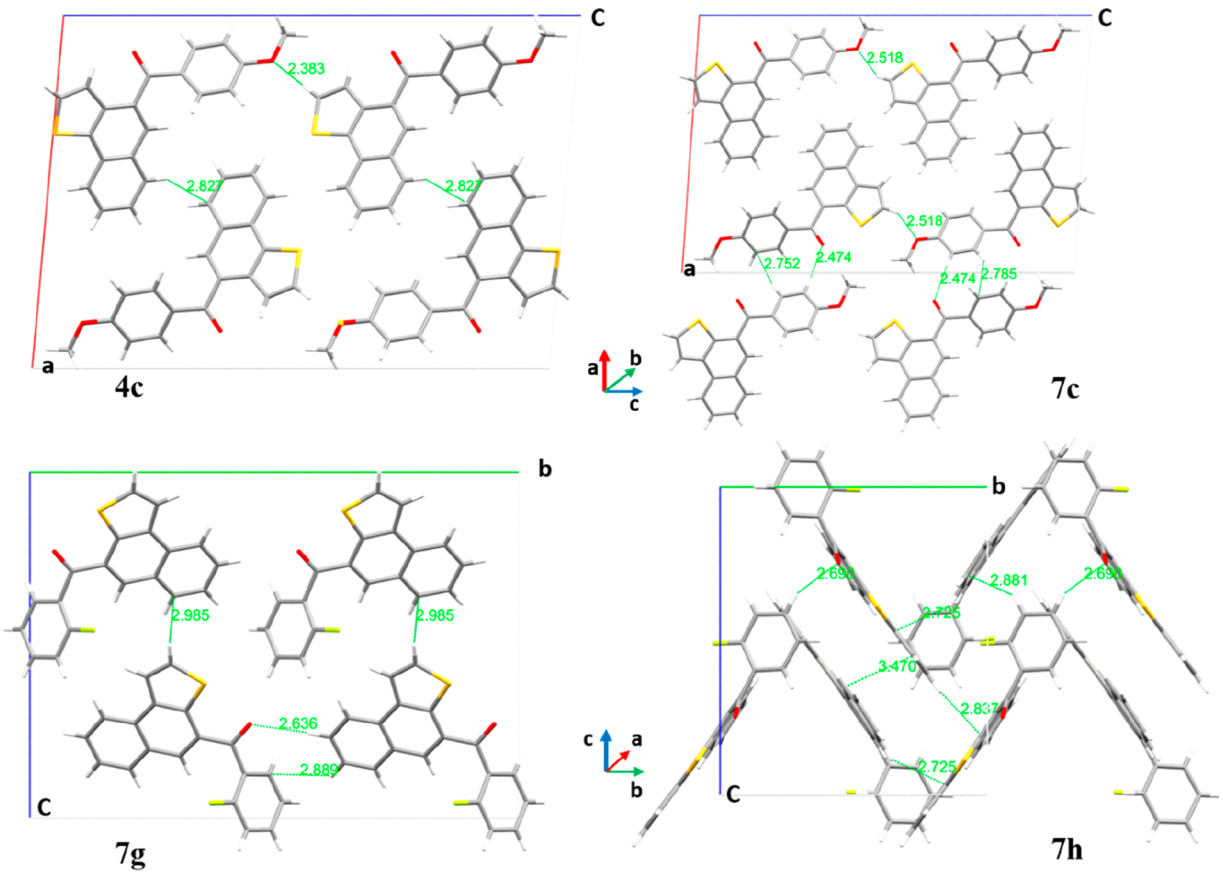

Figure 1. Crystal lattice of **4c**, **7c**, **7g**, and **7h** in the unit cell and selected shortest distance between neighboring molecules. Crystal structure of **4c** and **7c** viewed along the *b*-axis and **7g** and **7h** viewed along the *a*-axis.

TLC revealed complete conversion. The reaction mixture was then allowed to cool to room temperature and diluted with H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under vacuum, and purified by column chromatography (heptane/ethyl acetate = 10:1) to afford the corresponding products.

*Procedure B: General Procedure for Pd-Catalyzed One-Pot Sequential Sonogashira/Suzuki Reactions (Synthesis of **6a–j**).* To a solution of 2,3-dibromothiophene (**1**) (1.0 mmol) in 2 mL of DMF, 6 mol % of $Pd(PPh_3)_2Cl_2$ (0.048 g) and CuI (5 mol %,0.019 g) were added 3.5 eq. of Et_3N (0.5 mL) and 1.2 mmol of alkyne **3**. The reaction vial was flushed with argon and sealed. The reaction was then stirred in a stainless-steel heating block at 70 °C. After completion of the first coupling reaction (monitored by TLC), 8 mol % of $Pd(PPh_3)_2Cl_2$ (0.065 g), 1.2 mmol of boronic acid **2**, 3.0 eq. of K_2CO_3 (0.207 g), and 0.5 mL of EtOH were added. The reaction was stirred at 100 °C until TLC revealed complete conversion. The reaction mixture was allowed to cool to room temperature and diluted with H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum, and purified by column chromatography (heptane/ethyl acetate = 10:1) to afford the corresponding products. (To have better separation for compound **6h** and **6j**, after the first coupling reaction, the reaction crude was cleared with short column chromatography and the crude was used for second step).

*Procedure C: General Experimental Procedure for Synthesis of Naphtho[1,2-b]thiophenes **4a–i** and Naphtho[2,1-b]thiophenes **7a–j**.* Compounds **3a–i** (or **6a–j**) were dissolved toluene (0.25 M); subsequently, *p*-TsOH·H_2O (15 equiv) was added and the solution was stirred for 1 h in a stainless-steel heating block at 100 °C. After cooling to room temperature, a saturated $NaHCO_3$ solution was added to the reaction mixture, which was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and the residue was purified by column chromatography (heptane/EtOAc = 10:1).

Experimental Data for Products 4a–i. *4-Benzoylnaphtho[1,2-b]thiophene (**4a**).* The reaction of **3a** (0.5 mmol, 144 mg; 1 mmol, 288 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.42), an orange solid was obtained in 74% (73%) yield (0.37 mmol, 106 mg; 0.73 mmol, 210 mg); mp: 102–104 °C. IR (ATR): $\tilde{\nu}$ = 1636 (s), 1442 (m), 1358 (m), 1278 (s), 1208 (s), 1092 (m), 880 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 8.22–8.27 (m, 1H). 7.91 (d, J = 5.5 Hz, 1H), 7.82 (d, 1H), 7.72–7.77 (m, 2H), 7.66 (dd, J = 5.5 Hz, J = 0.5 Hz, 1H), 7.56–7.63 (m, 1H), 7.47–7.55 (m, 1H), 7.37–7.46 (m, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 196.8, 139.2, 138.4, 135.3, 132.8, 131.4, 130.5, 130.3, 130.2, 130.0, 129.3, 129.1, 128.9, 128.5, 128.4, 126.4, 126.0, 125.2, 123.7. MS (EI, 70 eV): m/z (%) = 288 (M^+, 100), 287 (17), 258 (5), 212 (11), 211 (75), 183 (42), 182 (6), 139 (30), 105 (22), 77 (27). HRMS (EI) m/z: calcd. for $C_{19}H_{12}OS$ [M^+] 288.0603, found 288.0601.

*4-((2-Methoxy)benzoyl)naphtho[1,2-b]thiophene (**4b**).* The reaction of **3b** (0.5 mmol, 159 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.25), a brown solid was obtained in 48% yield (0.24 mmol, 76.4 mg); mp: 114–116 °C. IR (ATR): $\tilde{\nu}$ = 1657 (s), 1599 (s), 1486 (s), 1459 (s), 1432 (s), 1296 (s), 1269 (s), 1249 (s), 1236 (s), 1177 (s), 1086 (s), 1024 (s), 952 (s), 907 (s), 839 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, J = 5.4 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.89 (s, 1H), 7.80 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.57–7.61 (m, 1H), 7.55 (d, J = 5.4 Hz, 1H), 7.39–7.48 (m, 3H), 6.94–7.03 (m, 2H), 3.61 (s, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 196.8, 157.8, 139.3, 134.9, 132.4, 132.1, 131.8, 130.9, 130.3, 130.1, 129.7, 129.5, 129.2, 127.9, 126.1, 125.9, 123.7, 120.5, 111.7, 55.7. MS (EI, 70 eV): m/z (%) = 318 (M^+,100), 301 (12), 211

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(33), 199 (12), 198 (80), 197 (15), 184 (14), 183 (45), 139 (38), 135 (62). HRMS (EI) m/z: calcd. for $C_{20}H_{14}O_2S$ [M^+] 318.0709, found 318.0709.

*4-((4-Methoxy)benzoyl)naphtho[1,2-b]thiophene (**4c**).* The reaction of **3c** (0.5 mmol, 159 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.25), a yellow solid was obtained in 71% yield (0.36 mmol, 112.2 mg); mp: 125 °C. IR (ATR): $\tilde{\nu}$ = 1638 (s), 1593 (s), 1506 (s), 1461 (s), 1434 (s), 1313 (s), 1284 (s), 1247 (s), 1173 (s), 1154 (s), 1094 (s), 1022 (s), 956 (s), 946 (s) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.07−8.14 (m, 1H), 7.84−7.88 (m, 2H), 7.80−7.84 (m, 2H), 7.69 (d, J = 5.4 Hz, 1H), 7.53−7.61 (m, 1H), 7.43−7.50 (m, 2H), 6.85−6.93 (m, 2H), 3.81 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 195.4, 163.6, 139.0, 135.4, 132.7, 132.1, 130.9, 130.2, 129.8, 129.7, 129.4, 128.9, 128.5, 127.8, 126.3, 125.8, 125.1, 123.7, 113.7, 55.5. MS (EI, 70 eV): m/z (%) = 318 (M^+ 100), 317 (16), 287 (12), 211 (21), 183 (22), 139 (21), 135 (71), 77 (12). HRMS (EI) m/z: calcd. for $C_{20}H_{14}O_2S$ [M^+] 318.0709, found 318.0704.

*4-((4-tert-Butyl)benzoyl)naphtho[1,2-b]thiophene (**4d**).* The reaction of **3d** (0.5 mmol, 172 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.25), a brown oil was obtained in 70% yield (0.35 mmol, 120.6 mg). IR (ATR): $\tilde{\nu}$ = 1735 (s), 1649 (s), 1603 (s), 1556 (s), 1465 (s), 1434 (s), 1362 (s), 1313 (s), 1282 (s), 1245 (s), 1187 (s), 1111 (s), 1084 (s), 952 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.1 Hz, 1H), 7.91 (s, 1H), 7.85 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.76−7.82 (m, 3H), 7.56−7.60 (m, 1H), 7.49 (d, J = 5.4 Hz, 1H), 7.41−7.48 (m, 3H), 1.30 (s, 9H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 196.5, 156.7, 139.2, 135.6, 135.4, 132.5, 131.7, 130.4, 130.3, 130.0, 129.8, 129.3, 128.8, 128.5, 126.3, 125.9, 125.4, 125.3, 123.7, 35.2, 31.2. MS (EI, 70 eV): m/z (%) = 344 (M^+ 100), 330 (13), 329 (56), 287 (14), 211 (26), 183 (35), 161 (18), 151 (16), 139 (19). HRMS (EI) m/z: calcd. for $C_{23}H_{20}OS$ [M^+] 344.1229, found 344.1228.

*4-((3-Methyl)benzoyl)naphtho[1,2-b]thiophene (**4e**).* The reaction of **3e** (0.5 mmol, 151 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.52), a brown oil was obtained in 68% yield (102.8 mg). IR (ATR): $\tilde{\nu}$ = 1649 (s), 1599 (s), 1583 (s), 1434 (s), 1280 (m), 1253 (m), 1205 (m), 1183 (m), 1144 (m), 1084 (m), 964 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.11−8.17 (m, 1H), 7.91 (s, 1H), 7.84−7.89 (m, 1H), 7.82 (d, J = 5.4 Hz, 1H), 7.65−7.70 (m, 1H), 7.56−7.65 (m, 2H), 7.45−7.53 (m, 2H), 7.27−7.41 (m, 2H), 2.36 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 197.1, 139.2, 138.5, 138.4, 135.4, 133.6, 131.6, 130.7, 130.5, 130.1, 130.0, 129.3, 128.8, 128.3, 127.7, 126.3, 126.0, 125.2, 123.7, 21.4. MS (EI, 70 eV): m/z (%) = 302 (M^+ 100), 30 (11), 287 (12), 211 (58), 183 (32), 139 (23), 119 (20), 91 (19). HRMS (EI) m/z: calcd for $C_{20}H_{14}OS$ [M^+] 302.0759, found 302.0761.

*4-((4-Propyl)benzoyl)naphtho[1,2-b]thiophene (**4f**).* The reaction of **3f** (0.5 mmol, 165 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.50), a yellow solid was obtained in 75% yield (0.38 mmol, 123.9 mg). IR (ATR): $\tilde{\nu}$ = 1649 (s), 1603 (s), 1556 (m), 1465 (m), 1434 (m), 1412 (m), 1309 (m), 1280 (vs) 1245 (s), 1210 (m), 1179 (s), 1156 (m), 1084 (s), 861 (m) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.09−8.16 (m, 1H), 7.91 (s, 1H), 7.84−7.89 (m, 1H), 7.73−7.81 (m, 3H), 7.55−7.65 (m, 1H), 7.43−7.53 (m, 2H), 7.20−7.28 (m, 2H), 2.62 (dd, J = 8.5 Hz, J = 6.7 Hz, 2H), 1.56−1.72 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 196.5, 148.4, 139.1, 135.9, 135.4, 131.8, 130.5, 130.5, 130.3, 129.9, 129.7, 129.3, 128.7, 128.5, 126.3, 125.9, 125.2, 123.7, 38.1, 24.2, 13.8. MS (EI, 70 eV): m/z (%) = 330 (M^+ 100), 287 (25), 273 (15), 211 (39), 183 (29), 147 (38), 139 (18), 91 (12). HRMS (EI) m/z: calcd for $C_{22}H_{18}OS$ [M^+] 330.1072, found 330.1073.

*4-Benzoyl-8-methoxynaphtho[1,2-b]thiophene (**4g**).* The reaction of **3g** (0.5 mmol, 159 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.30), a yellow solid was obtained in 87% yield (0.44 mmol, 138.5 mg); mp: 116 °C. IR (ATR): $\tilde{\nu}$ = 1649 (s), 1616 (s), 1482 (s), 1430 (s), 1360 (s), 1284 (s), 1218 (s), 1175 (s), 1022 (m), 960 (m), 849 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 5.4 Hz, 1H), 7.86 (s, 1H), 7.77−7.83 (m, 2H), 7.73 (d, J = 9.0 Hz, 1H), 7.48−7.57 (m, 2H), 7.39−7.46 (m, 2H), 7.35 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 8.9 Hz, J = 2.5 Hz, 1H), 3.93 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 196.2, 138.4, 137.6, 135.1, 132.8, 132.5, 131.3, 131.2, 130.3, 130.1, 129.8, 129.3, 129.0, 128.2, 127.1, 126.0, 123.8, 120.8, 21.5. MS (EI, 70 eV): m/z (%) = 318 (M^+ 100), 242 (12), 241 (72), 213 (28), 170 (17), 105 (10), 77 (18). HRMS (EI) m/z: calcd for $C_{20}H_{14}O_2S$ [M^+] 318.0709, found 318.0710.

*4-Benzoyl-5-methylnaphtho[1,2-b]thiophene (**4h**).* The reaction of **3h** (0.5 mmol, 172 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.45), a yellow solid was obtained in 65% yield (0.33 mmol, 120.6 mg); mp: 129−131 °C. IR (ATR): $\tilde{\nu}$ = 1659 (m), 1591 (m), 1576 (m), 1449 (m), 1313 (m), 1269 (m), 1251 (m), 1166 (m), 1152 (m), 946 (s), 841 (s). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.10−8.15 (m, 1H), 8.04−8.09 (m, 1H), 7.76−7.83 (m, 2H), 7.45−7.63 (m, 3H), 7.30−7.41 (m, 3H), 6.99 (d, J = 5.4 Hz, 1H), 2.49 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 199.0, 137.5, 136.6, 134.3, 133.8, 132.7, 130.1, 129.9, 129.2, 128.8, 128.1, 127.2, 126.3, 125.5, 125.5, 124.3, 123.7, 16.5. MS (EI, 70 eV): m/z (%) = 302 (M^+ 100), 287 (10), 285 (25), 284 (22), 225 (13), 197 (27), 152 (10), 77 (19). HRMS (EI) m/z: calcd for $C_{20}H_{14}OS$ [M^+] 302.0759, found 302.0753.

*4-Benzoyl-2-phenylnaphtho[1,2-b]thiophene (**4i**).* The reaction of **3i** (0.5 mmol, 182 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.42), a yellow solid was obtained in 76% yield (0.38 mmol, 127.4 mg); mp: 146−147 °C. IR (ATR): $\tilde{\nu}$ = 1640 (w), 1593 (w), 1477 (m), 1447 (m), 1315 (m), 1286 (m), 1276 (m), 1212 (m), 1175 (m), 921 (m), 909 (m), 837 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1H), 8.03−8.05 (m, 1H), 7.81−7.88 (m, 3H), 7.76−7.80 (m, 1H), 7.64−7.69 (m, 2H), 7.50−7.59 (m, 2H), 7.38−7.45 (m, 3H), 7.28−7.36 (m, 2H), 7.20−7.26 (m, 1H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 196.8, 144.6, 138.7, 138.4, 136.4, 134.1, 132.8, 131.1, 130.6, 130.4, 130.4, 130.3, 130.1, 129.2, 129.0, 128.5, 128.3, 126.5, 126.3, 123.6, 120.8. MS (EI, 70 eV): m/z (%) = 364 (M^+ 100), 287 (27), 259 (16), 258 (18), 215 (18), 105 (9), 77 (20). HRMS (EI) m/z: calcd for $C_{25}H_{16}OS$ [M^+] 364.0916, found 364.0913.

Experimental Data for Products 7a−j. *4-Benzoylnaphtho[2,1-b]thiophene (**7a**).* The reaction of **6a** (0.38 mmol, 96 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.37), a yellow solid was obtained in 87% yield (0.33 mmol, 83.2 mg); mp: 109 °C. IR (ATR): $\tilde{\nu}$ = 1636 (s), 1554 (s), 1480 (s), 1442 (s), 1358 (m), 1306 (m), 1278 (m), 1245 (m), 1208 (m), 1156 (m), 1092 (m), 1063 (m), 1024 (m), 900 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.22−8.27 (m, 1H), 8.07 (s, 1H), 7.91 (d, J = 5.5 Hz, 1H), 7.82 (m, 1H), 7.72−7.77 (m, 2H), 7.66 (dd, J = 5.5 Hz, J = 0.5 Hz, 1H), 7.56−7.63 (m, 1H), 7.47−7.55 (m, 1H), 7.37−7.46 (m, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 196.0, 138.3, 137.6, 135.0, 132.6, 132.1, 131.3, 130.3, 130.0, 129.9, 129.8, 129.4, 128.8, 128.4, 126.0, 123.8, 120.9. MS (EI, 70 eV): m/z (%) = 288 (M^+ 100), 287 (12), 211 (43), 183 (32), 139 (26), 105 (26), 77 (27). HRMS (EI) m/z: calcd for $C_{19}H_{12}OS$ [M^+] 288.0603 found 288.0588

*4-((3-Methyl)benzoyl)naphtho[2,1-b]thiophene (**7b**).* The reaction of **6b** (0.38 mmol, 116 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.40), a yellow oil was obtained in 76% yield (0.29 mmol, 88.1 mg). IR (ATR): $\tilde{\nu}$ = 1638 (s), 1618 (m), 1556 (m), 1480 (m), 1442 (m), 1360 (m), 1282 (s), 1197 (m), 1162 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.30 (dd, J = 8.3 Hz, J = 1.2 Hz, 1H), 8.12 (s, 1H), 7.96 (d, J = 5.5 Hz, 1H), 7.84−7.90 (m, 1H), 7.70 (d, J = 5.5 Hz, 1H), 7.52−7.67 (m, 3H), 7.43−7.51 (m, 1H), 7.30−7.38 (m, 2H), 2.37 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 196.2, 138.4, 137.6, 135.1, 132.8, 132.5, 131.3, 130.3, 130.1, 129.8, 129.3, 129.0, 128.2, 127.1, 126.0, 123.8, 120.8, 21.5. MS (EI, 70 eV):

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m/*z* (%) = 302 (M^+100), 287 (9), 211 (38), 183 (28), 139 (23), 119 (28), 91 (24) 65 (8). HRMS (EI) *m*/*z*: calcd for $C_{20}H_{14}OS$ [M^+] 302.0759, found 302.0757.

*4-((4-Methoxy)benzoyl)naphtho[2,1-b]thiophene (**7c**).* The reaction of **6c** (0.33 mmol, 106 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.22), a yellow solid was obtained in 83% yield (0.27 mmol, 88 mg); mp: 135 °C. IR (ATR): $\tilde{\nu}$ = 1636 (m), 1595 (m), 1510 (m), 1440 (m), 1358 (m), 1315 (m), 1261 (s), 1175 (s), 1018 (s), 841 (s), 767 (s), 709 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.27−8.35 (m, 1H), 8.10 (s, 1H), 7.96 (d, *J* = 5.5 Hz, 1H), 7.87−7.92 (m, 1H), 7.78−7.85 (m, 2H), 7.69 (dd, *J* = 5.5 Hz, *J* = 0.6 Hz, 1H), 7.65 (dd, *J* = 8.3 Hz, *J* = 1.3 Hz, 1H), 7.44−7.52 (m, 1H), 6.91−6.98 (m, 2H), 3.83 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 193.7, 162.1, 136.5, 134.4, 131.3, 130.3, 130.0, 129.6, 129.1, 128.8, 128.5, 128.3, 128.0, 126.8, 124.9, 122.7, 119.9, 112.7, 54.5. MS (EI, 70 eV): *m*/*z* (%) = 318 (M^+100), 211 (11), 183 (16), 139 (19), 135 (81), 92 (11), 77 (15). HRMS (EI) *m*/*z*: calcd. for $C_{20}H_{14}O_2S$ [M^+] 318.0709, found 318.0708.

*4-Benzoyl-5-methylnaphtho[2,1-b]thiophene (**7d**).* The reaction of **6d** (0.36 mmol, 108 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.40), a brown oil was obtained in 80% yield (0.29 mmol, 86 mg). IR (ATR): $\tilde{\nu}$ = 1663 (m), 1595 (m), 1447 (m), 1358 (m), 1265 (m), 1247 (m), 1212 (m), 1168 (m), 1072 (m), 962 (m), 824 (w), 756 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.32−8.36 (m, 1H), 8.07−8.11 (m, 1H), 7.93 (d, *J* = 5.5 Hz, 1H), 7.80−7.84 (m, 2H), 7.62−7.66 (m, 1H), 7.60 (dd, *J* = 4.2 Hz, *J* = 1.6 Hz, 1H), 7.51−7.58 (m, 2H), 7.46 (d, *J* = 5.4 Hz, 1H), 7.35−7.41 (m, 2H), 2.52 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 198.3, 136.9, 135.3, 134.0, 131.5, 130.0, 129.6, 128.9, 128.5, 127.2, 126.2, 125.9, 125.3, 124.3, 121.7, 17.1. MS (EI, 70 eV): *m*/*z* (%) = 302 (M^+22), 301 (26), 197 (20), 195 (20), 171 (22), 165 (10), 152 (22), 151 (14), 105 (45), 78 (15), 77 (100). HRMS (EI) *m*/*z*: calcd. for $C_{20}H_{14}OS$ [M^+] 302.0759, found 302.0751.

*4-((4-Methoxy)benzoyl)-5-methylnaphtho[2,1-b]thiophene (**7e**).* The reaction of **6e** (0.34 mmol, 114 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.25), a brown oil was obtained in 82% yield (0.28 mmol, 93 mg). IR (ATR): $\tilde{\nu}$ = 1651 (m), 1593 (m), 1570 (m), 1506 (m), 1434 (m), 1247 (m), 1216 (s), 1158 (s), 1022 (s), 962 (s), 843 (s), 756 (s) cm^{-1} ^1H NMR (250 MHz, $CDCl_3$): δ = 8.29−8.35 (m, 1H), 8.03−8.12 (m, 1H), 7.91 (d, *J* = 5.5 Hz, 1H), 7.72−7.82 (m, 2H), 7.50−7.65 (m, 2H), 7.44 (d, *J* = 5.4 Hz, 1H), 6.79−6.88 (m, 2H), 3.78 (s, 3H), 2.52 (s, 3H). ^{13}C {^1H} NMR (63 MHz, $CDCl_3$): δ = 196.7, 164.4, 135.2, 135.1, 132.5, 131.9, 130.6, 129.8, 129.5, 128.1, 127.0, 126.1, 125.8, 125.2, 124.2, 121.7, 114.1, 55.5, 16.9. MS (EI, 70 eV): *m*/*z* (%) = 332 (M^+37), 331 (32), 317 (17), 315 (15), 301 (39), 197 (42), 196 (24), 171 (49), 165 (22), 163 (20), 153 (18), 152 (47), 151 (27), 136 (17), 135 (100), 108 (45), 107 (37). HRMS (EI) *m*/*z*: calcd for $C_{21}H_{16}O_2S$ [M^+] 332.0865, found 332.0856.

*4-((3-Fluoro)benzoyl)naphtho[2,1-b]thiophene (**7f**).* The reaction of **6f** (0.38 mmol, 115 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.32), a brown solid was obtained in 78% yield (0.29 mmol, 90 mg); mp: 111−112 °C. IR (ATR): $\tilde{\nu}$ = 1642 (m), 1616 (m), 1583 (m), 1556 (m), 1480 (m), 1438 (m), 1362 (m), 1311 (m), 1288 (s), 1166 (s), 940 (s), 853 (s), 874 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 8.4 Hz, *J* = 1.1 Hz, 1H), 8.10 (s, 1H), 7.96 (d, *J* = 5.5 Hz, 1H), 7.89 (dd, *J* = 8.3 Hz, ^3J = 1.2 Hz, 1H), 7.71 (d, *J* = 5.5 Hz, 1H), 7.63−7.68 (m, 1H), 7.51−7.55 (m, 1H), 7.40−7.50 (m, 3H), 7.22−7.27 (m, 1H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 194.4 (d, *J* = 2.2 Hz). 162.5 (d, *J* = 248.3 Hz), 140.4, 140.3, 137.7, 134.8, 132.6, 131.4, 130.3, 130.2, 130.1, 129.9, 129.7, 125.6, 125.5, 123.8, 120.9, 119.0 (d, *J* = 21.4 Hz), 116.6 (d, *J* = 22.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ = −111.6. MS (EI, 70 eV): *m*/*z* (%) = 306 (M^+100), 212 (7), 211 (43), 184 (6), 183 (41), 139 (33), 123 (14), 95 (22), 75 (7). HRMS (EI) *m*/*z*: calcd for $C_{19}H_{11}FOS$ [M^+] 306.0709, found 306.0708.

*4-((2-Fluoro)benzoyl)naphtho[2,1-b]thiophene (**7g**).* The reaction of **6g** (0.3 mmol, 90 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.37), a yellow solid was obtained in 90% yield (0.27 mmol, 81 mg); mp: 144−145 °C. IR (ATR): $\tilde{\nu}$ = 1638 (m), 1607 (m), 1556 (m), 1480 (m), 1447 (m), 1358 (m), 1313 (m), 1288 (m), 1205 (m), 1166 (m), 948 (s), 903 (s), 886 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.39−8.49 (m, 1H), 8.17 (dd, *J* = 2.5 Hz, *J* = 0.7 Hz, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.94−8.03 (m, 1H), 7.85 (dd, *J* = 5.5 Hz, *J* = 0.6 Hz, 1H), 7.72−7.84 (m, 1H), 7.53−7.70 (m, 3H), 7.33−7.42 (m, 1H), 7.24−7.32 (m, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 192.7, 159.8 (d, *J* = 251.4 Hz), 137.6, 134.1, 133.4, 132.8 (d, *J* = 8.2 Hz), 131.7, 130.6, 130.5, 130.2, 129.9 (d, *J* = 28.5 Hz), 129.2, 127.1 (d, *J* = 15.6 Hz), 126.0, 124.4, 124.4, 123.8, 120.7, 116.4 (d, *J* = 21.6 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ = −112.1. MS (EI, 70 eV): *m*/*z* (%) = 306 (M^+100), 211 (38), 183 (33), 139 (26), 138 (6), 123 (25), 95 (14), 75 (6). HRMS (EI) *m*/*z*: calcd. for $C_{19}H_{11}FOS$ [M^+] 306.0509, found 306.0514.

*6-(2-Fluoro)benzoyl)benzo[b]naphtho[1,2-d]thiophene (**7h**).* The reaction of **6h** (0.33 mmol, 119 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.26), a yellow solid was obtained in 91% yield (0.30 mmol, 108 mg); mp: 227−230 °C. IR (ATR): $\tilde{\nu}$ = 1638 (m), 1607 (m), 1556 (m), 1480 (m), 1447 (m), 1358 (m), 1313 (m), 1288 (m), 1205 (m), 948 (s), 903 (s), 886 (s), 750 (s), 707 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.03 (d, *J* = 8.6 Hz, 1H), 8.82 (d, *J* = 8.2 Hz, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 8.05 (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 1H), 7.96 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H), 7.79 (ddd, *J* = 8.4 Hz, *J* = 6.9 Hz, *J* = 1.5 Hz, 1H), 7.47−7.59 (m, 6H), 7.28 (dd, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H), 7.16−7.21 (m, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 192.8, 159.8 (d, *J* = 251.8 Hz), 142.4, 136.5, 135.3 (d, *J* = 2.3 Hz), 134.9, 132.9 (d, *J* = 8.2 Hz), 132.8, 131.4, 131.2, 130.6 (d, *J* = 2.8 Hz), 130.4, 128.8, 127.1 (d, *J* = 15.5 Hz), 125.7, 125.5, 124.9, 124.6, 124.5, 123.5, 123.3, 116.5 (d, *J* = 21.6 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ = −111.8. MS (EI, 70 eV): *m*/*z* (%) = 356 (M^+ 100), 261 (17), 233 (33), 232 (0), 189 (15), 123 (19). HRMS (EI) *m*/*z*: calcd. for $C_{23}H_{13}FOS$ [M^+] 356.0665, found 356.0663.

*6-((2-Fluoro)benzoyl)-3-methoxybenzo[b]naphtho[1,2-d]-thiophene (**7i**).* The reaction of **6i** (0.26 mmol, 99 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0. 20), a yellow solid was obtained in 45% yield (0.12 mmol, 44 mg); mp: 170 °C. IR (ATR): $\tilde{\nu}$ = 1640 (vs), 1611 (vs), 1447 (s), 1309 (vs), 1220 (vs), 1203 (s), 925 (s), 907 (vs), 816 (vs), 750 (s), 738 (s), 713 (vs), 503 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.67−8.71 (m, 1H), 8.28 (d, *J* = 2.4 Hz, 1H), 8.12 (d, *J* = 2.5 Hz, 1H), 8.01−8.06 (m, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.44−7.59 (m, 4H), 7.27 (dd, *J* = 7.5 Hz, *J* = 1.1 Hz, 1H), 7.12−7.24 (m, 2H), 4.03 (s, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ = 192.3, 159.8 (d, *J* = 268.8 Hz), 142.4, 137.4, 135.3, 134.9, 134.5, 133.0, 132.6 (d, *J* = 8.2 Hz), 130.6, 127.2, 126.6, 125.9, 125.4, 124.8, 124.4 (d, *J* = 3.6 Hz), 123.9, 123.3, 117.0, 116.5 (d, *J* = 21.6 Hz), 116.2, 103.8, 55.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.1. MS (EI, 70 eV): *m*/*z* (%) = 386 (M^+100), 343 (12), 315 (10), 291 (13), 263 (24), 220 (55), 219 (25), 176 (18), 123 (57), 95 (42). HRMS (EI) *m*/*z*: calcd. for $C_{24}H_{15}FO_2S$[M^+] 386.0771, found 386.0776.

*4-Fluoro-6-((2-Fluoro)benzoyl)benzo[b]naphtho[1,2-d]-thiophene (**7j**).* The reaction of **6j** (0.4 mmol, 150 mg) was carried out through general procedure C. After extraction and column chromatography (heptane/ethyl acetate = 10:1, Rf = 0.25), a yellow solid was obtained in 65% yield (0.26 mmol, 98 mg); mp: 192−194 °C. IR (ATR): $\tilde{\nu}$ = 1696 (vs), 1651 (s), 1599 (m), 1570 (m), 1486 (m), 1440 (m), 1243 (m), 1191 (m), 1092 (m), 981 (m), 843 (m), 797 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.79 (dd, *J* = 11.6 Hz, *J* = 8.4 Hz, 2H), 8.52 (d, *J* = 2.6 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, *J* = 6.0 Hz, 1H), 7.63−7.48 (m, 4H), 7.29 (m, 1H), 7.24−7.16 (m, 2H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ = 192.8, 160.3 (d, *J* = 255.2 Hz), 159.9 (d, *J* = 251.8 Hz), 142.5, 137.6, 134.7, 133.7, 133.3 (d, *J* = 8.3 Hz), 131.0, 130.7, 130.6, 127.0

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(d, J = 7.2 Hz), 127.0, 126.7 (d, J = 15.2 Hz), 126.0, 125.1, 124.6, 124.5, 123.3, 121.2 (d, J = 15.1 Hz), 119.4 (d, J = 4.2 Hz), 116.5 (d, J = 21.6 Hz), 109.6 (d, J = 20.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −117.0, −111.5. MS (EI, 70 eV): m/z (%) = 374 (M^+100), 279 (23), 252 (14), 251 (69), 250 (23), 207 (57), 206 (16), 205 (28), 187 (10), 123 (99). HRMS (EI) m/z: calcd for $C_{23}H_{12}F_2OS$ [M^+] 374.0571, found 374.0567.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02838.

General experimental procedures, optimization tables, starting material synthesis including discussion and compound characterization data, crystallographic data, steady-state UV/vis and photoluminescence data, copies of NMR spectra (PDF)

Accession Codes

CCDCs 2090400−2090403 contain supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via. www.ccdc.cam.ac.uk/data_request/cif.

■ AUTHOR INFORMATION

Corresponding Authors

Peter Ehlers − *Institut für Chemie, Universität Rostock, 18059 Rostock, Germany; Leibniz Institut für Katalyse, Universität Rostock, 18059 Rostock, Germany;* orcid.org/0000-0001-6444-7563; Email: peter.ehlers@uni-rostock.de

Peter Langer − *Institut für Chemie, Universität Rostock, 18059 Rostock, Germany; Leibniz Institut für Katalyse, Universität Rostock, 18059 Rostock, Germany;* orcid.org/0000-0002-7665-8912; Email: peter.langer@uni-rostock.de

Authors

Maryam Sobhani − *Institut für Chemie, Universität Rostock, 18059 Rostock, Germany*

Alexander Villinger − *Institut für Chemie, Universität Rostock, 18059 Rostock, Germany;* orcid.org/0000-0002-0868-9987

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c02838

Notes

The authors declare no competing financial interest.

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III. Publication

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Synthesis of imidazo[1,2-*a*]benzoazepines by alkyne-carbonyl-metathesis†

Maryam Sobhani,[a] Rúben Manuel Figueira de Abreu,[a] Alexander Villinger,[a] Peter Ehlers *[a] and Peter Langer *[a,b]

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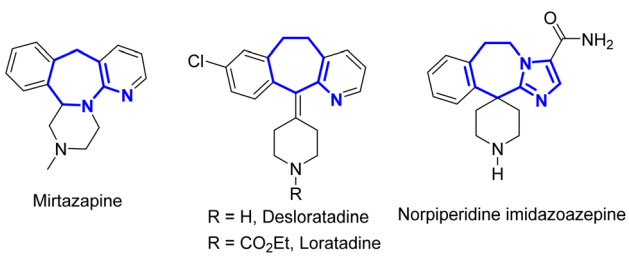
Imidazo[1,2-*a*]benzoazepines were prepared by Brønsted acid-mediated intramolecular alkyne-carbonyl metathesis (ACM). The starting materials, imidazole and benzimidazole derivatives, were prepared by *N*-alkylation, formylation and Sonogashira cross-coupling reaction. The final intramolecular ACM delivered the final products in good to excellent yields and with a wide tolerance towards functional groups.

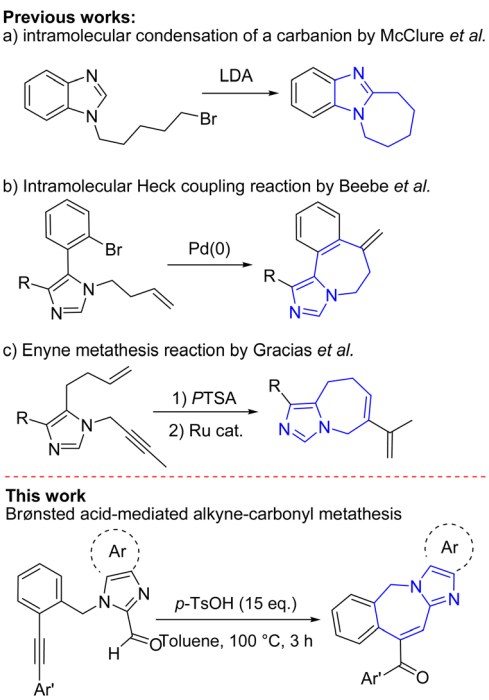
Introduction

The imidazole and benzimidazole core is present in a variety of natural products and medicinally important structures, including antiplatelet, antiparasitic, antiprotozoa, antiviral, and antibacterial agents.[1] Likewise, azepane-based molecules show a wide spectrum of biological activities and provide significant structural diversity, making them valuable for the development of new therapeutic medications.[2] So far, the FDA (Food and Drug Administration) has approved more than twenty azepane-based drugs, such as tofranil, lotensin, corlopam, and alcaftadine, which are nowadays routinely employed to treat a variety of diseases, such as depression, high blood pressure, heart failure, diabetic and allergic diseases.[3] In 2005, inspired by the structures of the antihistamines mirtazapine, desloratadine, and loratadine, Janssens *et al.* developed a spirocyclic norpiperidine imidazoazepine structure as a selective and nonsedating H_1 antihistamine (Scheme 1).[4]

Imidazoazepines are synthetically challenging structures which have previously been prepared by cyclization of suitable imidazole derivatives. McClure *et al.* reported the synthesis of benzimidazo[1,2-*a*]azepines by intramolecular nucleophilic substitution (Scheme 2, reaction (a)).[5] Beebe *et al.* prepared arylated imidazoles through the van Leusen method.[6] The products were subsequently transformed to imidazo[1,5-*a*]aze-



Scheme 1 The structure of some antihistamines.



Scheme 2 Methods for the synthesis of fused imidazo-azepines.

[a]*Universität Rostock, Institut für Chemie, A.-Einstein-Str. 3a, 18059 Rostock, Germany. E-mail: peter.ehlers@uni-rostock.de, peter.langer@uni-rostock.de; Fax: +49 381 498 6412; Tel: +49 381 498 6410*

[b]*Leibniz Institut für Katalyse an der Universität Rostock, A.-Einstein-Str. 29a, 18059 Rostock, Germany*

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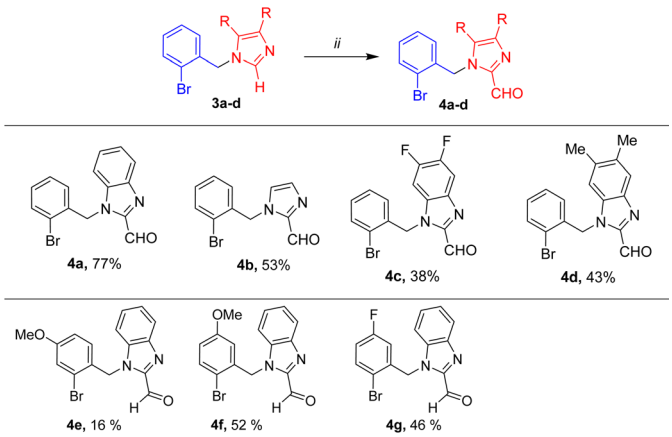
pines by intramolecular Heck reactions (Scheme 2, reaction (b)).[7] Gracias *et al.* synthesized imidazo[1,5-*a*]azepine derivatives by Ru catalyzed en-yne metathesis (Scheme 2, reaction (c)).[8] In recent years, the alkyne-carbonyl metathesis (ACM) reaction, promoted by either Lewis acid[9] or Brønsted acid,[10] has been used as an alternative to more classical olefination reactions in the synthesis of carbocycles, heterocycles, and polycyclic aromatic frameworks.[11,12] For example, Jana *et al.* reported the synthesis of seven-membered rings, such as dihydrobenzo[*b*]azepines, dibenzo[*b*,*f*]oxepines and benzo[*b*]oxepines, by iron(III) chloride-catalyzed intramolecular alkyne–carbonyl metathesis.[11b,c] Herein, we wish to report a new approach to imidazo[1,2-*a*]azepines *via* Brønsted acid mediated ACM reactions (Scheme 2). From a preparative point of view, this method allows for a convient synthesis of acylated derivatives which are not readily available by other methods. The starting materials are readily available from simple starting materials by alkylation and Sonogashira reactions. From a methodology viewpoint, applications of ACM reactions for the assembly of seven-membered rings have only scarcely been reported in the literature. Recently, we reported the synthesis of dibenzotropones by application of the ACM methodology.[12c]

Results and discussion

Our synthetic strategy is depicted in Scheme 3. The reaction of imidazoles and benzimidazoles **1a-d** with *ortho*-bromobenzyl bromide (**2**), following the method reported by Heaney *et al.*,[13] afforded *N*-alkylated imidazoles and benzimidazoles **3a-d** (ESI, Table S1†). Formylation of the latter gave products **4a-d** which were subsequently transformed to alkynes **5a-u** by Sonogashira coupling reactions. Cyclization of **5a-u** by ACM reactions finally afforded imidazo[1,2-*a*]azepines **6a-u**.

The formylation of **3a-d** was carried out by application of the Bouveault aldehyde synthesis.[14] Lithiation of carbon atom C-2 of the imidazole with (LDA) and subsequent addition of DMF gave the desired formylated (benz)imidazoles **4a-d** in moderate to good yields (Table 1).

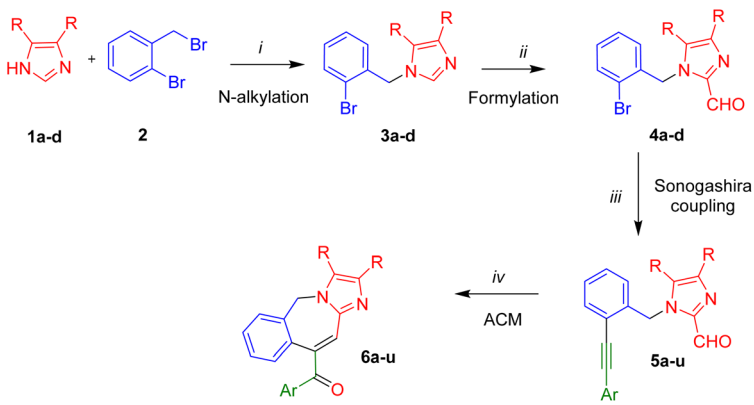
Table 1 Synthesis of **4a-d**



Conditions: ii, (1) LDA (1.1 equiv.), THF; (2) DMF (1.5 equiv.), −78 °C to 20 °C. Yields refer to isolated yields.

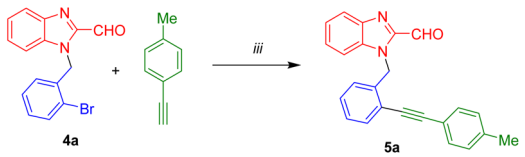
Subsequently, we studied and optimized the Sonogashira reaction of **4a** and *p*-tolylacetylene (Table 2). Application of the catalytic system $Pd(PPh_3)_2Cl_2$/CuI in the presence of triethylamine did not provide the desired product. However, employment of XPhos as the ligand (1,4-dioxane, slightly elevated temperature) allowed to prepare alkyne **5a** in 70% yield.

Subsequently, the preparative scope of the Sonogashira reaction was studied. The reaction of (benz)imidazoles **4a-d** with various alkynes afforded products **5a-u** (Table 3). Imidazole derivatives gave better yields as compared to their benzimidazole analogues. Relatively low yields were obtained for fluorinated benzimidazole **4c**, what can be explained by difficulties during column chromatography. The substitution pattern of the arylacetylene did not influence the yields very much. Both electron donating and withdrawing substituents were tolerated. Similar yields were obtained for substituents located in the *ortho* or *para* position of the phenyl ring. In fact,



Scheme 3 Synthesis of imidazo[1,2-*a*]azepines **6a-u**. Conditions: i, KOH (4 equiv.), DMSO, 20 °C, 5 h; ii, (1) LDA (1.1 equiv.), THF; (2) DMF (1.5 equiv.), −78 °C to 20 °C; iii, alkyne (2.0 equiv.), $Pd(CH_3CN)_2Cl_2$ (6 mol%), CuI (4 mol%), diisopropylamine (3 equiv.), X-Phos (12 mol%), 1,4-dioxane, 35 °C, 12 h; iv, PTSA (15 equiv.), toluene, 100 °C, 3 h.

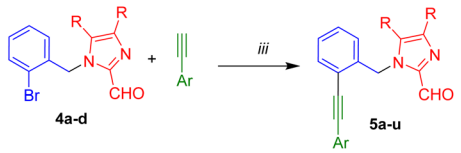
Table 2 Optimizing the reaction conditions for Sonogashira coupling

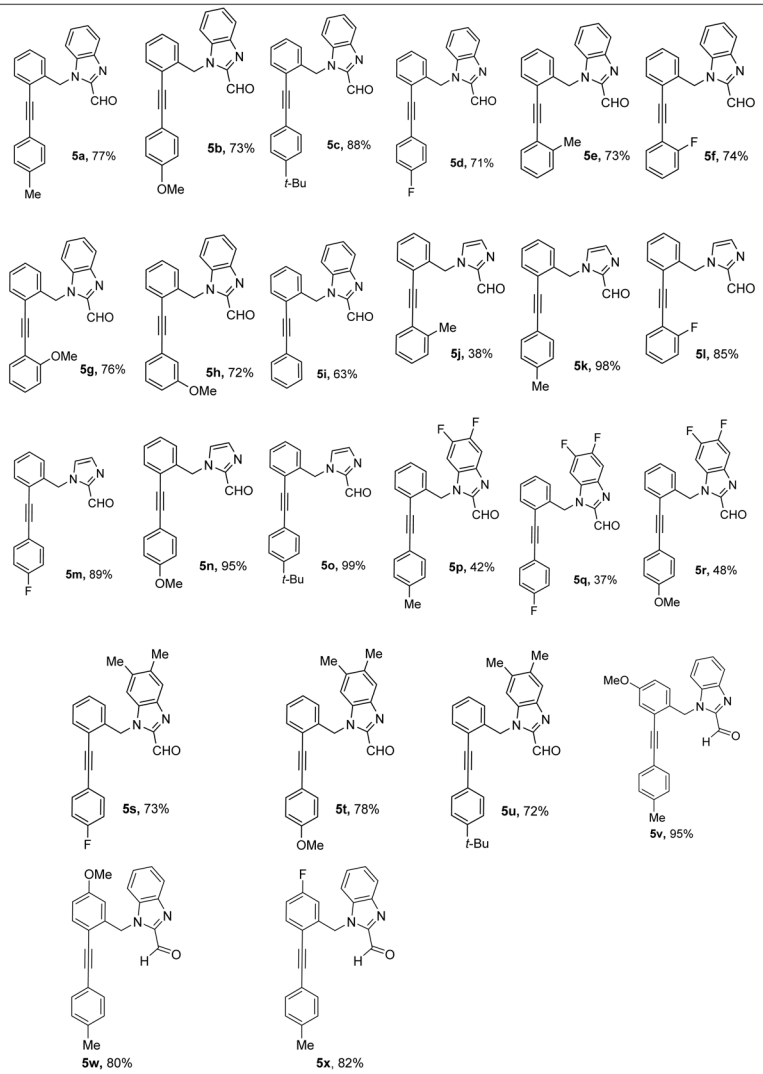


Entry	Catalyst	Base	Ligand	Conditions	Yield (%)
1	$Pd(PPh_3)_2Cl_2$ (6 mol%) CuI (4 mol%)	Et_3N	PPh_3 (12 mol%)	THF, rt.	—
2	$Pd(PPh_3)_2Cl_2$ (10 mol%) CuI (4 mol%)	Et_3N (15 eq.)	PPh_3 (12 mol%)	rt.	—
3	$Pd(CH_3CN)_2Cl_2$ (6 mol%) CuI (4 mol%)	$HN(i\text{-}Pr)_2$ (3 eq.)	X-Phos (12 mol%)	Dioxane, 35 °C	70

Yields refer to isolated yields.

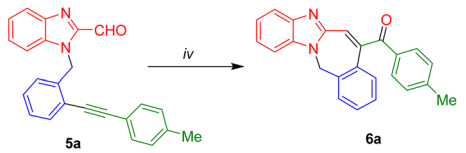
Table 3 Scope of the Sonogashira coupling reaction





Conditions iii: alkyne (2 equiv.), $Pd(CH_3CN)_2Cl_2$ (6 mol%), CuI (4 mol%), diisopropylamine (3.0 equiv.), X-Phos (12 mol%), 1,4-dioxane, 35 °C, 12 h. Yields refer to isolated yields.

Table 4 Optimization of the reaction conditions for the synthesis of **6a**



Entry	Brønsted acid (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	PTSA (15)	Toluene	80	5	61
2	PTSA (20)	Toluene	80	5	90
3	PTSA (15)	HFIP	60	1	71
4	TFA (15)	Toluene	60	5	0
5	TFA (30)	Toluene	60	5	0
6	PTSA (15)	Toluene	100	3	91
7	PTSA (15)	OFP	100	3	87
8	PTSA (10)	Toluene	100	3	48
9	MSA (10)	Toluene	100	3	51

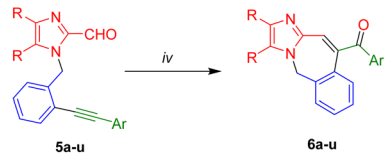
Yields refer to isolated yields.

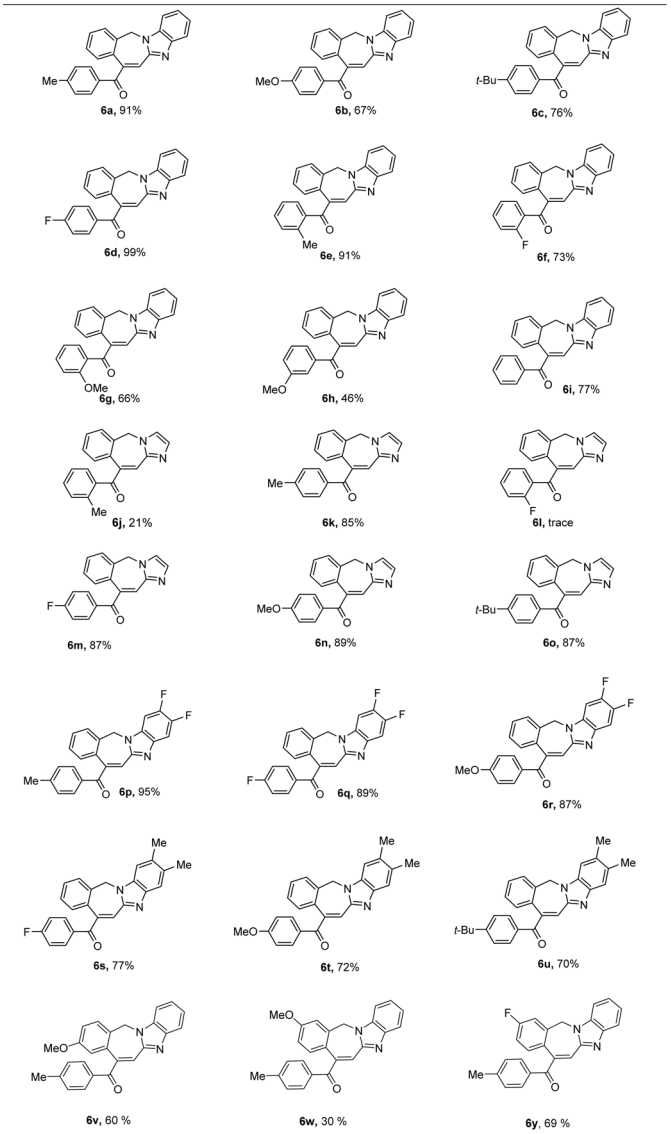
the *ortho* substituent does not exert a steric bias, due to the large distance to the reaction site. An exception was the *ortho*-tolylacetylene group which gave a significantly lower yield than the corresponding *para*-substituted derivative.

Finally, the intramolecular ACM reaction was studied and the conditions were optimized for derivative **5a** (Table 4). As in previous studies of our group,[12] we focused on the use of Brønsted acids, such as *para*-toluenesulfonic acid (PTSA), methanesulfonic acid (MSA) and trifluoroacetic acid (TFA). While TFA gave no conversion of the starting material, both sulfonic acids gave the desired ACM product in moderate yields. Increasing the temperature from 80 to 100 °C of PTSA from 15 to 20 equivalents allowed to increase the yield of product **6a** from 61 to 90% (Table 4, entries 1 and 2). Elevation of the temperature from 80 to 100 °C allowed to use only 15 equiv. of PTSA and to reduce the reaction time from 5 to 3 h (entry 6). Replacement of toluene by hexafluoro-2-propanol (HFIP) or octafluoro-1-pentanol (OFP) resulted in lower yields (entries 3 and 7). Thus, we chose PTSA (15 equiv.) as the Brønsted acid and carried out the reaction at 100 °C for 3 h.

The scope of the ACM reaction was studied next (Table 5). Under the optimized conditions a variety of products **6a-u** were prepared in mostly good to excellent yields Alkyl, methoxy, fluorine substituents on the acetylene moiety are all well tolerated. Benzimidazole based products **6a-i** were obtained in good to excellent yields regardless to the substitution pattern. In case of imidazole derived products, products **6k** and **6m-o** were isolated in very good yields. However, products **6j** and **6l**, derived from *ortho*-substituted starting materials **5j** and **5l**, gave only poor yields. It remains unclear at present, why the *ortho*-position of the substituents were disadvantageous only for imidazoles **6j** and **6l**, but not for the corresponding benzimidazole derivatives **6e** and **6f**. The location of the functional groups on the central benzyl ring has a higher impact on the reaction outcome. Compound **6v** and **6w** were obtained in quite different yields (60% for **6v** *vs.* 30% for **6w**), only differing by the position of the

Table 5 Synthesis of (benz)imidazo[1,2-*b*]azepines **6a-u**





Conditions: iv: PTSA (15 equiv.), toluene, 100 °C, 3 h. Yields refer to isolated yields.

methoxy group on the central benzene ring. However, exchange of the donating methoxy group by fluorine led to an isolated yield of 69% for **6x**.

Single crystals suitable for X-ray crystal structure analysis were obtained for compounds **6i,j,p,r** by slow evaporation of ethanol solutions. A boat conformation was observed for the seven-membered rings with different dihedral angles for all molecules (ESI, Fig. S2†). Both **6i** and **6j** crystalize in the monoclinic space group $P2_1/n$ (-*P2yn*) containing four molecules in

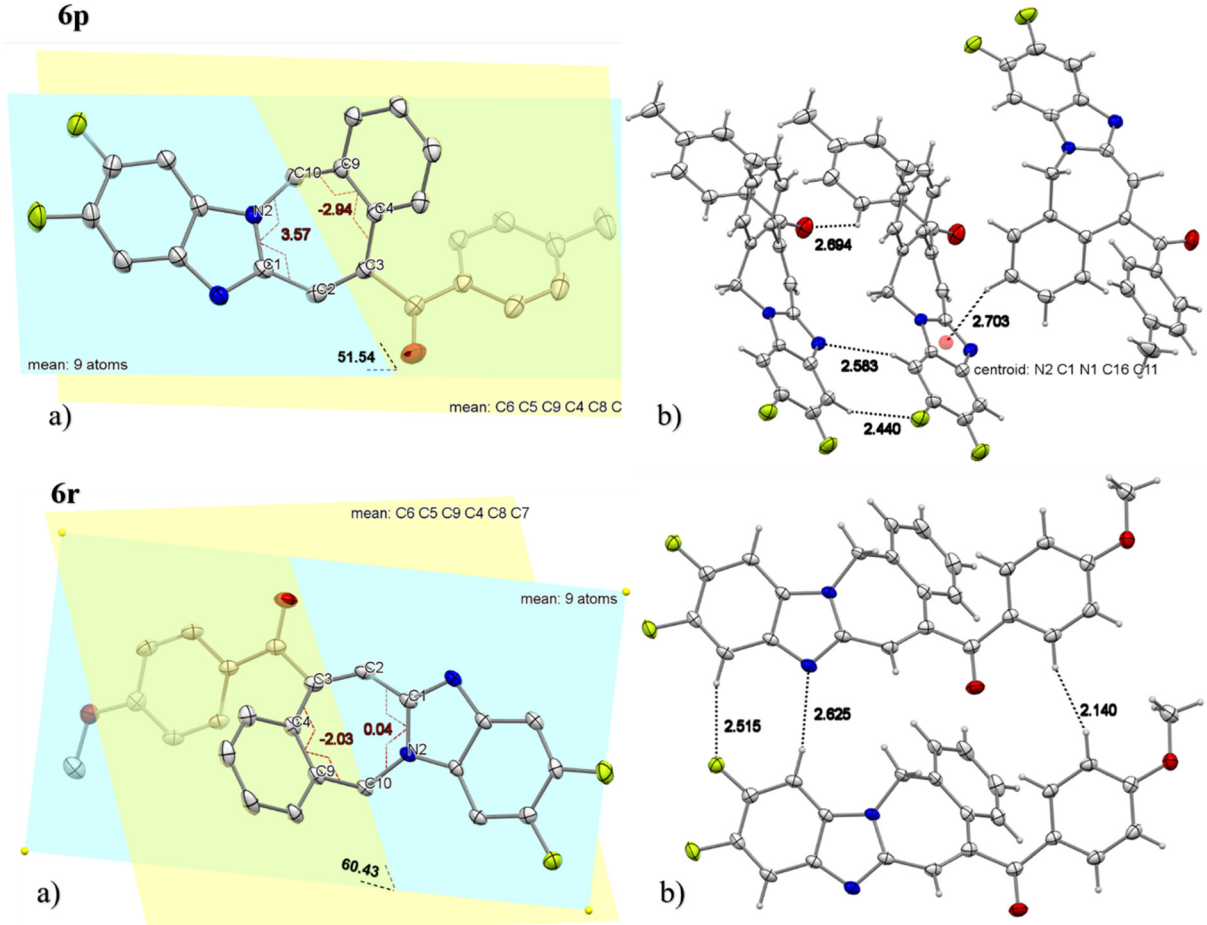


Fig. 1 Crystal structures of **6p** and **6r**: (a) structures with crystallographic labeling numbers and dihedral angles between the planes of the imidazole ring (blue plane) and the benzene ring (yellow plane). All hydrogens are omitted for clarity; (b) crystal lattice with intermolecular interactions.

the unit cell (ESI, Table S3†). Unlike **6i** and **6j**, derivative **6p** crystalizes in a different space group C_2 (C_{2y}) and in different form. A slipped herringbone packing along the *b*-axis was observed for **6p**. Besides intermolecular hydrogen bonds C–H···F, C–H···N and C–H···O, two molecules along the *c*-axis possess a close C–H/π interaction between imidazole moiety and the fused benzene ring (2.733 Å) (Fig. 1). The torsion angles between the benzoimidazole and benzene rings are 3.5° for C(2)–C(1)–N(2)–C(10) and −2.9° for C(3)–C(4)–C(9)–C(10), respectively (Fig. 1). Compound **6r** crystalizes in the triclinic space group $P\bar{1}$ ($-P_1$) with two molecules in the unit cell. This packing results in formation of C–H···N and C–H···F hydrogen bonds along the *b*-axis. The biggest dihedral angle is 60.4° and the smallest torsion angles are 3.5° for C(2)–C(1)–N(2)–C(10) and −2.9° for C(3)–C(4)–C(9)–C(10). It is noteworthy that no π–π interactions are observed for **6p** and **6r** which contain two additional fluorine substituents.

Conclusion

In summary, a variety of (benz)imidazo[1,2-*b*]azepines were prepared by Brønsted acid mediated ACM cyclization. The products were mostly obtained in good yields with a broad range of substitution pattern. The starting materials are readily available by a combination of *N*-alkylation, formylation and Sonogashira cross-coupling reactions.

Experimental section

Experimental information

The nuclear magnetic resonance spectra (1H/13C/^{19}F NMR) were recorded on a Bruker AVANCE 300 III, 250 II or 500. The analyzed chemical shifts δ are referenced to residual solvents signals of the deuterated solvents $CDCl_3$ (δ = 7.26 ppm/77.0 ppm). Multiplicities due to spin–spin correlation are reported as follows: s = singlet, d = doublet, dd = double doublet, t = triplet, pt = pseudo triplet, m = multiple and further described through their coupling constants *J*. Infrared spectra (IR) were measured as attenuated total reflection (ATR) experiments with a Nicolet 380 FT-IR spectrometer. The signals have been characterized through their wave numbers $\tilde{\nu}$ and their corresponding absorption as very strong (vs), strong (s), medium (m), weak (w) or very weak (vw). Basic and high-resolution mass spectra (MS/HRMS) were measured on instru-

ments which are paired with a preceding gas chromatograph (GC) or liquid chromatograph (LC). The samples have been ionized through electron impact ionization (EI) on an Agilent 6890/5973 or Agilent 7890/5977 GC-MS equipped with a HP-5 capillary column using helium carrier gas or by applying electron spray ionization (ESI) on an Agilent 1200/6210 Time-of-Flight (TOF) LC-MS. Melting points (mp) were determined by a Micro-Hot-Stage GalenTM III Cambridge Instruments and are not corrected.

Materials

The applied solvents toluene, hexane, acetonitrile, 1,4-dioxane, xylene and dichloromethane were purchased as dry solvents and employed without further purification. Solvents for extraction and column chromatography were distilled prior employment. Other reagents, catalysts, ligands, acids and bases have been utilized as received from commercial suppliers. Column chromatography was performed using Merck Silica gel 60 (particle size 63–200 μm).

Representative method for the preparation of starting materials

Representative procedure A for the synthesis of 3a-d. Imidazole (15.6 mmol; 1.06 g) was dissolved in dry DMF (20 mL) and after 5 min. NaH (2.0 equiv.; 32.1 mmol; 1.28 g) was added in portions to the clear solution (4.0 equiv. crushed KOH was used for benzimidazole). The suspensions were stirred until hydrogen formation stopped. Subsequently, 2-bromobenzyl bromide (1.0 equiv. 15.9 mmol; 3.96 g) was added slowly. After the reaction was finished (monitored by TLC). The reaction was neutralized with an HCl solution (1 M) and diluted with water (40 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (heptane/ethyl acetate).

Representative procedure B for the synthesis of 4a-d. *n*-Butyllithium 1.1 equiv. (16 mmol, 1.4 mL of a 2.5 mol dm^{-3} solution in hexanes) was added to a solution of diisopropylamine (1.2 equiv.; 18 mmol; 2.5 mL) at −78 °C. After 20 minutes at −78 °C, a solution of **3** (14.5 mmol; 4.15 g) in 10 mL THF was added dropwise to the reaction mixture. The reaction was stirred for 1 h at −78 °C. Subsequently, DMF (1.5 equiv.; 22 mmol; 1.7 mL) was added to the reaction mixture and the reaction mixture was allowed to warm to ambient temperature and stirred for further 4 h. The reaction was quenched with a saturated NH_4Cl solution (30 mL) and diluted with water (30 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (heptane/ethyl acetate).

Representative procedure C for the synthesis of 5a-u. In a pressure tube under an atmosphere of argon, $Pd(CH_3CN)_2Cl_2$ (6 mol%; 0.05 mmol; 13.8 mg), CuI (4 mol%, 0.04 mmol; 6.83 mg), X-Phos (12 mol%; 0.103 mmol; 49.1 mg) and **4** (0.86 mmol; 300 mg) were dissolved in diisopropylamine (3.0 equiv.; 2.6 mmol; 0.37 mL) and 1,4-dioxane (3 mL). The suspension was stirred for 5 min and warmed to 35 °C. Thereafter the alkyne (2.0 eq.; 1.8 mmol) was added slowly to the reaction mixture. The reaction was stirred for 12–15 hours at 35 °C. After addition of water, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum and finally purified by column chromatography (heptane/ethyl acetate).

Representative procedure D for the synthesis of 6a-u. A mixture of **5** (0.271 mmol; 105 mg), PTSA (15 equiv.; 3.70 mmol; 705 mg) was suspended in dry toluene (5 mL) and stirred at 100 °C for 3 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (10 mL) and diluted with water (20 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (heptane/ethyl acetate).

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(*p*-tolyl) methanone (6a). According to procedure D, compound **6a** was obtained as a white solid in 91% yield (91 mg, 0.26 mmol, R_f = 0.20 heptane/ethyl acetate, 1 : 1); mp: 236–238 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1659 (m), 1601 (m), 1459 (m), 1442 (m), 1418 (m), 742 (vs), 1177 (m), 898 (m), 764 (s), 1238 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 5.17 (s, 2H), 7.14–7.17 (m, 1H), 7.19–7.28 (m, 4H), 7.29–7.36 (m, 3H), 7.41–7.45 (m, 1H), 7.47–7.52 (m, 1H), 7.70–7.74 (m, 1H), 7.84–7.89 (m, 2H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 197.1, 144.9, 144.4, 144.0, 135.6, 135.2, 134.1, 130.5, 130.0, 129.8, 129.6, 128.8, 128.7, 124.3, 123.8, 122.9, 120.2, 109.1, 47.6, 21.8 (signal of two carbons are absent, which relates to signal overlap). MS (EI, 70 eV): *m*/*z* (%) = 350 (M^+, 100), 335 (4), 322 (21), 321 (71), 307 (4), 231 (24), 230 (6), 229 (14), 204 (9), 203 (5), 175 (8). HRMS (EI): calcd for $C_{24}H_{19}N_2O$ $[M]^+$ 350.1413 found: 350.1415.

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-methoxyphenyl)methanone (6b). According to procedure D, compound **6b** was obtained as a yellow solid in 67% yield (67 mg, 0.18 mmol, R_f = 0.22 heptane/ethyl acetate, 1 : 1); mp: 234–236 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1653 (m), 1597 (s), 1574 (m), 1455 (m), 1440 (m), 1414 (m), 742 (vs), 1164 (s), 837 (s), 1022 (vs), 775 (s), 1243 (vs). ^{1}H NMR (250 MHz, $CDCl_3$):δ = 8.01–7.95 (m, 2H), 7.73 (dd, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.51 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.47–7.42 (m, 1H), 7.39–7.27 (m, 3H), 7.30–7.11 (m, 3H), 6.96–6.89 (m, 2H), 5.19 (s, 2H), 3.84 (s, 3H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 195.1, 163.2, 148.0, 143.4, 134.7, 134.2, 133.3, 131.8, 128.9, 128.8, 128.4, 127.8, 127.7, 122.7, 121.9, 119.2, 113.1, 108.0, 54.6, 46.6 (signal of two carbons are absent, which may relates to signal overlap). MS (EI, 70 eV): *m*/*z* (%) = 366 (M^+, 84), 338 (35), 337 (92), 231 (27), 230 (26), 229 (74), 204 (43), 203 (19), 136 (18), 135 (82). HRMS (ESI-TOF): calcd for $C_{24}H_{19}N_2O_2$ $[M + H]^+$ 367.1447, found: 367.1439.

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-(*tert*-butyl)phenyl)methanone (6c). According to procedure D, compound **6c** was obtained as a yellow solid in 76% yield (76 mg, 0.19 mmol, R_f = 0.21 heptane/ethyl acetate, 1 : 1); mp = 274–276 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1702 (m), 1661 (m), 1601 (m), 1457 (m), 1442 (m), 1257 (s), 1107 (m), 847 (m), 771 (m), 740 (vs). ^{1}H NMR (250 MHz, $CDCl_3$):δ = 7.94–7.88 (m, 2H), 7.71 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.52–7.40 (m, 4H), 7.37–7.23 (m, 4H), 7.20 (dd, J = 3.2 Hz, J = 1.7 Hz, 1H), 7.18–7.16 (m, 1H), 5.16 (s, 2H), 1.29 (s, 9H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$) δ = 197.3, 157.7, 149.0, 144.4, 144.1, 135.6, 135.3, 134.4, 134.1, 130.3, 129.9, 128.7, 125.9, 124.9, 123.7, 122.8, 120.3, 109.0, 47.5, 35.3, 31.1 (signal of two carbons are absent, which relates to signal overlap). MS (EI, 70 eV): m/z (%) = 392 (M$^+$, 100), 364 (27), 363 (90), 231 (32), 229 (27), 204 (19), 161 (37), 118 (26), 117 (19). HRMS (ESI-TOF): calcd for $C_{27}H_{25}N_2O$ [M + H]$^+$ 393.1967, found: 393.1965

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-fluorophenyl)methanone (6d). According to procedure D, compound **6d** was obtained as a yellow solid in 99% yield (99 mg, 0.28 mmol, R_f = 0.19, heptane/ethyl acetate, 1 : 1). mp: 250–252 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1665 (s), 1593 (s), 1459 (s), 1418 (vs), 1236 (s), 1222 (s), 1150 (m), 847 (m), 771 (s), 740 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.00–7.95 (m, 2H), 7.71 (d, J = 8.1 Hz, 1H), 7.50–7.41 (m, 2H), 7.36–7.27 (m, 3H), 7.26–7.19 (m, 2H), 7.14–7.08 (m, 3H), 5.15 (s, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ = −103.5. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ = 195.9, 166.1 (d, J = 256.5 Hz), 148.7, 144.4, 143.6, 135.4, 135.3, 134.4, 133.1, 133.0 (d, J = 9.6 Hz)., 130.1, 129.8, 128.9, 128.8, 125.0, 123.9, 122.9, 120.4, 116.1 (d, J = 22.0 Hz), 109.1, 47.5. MS (EI, 70 eV): m/z (%) = 354 (M$^+$, 100), 353 (14), 326 (11), 325 (32), 231 (33), 230 (11), 229 (28), 204 (16), 123 (50), 95 (52). HRMS (ESI-TOF): calcd for $C_{23}H_{16}FN_2O$ [M + H]$^+$ 355.1247, found: 355.1244

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(*o*-tolyl) methanone (6e). According to procedure D, compound **6e** was obtained as a yellow solid in 91% yield (123 mg, 0.351 mmol, R_f = 0.30 heptane/ethyl acetate, 1 : 1); mp = 165–167 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1669 (m), 1601 (m), 1485 (w), 1454 (m), 1415 (m), 1240 (m), 1034 (m), 797 (w), 735 (vs), 721 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.52 (m, 1H), 7.42–7.03 (m, 12H), 4.98 (s, 2H), 2.34 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 200.0, 148.8, 144.8, 144.4, 138.3, 137.8, 135.7, 134.7, 134.5, 131.7, 131.6, 130.7, 130.1, 130.0, 128.8, 128.7, 128.7, 126.1, 124.1, 123.1, 120.5, 109.3, 47.7, 20.6. MS (EI, 70 eV): m/z (%) = 350 (M$^+$, 100), 349 (62), 333 (23), 322 (17), 321 (62), 231 (21), 230 (10), 229 (29), 204 (23), 119 (44). HRMS (ESI-TOF) m/z = calcd for $C_{24}H_{19}N_2O$ [M + H]$^+$ 351.1497, found: 351.1499.

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(2-fluorophenyl)-methanone (6f). According to procedure D, compound **6f** was obtained as a beige solid in 73% yield (77 mg, 0.217 mmol, R_f = 0.21 heptane/ethyl acetate, 1 : 1); mp = 160–163 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1650 (m), 1605 (m), 1446 (m), 1351 (m), 1275 (m), 1207 (m), 1100 (m), 1059 (m), 888 (m), 762 (s), 737 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.79 (m, 2H), 7.62–7.49 (m, 4H), 7.46–7.29 (m, 6H), 7.10 (ddd, J = 10.5, J = 8.3, J = 1.0 Hz, 1H), 5.25 (s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −109.9 (s). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 194.2, 160.9 (d, J = 254.5 Hz), 148.7, 145.4, 144.2, 135.7, 134.7 (d, J = 8.8 Hz), 134.5, 134.2, 131.3 (d, J = 2.0 Hz), 130.0, 129.9, 128.7, 128.5, 126.7, 126.6 (d, J = 3.0 Hz), 124.9 (d, J = 3.6 Hz), 124.1, 123.1, 120.4, 116.7 (d, J = 22.0 Hz), 109.3, 47.6. MS (EI, 70 eV): m/z (%) = 354 (M$^+$, 100), 325 (14), 232 (8), 231 (44), 230 (6), 229 (11), 204 (7), 177 (7), 123 (27). HRMS (EI) m/z = calcd for $C_{23}H_{15}FN_2O$ [M]$^+$ 354.11554, found: 354.11629.

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(2-methoxyphenyl)-methanone (6g). According to procedure D, compound **6g** was obtained as a white solid in 66% yield (67 mg, 0.183 mmol, R_f = 0.13 heptane/ethyl acetate, 1 : 1); mp = 190–193 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1648 (m), 1590 (m), 1454 (m), 1413 (m), 1289 (m), 1246 (m), 1009 (m), 851 (m), 741 (s). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, J = 8.1 Hz, 1H), 7.43 (dd, J = 7.5, J = 1.7 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.28–7.19 (m, 4H), 7.17–7.01 (m, 4H), 6.85 (m, 1H), 6.71 (d, J = 8.4 Hz, 1H), 4.94 (s, 2H), 3.48 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ = 198.0, 158.1, 149.2, 145.9, 144.5, 135.7, 134.8, 134.5, 133.5, 130.6, 130.3, 129.6, 128.4, 128.3, 126.2, 123.8, 122.9, 121.1, 120.3, 111.9, 109.2, 55.7, 47.6 (signal of one carbon is absent, which relates to signal overlap). MS (EI, 70 eV): m/z (%) = 366 (M$^+$, 51), 337 (24), 321 (19), 246 (42), 245 (32), 231 (22), 230 (17), 229 (43), 204 (28), 135 (100). HRMS (ESI-TOF) m/z = calcd for $C_{24}H_{19}N_2O_2$ [M + H]$^+$ 367.1447, found: 367.1449.

(12*H*-Benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(3-methoxyphenyl)-methanone (6h). According to procedure D, compound **6k** was obtained as a beige solid in 46% yield (73 mg, 0.199 mmol, R_f = 0.19 heptane/ethyl acetate, 1 : 1); mp = 200–206 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1658 (m), 1590 (m), 1456 (s), 1419 (s), 1259 (s), 1217 (m), 1034 (m), 797 (m), 764 (s), 739 (vs), 710 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.67 (m, 1H), 7.49 (m, 3H), 7.43 (dd, J = 7.5, J = 1.5 Hz, 1H), 7.39–7.28 (m, 3H), 7.33–7.21 (m, 2H), 7.25–7.13 (m, 2H), 7.10 (ddd, J = 8.2, J = 2.6, J = 1.1 Hz, 1H), 5.16 (s, 2H), 3.80 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 197.4, 160.1, 148.9, 144.3, 144.2, 138.2, 135.6, 135.3, 134.5, 130.1, 130.0, 128.9, 125.1, 123.9, 123.4, 123.0, 120.5, 120.4, 114.1, 109.2, 55.6, 47.7 (signal of two carbons are absent, which relates to signal overlap). MS (EI, 70 eV): m/z (%) = 366 (M$^+$, 40), 338 (28), 337 (100), 307 (14), 294 (7), 229 (21), 204 (13), 135 (15), 107 (17), 92 (16). HRMS (ESI-TOF) m/z = calcd for $C_{24}H_{19}N_2O_2$ [M + H]$^+$ 367.1447, found: 367.1440.

(12-Dihydro-5*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl) (phenyl)-methanone (6i). According to procedure D, compound **6i** was obtained as a white solid in 77% yield (77 mg, 0.229 mmol, R_f = 0.15 heptane/ethyl acetate, 1 : 1); mp = 189–192 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1648 (m), 1590 (m), 1413 (m), 1345 (w), 1289 (m), 1248 (m), 1224 (m), 1158 (w), 1009 (m), 853 (m), 756 (s), 741 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.84 (m, 2H), 7.67–7.61 (m, 1H), 7.51–7.43 (m, 1H), 7.43–7.31 (m, 4H), 7.29–7.20 (m, 3H), 7.16 (m, 2H), 7.12–7.06 (m, 1H), 5.08 (s, 2H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 197.6, 148.9, 144.4, 144.0, 136.9, 135.6, 135.4, 134.5, 133.8, 130.4, 130.1, 130.0, 129.0, 128.9, 128.8, 125.3, 123.9, 123.0, 120.4, 109.2, 47.6. MS

(EI, 70 eV): *m*/*z* (%) = 336 (M^+, 100), 335 (17), 308 (15), 307 (53), 306 (9), 305 (5), 232 (6), 231 (32), 230 (8), 229 (14). HRMS (ESI-TOF) *m*/*z* = calcd for $C_{23}H_{17}N_2O$ $[M + H]^+$ 337.1341, found: 337.1339.

(5*H*-Benzo[*e*]imidazo[1,2-*a*]azepin-10-yl)(*o*-tolyl)methanone (6j). According to procedure D, compound **6j** was obtained as a brown solid in 21% yield (44 mg, 0.147 mmol, R_f = 0.17 (ethyl acetate); mp = 112–115 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1652 (s), 1599 (m), 1570 (w), 1425 (m), 1285 (m), 1232 (s), 1131 (m), 1036 (m), 886 (m), 739 (vs), 731 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.47 (m, 2H), 7.44–7.35 (m, 5H), 7.31–7.22 (m, 3H), 7.09 (s, 1H), 5.00 (s, 2H), 2.50 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 200.1, 141.0, 138.3, 137.6, 135.2, 134.5, 131.5, 131.1, 130.5, 129.6, 129.6, 129.3, 128.6, 128.5, 125.9, 121.7, 51.1, 20.3 (signal of two carbons are absent, which relates to signal overlap). MS (EI, 70 eV): *m*/*z* (%) = 300 (M^+, 100), 299 (93), 283 (28), 272 (12), 271 (54), 231 (12), 181 (13), 127 (19), 119 (44). HRMS (EI) *m*/*z* = calcd for $C_{20}H_{16}N_2O$ $[M]^+$ 300.12571, found: 300.12502.

(5*H*-Benzo[*e*]imidazo[1,2-*a*]azepin-10-yl)(*p*-tolyl)methanone (6k). According to procedure D, compound **6k** was obtained as a white solid in 85% yield (85 mg, 0.283 mmol, R_f = 0.11 (ethyl acetate); mp = 172–174 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1650 (s), 1599 (s), 1467 (m), 1242 (s), 1186 (m), 1176 (m), 908 (m), 834 (m), 760 (s), 745 (vs), 725 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.0 Hz, 2H), 7.41–7.36 (m, 2H), 7.32–7.27 (m, 4H), 7.25–7.19 (m, 2H), 7.08 (s, 1H), 5.06 (s, 2H), 2.44 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ = 197.6, 144.6, 143.8, 140.7, 135.8, 134.9, 134.6, 131.0, 130.5, 129.9, 129.6, 129.6, 128.8, 128.7, 125.2, 121.2, 51.2, 21.9. MS (EI, 70 eV): *m*/*z* (%) = 300 (M^+, 100), 299 (15), 272 (16), 271 (66), 209 (6), 181 (9), 119 (51), 91 (24). HRMS (ESI-TOF) *m*/*z* = calcd for $C_{20}H_{17}N_2O$ $[M + H]^+$ 301.1341, found: 301.1334.

(5*H*-Benzo[*e*]imidazo[1,2-*a*]azepin-10-yl)(4-fluorophenyl) methanone (6m). According to procedure D, compound **6m** was obtained as a white solid in 87% yield (91 mg, 0.299 mmol, R_f = 0.11 (ethyl acetate); mp = 186–189 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1660 (s), 1605 (s), 1592 (s), 1504 (m), 1465 (m), 1329 (m), 1238 (s), 1226 (s), 1147 (s), 904 (m), 844 (s), 770 (vs), 748 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.96 (m, 2H), 7.41–7.37 (m, 2H), 7.34–7.28 (m, 2H), 7.24 (d, *J* = 1.2 Hz, 1H), 7.20–7.12 (m, 3H), 7.08 (d, *J* = 1.1 Hz, 1H), 5.06 (s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −104.2 (s). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 196.2, 165.9 (d, *J* = 255.8 Hz), 143.5, 139.9, 135.4, 134.8, 133.5, 133.4, 132.8 (d, *J* = 9.4 Hz), 131.1, 129.7, 129.6, 128.7, 125.6, 121.3, 116.0 (d, *J* = 22.0 Hz), 51.0. MS (EI, 70 eV): *m*/*z* (%) = 304 (M^+, 100), 303 (26), 276 (12), 275 (41), 274 (10), 209 (10), 181 (26), 154 (14), 127 (38). HRMS (ESI-TOF) *m*/*z* = calcd for $C_{19}H_{14}FN_2O$ $[M + H]^+$ 305.1090, found: 305.1088.

(5*H*-Benzo[*e*]imidazo[1,2-*a*]azepin-10-yl)(4-methoxyphenyl) methanone (6n). According to procedure D, compound **6n** was obtained as a beige solid in 89% yield (151 mg, 0.477 mmol, R_f = 0.06 (ethyl acetate); mp = 150–152 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1646 (m), 1592 (s), 1572 (m), 1506 (m), 1465 (m), 1248 (vs), 1164 (s), 1022 (m), 844 (m), 768 (s), 733 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.96 (m, 2H), 7.40–7.36 (m, 2H), 7.34–7.18 (m, 4H), 7.08 (d, *J* = 1.1 Hz, 1H), 7.00–6.94 (m, 2H), 5.06 (s, 2H), 3.89 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 196.5, 164.1, 143.9, 140.8, 136.0, 134.9, 132.8, 130.9, 129.9, 129.7, 129.6, 128.8, 128.7, 124.4, 121.1, 114.1, 55.7, 51.1. MS (EI, 70 eV): *m*/*z* (%) = 316 (M^+, 100), 315 (18), 288 (21), 287 (53), 179 (9), 154 (11), 136 (11), 135 (87), 128 (11). HRMS (ESI-TOF) *m*/*z* = calcd for $C_{20}H_{17}N_2O_2$ $[M + H]^+$ 317.1290, found: 317.1288.

(5*H*-Benzo[*e*]imidazo[1,2-*a*]azepin-10-yl)(4-(*tert*-butyl)phenyl) methanone (6o). According to procedure D, compound **6o** was obtained as a white solid in 87% yield (110 mg, 0.321 mmol, R_f = 0.13 (ethyl acetate); mp = 243–245 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1652 (s), 1601 (s), 1469 (m), 1333 (m), 1259 (vs), 1186 (m), 1108 (m), 910 (m), 851 (m), 764 (vs), 737 (vs), 700 (vs). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.89 (m, 2H), 7.52–7.47 (m, 2H), 7.39–7.35 (m, 2H), 7.34–7.27 (m, 2H), 7.26–7.21 (m, 2H), 7.07 (d, *J* = 1.1 Hz, 1H), 5.05 (s, 2H), 1.35 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 197.7, 157.4, 143.8, 140.6, 135.8, 134.9, 134.6, 131.0, 130.3, 129.9, 129.6, 128.8, 128.7, 125.9, 125.4, 121.2, 51.1, 35.3, 31.2. MS (EI, 70 eV): *m*/*z* (%) = 342 (M^+, 76), 342 (76), 327 (13), 314 (26), 313 (100), 299 (14), 285 (11), 181 (20), 161 (37), 154 (12). HRMS (ESI-TOF) *m*/*z* = calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1810, found: 343.1806.

(2,3-Difluoro-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(*p*-tolyl)-methanone (6p). According to procedure D, compound **6p** was obtained as a beige solid in 95% yield (99 mg, 0.256 mmol, R_f = 0.14 heptane/ethyl acetate, 3 : 2); mp = 257–260 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1667 (m), 1607 (m), 1454 (s), 1333 (s), 1244 (s), 1145 (s), 1108 (s), 1013 (m), 861 (vs), 758 (vs), 708 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.89 (m, 2H), 7.59–7.47 (m, 2H), 7.43 (m, 1H), 7.39–7.28 (m, 5H), 7.23 (dd, *J* = 7.7, *J* = 1.4 Hz, 1H), 5.18 (s, 2H), 2.45 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −139.40 (d, *J* = 20.4 Hz), −142.00 (d, *J* = 20.6 Hz). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ = 196.9, 150.5 (d, *J* = 3.2 Hz), 149.0 (dd, *J* = 245.5 Hz, *J* = 16.0 Hz), 148.2 (dd, *J* = 242.7, *J* = 15.1 Hz), 145.0, 144.5, 139.6, 139.5, 135.5, 134.7, 134.0, 130.5, 130.2, 129.9 (d, *J* = 17.8 Hz), 129.6, 129.0, 128.7, 123.8, 107.4 (d, *J* = 19.7 Hz), 97.1 (d, *J* = 23.1 Hz), 48.0, 21.8. MS (EI, 70 eV): *m*/*z* (%) = 386 (M^+, 100), 385 (13), 358 (20), 357 (60), 267 (9), 240 (6), 193 (6), 119 (53), 91 (25). HRMS (ESI-TOF) *m*/*z* = calcd for $C_{24}H_{17}F_2N_2O$ $[M + H]^+$ 387.1309, found: 387.1312.

(2,3-Difluoro-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-fluoro-phenyl)-methan-one (6q). According to procedure D, compound **6q** was obtained as a beige solid in 89% yield (85 mg, 0.218 mmol, R_f = 0.12 heptane/ethyl acetate, 3 : 2); mp = 276–279 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1669 (s), 1592 (s), 1483 (m), 1463 (s), 1341 (s), 1224 (vs), 1147 (s), 1108 (m), 1040 (m), 871 (vs), 764 (vs), 708 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10–8.02 (m, 2H), 7.59–7.49 (m, 2H), 7.46 (m, 1H), 7.40–7.32 (m, 3H), 7.24–7.15 (m, 3H), 5.19 (s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −103 (s), −138.9 (d, *J* = 20.6 Hz), −141.5 (d, *J* = 20.2 Hz). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ = 195.8, 166.3 (d, *J* = 256.8 Hz), 150.4, 149.2 (dd, *J* = 246.0, *J* = 15.9 Hz), 148.4 (dd, *J* = 242.9, *J* = 15.1 Hz), 144.1, 139.7 (d, *J* = 10.5 Hz), 135.3, 134.9, 133.2, 133.1, 133.0 (d, *J* = 3.0 Hz), 130.5, 130.0, 129.9, 129.1 (d, *J* =

26.3), 124.3, 116.3 (d, J = 22.1 Hz), 107.6 (d, J = 19.8 Hz), 97.2 (d, J = 23.1 Hz), 48.2. MS (EI, 70 eV): m/z (%) = 390 (M^+, 100), 389 (16), 362 (8), 361 (32), 267 (21), 265 (6), 240 (6), 123 (47), 95 (22). HRMS (ESI-TOF) m/z = calcd for $C_{23}H_{14}F_3N_2O$ $[M + H]^+$ 391.1058, found: 391.1049.

(2,3-Difluoro-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-methoxyphenyl)-methanone (6r). According to procedure D, compound **6r** was obtained as a white solid in 87% yield (105 mg, 0.261 mmol, R_f = 0.22 heptane/ethyl acetate, 1 : 1); mp = 243–245 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1646 (m), 1596 (s), 1572 (m), 1460 (s), 1446 (s), 1250 (vs), 1162 (s), 1143 (s), 1026 (s), 863 (s), 764 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06–8.00 (m, 2H), 7.59–7.47 (m, 2H), 7.43 (m, 1H), 7.39–7.28 (m, 3H), 7.23 (dd, J = 7.8, J = 1.4 Hz, 1H), 7.02–6.96 (m, 2H), 5.18 (s, 2H), 3.90 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −139.40 (d, J = 20.5 Hz), −141.92 (d, J = 20.6 Hz). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ = 195.8, 164.3, 150.5 (d, J = 3.2 Hz), 148.9 (dd, J = 245.6 Hz, J = 16.0 Hz), 148.2 (dd, J = 242.6 Hz, J = 15.1 Hz), 144.6, 139.5 (d, J = 11.0 Hz), 135.6, 134.7, 132.8, 130.1, 129.9, 129.8, 129.3, 129.0, 128.7, 123.1, 114.2, 107.4 (d, J = 19.6 Hz), 97.1 (d, J = 23.3 Hz), 55.7, 48.0. MS (EI, 70 eV): m/z (%) = 402 (M^+, 100), 401 (10), 374 (14), 373 (36), 136 (7), 135 (90), 107 (7), 92 (9), 77 (14). HRMS (ESI-TOF) m/z = calcd for $C_{24}H_{17}F_2N_2O_2$ $[M + H]^+$ 403.1248, found: 403.1248.

(2,3-Dimethyl-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-fluorophenyl)methanone (6s). According to procedure D, compound **6s** was obtained as a white solid in 77% yield (77 mg, 0.20 mmol, R_f = 0.22 heptane/ethyl acetate, 1 : 1); mp = 251–253 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1677 (vs), 1599 (vs), 1508 (vs), 1409 (s), 1249 (s), 1241 (vs), 1173 (vs), 1024 (s), 835 (s), 775 (m), 750 (vs). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04–7.97 (m, 2H), 7.49 (s, 1H), 7.47–7.43 (m, 1H), 7.39–7.33 (m, 2H), 7.29–7.23 (m, 2H), 7.17–7.09 (m, 3H), 5.14 (s, 2H), 2.38 (s, 3H), 2.31 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ = −103.5. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 196.0, 166.1 (d, J = 256.5 Hz), 147.8, 142.9, 142.8, 135.5, 135.3, 133.6, 133.2, 133.1, 133.0, 132.9, 132.2, 129.9, 129.8, 128.7 (d, J = 9.0 Hz), 125.3, 120.1, 116.1 (d, J = 22.0 Hz), 109.2, 47.6, 20.8, 20.3. MS (EI, 70 eV): m/z (%) = 382 (M^+, 100), 381 (10), 354 (7), 353 (12), 260 (6), 259 (34), 258 (7), 244 (8), 243 (9), 229 (4). HRMS (EI): calcd for $C_{25}H_{19}FN_2O$ $[M]^+$ 382.1475, found: 382.1472.

(2,3-Dimethyl-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(4-methoxyphenyl)methanone (6t). According to procedure D, compound **6t** was obtained as a white solid in 72% yield (72 mg, 0.18 mmol, R_f = 0.22 heptane/ethyl acetate, 1 : 1); mp: 232–234 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1642 (vs), 1599 (s), 1574 (vs), 1461 (s), 1422 (vs), 1253 (m), 1164 (m), 1022 (m), 841 (s), 781 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00–7.94 (m, 2H), 7.47 (s, 1H), 7.45–7.41 (m, 1H), 7.35–7.30 (m, 1H), 7.28 (s, 1H), 7.26–7.24 (m, 1H), 7.22 (dd, J = 7.3 Hz, J = 1.4 Hz, 1H), 7.17–7.13 (m, 1H), 6.94–6.89 (m, 2H), 5.13 (s, 2H), 3.83 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 196.2, 164.2, 148.1, 143.7, 135.9, 135.3, 133.4, 132.8, 132.2, 129.8, 129.5, 128.8, 128.7, 123.9, 119.9, 114.1, 109.2, 55.6, 47.6, 20.8, 20.3 (three carbon signals were not observed, which relates to signal overlap). MS (EI, 70 eV): m/z (%) = 394 (M^+, 100), 393 (4), 366 (6), 365 (16), 351 (3), 260 (4), 259 (18), 244 (6), 243 (9), 229 (3), 197 (6). HRMS (EI): calcd for $C_{26}H_{22}N_2O_2$ $[M]^+$ 394.1674, found: 394.1667.

(4-(*tert*-Butyl)phenyl)(2,3-dimethyl-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)methanone (6u). According to procedure D, compound **6u** was obtained as a dark yellow solid in 70% yield (70 mg, 0.17 mmol, R_f = 0.22 heptane/ethyl acetate, 1 : 1); mp = 248–250 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1657 (s), 1601 (vs), 1457 (vs), 1335 (vs), 1251 (m), 1187 (vs), 898 (m), 847 (m), 775 (s), 703 (s). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.91 (d, J = 1.9 Hz, 1H), 7.89–7.86 (m, 1H), 7.48–7.39 (m, 4H), 7.33 (dd, J = 7.1 Hz, J = 1.7 Hz, 1H), 7.28 (s, 1H), 7.26–7.22 (m, 1H), 7.21–7.15 (m, 2H), 5.10 (s, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 1.29 (s, 9H). ^{13}C {^{1}H} NMR (63 MHz, $CDCl_3$): δ = 197.5, 157.5, 148.1, 143.3, 143.0, 135.8, 135.3, 134.3, 133.4, 133.0, 132.0, 130.3, 129.9, 129.7, 128.7, 128.6, 125.8, 125.2, 120.0, 109.2, 47.6, 35.2, 31.1, 20.8, 20.3. MS (EI, 70 eV): m/z (%) = 420 (M^+, 100), 405 (5), 391 (20), 377 (3), 375 (3), 363 (3), 260 (5), 259 (19), 244 (6), 243 (7), 188 (8). HRMS (EI): calcd for $C_{29}H_{28}N_2O$ $[M]^+$ 420.2196, found: 420.2199.

(9-Methoxy-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(*p*-tolyl)methanone (6v). According to general procedure D, compound **6v** was obtained as a white in 70% yield (23.4 mg, 61.5 μmol, R_f = 0.32, heptane/ethyl acetate, 4 : 6); m.p. = 152–155 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2921 (m), 1662 (s), 1605 (s), 1454 (s), 1444 (s), 1343 (m), 1256 (s), 1240 (s), 1040 (s), 846 (s), 832 (s), 743 (vs), 484 (m). ^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.96–7.91 (m, 2H), 7.79 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.43–7.34 (m, 3H), 7.33–7.27 (m, 3H), 6.92 (dd, J = 8.4, 2.6 Hz, 1H), 6.73 (d, J = 2.6 Hz, 1H), 5.20 (s, 2H), 3.67 (s, 3H), 2.45 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 197.1, 159.7, 148.9, 145.0, 144.3, 144.2, 136.7, 134.3, 134.2, 130.6, 130.0, 129.7, 128.0, 124.7, 123.8, 123.0, 120.4, 120.3, 115.5, 115.2, 109.2, 55.6, 47.0, 21.9 (signal of one carbon is absent, which may relate to signal overlap). MS (EI, 70 eV): m/z (%) = 380 (100), 379 (11), 352 (16), 351 (51), 261 (21), 218 (16), 217 (10), 190 (12). HRMS (ESI-TOF) m/z = calcd for $C_{25}H_{21}N_2O_2$ $[M + H]^+$ 381.1603, found 381.1605.

(10-Methoxy-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(*p*-tolyl)methanone (6w). According to general procedure D, compound **6w** was obtained as a brown in 30% yield (16.4 mg, 43.1 μmol, R_f = 0.20, heptane/ethyl acetate, 4 : 6); m.p. = 129–132 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2921 (m), 1654 (m), 1592 (s), 1448 (m), 1327 (m), 1277 (m), 1254 (s), 1236 (s), 1224 (s), 1151 (m), 1116 (m), 1098 (m), 807 (s), 741 (vs), 506 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.89 (d, J = 8.7 Hz, 1H), 7.78–7.73 (m, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.35–7.28 (m, 1H), 7.29–7.23 (m, 2H), 7.23–7.16 (m, 3H), 7.06 (d, J = 2.5 Hz, 1H), 6.95 (dd, J = 8.7, 2.6 Hz, 1H), 5.46 (s, 2H), 3.92 (s, 3H), 2.36 (s, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ [ppm] = 196.5, 163.3, 151.8, 150.2, 143.6, 139.9, 139.6, 134.7, 133.9, 132.7, 130.2, 129.8, 129.5, 126.8, 123.4, 123.2, 120.3, 115.0, 113.7, 113.6, 109.6, 55.9, 48.4, 21.4 (signal of one carbon is absent, which may relate to signal overlap). MS (EI, 70 eV): m/z (%) = 380 (100), 379 (27), 365 (10), 352 (25), 351 (72), 338 (15), 307 (17), 264 (14), 263 (16), 249 (22), 236 (45), 194 (13), 190 (13). HRMS

(ESI-TOF) m/z = calcd for $C_{25}H_{21}N_2O_2$ $[M + H]^+$ 381.1603, found 381.1605.

(10-Fluoro-12*H*-benzo[*e*]benzo[4,5]imidazo[1,2-*a*]azepin-7-yl)(*p*-tolyl)methanone (6x). According to general procedure D, compound **6y** was obtained as a white in 69% yield (36.2 mg, 98.3 μmol, R_f = 0.19, heptane/ethyl acetate, 6 : 4); m.p. = 246–249 °C. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2919 (m), 1660 (m), 1607 (m), 1454 (m), 1444 (m), 1411 (m), 1238 (s), 1166 (m), 921 (m), 826 (s), 741 (vs), 558 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.93 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.43–7.28 (m, 5H), 7.27–7.20 (m, 2H), 7.02 (td, J = 8.4, 2.6 Hz, 1H), 5.22 (s, 2H), 2.46 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −110.2. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ [ppm] = 197.08, 163.39 (d, J = 252.4 Hz), 145.17, 143.32, 137.64 (d, J = 7.5 Hz), 134.11, 132.18, 132.06, 131.98, 130.62, 129.78, 124.47, 124.10, 123.22, 120.45, 116.12, 115.83, 109.13, 47.27, 21.94 (signal of four carbons are absent, which may relate to signal overlap). MS (EI, 70 eV): m/z (%) = 368 (91), 340 (24), 339 (82), 249 (14), 247 (13), 119 (100), 91 (57). HRMS (ESI-TOF) m/z = calcd for $C_{24}H_{18}FN_2O$ $[M + H]^+$ 369.1403, found 369.1404.

Conflicts of interest

There are no conflicts to declare.

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