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Novel synthetic methods based on hypervalent iodine compounds as functional groups donors: N–heterocyclic carbene catalysis and beyond

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Data Podpis autora pracy

Keywords

N–heterocyclic carbenes, organocatalysis, hypervalent iodine compounds, group transfer reactions

The thesis title in Polish

Nowe metody syntetyczne oparte o związki hiperwalencyjnego jodu jako donory grup funkcyjnych: kataliza N–heterocyklicznymi karbenami i nie tylko

I am puzzled as the oyster

I am troubled as the tide

Should I stand amid your breakers?

Or should I lie with death my bride?

Tim Buckley – Song to the Siren

Abstract

This thesis describes the development of novel synthetically useful reactions employing hypervalent iodine compounds as group transfer reagents. The aims of the thesis are: (1) to review the current knowledge in the area, in particular group transfer reactions from hypervalent iodine reagents utilizing organocatalysis, (2) to develop *N*–heterocyclic carbene catalyzed functionalizations of aldehydes with vinyliodonium and alkynyliodonium salts, and (3) to develop a metal-free vinylation of phosphorus-based nucleophiles with vinylbenziodoxolones.

The first part outlines the general characteristics of hypervalent iodine and its chemistry, focusing on the group transfer reactions. Over the last 15 years a variety of group transfer reactions from iodine(III) compounds have been invented, wherein a plethora of both organic and inorganic moieties are transferred to a variety of acceptors. Although many of such processes occur spontaneously, some require catalysis to promote their progress and in most cases transition metals have been used in this role. However, in recent years organocatalysis has been increasingly applied to assist the reactions with hypervalent iodine compounds, which allows to fully capitalize on the environmental and economic advantages of these reagents. A thorough literature review concerning the state of the art in the organocatalytic group transfer reactions employing hypervalent iodine compounds is given. In this review, I demonstrate that organocatalysis in many instances can successfully replace metal catalysis and, moreover, it allows to access to completely novel reactivity patterns, unavailable for the other types of catalytic activation.

The second part of the thesis presents my work on using vinyl- and alkynyliodonium salts to develop novel transformations of aldehydes, initiated by their activation with an *N*–heterocyclic carbene organocatalyst. I assumed that a nucleophilic Breslow intermediate, formed from the aldehyde and the carbene, may react with highly electrophilic iodonium salts delivering a ketone, overall resulting in a formal C–H functionalization of the formyl group. The careful optimization of the reactions conditions allowed for a selective and high-yielding transfer of vinyl and alkynyl groups. The new processes are characterized with very mild conditions and broad scopes of the transferred substituents, delivering a variety of functionalized enones and ynones. In the case of the alkynylation reaction, I performed thorough mechanistic studies using both experimental and computational methods, such as ^{13}C–labeling experiments, kinetic studies, and DFT calculations. The established mechanistic pathway proceeds *via* a direct substitution of iodine by the Breslow intermediate, taking place at the α–acetylenic

carbon. This is the first known example wherein such mechanism is operating exclusively. Additionally, the kinetic studies, validated by the computed free energy profile, identified the formation of the Breslow intermediate as the rate-determining step of the catalytic cycle. This demonstrated that the following C–C bond-formation between the Breslow intermediate and the alkynyliodonium salt is a facile, low-barrier process, in line with the original assumption.

The third part deals with studies on the vinylation of phosphorus-based nucleophiles with a cyclic hypervalent iodine compound – vinylbenziodoxolone. This novel vinyl transfer reagent was introduced in 2015, and it was found to exhibit an extraordinary β–regioselectivity of the vinyl transfer to C–nucleophiles, which is the opposite to that observed for vinyliodonium salts. The application of this reagent toward phosphorus-based nucleophiles was found to also display the similar selectivity, leading to valuable β–vinyl-phosphorus compounds. Based on this finding, an efficient method for the synthesis of a variety of β–vinyl phosphine oxides and phosphinates has been successfully developed.

Abstract in Polish

Przedstawiona rozprawa doktorska dotyczy opracowania nowych i syntetycznie użytecznych transformacji wykorzystujących związki hiperwalencyjnego jodu jako reagenty transferu grup. Cele pracy to: (1) przegląd aktualnej wiedzy w obszarze reakcji transferu grup ze związków hiperwalencyjnego jodu, wykorzystujących organokatalizę, (2) opracowanie metod funkcjonalizacji aldehydów przez sole winylojodoniowe oraz alkinylojodoniowe, katalizowanych przez *N*–heterocykliczne karbeny oraz (3) opracowanie reakcji winylowania nukleofili fosforowych z użyciem winylobenzjodoksolonów bez użycia związków metali.

Część pierwsza to przegląd literaturowy dotyczący aktualnej wiedzy na temat transformacji opartych o użycie związków hiperwalencyjnego jodu i wykorzystujących organokatalizatory do ich promowania. W ciągu ostatnich piętnastu lat odkryto wiele reakcji wykorzystujących związki hiperwalencyjnego jodu, podczas których organiczne i nieorganiczne grupy zostają przeniesione na różnorodne akceptory. Wiele z tych procesów zachodzi samorzutnie, jednak niektóre wymagają użycia katalizy, w większości przypadków jako katalizatory zastosowano związki metali przejściowych. Niemniej jednak, w ostatnich latach zaczęto coraz częściej wykorzystywać do tego celu organokatalizę. W przeglądzie tym pokazuję, że organokatalizatory nie tylko są w stanie zastąpić metale przejściowe, ale także pozwalają na uzyskanie zupełnie nowych rodzajów reaktywności.

Część druga skupia się na wykorzystaniu soli winylo– oraz alkinylojodoniowych do opracowania nowych transformacji aldehydów, przez ich aktywację za pomocą *N*–heterocyklicznego karbenu. Założyłem, że nukleofilowy związek przejściowy Breslowa, powstający w reakcji pomiędzy aldehydem i karbenem, może reagować z silnie elektrofilową solą jodoniową prowadząc do powstania ketonu – produktu formalnej funkcjonalizacji wiązania C–H grupy formylowej. Dogłębna optymalizacja warunków reakcji pozwoliła na selektywny oraz wydajny transfer grupy winylowej oraz alkinylowej. Opracowane reakcje charakteryzują się łagodnymi warunkami oraz szerokim zakresem stosowalności, prowadząc do powstania różnorodnych wysoce sfunkcjonalizowanych enonów oraz ynonów. Dla reakcji alkinylacji przeprowadziłem dokładne i wyczerpujące badania mechanistyczne za pomocą metod eksperymentalnych, takich jak badania kinetyki reakcji, eksperymenty ze znakowaniem izotopem ^{13}C, oraz obliczeniowych opartych o teorię funkcjonałów gęstości. Ustalony mechanizm przebiega poprzez bezpośrednią substytucję jodu przez związek przejściowy Breslowa przy α–acetylenowym atomie węgla, co jest pierwszym znanym przykładem, gdy taki proces jest jedyną możliwą ścieżką. Dodatkowo, badania kinetyczne podparte

obliczonym profilem energetycznym reakcji pokazują, iż to powstawanie związku pośredniego Breslowa jest etapem determinującym szybkość obrotu cyklu katalitycznego. Następcze tworzenie wiązania węgiel–węgiel pomiędzy tymże produktem pośrednim a solą alkinylojodoniową jest szybkim procesem szybkim o niskiej barierze energetycznej, zgodnie z pierwotnie przyjętym założeniem.

Cześć trzecia rozprawy omawia badania nad reakcją winylacji nukleofili fosforowych z wykorzystaniem cyklicznego związku hiperwalencyjnego jodu – winylobenzjodoksolonu. Ten nowy związek, odkryty w 2015 roku, w reakcjach transferu grupy winylowej wykazuje niezwykłą, w porównaniu do soli winylojodoniowych, wysoką β–regioselektywność wobec nukleofili węglowych. W trakcie moich badań ustaliłem, że podobna selektywność występuje również w przypadku nukleofili fosforowych, prowadząc do powstania wartościowych β–winylowych związków fosforu. W oparciu o to odkrycie, opracowałem ogólną metodę syntetyczną pozwalającą na wydajne otrzymywanie różnorodnych β–winylotlenków fosfin oraz β–winylofosfinianów.

List of Publications

The thesis is based on the following papers, referred to in the text by their Roman numerals I–IV. Reprints were made with the kind permission of the publishers (**Appendix A**). The contribution of the author to each publication is clarified in **Appendix B**.

I. **Organocatalytic Group Transfer Reactions with Hypervalent Iodine Reagents**
Manoj K. Ghosh, Adam A. Rajkiewicz, Marcin Kalek
Synthesis **2019**, *51*, 359–370

II. ***N*–Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts To Generate α,β-Unsaturated Ketones**
Adam A. Rajkiewicz, Marcin Kalek
Org. Lett. **2018**, *20*, 1906–1909

III. ***N*–Heterocyclic Carbene-Catalyzed Synthesis of Ynones via C–H Alkynylation of Aldehydes with Alkynyliodonium Salts — Evidence for Alkynyl Transfer *via* Direct Substitution at Acetylenic Carbon**
Adam A. Rajkiewicz, Natalia Wojciechowska, Marcin Kalek
ACS Catal. **2020**, *10*, 831–841

IV. **Transition Metal-Free and Regioselective Vinylation of Phosphine Oxides and H-Phosphinates with VBX Reagents**
Laura Castoldi, Adam A. Rajkiewicz, Berit Olofsson
Chem. Commun. **2020**, *accepted* (DOI: 10.1039/D0CC05992G)

Papers by the author not submitted as part of the thesis:

V. **Ruthenium Catalysts Supported by Amino-Substituted *N*-Heterocyclic Carbene Ligands for Olefin Metathesis of Challenging Substrates**
Vincent César, Yin Zhang, Wioletta Kośnik, Adam Zieliński, Adam A. Rajkiewicz, Mirko Ruamps, Stéphanie Bastin, Noël Lugan, Guy Lavigne, Karol Grela
Chem. Eur. J. **2017**, *23*, 1950–1955

VI. **Boron–boron, Carbon–carbon and Nitrogen–nitrogen Bonding in *N*–Heterocyclic Carbenes and Their Diazaboryl and Triazole Analogues: Wanzlick Equilibrium Revisited**
Katarzyna Młodzikowska, Adam A. Rajkiewicz, Karol Grela, Bartosz Trzaskowski
New J. Chem. **2018**, *42*, 6183–6190

VII. **Modification of Polyhedral Oligomeric Silsesquioxanes (POSS) Molecules by Ruthenium Catalyzed Cross Metathesis**
Justyna Czaban-Jóźwiak, Łukasz Woźniak, Artur Ulikowski, Katarzyna Kwiecińska, Adam A. Rajkiewicz, Karol Grela
Molecules **2018**, *23*, 1722

VIII. **2-Methyltetrahydrofuran as a Solvent of Choice for Spontaneous Metathesis/Isomerization Sequence**
Adam A. Rajkiewicz, Krzysztof Skowerski, Bartosz Trzaskowski, Anna Kajetanowicz, Karol Grela
ACS Omega **2019**, *4*, 1831–1837

IX. **Benzoxazepine-Derived Selective, Orally Bioavailable Inhibitor of Human Acidic Mammalian Chitinase**
Gleb Andryianau, Michal Kowalski, Michal C. Piotrowicz, Adam A. Rajkiewicz, Barbara Dymek, Piotr L. Sklepkiewicz, Elzbieta Pluta, Filip Stefaniak, Wojciech Czestkowski, Sylwia Olejniczak, Marzena Mazur, Piotr Niedziejko, Robert Koralewski, Krzysztof Matyszewski, Mariusz Gruza, Agnieszka Zagozdzon, Magdalena Salamon, Aleksandra Rymaszewska, Mikolaj Welzer, Karolina Dzwonek, Jakub Golab, Jacek Olczak, Agnieszka Bartoszewicz, Adam Golebiowski
ACS Med. Chem. Lett. **2020**, *11*, 1228–1235

X. **Preparation of Functionalized α,β-Unsaturated Sulfonamides *via* Olefin Cross-Metathesis**
Łukasz Woźniak, Adam A. Rajkiewicz, Louis Monsigny, Anna Kajetanowicz, Karol Grela
Org. Lett. **2020**, *22*, 4970–4973

Table of Contents

Abbreviations

In this thesis, abbreviations are used in agreement with the standard of the subject. Only nonstandard and unconventional abbreviations that appear in the thesis are listed here:

2c-2e = two-center two-electron
3c-4e = three-center four-electron
BTMG = 2–*tert*–butyl–1,1,3,3–tetramethylguanidine
DABCO = 1,4–diazabicyclo[2.2.2]octane
DBU = 1,8–diazabicyclo[5.4.0]undec–7–ene
DCE = 1,2–dichloroethane
DFT = density functional theory
DG = directing group
DIPEA = *N*,*N*–diisopropylethylamine
DMAP = *N*,*N*–dimethylpyridine–4–amine
DPE = 1,1–diphenylethene
EBX = ethynylbenziodoxolone
ee = enantiomeric excess
equiv. = equivalent
EWG = electron-withdrawing group
MB = methylene blue
MesAcr = 9–mesityl–10–methylacridinium tetrafluoroborate
mol% = molar percent
nd = not detected
NHC = *N*–heterocyclic carbene
PIDA = phenyliodine diacetate
PTC = phase-transfer catalysis
Qx = quinoxalin–2–yl
SET = single electron transfer
SMD = solvation model based on full electron density
S_N2 = bi-molecular nucleophilic substitution
TBAI = tetra–*n*–butylammonium bromide (nBu$_4$NBr)
TClP = 2,4,6–trichlorophen–1–yl
TEMPO = (2,2,6,6–tetramethylpiperidine–1–yl)oxyl
TfO = trifluoromethanesulfonate, triflate
TfOH = trifluoromethanesulfonic acid, triflic acid
TIPS = triisopropylsilyl

TMEDA = *N*,*N*,*N*′,*N*′–tetramethylethane–1,2–diamine
TMS = trimethylsilyl
TsO = 4–methylbenzene–1–sulfonic acid, tosylate
VBX = vinylbenziodoxolone

Preface

It was 1845, when for the first time in history word *synthesis* was used as a description of the process of assembling chemical compounds. Herman Kolbe in *Annalen Der Chemie und Pharmacie*[1] wrote:

"In contrary to the so far known organic acids, [which were generated due to decomposition of organic material and influence of strong agents under conditions, which allow broad interpretation of occurred decomposition] those described in this article were generated through ***synthesis*** *from small molecules of simple composition, so that there is no doubt about the products composition, and therefore can be described as the prototypes of the product type."*

This was the first example of using entities for building-up more complex molecules in a rational way. Since that moment, organic synthesis has been continuously evolving to higher levels of composure and elegance. The most extraordinary and sophisticated of the developments raised in the eras of great chemists: Robert Woodward, Roald Hoffmann, Elias James Corey, and Kyriacos Nicolaou, and emerged into the great methodology breakthroughs rewarded in The Nobel Prizes. Nowadays, the organic synthetic chemistry is well established and highly advanced, however, there are still outstanding challenges to face – the sustainability of reactants and their toxicity, the contamination of products by transition metal catalysts residues, atom economy, functional group tolerance and, in a number of cases, still far from perfect chirality transfer. Thus, every novel and innovative approach brings the synthetic organic chemistry closer to unraveling above problems. I strongly believe that it is not *just another brick in the wall* of scientific reports – each *brick* is vital and influential to the fundamental understanding of chemical processes, which allows us, the chemists, to create integral synthetic tools for our prosperity and the prosperity of the Earth.

[1] Kolbe, H., *Ann. Chem. Pharm.* **1845,** *54*, 145-188.

Chapter I. Introduction

1. Hypervalency of Main Group Elements

In the beginning of the 20th century, a plethora of theories about reactivity of chemical compounds have been established and one of the most significant was the *octet rule*. In 1916 Walther Kossel identified that noble gases do not undergo chemical reactions under ordinary conditions.[2] Upon this observation, he concluded that atoms of noble gases are stable and on the basis of this conclusion, he proposed a theory of valency:

"During the formation of a chemical bond, atoms combine together by gaining, losing, or sharing electrons in such a way that they acquire the nearest noble gas configuration."

Few years later Irving Langmuir refined proposed concepts further and coined the names *cubic octet atom* and *octet theory*.[3] This theory emerged then into what is now known as the *octet rule*, which describes **the tendency of element to bond in such a way that each atom has eight electrons in its valence shell, obtaining the same electronic configuration as a noble gas**. Nevertheless, a number of known chemical moieties did not seem to come under the above rule of bonding. The traditional Lewis 2c-2e (*two-center two-electron*) covalent bond[4] was insufficient to describe the structure of molecules such as phosphorus pentachloride (PCl_5) or hexafluorosilicate anion (SiF_6^{2-}), whose central atoms seem to possess more than 8 valence electrons.

To describe such bonding in the compounds of the main-block elements, Jeremy Musher was the first who introduced the term *hypervalent*.[5] He classified as hypervalent molecules all these formed by elements in groups V–VIII of the periodic table in any of their valences other than their lowest stable chemical valence. **Such molecules exceed the number of valences, thus utilize more electron pairs than allowed by the *octet rule*.** To characterize the bonding, Musher applied a 3c-4e (*three-center four-electron*) bond outlined by George Pimentel in 1951.[6] The orbital picture of the hypervalent bond is depicted in **Figure 1**, exemplified by triiodide anion (I_3^-).

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[2] Kossel, W., *Ann. Phys.* **1916**, *354*, 229-362.
[3] Langmuir, I., *J. Am. Chem. Soc.* **1919**, *41*, 868-934.
[4] Lewis, G. N., *J. Am. Chem. Soc.* **1916**, *38*, 762-785.
[5] Musher, J. I., *Angew. Chem. Int. Ed.* **1969**, *8*, 54-68.
[6] Pimentel, G. C., *J. Chem. Phys.* **1951**, *19*, 446-448.

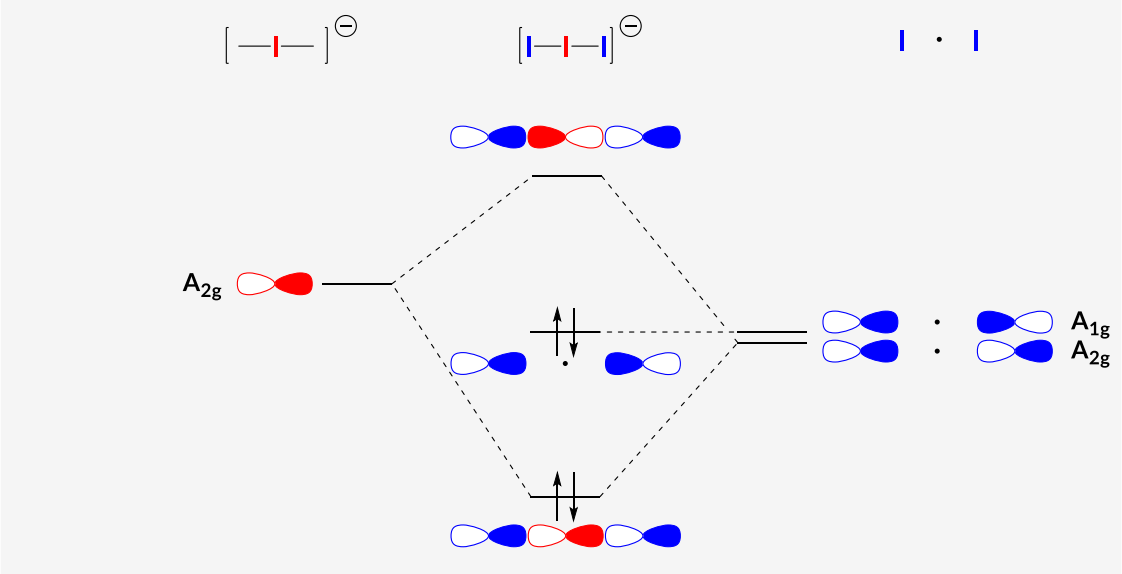

Figure 1. Molecular orbitals of 3c-4e bond in triiodide anion.

The orbitals involved in the formation of the 3c-4e bond are the p_z orbital of the central iodine (red), belonging to A_{2g} representation, and the symmetrically adapted orbitals A_{1g} and A_{2g} (blue), obtained by the mixing of the p_z orbitals of the outside atoms. As the mixing is only allowed between the orbitals having the same symmetry, the mixing of the two A_{2g} orbitals results in bonding and antibonding molecular orbitals, while orbital A_{1g} remains unchanged and it constitutes a non-bonding molecular orbital. Because in I_3^- there are four electrons to be distributed, the bonding and non-bonding orbitals are occupied. Therefore, only 2 electrons are responsible for the bonding of all 3 atoms, rendering the hypervalent bond considerably weak. This leads to an overall electrophilic and oxidative character of hypervalent molecules and their high reactivity, in terms of both kinetics and thermodynamics. Due to the localization of the non-bonding occupied orbital at the outside atoms, electronegative ligands lend stabilization to the hypervalent compounds.

Currently, hypervalency is used in defining and characterization of tetra-, penta- and hexavalent phosphorus, silicon, and sulfur compounds, noble gas compounds (*e.g.*, KrF_2, XeF_4), halogen bonding (as an example of secondary bonding), hydrogen bonding, and hypervalent halogen molecules, including halogen polyfluorides (ClF_5, IF_7).

2. Hypervalent Iodine Compounds

Iodine, as an element, was isolated from the ash of seaweed by French chemist Bernard Courtois in 1811.[7] It was named 3 years later by Joseph Louis Gay-Lussac,[8] who suggested the name "*iode*", from Greek word ιοειδής (*ioeides*), meaning "violet", due to the purple color of iodine vapors. Organoiodine compounds have been used in organic chemistry since the 19th century, notably in the Hofmann's alkynylation of amines, the Williamson synthesis of ethers and Wurtz coupling reaction. In organic compounds iodine is in most cases monovalent with a formal oxidation state +I.[9] Moreover, due to its large radius, susceptibility to polarization, and low electronegativity, it is prone to form stable, polycoordinate hypervalent compounds.[10]

The first synthesis and isolation of hypervalent organoiodine compound, phenyliodine dichloride, was achieved by a German chemist Willgerodt in 1886.[11] This was rapidly followed by the preparation of phenyliodine diacetate (PIDA),[12] diphenyliodonium hydrogen sulfate – the first iodonium salt,[13] and many others, thus until 1914 nearly 500 organic hypervalent iodine compounds have been known.[14] Despite this early discovery, the chemistry of hypervalent iodine remains an active area of research and novel reagents are still being investigated and applied in organic synthesis (**Figure 2**).

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[7] Courtois, B., *Ann. Chim.* **1813,** *88*, 304-310.

[8] Gay-Lussac, J. L., *Ann. Chim.* **1814,** *91*, 5-160.

[9] Due to a strong resemblance of organic hypervalent iodine compounds to organometallic complexes of late transition metals, the convention is to ascribe the oxidation state of iodine atom similarly to the oxidation state of metals in complexes. Thus, according to this convention, which will be used in this thesis, for example, the oxidation state of iodine in iodobenzene is +I, while in $PhICl_2$ and $PhI(OAc)_2$ it is +III.

[10] For examples of reviews about hypervalent iodine compounds, see: (a) Stang, P. J.; Zhdankin, V. V., *Chem. Rev.* **1996,** *96*, 1123-1178; (b) Zhdankin, V. V.; Stang, P. J., *Chem. Rev.* **2002,** *102*, 2523-2584; (c) Zhdankin, V. V.; Stang, P. J., *Chem. Rev.* **2008,** *108*, 5299-5358; (d) Yoshimura, A.; Zhdankin, V. V., *Chem. Rev.* **2016,** *116*, 3328-3435; (e) Olofsson, B.; Marek, I.; Rappoport, Z., *The Chemistry of Hypervalent Halogen Compounds*. John Wiley & Sons, Ltd.: **2019**.

[11] Willgerodt, C., *J. Prakt. Chem.* **1886,** *33*, 154-160.

[12] Willgerodt, C., *Ber. Dtsch. Chem. Ges.* **1892,** *25*, 3494-3502.

[13] Hartmann, C.; Meyer, V., *Ber. Dtsch. Chem. Ges.* **1894,** *27*, 426-432.

[14] Willgerodt, C., *Die Organischen Verbindungen mit Mehrwertigen Jod*. Ferdinand Enke Verlag: Stuttgart, 1914.

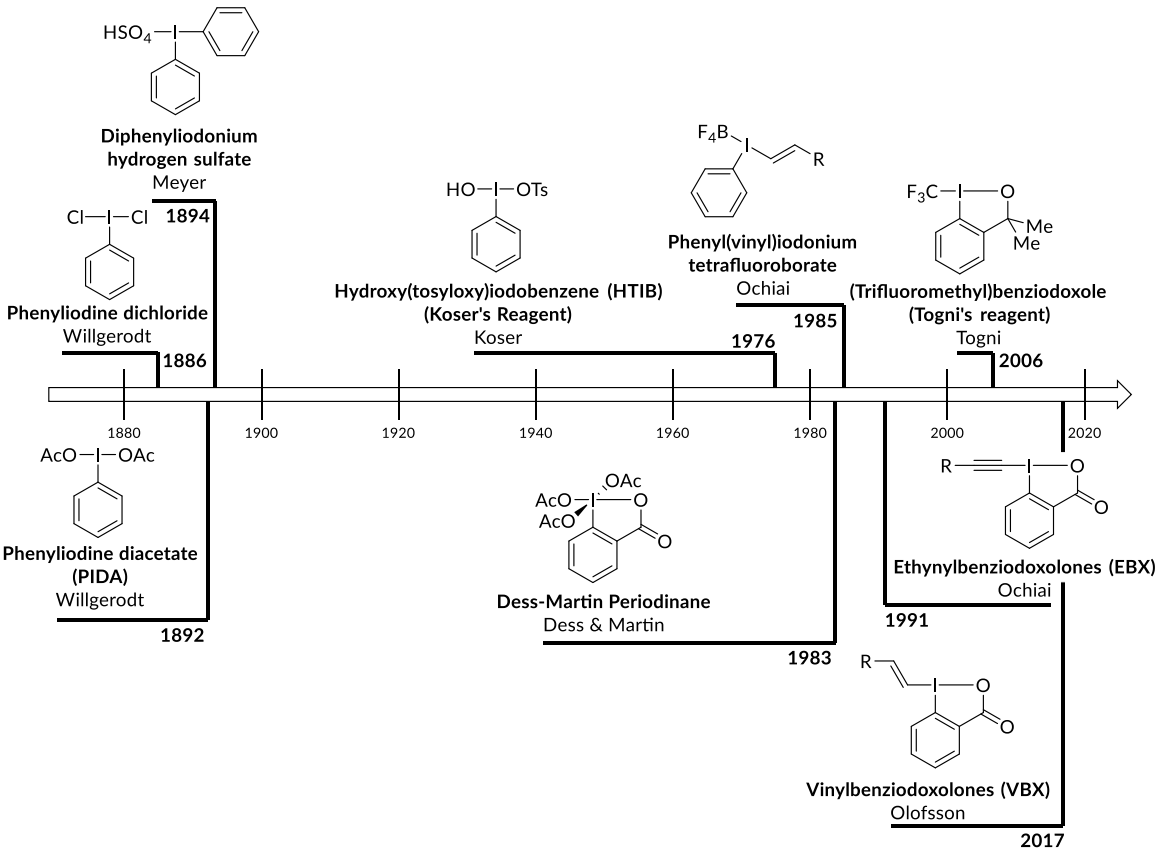

Figure 2. Timeline of the development in organic hypervalent iodine compounds.

2.1. Structural Features of Hypervalent Iodine Compounds

There are two general classes of organic hypervalent iodine compounds: iodine(III) compounds, also called λ^3–iodanes, and iodine(V) compounds, λ^5–iodanes (**Figure 3**).

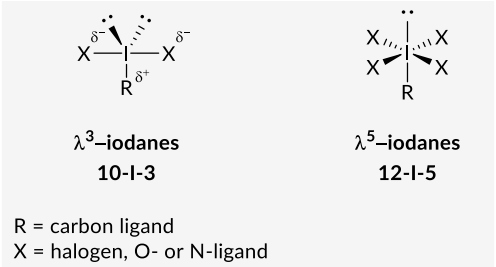

Figure 3. General structure of hypervalent iodine compounds. The Martin-Arduengo-Kochi N-X-L descriptors are also given (N = number of valence electron, X = central atom, L = number of ligands).

The iodine atom in trivalent compounds has a total of 10 electrons in the valence shell and a T-shaped geometry. Two of the ligands (X) occupy the apical positions, while R ligand is placed in an equatorial position, and the experimentally determined angles between ligands are close to 90°. Apical ligands create the 3c–4e bond with iodine

central atom - highly polarized, moreover longer and weaker than typical covalent bond, which is commonly referred to as a "hypervalent bond" and is responsible for a high electrophilic reactivity of λ^3–iodanes. On the other hand, the structure of λ^5–iodanes is square pyramid, with the organic group R in the apical position and four ligands X in the basal positions. This type of compounds bears two 3c–4e bonds accommodated on the four X ligands and angles between both X–X and X–R ligands are close to 90°. To classify hypervalent compounds of main group elements, the **N-X-L notation** has been introduced by the research groups of Martin, Arduengo, and Kochi, where: **N** describes the number of valence electrons; **X** – depicts the chemical symbol of the central atom; and **L** is the number of ligands bonded to the central atom.[15] Using this notation, λ^3–iodanes are described as **10-I-3**, and λ^5–iodanes as **12-I-5**.

As mentioned in section 1, electronegative outside atoms of the hypervalent bond stabilize the hypervalency. Therefore, in stable hypervalent iodine compounds ligands X are usually halogen-, O-, or N-based groups. However, in λ^3–iodanes it is possible that one of the X ligands is an organic moiety. This creates an opportunity to use such I(III) compounds as efficient organic groups donors. Conversely, to maintain the high +V oxidation state of iodine in λ^5–iodanes, all four X ligands need to be strongly electronegative, and thus, the applications of these species in organic chemistry is limited to being oxidants.

2.2. Properties and Applications of Hypervalent Iodine Compounds

Hypervalent iodine compounds, both λ^3– and λ^5–iodanes, are well-established oxidants in synthetic organic chemistry.[10a-d, 16] They display reactivity similar to Hg(II), Tl(III) and Pb(IV) reagents, but they lack the inherent toxicity of these heavy metals. However, the recent rebirth of the interest in this class of compounds originates from a close resemblance between the hypervalent I(III) compounds bearing an organic group at the hypervalent bond and organometallic complexes of late transition metals, such as Pd or Au, on high oxidation states. In particular, the properties of organic λ^3–iodanes make them very competent group transfer reagents in coupling reactions.

In contrast to catalytic transition metal-catalyzed cross-couplings, the reactions involving hypervalent iodine species typically make use of a stoichiometric amount of

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[15] Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K., *J. Am. Chem. Soc.* **1980**, *102*, 7753-7759.

[16] (a) Ladziata, U.; Zhdankin, V. V., *Arkivoc* **2006**, 26-58; (b) Zhdankin, V. V., *Arkivoc* **2009**, *i*, 1-62; (c) Akira Yoshimura; Zhdankin, V. V., *Arkivoc* **2017**, *i*, 99-116; (d) Zhdankin, V. V., *Arkivoc* **2020**, *iv*, 1-11.

the reagent. This does not constitute a major drawback, due to the low price and toxicity of iodine. In other words, the oxidative addition step of a catalytic metal-catalyzed cross-coupling mechanism is replaced by the preparation of stable and cheap iodine(III) compound (**Figure 4**). The following reaction steps, *i.e.*, the ligand exchange and the reductive elimination, are the same for both processes. The ligand exchange occurs due to the appreciable electrophilic character of iodine(III) and proceeds smoothly for several type of nucleophiles, such as alcohols, phenols, amines and other heteroatom-based nucleophiles. Last step, the reductive elimination, leads to the formation of a bond between the ligand with a parallel reduction of iodine(III) to organic iodide, which is usually discarded, but it can be recovered, recycled and used for further syntheses.

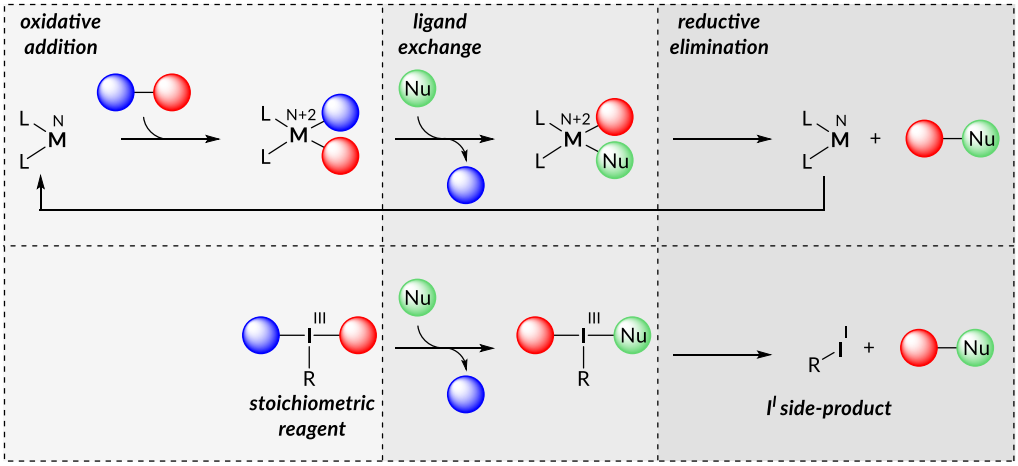

Figure 4. Comparison of the elementary steps of a catalytic transition metal-catalyzed coupling reaction and the reactivity pattern of hypervalent iodine compounds.

The group transfer reagents based on hypervalent iodine can be divided into acyclic and cyclic ones (**Figure 5a** and **5b**, respectively). The first class can be further divided into two groups of compounds: (a) aryliodine dihalides and dicarboxylates, wherein the iodine(III) center bears one carbon ligand and two electronegative ligands occupying the hypervalent positions; (b) compounds known also as iodonium salts, bearing two carbon ligands and one electronegative ligand (in most cases triflate, tosylate, or tetrafluoroborate) (**Figure 5a**). The iodonium salts can contain aryl, vinyl, and alkynyl transferable groups. Alkyl substituents are not tolerated, because similarly as in transition metal complexes, they undergo a β–elimination of hydrogen. The cyclic iodine(III) compounds have the aromatic ring fused to a 5-membered ring encompassing the I–O bond (**Figure 5b**). The oxygen atom can be a part of either an alkoxide or carboxylate. Typical groups, which undergo the transfer reaction are vinyl, alkynyl, and trifluoromethyl, as well as halogens and pseudohalogens, such as F, CN, and N_3. The five-membered heterocyclic iodine compounds have considerably higher thermal stability compared to the noncyclic analogs, due to the bridging of the equatorial and

the apical positions at hypervalent iodine center by the five-membered ring.[17] The increased stability of benziodoxoles made possible the preparation of otherwise unstable hypervalent iodine derivatives with peroxide, azido, cyano, and trifluoromethyl substituents. On the downside, the cyclic compounds often display lower reactivity than the corresponding iodonium salts.

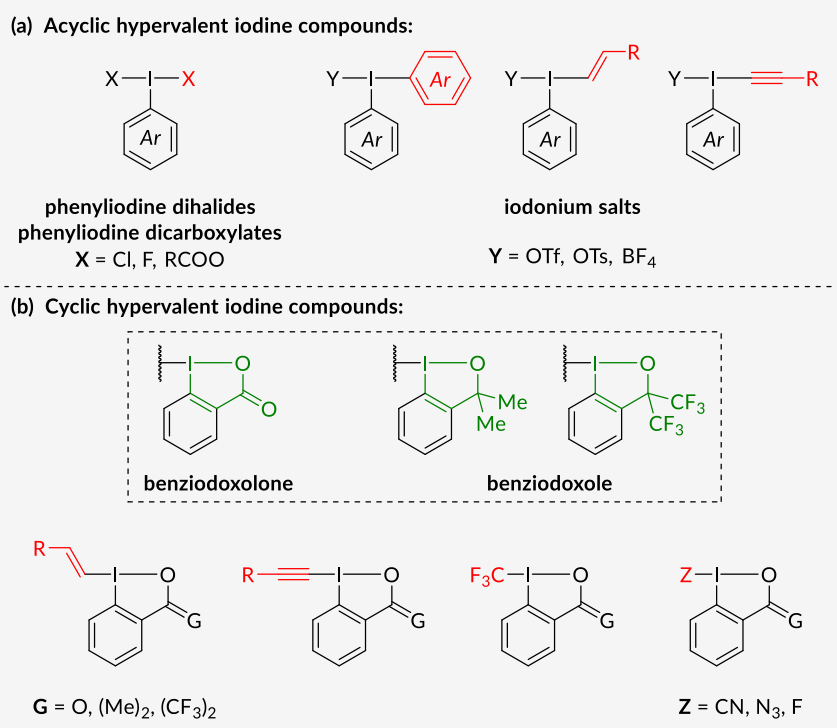

Figure 5. Classes of hypervalent iodine group transfer reagents. The transferable group is indicated in red.

Over the last 20 years, a large group of reactions have been developed, wherein an array of groups is transferred from hypervalent iodine reagents to a variety of acceptors. **Figure 6** presents selected representative examples of such reactions. For instance, synthetically useful 1,1–difluorinations of olefins with 4–tolyliodine difluoride have been developed by Murphy (**Figure 6a**).[18] The reaction in the presence of a catalytic amount of boron trifluoride provides a fluorinative rearrangement products, such as α,α–difluoromethyl styrenes (from allenes), cyclic β,β–difluoroalkyl arenes, and allylic

[17] Amey, R. L.; Martin, J. C., *J. Org. Chem.* **1979**, *44*, 1779-1784.

[18] (a) Zhao, Z.; Racicot, L.; Murphy, G. K., *Angew. Chem. Int. Ed.* **2017**, *56*, 11620-11623; (b) Zhao, Z.; To, A. J.; Murphy, G. K., *Chem. Commun.* **2019**, *55*, 14821-14824.

gem–difluorides (from methylidene substituted cycloalkanes or allenes) *via* ring expansion of benzo–fused carbocycles. The group of Olofsson has developed a number

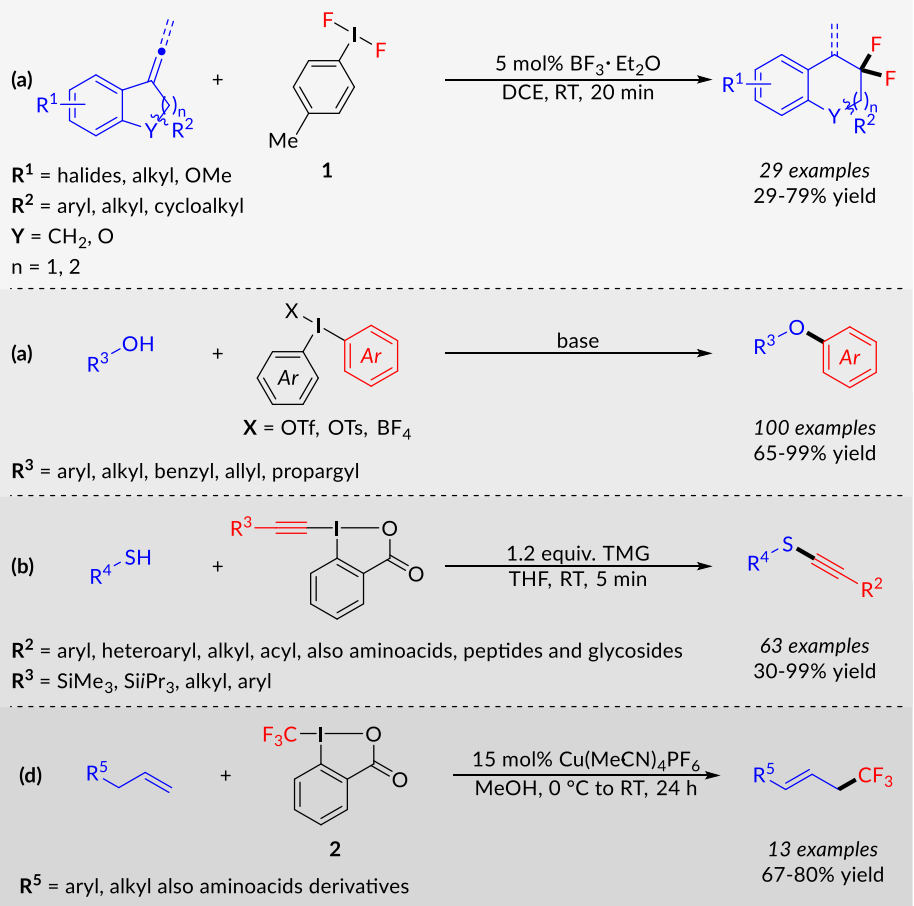

Figure 6. Examples of applications of hypervalent iodine compounds as group transfer reagents.

of aryl transfers from aryliodonium salts to several hetero-nucleophiles, such as phenols,[19a-c] alcohols,[19d, 19e] and amines (**Figure 6a**).[19f] This methodology is a comprehensive and almost unlimited alternative to the metal-catalyzed cross-couplings, such as Ullman or Buchwald-Hartwig coupling reactions. Waser developed a variety of transformations based on the alkynyl transfer from cyclic ethynylbenziodoxolone reagents. For instance, sulfur nucleophiles have been found to be an extraordinarily susceptible group of acceptors, delivering both aliphatic and aromatic ethynyl sulfides,

[19] (a) Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B., *Org. Lett.* **2011**, *13*, 1552-1555; (b) Jalalian, N.; Petersen, T. B.; Olofsson, B., *Chem. Eur. J.* **2012**, *18*, 14140-14149; (c) Lindstedt, E.; Ghosh, R.; Olofsson, B., *Org. Lett.* **2013**, *15*, 6070-6073; (d) Ghosh, R.; Lindstedt, E.; Jalalian, N.; Olofsson, B., *ChemistryOpen* **2014**, *3*, 54-57; (e) Lindstedt, E.; Stridfeldt, E.; Olofsson, B., *Org. Lett.* **2016**, *18*, 4234-4237; (f) Purkait, N.; Kervefors, G.; Linde, E.; Olofsson, B., *Angew. Chem. Int. Ed.* **2018**, *57*, 11427-11431.

including ones of high biological importance (**Figure 6c**).[20] Cyclic hypervalent iodine compounds are also a very convenient platform for electrophilic trifluoromethylation, however, the activation by a transition metal catalyst is often required. In 2011, Buchwald described an elegant method for the allylic trifluoromethylation using Togni's II reagent **2** (**Figure 6d**).[21] The reaction requires a Cu catalyst and it affords various functionalized trifluoromethylated products, including biologically relevant aminoacids derivatives.

[20] (a) Frei, R.; Waser, J., *J. Am. Chem. Soc.* **2013,** *135*, 9620-9623; (b) Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J., *J. Am. Chem. Soc.* **2014,** *136*, 16563-16573; (c) Wodrich, M. D.; Caramenti, P.; Waser, J., *Org. Lett.* **2016,** *18*, 60-63.

[21] Parsons, A. T.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2011,** *50*, 9120-9123.

3. Organocatalytic Group Transfer Reactions with Hypervalent Iodine Reagents (Paper I)

3.1. Background

Modern hypervalent iodine compounds occupy a well-established place in synthetic organic chemistry.[10e, 22] In particular, iodine(III) reagents which are efficient functional group or atom donors to organic substrates constitute a prominent class among the hypervalent iodine species. Over the last 20 years a variety of reactions have been invented, wherein a plethora of both organic and inorganic moieties, such as aryl, vinyl, alkynyl, CF_3, CN, N_3, F, NTs_2, and others, are transferred to a variety of acceptors.[23] Among these synthetically useful transformations, some require catalysis to promote their progress or to drive them towards the formation of desired products. In the majority of cases transition metal catalysis has been used,[23k, 24] however, in recent years the application of organocatalysis to promote reactions with hypervalent iodine compounds has begun to emerge. The organocatalysis could not only replace metals catalysts, but in many instances, it allowed to access completely novel reactivity patterns. Moreover, the strength of organocatalysis lies in its ability to provide a very efficient asymmetric induction and this property has been exploited in several enantioselective group transfers utilizing hypervalent iodine reagents.

From the mechanistic perspective, there exist different possible pathways that the group transfer from iodine(III) regents may follow,[25] each providing different opportunities to exploit the organocatalysis (**Figure 7**). In the first pathway, a nucleophilic acceptor attacks the hypervalent iodine species (**Figure 7a**). The reaction

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[22] (a) Zhdankin, V. V., *Hypervalent Iodine Chemistry*. Wiley: Chichester, **2014**; (b) Wirth, T., *Hypervalent Iodine Chemistry*. Springer International Publishing: Cham, **2016**.

[23] (a) Merritt, E. A.; Olofsson, B., *Angew. Chem. Int. Ed.* **2009,** *48*, 9052-9070; (b) Merritt, E. A.; Olofsson, B., *Synthesis* **2011,** *2011*, 517-538; (c) Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J., *Chem. Commun.* **2011,** *47*, 102-115; (d) Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C., *Org. Biomol. Chem.* **2014,** *12*, 4278-4289; (e) Romero, R. M.; Wöste, T. H.; Muñiz, K., *Chem. Asian J.* **2014,** *9*, 972-983; (f) Kaschel, J.; Werz, D. B., *Angew. Chem. Int. Ed.* **2015,** *54*, 8876-8878; (g) Charpentier, J.; Früh, N.; Togni, A., *Chem. Rev.* **2015,** *115*, 650-682; (h) Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J., *Angew. Chem. Int. Ed.* **2016,** *55*, 4436-4454; (i) Kohlhepp, S. V.; Gulder, T., *Chem. Soc. Rev.* **2016,** *45*, 6270-6288; (j) Lauriers, A. J.-D.; Legault, C. Y., *Asian J. Org. Chem.* **2016,** *5*, 1078-1099; (k) Fañanás-Mastral, M., *Synthesis* **2017,** *49*, 1905-1930; (l) Chatterjee, N.; Goswami, A., *Eur. J. Org. Chem.* **2017,** *2017*, 3023-3032; (m) Muñiz, K., *Acc. Chem. Res.* **2018,** *51*, 1507-1519.

[24] Sousa e Silva, F. C.; Tierno, A. F.; Wengryniuk, S. E., *Molecules* **2017,** *22*, 780.

[25] Sreenithya, A.; Surya, K.; Sunoj, R. B., *WIREs Comput. Mol. Sci.* **2017,** *7*, e1299.

may occur by either a direct attack on ligand R with the release of aryl iodide as a leaving group or *via* the association of the nucleophile to the iodine(III) center (ligand exchange), followed by the bond formation between the acceptor and R (reductive elimination). In this scenario an organocatalyst can be utilized to generate a proper nucleophilic species from the acceptor or, *vice versa*, to increase the electrophilicity of the iodine(III) compound. The second mechanistic pathway involves the initial formation of a radical R• via a SET process, which is feasible due to the low dissociation energy of the weak hypervalent R–I bond (**Figure 7b**). The radical R• reacts then with the acceptor providing the functionalized product. In this case, organocatalysis can be employed to promote the generation of the radical from the iodine(III) precursor. Finally, there is a large group of reactions, wherein hypervalent iodine compounds are utilized to first transfer the R group to a metal complex that subsequently delivers it to the acceptor (**Figure 7c**). Naturally, this type of processes by necessity require a metal catalyst, but there is still room for the application of organocatalysis, which results in cooperatively catalyzed transformations.

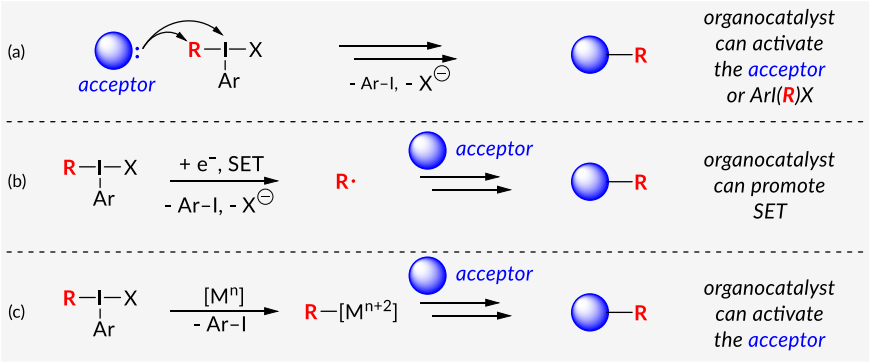

Figure 7. General mechanistic possibilities for the group transfer from iodine(III) reagents and the respective opportunities for the use of organocatalysis.

3.2. Organocatalytic Activation of Acceptor

3.2.1. Amine Catalysis *via* Formation of Enamine or Unsaturated Iminium

Activation of aldehydes and ketones with amine catalysts to form enamine species is one of the most robust approaches for the α-functionalization of carbonyl compounds.[26] Notably, it was one of the first organocatalytic approaches to be used in the combination with hypervalent iodine group-transfer reagents. In 2005 Cordova and co-workers reported a proline-catalyzed α-hydroxylation of cyclohexanones with

[26] (a) Waser, M., *Asymmetric Organocatalysis in Natural Product Syntheses*. Springer: Vienna, **2012**; Vol. 7; (b) List, B.; Maruoka, K., *Science of Synthesis: Asymmetric Organocatalysis 1: Lewis Base and Acid Catalysts*. Thieme: Stuttgart, **2012**.

iodosobenzene (PhIO).[27] However, this work did not receive a lot of attention, due to only moderate yields and enantioselectivities obtained.

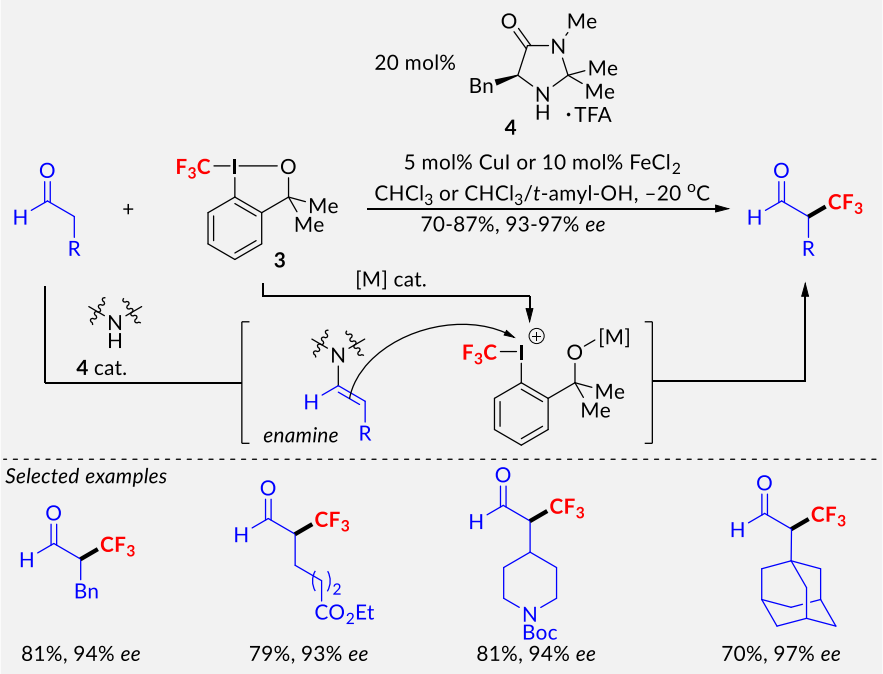

Figure 8. Chiral amine/Lewis acid co-catalyzed enantioselective α-trifluoromethylation of aldehydes with CF_3-benziodoxole.

The breakthrough has happened 5 years later: in 2010, the group of Macmillan described the first high yielding and highly enantioselective α–functionalization of aldehydes, using chiral amine catalyst **4** and Togni's I reagent **3** as the CF_3-group donor (**Figure 8**).[28] The key to the success of this reaction was the activation of **3** by an additional Lewis acid catalyst, CuI or $FeCl_2$.

In the next years, the scope of this methodology has been expanded to α-arylation and α-olefination, by replacing CF_3–benziodoxole **3** with diaryliodonium and aryl(vinyl)iodonium salts, respectively (**Figure 9**). In the case of iodonium salts, the mechanism of activation by Cu(I) co-catalyst proceeds *via* the initial oxidative addition to the Cu center, resulting in the formation of copper(III) species, which react further with the enamine. To secure a selective transfer from unsymmetric diaryliodonium salts, a mesityl group was used as an auxiliary non-transferable aryl.[29a] An exclusive transfer of the vinyl substituent was observed for simple phenyl(vinyl)iodonium salts.[29b]

[27] Engqvist, M.; Casas, J.; Sundén, H.; Ibrahem, I.; Córdova, A., *Tetrahedron Lett.* **2005**, *46*, 2053-2057.
[28] Allen, A. E.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2010**, *132*, 4986-4987.
[29] (a) Allen, A. E.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2011**, *133*, 4260-4263; (b) Skucas, E.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2012**, *134*, 9090-9093.

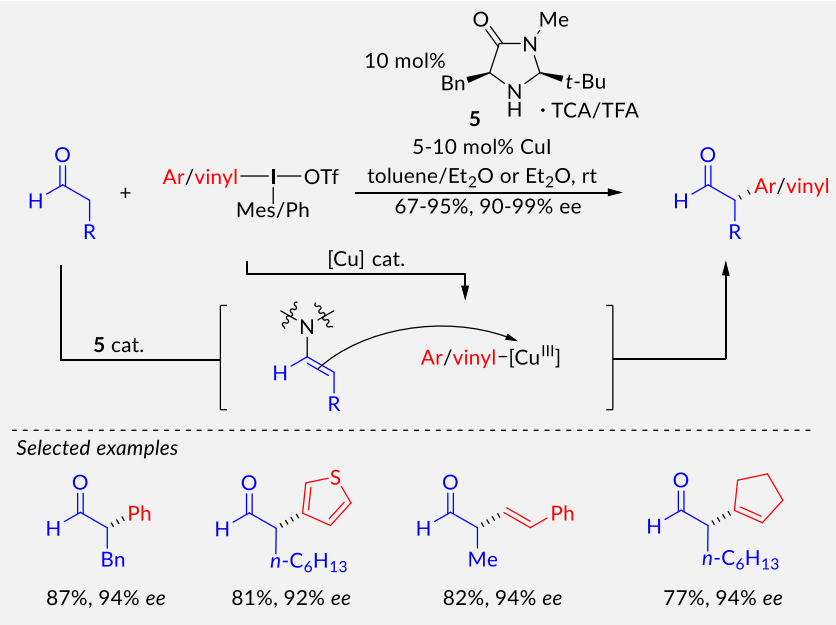

Figure 9. Chiral amine/copper co-catalyzed enantioselective α-arylation/vinylation of aldehydes with iodonium salts.

Huang and co-workers also utilized the enamine activation and developed a cascade α–vinylidenation/γ–alkynylation of aldehydes with silylethynylbenziodoxolone reagent **6** (TIPS-EBX), co-catalyzed by either gold(I) or gold(III) complexes with polypyridine ligands (**Figure 10**).[30] The initial step is the alkynylation of enamine with Au-activated EBX. A subsequent deprotonation of the resulting iminium intermediate generates ynenamine that undergoes another alkynylation in the γ-position, providing a broad scope of multi-functionalized products. The reaction assembles functional group-rich structures and it displays a broad scope.

[30] Wang, Z.; Li, X.; Huang, Y., *Angew. Chem. Int. Ed.* **2013**, *52*, 14219-14223.

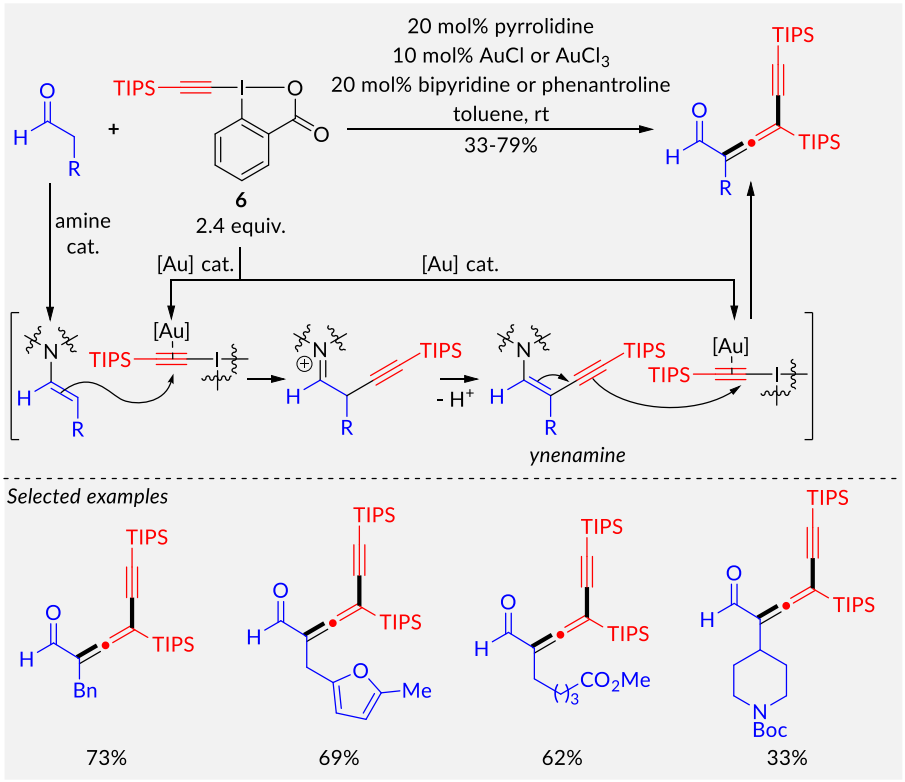

Figure 10. Amine/gold co-catalyzed cascade α-vinylidenation/γ-alkynylation of aldehydes with TIPS-ethynylbenziodoxolones (TIPS-EBX).

To summarize, catalytically generated enamines can be functionalized with hypervalent iodine reagents to provide valuable products. However, the nucleophilicity of enamine species seems to be somewhat insufficient for a direct functionalization with iodine(III) reagents and, thus, an additional activation by a metal co-catalyst is generally required.

In 2006 Macmillan and co-workers reported an enantioselective epoxidation of α,β–unsaturated aldehydes with PhIO **7**, *via* the formation of unsaturated iminium species (**Figure 11**).[31] The reaction is unique in a way that the hypervalent iodine compound acts as a nucleophile during the process. An additional interesting aspect is that monomeric PhIO is generated gradually *in situ* from PhINTs precursor, to prevent the catalyst decomposition caused by PhIO.

[31] Lee, S.; MacMillan, D. W. C., *Tetrahedron* **2006**, *62*, 11413-11424.

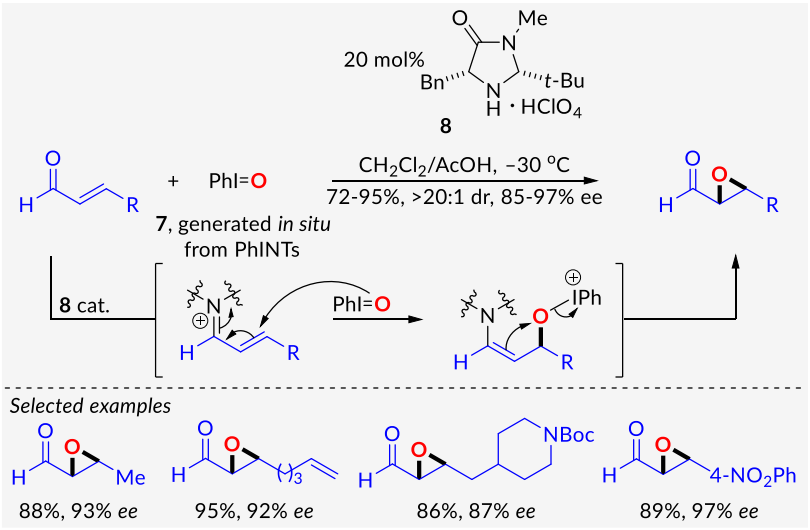

Figure 11. Chiral amine catalyzed enantioselective epoxidation of α,β-unsaturated aldehydes with PhIO.

3.2.2. NHC–Catalysis *via* Formation of Acyl Anion Equivalent or Enolate

Catalytic activation of aldehydes by *N*–heterocyclic carbenes (NHCs) provides so-called Breslow intermediate (see **Section 4**, below), constituting a nucleophilic acyl anion equivalent. In a seminal report from 2013, Gaunt and co-workers have shown that the NHC-derived acyl anion equivalents are prone to react with diaryliodonium triflates, effecting a direct C–H arylation of aromatic aldehydes (**Figure 12**).[32] The reaction utilizes a simple commercially available perfluorophenyl-substituted triazolium NHC-precatalyst **9** and it produces an array of bis(hetero)aryl ketones in moderate to excellent yields. In addition to symmetric diaryliodonium salts, unsymmetric salts with a 1,3-dimethyluracil-5-yl auxiliary non-transferable group were used.

Another type of aldehyde activation by NHC was employed in an α–trifluoromethylation/esterification of α-chloroaldehydes with Togni's II reagent **2**, developed by Besset and co-workers (**Figure 13**).[33] The presence of a leaving group causes the transformation of the Breslow intermediate into the corresponding enolate, which then reacts with the hypervalent iodine compound. The resulting acylazolium is subsequently esterified with methanol co-solvent. Mild reaction conditions deliver a variety of both α–aryl- and α–alkyl-substituted products and the reaction demonstrates good functional group tolerance.

[32] Toh, Q. Y.; McNally, A.; Vera, S.; Erdmann, N.; Gaunt, M. J., *J. Am. Chem. Soc.* **2013**, *135*, 3772-3775.
[33] Gelat, F.; Patra, A.; Pannecoucke, X.; Biju, A. T.; Poisson, T.; Besset, T., *Org. Lett.* **2018**, *20*, 3897-3901.

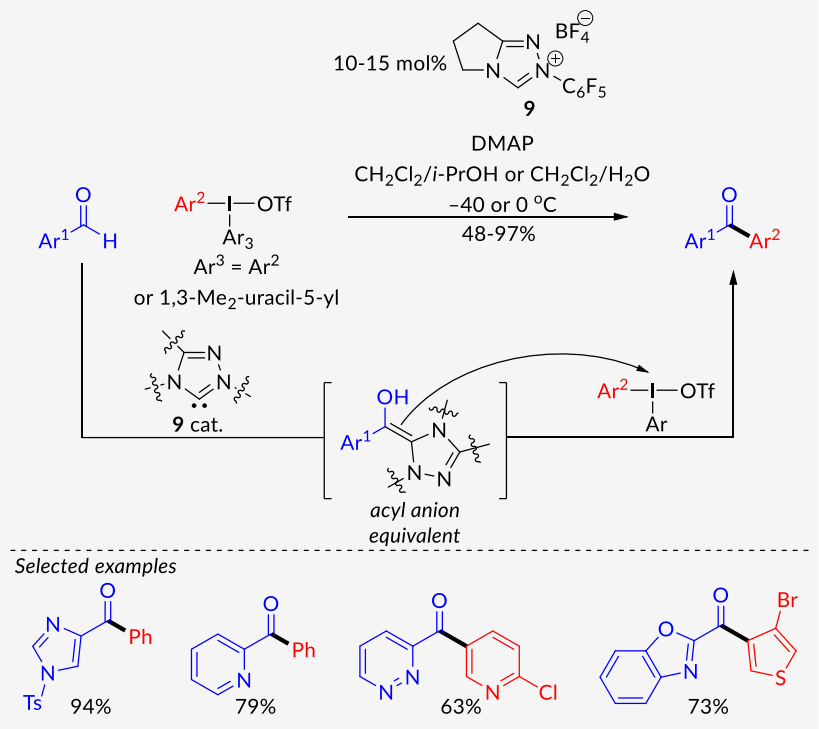

Figure 12. NHC-catalyzed C-H arylation of aldehydes with diaryliodonium salts.

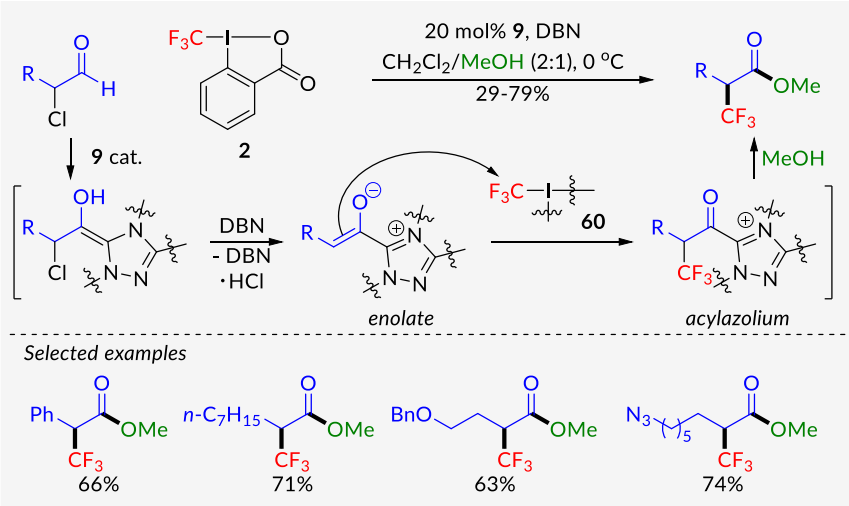

Figure 13. NHC-catalyzed α–trifluoromethylation/esterification of α–chloroaldehydes with Togni's II reagent **2**.

Very recently, the group of Sun reported a related NHC-catalyzed γ–trifluoromethylation/esterification of α,β–unsaturated aldehydes containing a leaving group in the γ-position (**Figure 14**).[34] The reaction proceeds through a mechanism similar to that shown in **Figure 13**, but with a vinylogous enolate intermediate and it allows to obtain a γ–perfluoroalkylated α,β–unsaturated esters in good yields.

[34] Yang, W.; Ma, D.; Zhou, Y.; Dong, X.; Lin, Z.; Sun, J., *Angew. Chem. Int. Ed.* **2018**, *57*, 12097-12101.

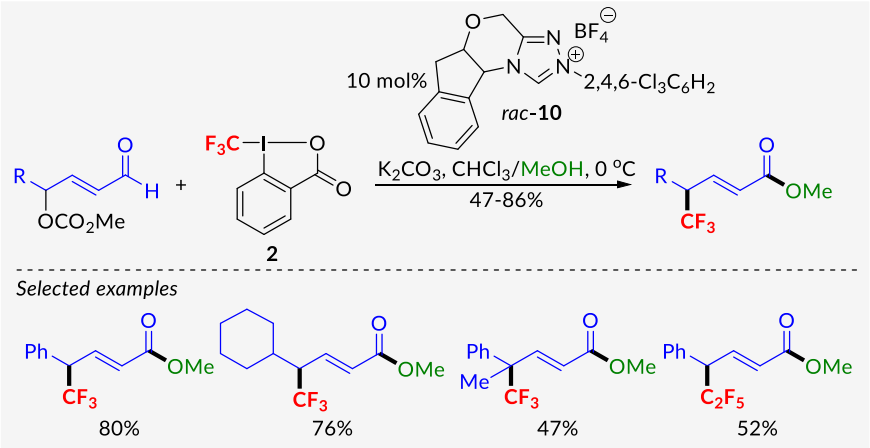

Figure 14. NHC-catalyzed γ-trifluoromethylation/esterification of α,β–unsaturated aldehyde containing leaving group with Togni's II reagent **2**.

3.2.3. Chiral Cation–Directed Catalysis and Brønsted Base Catalysis *via* Pairing with Stabilized Enolates

The formation of ion- or hydrogen-bonded pairs between chiral cations and stabilized enolates has been broadly exploited as a way of the organocatalytic introduction of chirality.[35]

The first application of hypervalent iodine group-transfer reagent *via* this approach has been described by Jérôme Waser, who in 2010 reported that cinchonidine-derived quaternary ammonium salt catalyzes an enantioselective ethynylation of cyclic β–ketoester using silylethynylbenziodoxolone **6** (TMS-EBX) with 40% *ee* under phase-transfer catalysis (PTC) conditions.[36a] Further evaluation of a variety of chiral phosphonium and ammonium salts allowed increasing the enantioselectivity to 79%.[36b] Finally, Marouka and co-workers broke the barrier of 90% *ee* in an analogous reaction, by the application of a sterically hindered ammonium PTC catalyst **13** and ethynyl[bis(trifluoromethyl)]benziodoxole reagent **12** (**Figure 15**).[37]

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[35] (a) Brak, K.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2013,** *52*, 534-561; (b) Shirakawa, S.; Maruoka, K., *Angew. Chem. Int. Ed.* **2013,** *52*, 4312-4348; (c) Schörgenhumer, J.; Tiffner, M.; Waser, M., *Beilstein J. Org. Chem.* **2017,** *13*, 1753-1769.

[36] (a) Fernández González, D.; Brand, J. P.; Waser, J., *Chem. Eur. J.* **2010,** *16*, 9457-9461; (b) Fernández González, D.; Brand, J. P.; Mondière, R.; Waser, J., *Adv. Synth. Catal.* **2013,** *355*, 1631-1639.

[37] Wu, X.; Shirakawa, S.; Maruoka, K., *Org. Biomol. Chem.* **2014,** *12*, 5388-5392.

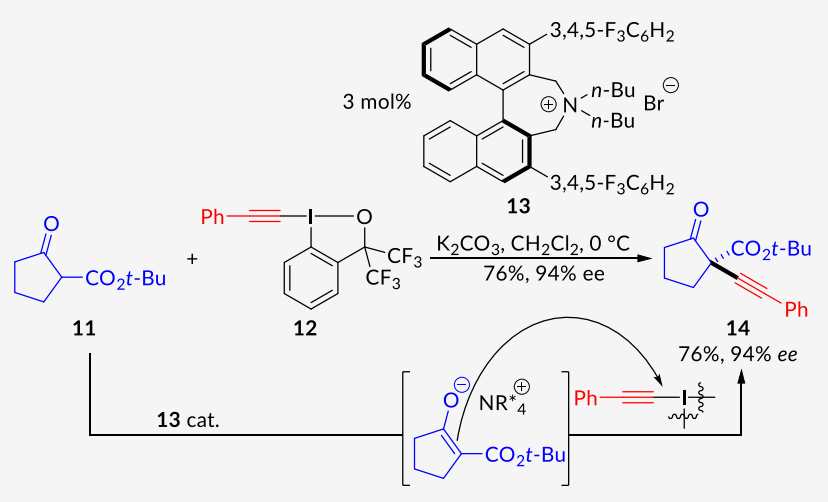

Figure 15. Ethynylation of cyclic β–ketoesters with benziodoxole **11** under PTC conditions using chiral quaternary ammonium salt.

In 2013, Veselý and co-workers utilized another cinchonidine-based ammonium salt **15** to catalyze the ethynylation of α–fluorosulfones bearing electron-withdrawing substituents with TMS-EBX **6** (**Figure 16**).[38] The obtained enantioselectivities were moderate. Further, they also attempted the asymmetric ethynylation of pyrazolones with **6**, but none of the tested *Cinchona* alkaloid-based catalysts delivered decent results in terms of the chirality transfer.[39]

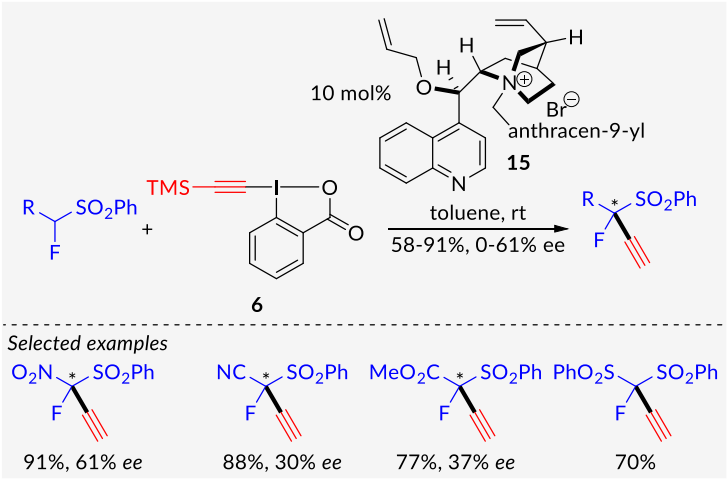

Figure 16. Ethynylation of α–fluorosulfones with TMS-EBX using cinchonidine-derived quaternary ammonium salt catalyst.

The group of Mario Waser investigated an array of quaternary ammonium salts and tertiary amines for their ability to catalyze enantioselective CN and N_3 groups transfer from the corresponding benziodoxolone reagents **16** and **17** to cyclic

[38] Kamlar, M.; Putaj, P.; Veselý, J., *Tetrahedron Letters* **2013,** *54*, 2097-2100.
[39] Kamlar, M.; Císařová, I.; Veselý, J., *Org. Biomol. Chem.* **2015,** *13*, 2884-2889.

β–ketoesters. Cinchonidine **18** was determined to be the best catalyst among the tested ones, however, *ee* did not exceed 66% (**Figure 17**).[40]

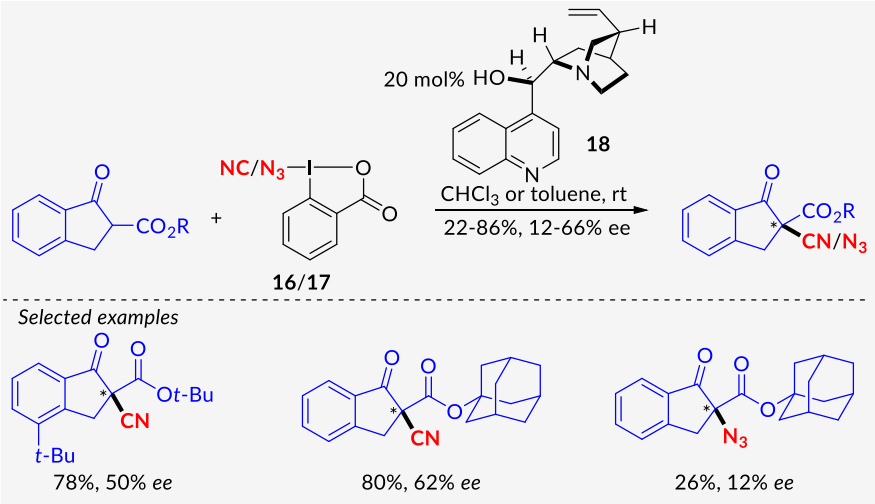

Figure 17. Cinchonidine-catalyzed cyanation and azidation of cyclic β–ketoesters with CN/N_3–benziodoxolones.

3.3. Organocatalytic Activation of Hypervalent Iodine Reagent

3.3.1. Brønsted and Lewis Acid Catalysis

Acid organocatalysis has been found as a useful mean to promote many enantioselective reactions.[41] Organic Brønsted and Lewis acids have also been used in several reactions involving group-transfer hypervalent iodine reagents. The main mechanism of action of the acid catalyst is to increase the electrophilicity of the iodine species, making the group transfer to nucleophilic acceptors more facile.

In the chemistry of cyclic hypervalent iodine compounds the activation by acids is frequently employed, thus, not surprisingly this group of transfer reagents have been used in the combination with organic acid catalysts. In 2011, Togni and co-workers developed a Ritter-type reaction, between azoles and CF_3-benziodoxole **3** in MeCN, in the presence of catalytic amounts of triflimide (**Figure 18**).[42] Protonation of the oxygen

[40] (a) Chowdhury, R.; Schörgenhumer, J.; Novacek, J.; Waser, M., *Tetrahedron Lett.* **2015**, *56*, 1911-1914; (b) Tiffner, M.; Stockhammer, L.; Schörgenhumer, J.; Röser, K.; Waser, M., *Molecules* **2018**, *23*, 1142.

[41] (a) Akiyama, T.; Mori, K., *Chem. Rev.* **2015**, *115*, 9277-9306; (b) Min, C.; Seidel, D., *Chem. Soc. Rev.* **2017**, *46*, 5889-5902; (c) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G., *Chem. Eur. J.* **2018**, *24*, 3925-3943.

[42] Niedermann, K.; Früh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A., *Angew. Chem. Int. Ed.* **2011**, *50*, 1059-1063.

atom in the iodoxole ring of **3** by $HNTf_2$ weakens the I–O bond and this way promotes the transfer of the CF_3 group to acetonitrile. The resulting *N*–trifluoromethyl nitrilium ion reacts then with a heterocyclic substrate, furnishing *N'*–substituted *N*–trifluoromethylimidoyl azole product.

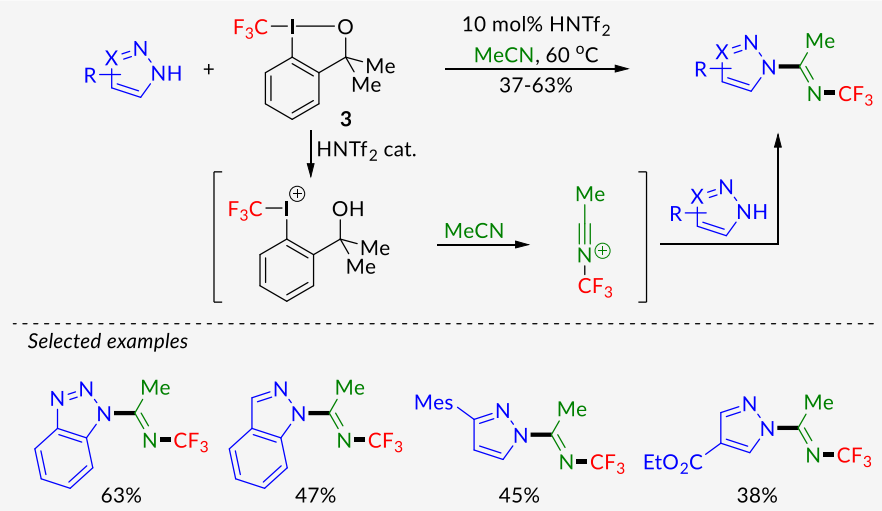

Figure 18. Triflimide-catalyzed Ritter-type trifluoromethylation of azoles with CF_3-benziodoxole.

As a result of further investigations, the same group described a direct *N*–trifluoromethylation of azoles utilizing $HNTf_2$ catalyst, as well (**Figure 19**).[43] In order to secure satisfactory reactivity, azoles were silylated *in situ* prior to the reaction with **3**. A small amount of $LiNTf_2$ was used to prevent interference of side-formed fluorides and to increase the efficiency of product formation.

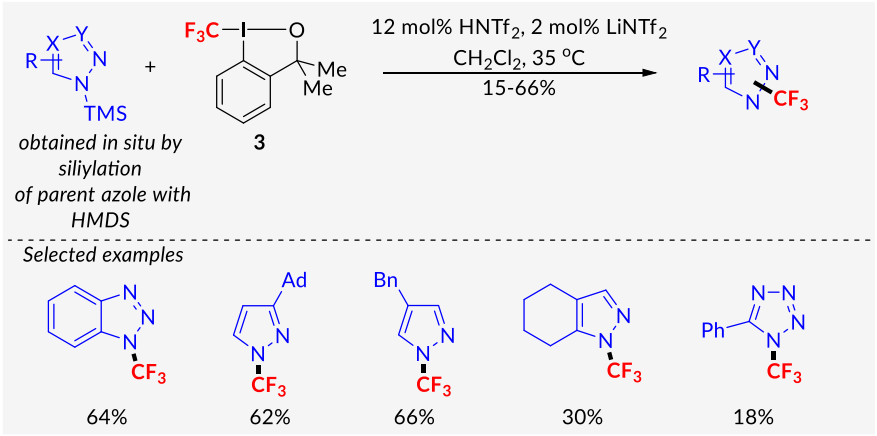

Figure 19. Triflimide-catalyzed trifluoromethylation of azoles with CF_3-benziodoxole.

An organic Lewis acid has also been applied for the activation of a benziodoxole reagent. Recently, Minakata described a cyanation of silyl enol ethers with

[43] Niedermann, K.; Früh, N.; Senn, R.; Czarniecki, B.; Verel, R.; Togni, A., *Angew. Chem. Int. Ed.* **2012**, *51*, 6511-6515.

cyanobenziodoxole **19** catalyzed by tris(pentafluorophenyl)borane (**Figure 20**).[44] Mild reaction conditions secure the formation of variety of α–cyanoketones products. Spectroscopic investigation clearly demonstrates the interaction of the borane with the CN group, not the oxygen atom, of **18** as the possible mechanism of catalysis.

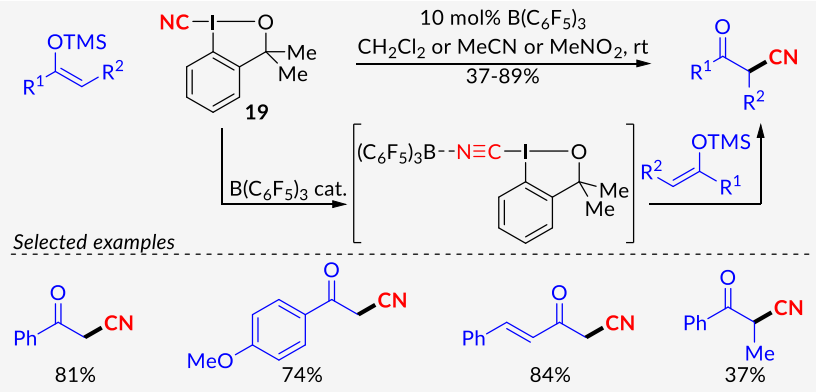

Figure 20. Borane-catalyzed cyanation of silyl enols ethers with CN-benziodoxole.

In 2015, the group of Nagorny described an arylation of carboxylic acids with diaryliodonium triflates, co-catalyzed by thiophosphoramide hydrogen-bond-donor **20** and $Cu(OTf)_2$ (**Figure 21**).[45] The reaction proceeds under noticeably milder conditions compared to earlier uncatalyzed protocols.[19b, 46] The role of **20** is to bond with triflate anion resulting in the enhancement of the electrophilicity of the concomitant cation. Interestingly, the arylation yield was improved by both thiophosphoramide and $Cu(OTf)_2$ independently, but when the two reagents were used simultaneously a further improvement in efficiency was achieved. Thus, it indicates that **20** enhances the reactivity of both iodonium salt and cationic organocopper intermediate, and the latter effect is significant.

[44] Nagata, T.; Matsubara, H.; Kiyokawa, K.; Minakata, S., *Org. Lett.* **2017**, *19*, 4672-4675.
[45] Bhattarai, B.; Tay, J.-H.; Nagorny, P., *Chem. Commun.* **2015**, *51*, 5398-5401.
[46] Petersen, T. B.; Khan, R.; Olofsson, B., *Org. Lett.* **2011**, *13*, 3462-3465.

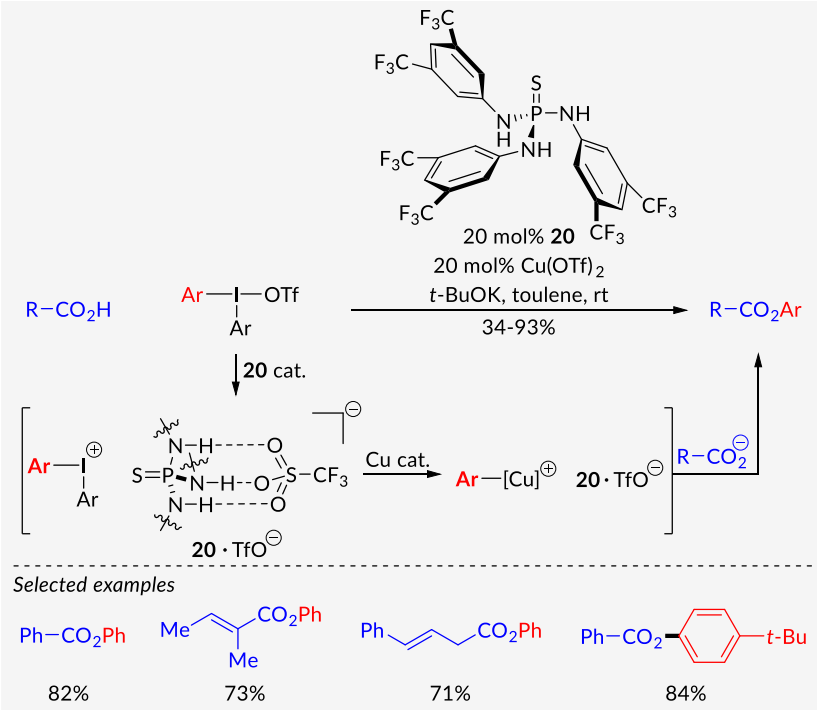

Figure 21. Thiophosphoramide/copper co-catalyzed arylation of carboxylates with diaryliodonium salts.

An alluring example of a Lewis acid umpolung activation of iodonium ylides with 2-iodoimidazolium catalysts was described by Takemoto in 2017. The iodonium ylide acts as a 1,3-dicarbonyl moiety transfer reagent to silyl enol ethers, delivering formal cross-enolate coupling products (**Figure 22**).[47] Using experimental and computational evidence, the authors demonstrated that 2-iodoimidazolium cations **21** or **22** form an explicit halogen bond with iodonium ylide, activating it toward the nucleophilic attack.

[47] Saito, M.; Kobayashi, Y.; Tsuzuki, S.; Takemoto, Y., *Angew. Chem. Int. Ed.* **2017**, *56*, 7653-7657.

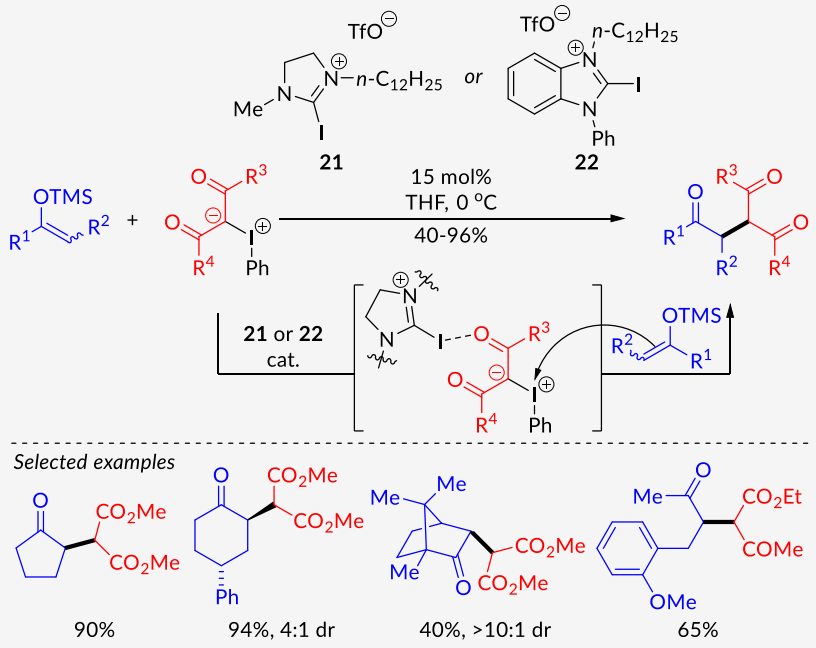

Figure 22. 2-Iodoimidazolium-catalyzed transfer of 1,3-dicarbonyl from iodonium ylides to silyl enol ethers.

By the involvement of Brønsted base co-catalyst the scope of this methodology could be expanded to protonucleophiles. 3–Substituted oxindoles were exploited as substrates, furnishing interesting building blocks for the synthesis of indole-derived natural products, possessing all-carbon quaternary centers at the C3–position (**Figure 23**).[47]

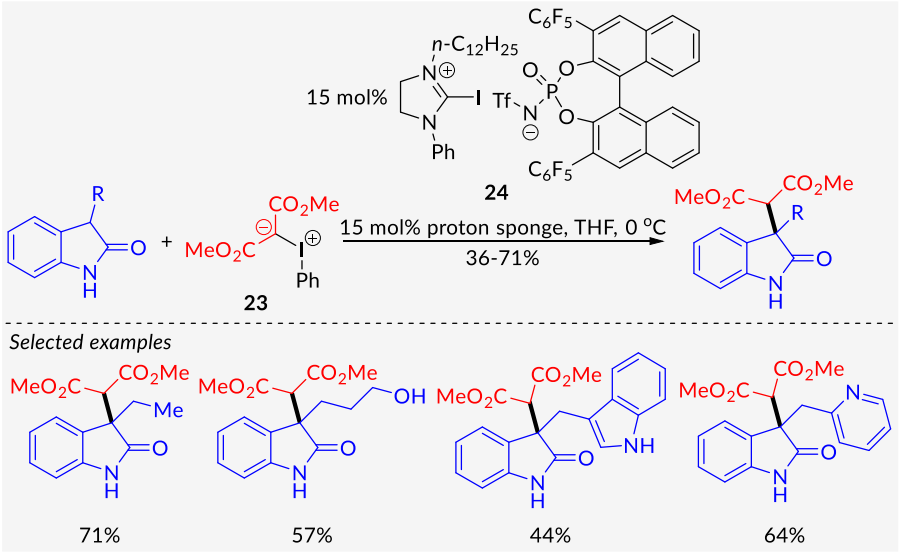

Figure 23. 2-Iodoimidazolium/proton sponge co-catalyzed transfer of 1,3-dicarbonyl from iodonium ylides to oxindoles.

3.3.2. Lewis Base Catalysis

In the literature there exists an isolated example of the application of a Lewis base to activate a hypervalent iodine group-transfer reagent. Namely, in 2011 the group of Nicolaou has developed an enantioselective dichlorination of allylic alcohols with aryliodine dichloride **25**, catalyzed by a dimeric *Cinchona* alkaloid derivative $(DHQ)_2PHAL$ **26** (**Figure 24**).[48] The reaction delivers a range of 2,3-dichloroalcohols in synthetically useful yields and moderate to good *ee*. The diastereospecific course of the dichlorination points to the formation of chloronium cation intermediate. Authors proposed that **26** promotes the chlorine transfer by attacking reagent **25** with one of the quinuclidine nitrogen atoms. The chlorine atom is then delivered to the olefin in an enantioselective fashion, assisted by the hydrogen bonding between the hydroxyl group of the alcohol and the phthlazine nitrogens.

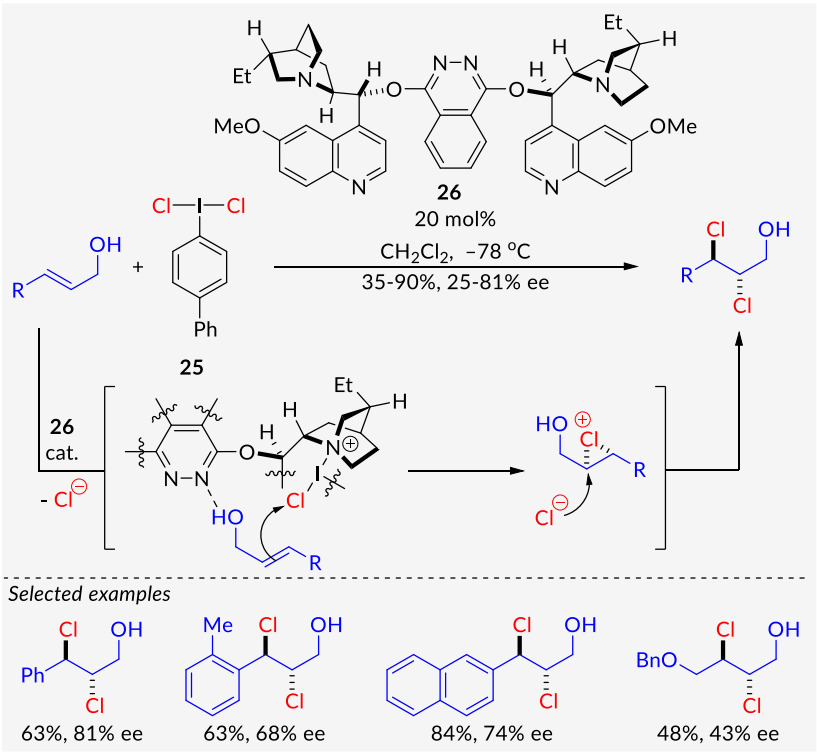

Figure 24. $(DHQ)_2PHAL$-catalyzed enantioselective dichlorination of allylic alcohols with aryliodine dichloride **25**.

[48] Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S., *J. Am. Chem. Soc.* **2011**, *133*, 8134-8137.

3.3.3. Radical Reactions with Organic Promoters and Catalysts

The capability of hypervalent iodine compounds to undergo free radical reactions has already been realized in the 1980s and 1990s. The discoveries from this early period demonstrated that iodine(III) species can both be the source of radicals (*via* the photochemical or thermal homolysis of X–I(R)X bond) and participate in the radical reactions.[49] In particular, recently the radical photochemical reactions have attracted considerable attetntion[50] and there is a small but robust group of transformations utilizing organic molecules to promote the group transfers from iodine(III) reagents *via* radical pathway.

In 1995, Magnus reported a TEMPO-catalyzed 1,2-bisazidation of silyl enol ethers with $PhI(N_3)_2$ **27**, formed *in situ* from iodosobenzene and TMS-azide (**Figure 25**).[51] The mechanism involves the creation of an azido radical upon the action of TEMPO on **27**. Once formed, the azido radical is engaged in a radical chain, involving a selective $N_3^{\bullet}$ addition to the 2-position of silyl enol ether. The ion pair of oxonium and azide, formed in the second step, undergoes a recombination, yielding the final product.

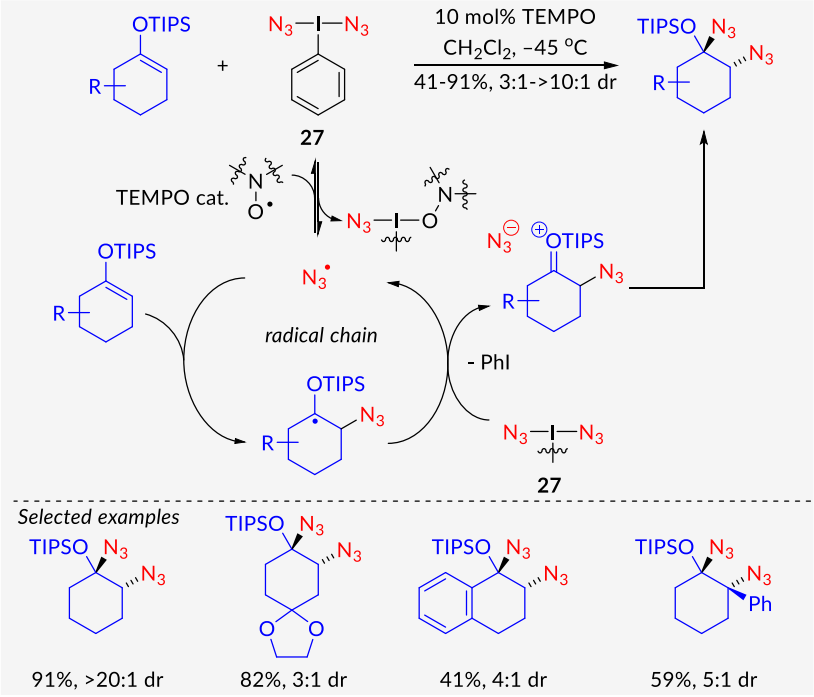

Figure 25. TEMPO-promoted 1,2-bis azidation of silyl enol ethers with *in situ* generated phenyliodine diazide.

[49] Togo, H.; Katohgi, M., *Synlett* **2001**, *2001*, 0565-0581.
[50] Wang, L.; Liu, J., *Eur. J. Org. Chem.* **2016**, *2016*, 1813-1824.
[51] (a) Magnus, P.; Roe, M. B.; Hulme, C., *J. Chem. Soc., Chem. Commun.* **1995**, 263-265; (b) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C., *J. Am. Chem. Soc.* **1996**, *118*, 3406-3418.

The group of Vankar, inspired by above reaction, over 20 years later developed a TEMPO-promoted synthesis of 2-azido-2-deoxysugars from glycals (**Figure 26**).[52] The reaction proceeds with a complete regio- and diastereoselectivity, providing various azide-containing carbohydrate analogs.

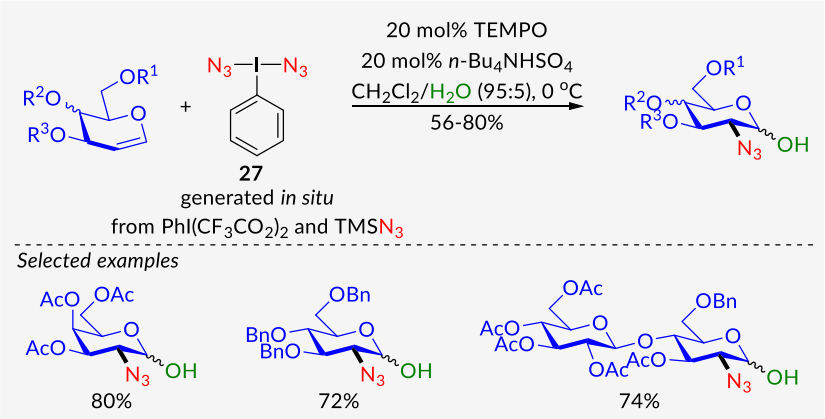

Figure 26. TEMPO-promoted synthesis of 2-azido-2-deoxysugars from glycals and *in situ* generated phenyliodine diazide.

Another organic initiator used to provide radicals from hypervalent iodine reagents is tetra-*n*-butylammonium iodide (*n*-Bu_4NI, TBAI). Studer and co-workers were the first who applied TBAI in this context, in their trifluoromethylation/cyclization of isonitriles to deliver 6–triflurомethylphenanthridines, employing Togni's II reagent **2** (**Figure 27**).[53] The reaction is initiated by the oxidation of TBAI iodide anion to iodine by **2** with a parallel generation of a trifluoromethyl radical. $CF_3^{\bullet}$ enters then a radical chain process sustained by isonitrile substrate and **2**. The same research group has later extended this methodology to the synthesis of 2-trifluoromethylated indoles.[54]

It needs to be noted that the mechanism of catalysis with TBAI remains still disputed. Nearly coincidently with the Studer's publication, Nevado and co-workers also reported a trifluoromethylation/cyclization sequence, in which they used the same combination of **2** and TBAI (**Figure 28**).[55] In this case, based on the lack of interference by TEMPO, the authors proposed an ionic mechanism rather than a radical one.

[52] Chennaiah, A.; Vankar, Y. D., *Org. Lett.* **2018,** *20*, 2611-2614.

[53] Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A., *Angew. Chem. Int. Ed.* **2013,** *52*, 10792-10795.

[54] Zhang, B.; Studer, A., *Org. Lett.* **2014,** *16*, 1216-1219.

[55] Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C., *Angew. Chem. Int. Ed.* **2013,** *52*, 13086-13090.

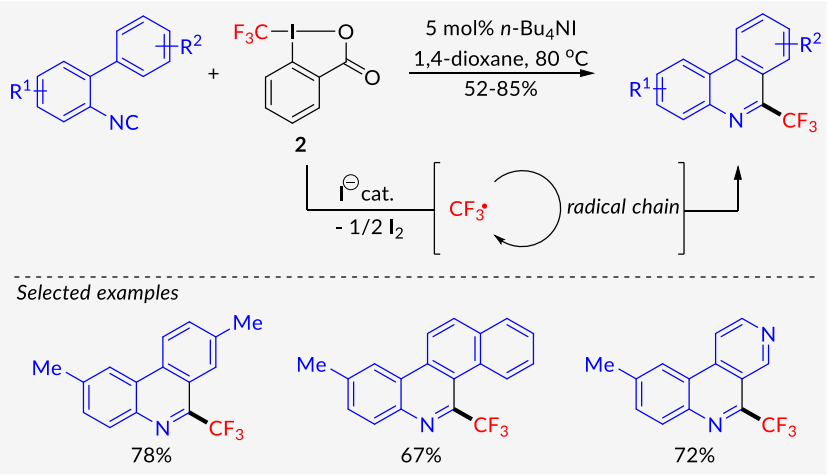

Figure 27. TBAI-promoted trifluoromethylation/cyclization of isonitriles with CF_3-benziodoxolone.

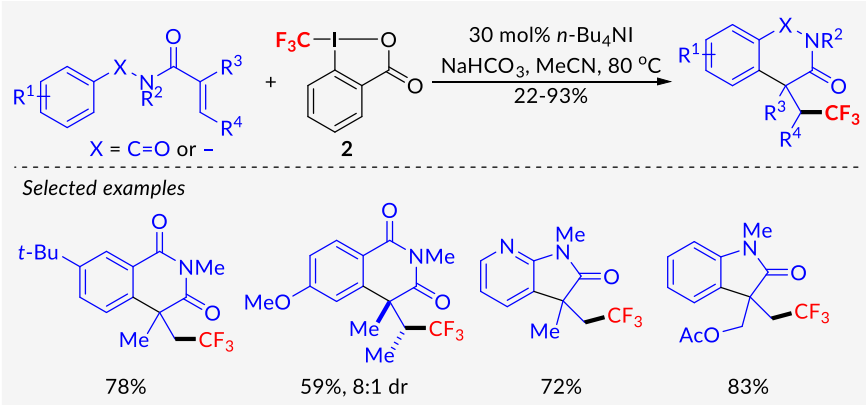

Figure 28. TBAI-promoted trifluoromethylation/cyclization of α,β–unsaturated amides with CF_3-benziodoxolone.

A very similar inconsistency in the mechanistic interpretation occurs for the TBAI-catalyzed C–H azidation of aldehydes with azidobenziodoxolone **17**, described by Zhdankin in 2015 (**Figure 29**),[56] and a similar C–H trifluoromethylation of aryl–*N*,*N*–dimethyl hydrazones with **2**, developed by Studer in 2017 (**Figure 30**).[57] The authors of the former report postulated the generation of IN_3, which would act as the actual azidation reagent, whereas in the latter case a radical chain pathway, through a free $CF_3^{\bullet}$, was implicated.

[56] Shinomoto, Y.; Yoshimura, A.; Shimizu, H.; Yamazaki, M.; Zhdankin, V. V.; Saito, A., *Org. Lett.* **2015**, *17*, 5212-5215.

[57] Janhsen, B.; Studer, A., *J. Org. Chem.* **2017**, *82*, 11703-11710.

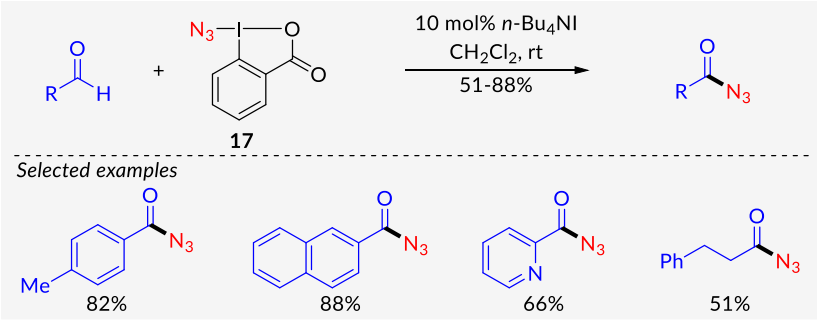

Figure 29. TBAI-promoted C-H trifluoromethylation of aldehydes with N_3-benziodoxolone.

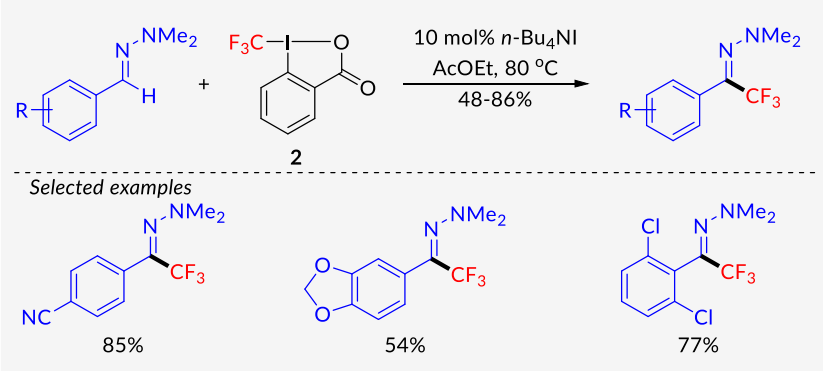

Figure 30. TBAI-promoted C–H trifluoromethylation of aryl–*N*,*N*–dimethyl hydrazones with CF_3-benziodoxolone.

In 2015 Liu and co-workers employed tertiary phosphine **28** to catalyze bistrifluoromethylation of aminoalkenes in two remote sites using Togni's II reagent **2** (**Figure 31**).[58] Due to its ability to undergo a one-electron oxidation, **28** induces the formation of $CF_3^{\bullet}$ radical from **2**. The addition of $CF_3^{\bullet}$ to the alkene, followed by a 1,5–hydrogen shift, generates a more favored benzylic radical. Next, the phosphonium radical cation reclaims the electron, after further deprotonation, furnishing an intermediate alkene **29**. Alternatively, the reaction can occur to by the propagation of the radical chain. The repetitive trifluoromethylation of **29**, proceeding in a similar fashion, secures the formation of final product.

[58] Yu, P.; Zheng, S.-C.; Yang, N.-Y.; Tan, B.; Liu, X.-Y., *Angew. Chem. Int. Ed.* **2015**, *54*, 4041-4045.

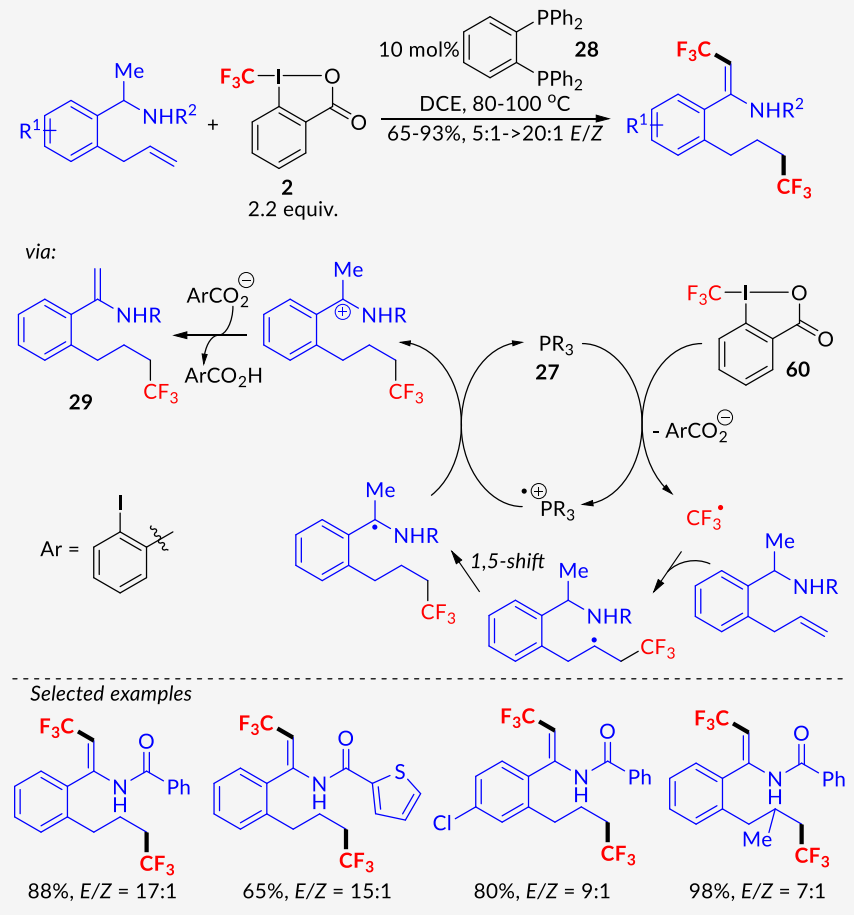

Figure 31. Phosphine-catalyzed bistrifluoromethylation of aminoalkenes with CF_3-benziodoxolone. Note that only the mechanism for the first CF_3-transfer is shown, the subsequent trifluoromethylation of intermediate **29** proceeds in a similar fashion, but without the 1,5–hydrogen shift.

A year later, the same group demonstrated that a tertiary amine **30** (1,5-diazabicyclo[4.3.0]nonene-5, DBN) is able to catalyze the formation of $CF_3^{\bullet}$ radicals from **8**, as well. This was employed in a trifluoromethylation/cyclization of unactivated alkenes with CF_3-benziodoxolone **2** (**Figure 32**).[59] A similar catalytic cycle to that shown in **Figure 31** is also expected for **30**, i.e. the generation of $CF_3^{\bullet}$ *via* the transient oxidation of the amine catalyst to an ammonium radical cation.

The first photo-organocatalytic group transfer reaction with a hypervalent iodine reagent was developed by Scaiano in 2014. The application of methylene blue **31** (MB) as the catalyst, under visible light irradiation, allows to obtain various trifluoromethylated pyrrole and thiophenes (**Figure 33**).[60] The exited state of **31** has an oxidizing character and additional TMEDA serves as a supporting electron donor, which

[59] Yang, N.-Y.; Li, Z.-L.; Ye, L.; Tan, B.; Liu, X.-Y., *Chem. Commun.* **2016,** *52*, 9052-9055.
[60] Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C., *ACS Catal.* **2014,** *4*, 2530-2535.

undergoes the first SET. The MB• radical induces then the generation of CF_3• from **2**, that after a number of further steps affords the trifluoromethylated product.

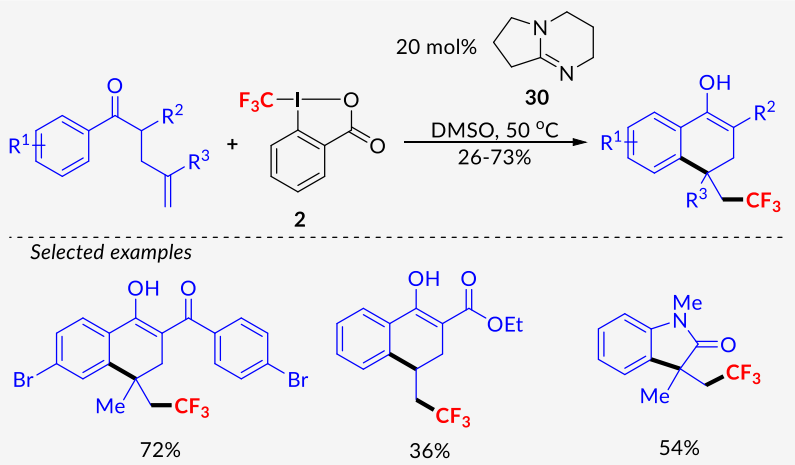

Figure 32. Amine-catalyzed trifluoromethylation/cyclization of unactivated alkenes with CF_3-benziodoxolone.

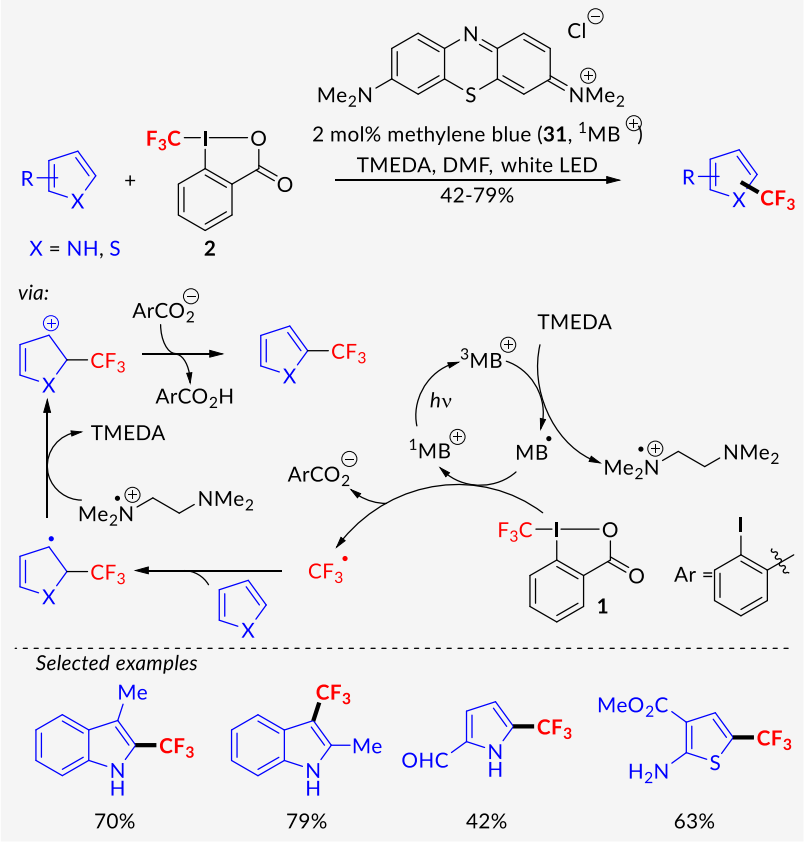

Figure 33. Methylene blue-photocatalyzed trifluoromethylation of pyrroles and thiophene with CF_3-benziodoxolone.

In 2016, the group of Cheng showed that a simple and inexpensive 9,10–dicyanoanthracene photocatalyst **32** is able to effectively induce a decarboxylative

alkynylation of carboxylic acids with ethynylbenziodoxolones (**Figure 34**).[61] The reaction have been earlier limited to using of transition metal catalysts only.[62] In this case, the photocatalyst promotes the generation of a carboxyl radical from carboxylic acid, which undergoes decarboxylation and produces an alkyl radical intermediate that then reacts with cyclic hypervalent iodine reagent.

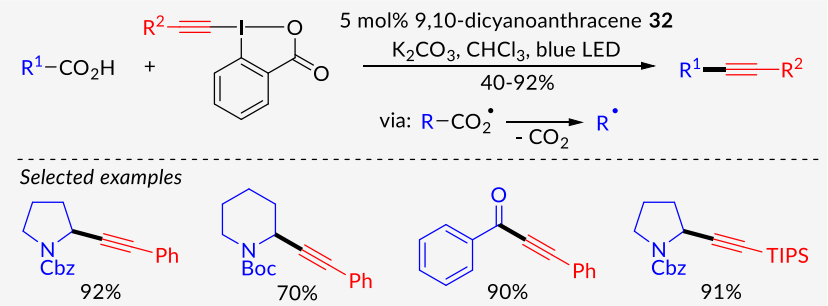

Figure 34. 9,10-Dicyanoanthracene-photocatalyzed decarboxylative alkynylation of carboxylic acids with ethynylbenziodoxolones.

9-Mesityl-10-methylacridinium **33** (MesAcr) was used by the group of Frenette as a photocatalyst in the alkylation of nitrogen heteroaromatics with phenyliodine(III) dicarboxylates (**Figure 35**).[63] It is worth mentioning that organocatalyst **33** displayed better activity in this reaction compared to Ru- and Ir-based alternatives. The mechanistic investigations showed that the key radical-generating step of the mechanism involves a one-electron reduction of iodonium species, and not of a free carboxylic acid.

Zhang and co-workers have developed an outstanding light-induced multicomponent radical coupling catalyzed by Eosine Y **34**. The transformation involves sequence of arylation/sulfonylation/cyclization of arylpropargylamines with diaryliodonium tosylates and DABCO · $(SO_2)_2$ serving as the aryl and SO_2 sources, respectively (**Figure 36**).[64] The reaction is believed to be initiated by a SET process upon the reduction of iodonium salt by the excited state of **34**, that generates an aryl radical. A series of radical additions, followed by deprotonation and second SET reduction affords 1,2-dihydroquinoline intermediate, which after an oxidative aromatization delivers the final product.

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[61] Yang, C.; Yang, J.-D.; Li, Y.-H.; Li, X.; Cheng, J.-P., *J. Org. Chem.* **2016,** *81*, 12357-12363.

[62] (a) Zheng, Y.; Jiao, Y.; Jaroniec, M.; Qiao, S. Z., *Angew. Chem. Int. Ed.* **2015,** *54*, 52-65; (b) Zhou, Q.-Q.; Guo, W.; Ding, W.; Wu, X.; Chen, X.; Lu, L.-Q.; Xiao, W.-J., *Angew. Chem. Int. Ed.* **2015,** *54*, 11196-11199; (c) Le Vaillant, F.; Courant, T.; Waser, J., *Angew. Chem. Int. Ed.* **2015,** *54*, 11200-11204.

[63] Genovino, J.; Lian, Y.; Zhang, Y.; Hope, T. O.; Juneau, A.; Gagné, Y.; Ingle, G.; Frenette, M., *Org. Lett.* **2018,** *20*, 3229-3232.

[64] Sun, D.; Yin, K.; Zhang, R., *Chem. Commun.* **2018,** *54*, 1335-1338.

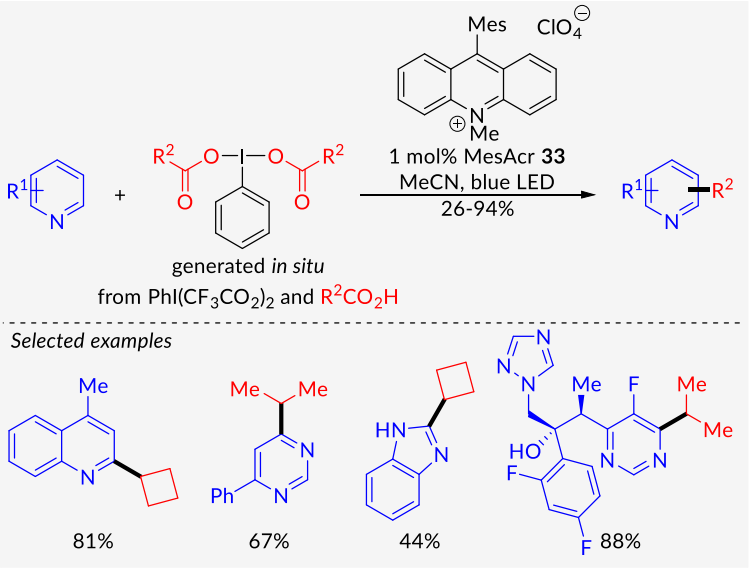

Figure 35. 9-Mesityl-10-methylacridinium-photocatalyzed decarboxylative alkylation of nitrogen heteroaromatics with phenyliodine dicarboxylates.

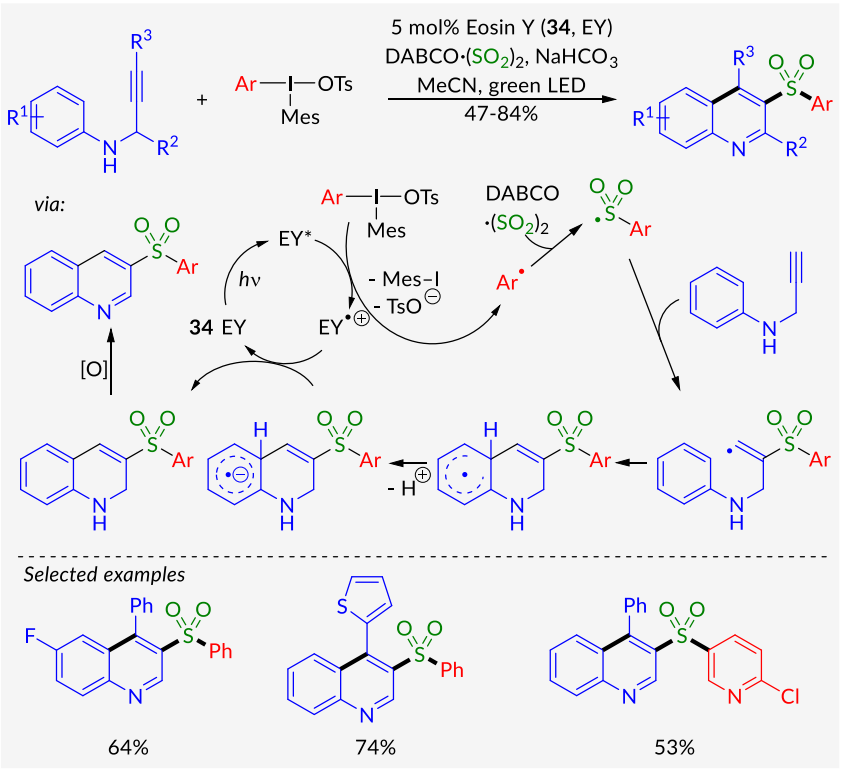

Figure 36. Eosin Y-photocatalyzed arylation/sulfonylation/cyclization of arylpropargylamines with diaryliodonium tosylates.

The group of Waser reported a cascade fragmentation/alkynylation of cyclic oxime ethers with ethynylbenziodoxolones (EBXs) using a fine-tuned organic photoredox catalyst **35** based on 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile scaffold

(**Figure 37**).[65] The exited photocatalyst promotes the formation of a radical from the carboxylic group of the acceptor. After the release of CO_2 and acetone, followed by ring opening, the resulting alkyl radical reacts with the hypervalent iodine reagent and delivers an array of functionalized nitriles.

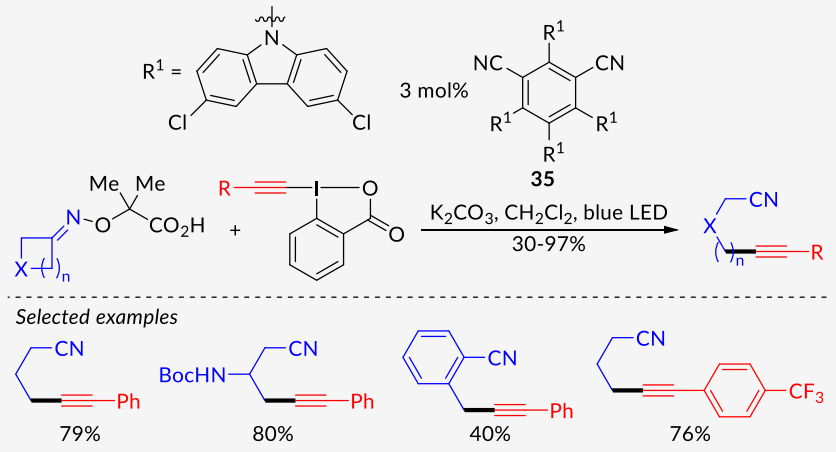

Figure 37. 2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile-photocatalyzed fragmentation/alkynylation of cyclic oxime ethers with ethynylbenziodoxolones.

3.4. Summary and Outlook

To summarize, the presented reactions establish robust synthetic methods, allowing for the direct formation of variety chemical bonds difficult to access by classical tools of organic chemistry. The most important point is that the application of organocatalysts results in equally well or even better outcomes than the equivalent metal catalysis, as illustrated by for example the acid– and photocatalyzed reactions. The fusion of environmental benign character of hypervalent iodine compounds and organocatalysts is the key driving force for the development of novel and more sustainable reactions employing the combination of these two types of reagents. Naturally, the use of organocatalysts is not perfect – for instance, a frequent need of high catalyst loadings remains outstanding major challenges in this area.

[65] Le Vaillant, F.; Garreau, M.; Nicolai, S.; Gryn'ova, G.; Corminboeuf, C.; Waser, J., *Chem. Sci.* **2018**, *9*, 5883-5889.

4. *N*–Heterocyclic Carbene Organocatalysis

The catalysis using small organic molecules is one of the most intensively developing areas in organic chemistry. This approach has also been quickly adopted among the chemical synthesis community. The fundamental advantages of organocatalysis are the ease and low cost of carrying out such reactions in the laboratory. The advent of organocatalysis brought the prospect of a variety of catalytic modes, and the potential for savings in cost, time, and energy, easier experimental procedures, and reductions in toxic chemical waste. The organic molecules are generally resistant to oxygen and moisture in the atmosphere, so there is no need for advanced glassware, storage containers, and experimental techniques, or for ultra-dry reagents and solvents. A wide variety of organic reagents — such as amino acids, carbohydrates, and hydroxy acids — are naturally and readably available from biological sources as single enantiomers. Organocatalysts are therefore usually cheap to prepare and accessible in a range of quantities, suitable from small-scale up to industrial-scale reactions. Small organic molecules are typically non-toxic and environmentally friendly, increasing the safety in chemical research across many settings, including the industry and academic institutions. From the plethora of applications, one of the mostly exploited is nucleophilic organocatalysis, based on molecules such as secondary amines,[66] amides and their various derivatives,[67] phosphines,[68] and finally ***N*–heterocyclic carbenes**.

[66] Erkkilä, A.; Majander, I.; Pihko, P. M., *Chem. Rev.* **2007**, *107*, 5416-5470.

[67] Doyle, A. G.; Jacobsen, E. N., *Chem. Rev.* **2007**, *107*, 5713-5743.

[68] (a) Methot, J. L.; Roush, W. R., *Adv. Synth. Catal.* **2004**, *346*, 1035-1050; (b) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O., *Chem. Rev.* **2018**, *118*, 10049-10293.

4.1. Structural Features and Properties of *N*–Heterocyclic Carbenes

The first successful isolation and characterization of an *N*–heterocyclic carbene (NHC) has been achieved by Arduengo in 1991[69] and it was quickly announced as one of the most significant milestones in general field of organic chemistry. Cryptic, but fundamental questions about properties, reactivity, structure, and character of NHCs have been answered, allowing great development and enhancement in several areas, such as organometallic chemistry, material science, and organic synthesis. There is no doubt about ranking NHCs among the most powerful tools in organic chemistry.

Carbene is a chemical entity containing a neutral two-valent carbon atom having two free valence electrons. It possesses 6 valence electrons making it a hypovalent species. Due to the open valence shell it can occur as both singlet and triplet. For simple hydrocarbon–based carbenes the ground state is the triplet, in line with Hund's rule of maximum multiplicity. Nonetheless, the singlet state can be stabilized by introducing substituents, which possess lone electron pairs, in particular nitrogen atoms, hence *N*–heterocyclic carbenes. The withdrawal of electron density from carbonic center by nitrogen atoms and a parallel π–donation from nitrogen's occupied orbitals to the empty p orbital of carbene increases the stability of the singlet state and effect on its highly nucleophilic character (**Figure 38**).

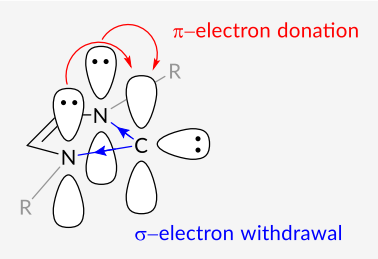

Figure 38. Electronic structure of an *N*–heterocyclic carbene.

The discovery and development of *N*–heterocyclic carbenes is undoubtedly one of the greatest scientific stories of late chemistry research. Many contributions from different research groups on the structure, coordination chemistry and reactivity have led to a multitude of applications across a variety of chemistry fields. Their application in organic and organometallic chemistry offers new possibilities and opens totally new horizons – one of them is **NHC organocatalysis**.

[69] Arduengo, A. J.; Harlow, R. L.; Kline, M., *J. Am. Chem. Soc.* **1991**, *113*, 361-363.

4.2. Principles of *N*–Heterocyclic Carbene "Umpolung"

The key aspect related to the *N*–heterocyclic organocatalysis is the concept of "umpolung". Known also as a "inverted polarity", *the phenomenon is the intended chemical modification of a certain functional group with the aim of "forced" reversal of the polarity of that group.* The name umpolung has been coined by Dieter Seebach and Elias J. Corey as a consequence of their research on 1,3–dithianes.[70] They postulated that sulfur–stabilized carboanion could be a suitable nucleophile in reactions with common electrophiles such as alkyl halides, aldehydes, or ketones. Moreover, this carboanion can be considered as a masked acylating equivalent, due to the ease of inverting carbonyl group to dithiane and reverse. Nevertheless, this precedence was not the only one of its kind. Nearly 150 years before, Wöhler and Liebig discovered a condensation reaction, catalyzed by cyanide anions, between two molecules of benzaldehyde leading to benzoin (2–hydroxy–2–phenylacetophenone) – now known as the *beznoin condensation*.[71] However, the explanation of the nature of the transformation was unknown until the report by Lapworth in 1904.[72] He demonstrated that the key step for this reaction is the addition of cyanide to carbonyl function, leading to a strongly nucleophilic intermediate – *nitrile enolate*. This intermediate reacts with the second molecule of aldehyde and after the repulsion of CN^- provides benzoin product. This transformation became a classic example of the polarity inversion phenomenon.

In 1943, Ukai reported that related acyloin condensation proceeds smoothly with diverse thiazolium salts acting as organocatalysts.[73] However, the mechanism of the transformation was unrevieled until the Breslow's work from 1958 (**Figure 39**).[74] He established that, similarly to cyanide, a thiazole carbene (Breslow proposed betaine–type structure rather than carbene, as its resonance structure) undergoes a nucleophilic addition to the carbonyl group, leading to stable and isolable intemediate (after, named in his honor as a Breslow intermediate). This highly nucleophilic species reacts with the second molecule of aldehyde providing the product of acyloin condensation, and regenerating the thiazole catalyst.

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[70] (a) Seebach, D.; Corey, E. J., *J. Org. Chem.* **1975,** *40*, 231-237; (b) Gröbel, B.-T.; Seebach, D., *Synthesis* **1977,** *1977*, 357-402; (c) Seebach, D., *Angew. Chem. Int. Ed. Engl.* **1979,** *18*, 239-258.

[71] Wöhler; Liebig, *Ann. Pharm.* **1832,** *3*, 249-282.

[72] Lapworth, A., *J. Chem. Soc., Trans.* **1904,** *85*, 1206-1214.

[73] Ukai, T.; Tanaka, R.; Dokawa, T., *J. Pharm. Soc. Jpn.* **1943,** *63*, 296–304.

[74] Breslow, R., *J. Am. Chem. Soc.* **1958,** *80*, 3719-3726.

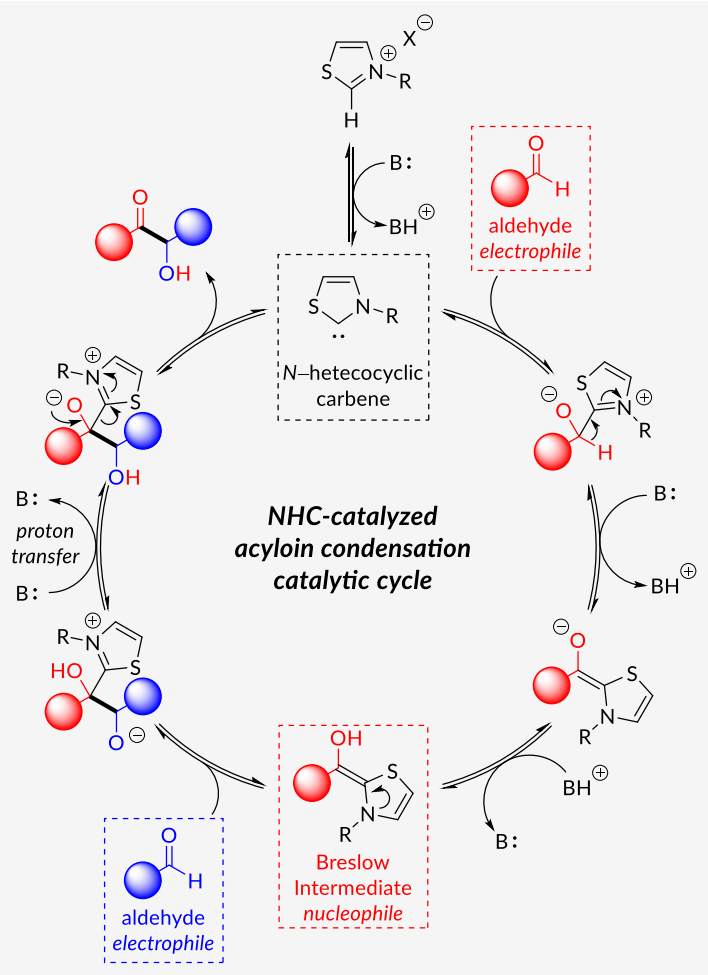

Figure 39. The catalytic cycle of NHC–catalyzed acyloin condensation.

Such catalytic behavior is accessible for NHC due to their electronic (both, electron–donor and electron–acceptor) properties, leading to various reactivities (**Figure 40**):

- **Reactivity I: Nucleophilicity** – the singlet carbene is a highly nucleophilic species and it can react with electrophiles, such as aldehydes, to provide a tetrahedral intermediate.
- **Reactivity II: α–Acidity** – the azolium moiety in the tetrahedral intermediate is strongly electron-withdrawing and it increases the acidity of the former formyl hydrogen, which can eliminate in the presence of base providing the Breslow intermediate.
- **Reactivity III: Enamine Reactivity** – nucleophilic Breslow intermediate is prone to react with electrophiles, acting as an acylating reagent.
- **Reactivity IV: Leaving group (type 1)** – the azolium moiety is a good leaving group; *via* elimination, the final **Product 1** is furnished, regenerating free NHC.

- **Reactivity V: Oxidation** – alternatively, the Breslow intermediate may undergo an oxidation to afford an acylazolium species.[75]
- **Reactivity VI: Leaving group (type 2)** – acylazolium is prone to nucleophilic substitution delivering **Product 2** and regenerating NHC catalyst.

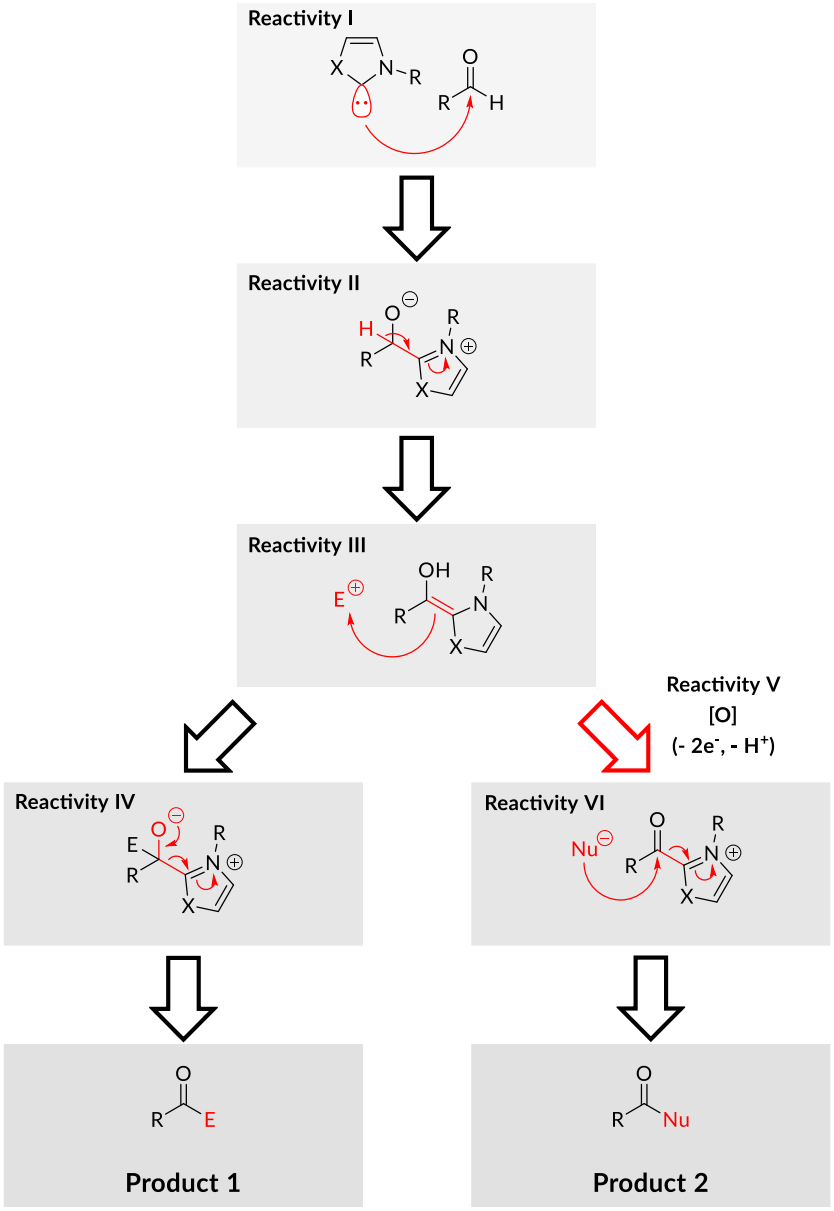

Figure 40. Types of reactivity displayed by the different intermediates containing NHC–catalyst.

The reactivity patterns of NHC toward aldehydes *via* the formation of Breslow intermediate, described above, are relevant to the subject of this thesis. Upon the modification of the carbonyl substrate, *e.g.,* the introduction of unsaturation or additional leaving groups, it is possible to attain additional reactivity modes (*e.g.*, *via* enolate or

[75] Dzieszkowski, K.; Rafiński, Z., *Catalysts* **2018**, *8*, 549.

extended Breslow intermediate). These give rise to many more synthetically useful processes catalyzed by NHCs.[76]

4.3. Synthetic Applications of *N*–Heterocyclic Carbene Catalysis *via* Breslow Intermediate Reactivity

The NHC-catalyzed benzoin condensation is very versatile and many of its cross variants have been developed. For instance, Glorius exploited this approach to the efficient synthesis of hydroxymethyl ketones (**Figure 41a**), *via* a formal hydroxymethylation of Breslow species.[77a] The reaction occurs *via* benzoin condensation between aldehydes and paraformaldehyde **36**, in the presence thiazole–based precatalyst **37**. You has developed an intermolecular cyclization forming α–hydroxydihydroquinolinone derivatives (**Figure 41b**).[77b] The application of D–camphor-derived NHC precatalyst **38** allowed for the synthesis of products with a good yield and a remarkable chirality transfer. Ye and co-workers described a very interesting NHC–catalyzed method for the synthesis of α–amino–α–trifluoromethyl ketones, which are biologically relevant compounds and play important role in the pharmaceutical industry (**Figure 41c**).[77c] The success of the reaction, efficiency, and excellent enantioselectivity were achieved by a thoughtful tuning of the catalyst, cumulating in structure **39**. The possible competing reactions through the corresponding extended Breslow intermediate or enolate were suppressed thanks to the free hydroxy group of **39** and the *N*–benzyl substituent, which decreases the steric hindrance of carbene leading to the typical Breslow intermediate reactivity.

Another essential transformation proceeding *via* the Breslow intermediate is a NHC-catalyzed reaction between aldehyde and electron–poor olefin, discovered by Hermann Stetter in 1976.[78] The process creates carbon–carbon bonds through a 1,4–addition and delivers highly functionalized ketones. An interesting variation of Stetter reaction has been used by Glorius to chiral synthesis of α–aminoacid derivatives (**Figure 42a**).[79a] The reaction between aldehyde and *N*–protected enamine is very

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[76] For an extensive review about *N*–heterocyclic carbene organocatalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A., *Chem. Rev.* **2007,** *107*, 5606-5655; (b) Marion, N.; Díez-González, S.; Nolan, S. P., *Angew. Chem. Int. Ed.* **2007,** *46*, 2988-3000; (c) Biju, A. T.; Kuhl, N.; Glorius, F., *Acc. Chem. Res.* **2011,** *44*, 1182-1195; (d) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T., *Chem. Rev.* **2015,** *115*, 9307-9387; (e) Wang, N.; Xu, J.; Lee, J. K., *Org. Biomol. Chem.* **2018,** *16*, 8230-8244; (f) Biju, A. T.; Breslow, R., *N–Heterocyclic Carbenes in Organocatalysis.* John Wiley & Sons, Ltd.: **2019**.

[77] (a) Kuhl, N.; Glorius, F., *Chem. Commun.* **2011,** *47*, 573-575; (b) Jia, M.-Q.; You, S.-L., *ACS Catal.* **2013,** *3*, 622-624; (c) Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S., *Angew. Chem. Int. Ed.* **2013,** *52*, 5803-5806.

[78] Stetter, H., *Angew. Chem. Int. Ed. Engl.* **1976,** *15*, 639-647.

[79] (a) Jousseaume, T.; Wurz, N. E.; Glorius, F., *Angew. Chem. Int. Ed.* **2011,** *50*, 1410-1414; (b) Read de Alaniz, J.; Rovis, T., *J. Am. Chem. Soc.* **2005,** *127*, 6284-6289.

attractive due to simple and readily available starting materials, mild conditions, and high stereoselectivity. The Stetter reaction can also occur in an intramolecular fashion. Rovis described a highly enantio– and diastereoselective Stetter–type cyclization leading to cyclic ketone derivatives and dihydrobenzopyranone–type compounds (**Figure 42b**).[79b] The reaction proceeds smoothly for a variety of trisubstituted Michael acceptors with great control of chirality on the newly formed stereocenters.

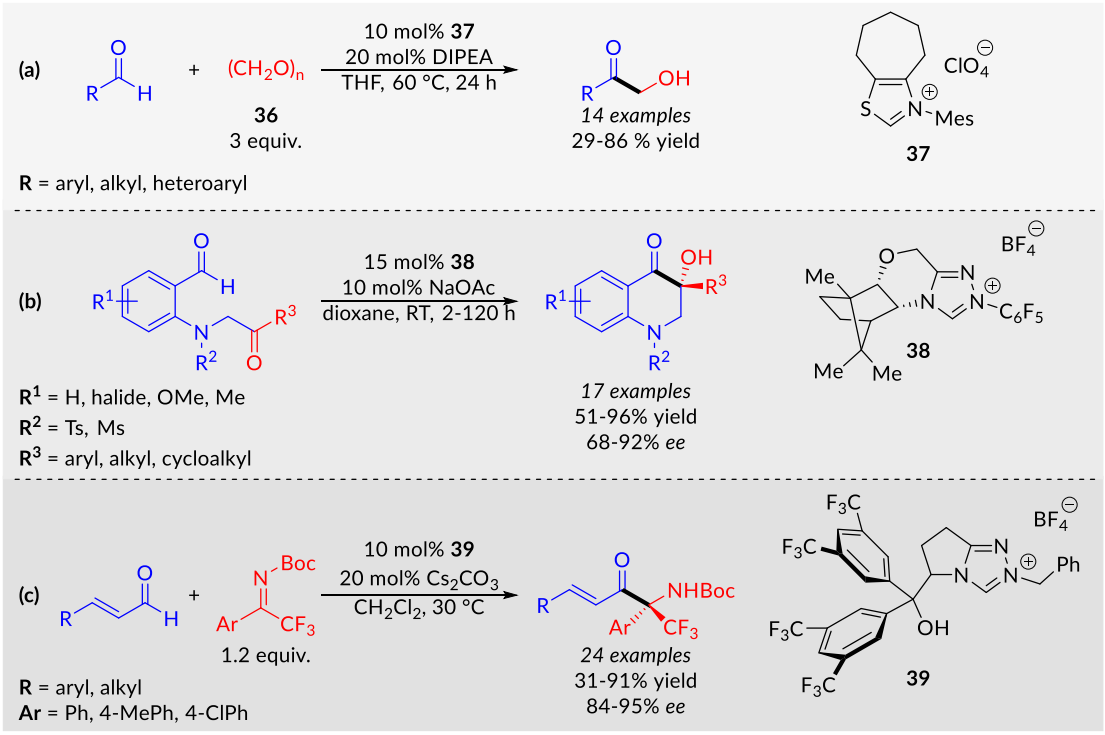

Figure 41. Synthetic applications of Breslow intermediate in benzoin condensation-type reactions.

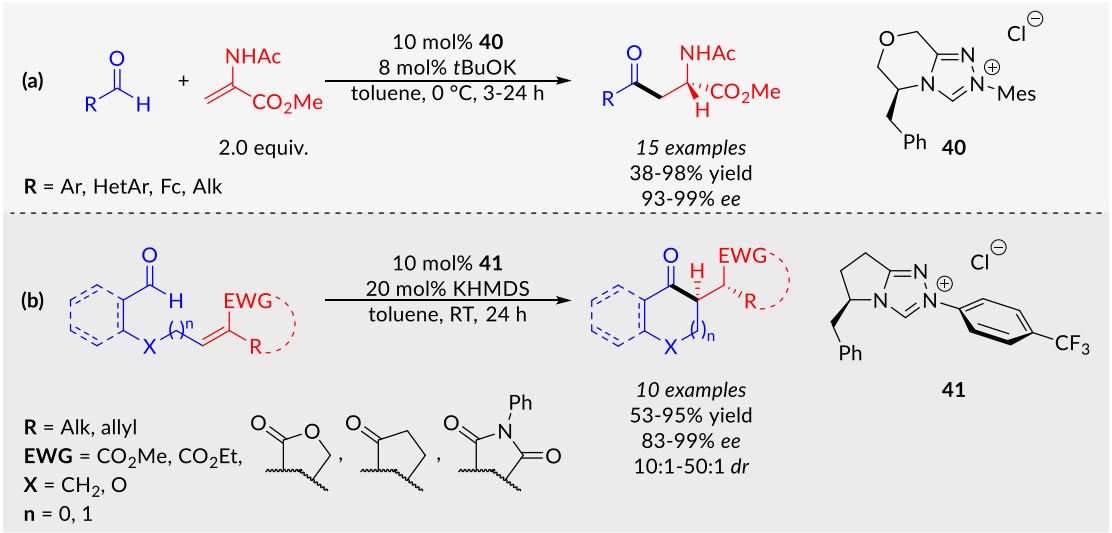

Figure 42. Synthetic applications of Breslow intermediate in Stetter-type reactions.

Apart from the classic benzoin and Stetter reactions, the Breslow intermediate were discovered to react with many other non-standard electrophilic species. It opened

the field for discovery of novel and outstanding chemical transformations, showing the powerfulness of *N*–heterocyclic carbene organocatalysis. In 2011, Glorius presented an extraordinary cyclopropanation of Breslow intermediate utilizing cyclopropenes as electrophiles (**Figure 43a**).[80a] Mild reaction conditions allows to obtain a variety of aryl–cyclopropyl ketones with a good cis selectivity. In 2020, Sajiki proposed a simple but very useful method for the deuteration of formyl group (**Figure 43b**),[80b] using D_2O as a deuterium source. The process occurs *via* electrophilic attack of deuterium cation on Breslow intermediate.

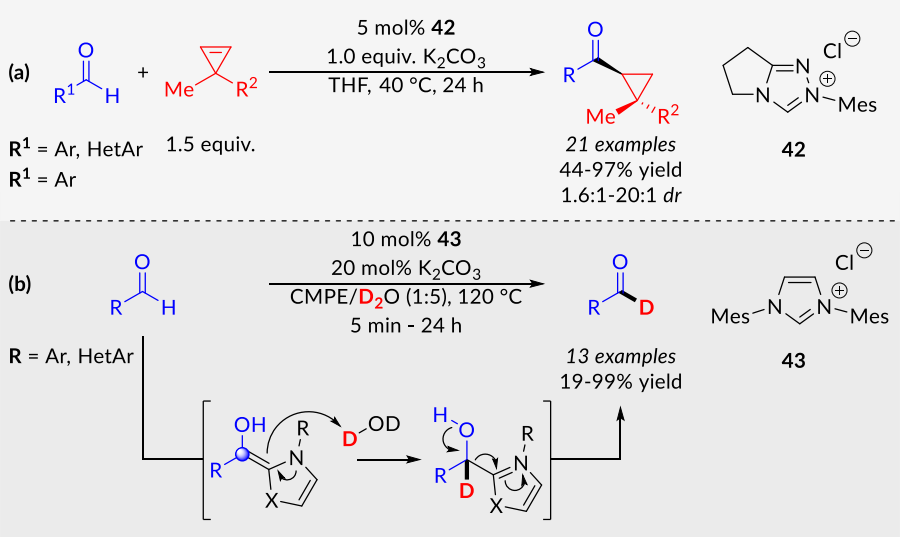

Figure 43. Examples of the reactions of Breslow intermediate with non-standard electrophiles.

[80] (a) Bugaut, X.; Liu, F.; Glorius, F., *J. Am. Chem. Soc.* **2011**, *133*, 8130-8133; (b) Sawama, Y.; Miki, Y.; Sajiki, H., *Synlett* **2020**, *31*, 699-702.

Aim of The Thesis

This thesis aims at the development of novel chemical transformations utilizing hypervalent iodine compounds as group transfer reagents. Its second major objective is to discern the nature of these reactions and to acquire the understanding of the underlying mechanisms, possibly creating opportunities for future advancements.

The first specific goal of the thesis is to develop novel synthetic methods based on the activation of aldehydes with *N*–heterocyclic carbene catalyst to prime them for a group transfer from hypervalent iodine reagents. At the start of my PhD studies, there existed only a single reaction employing such strategy, the arylation of aldehydes described by Gaunt and co-workers. I envisioned the expansion of its scope to the vinylation and alkynylation of aldehydes that would result in the formation of enons and ynones – useful and versatile building blocks in synthetic organic chemistry. The approach is based on the application of vinyl- and alkynyliodonium salts to functionalize the C–H bond in the aldehydes. Furthermore, it was planned to investigate the mechanisms of the developed reactions using both experimental and computational techniques.

The second specific aim of the thesis is to develop a metal-free β–vinylation of phosphorus-based nucleophiles using vinylbenziodoxolone reagents. This new class of hypervalent iodine compounds has been reported to react with carbon nucleophiles effecting a vinyl transfer with an unusual "reversed" β–regioselectivity. I decided to investigate if vinylbenziodoxolone can also be used to transfer the vinyl moiety to important phosphorus nucleophiles and whether in this case the similar intriguing β–selectivity can also be achieved.

Chapter II. N–Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts to Generate Vinyl Ketones (Paper II)

1. Background

α,β–Unsaturated ketones establish a honored group of reagents in organic chemistry. Their most essential synthetic applications such as a Michael addition,[81] Diels–Alder reaction,[82] and Morita–Baylis–Hillman reaction[83] are ones of the most used processes in organic chemist toolbox. Moreover, this class of compounds is also well represented among natural products and pharmaceutically important molecules.[84] There is a plethora of synthetic routes for the preparation of the vinyl ketone moiety.[85] However, there exist only a handful of methodologies, wherein vinyl ketones are obtained by the simplest logical disconnection – a direct olefination of the C–H bond of aldehydes. The most explored in this context are the hydroacylations of alkynes. These reactions catalyzed by transition metal complexes proceed by the activation of the formyl C–H bond *via* an oxidative addition to the metal center (**Figure 44a**).[86] In 2013, Lei and co-workers described an alternative strategy that relies on a homolytic cleavage

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[81] (a) Nair, D. P.; Podgórski, M.; Chatani, S.; Gong, T.; Xi, W.; Fenoli, C. R.; Bowman, C. N., *Chem. Mater.* **2014,** *26*, 724-744; (b) Pellissier, H., *Adv. Synth. Catal.* **2015,** *357*, 2745-2780; (c) Schmid, T. E.; Drissi-Amraoui, S.; Crévisy, C.; Baslé, O.; Mauduit, M., *Beilstein J. Org. Chem.* **2015,** *11*, 2418-2434.

[82] (a) Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H., *Angew. Chem. Int. Ed.* **2014,** *53*, 11146-11157; (b) Heravi, M. M.; Ahmadi, T.; Ghavidel, M.; Heidari, B.; Hamidi, H., *RSC Adv.* **2015,** *5*, 101999-102075; (c) Gregoritza, M.; Brandl, F. P., *Eur. J. Pharm. Biopharm.* **2015,** *97*, 438-453.

[83] (a) Wei, Y.; Shi, M., *Chem. Rev.* **2013,** *113*, 6659-6690; (b) Hu, F.-L.; Shi, M., *Org. Chem. Front.* **2014,** *1*, 587-595; (c) Subhendu, B.; Sanjay, B., *Curr. Org. Chem.* **2014,** *18*, 3078-3119.

[84] (a) Amslinger, S., *ChemMedChem* **2010,** *5*, 351-356; (b) Sahu, N. K.; Balbhadra, S. S.; Choudhary, J.; Kohli, D. V., *Curr. Med. Chem.* **2012,** *19*, 209-225; (c) Arshad, L.; Jantan, I.; Bukhari, S. N. A.; Haque, M. A., *Front. Pharmacol.* **2017,** *8*.

[85] (a) Muzart, J., *Eur. J. Org. Chem.* **2010,** *2010*, 3779-3790; (b) Lee, H.-W.; Kwong, F.-Y., *Eur. J. Org. Chem.* **2010,** *2010*, 789-811; (c) Zhu, Y.; Sun, L.; Lu, P.; Wang, Y., *ACS Catal.* **2014,** *4*, 1911-1925; (d) Pearson, C. M.; Snaddon, T. N., *ACS Cent. Sci.* **2017,** *3*, 922-924.

[86] (a) Willis, M. C., *Chem. Rev.* **2010,** *110*, 725-748; (b) Leung, J. C.; Krische, M. J., *Chem. Sci.* **2012,** *3*, 2202-2209; (c) Ghosh, A.; Johnson, K. F.; Vickerman, K. L.; Walker, J. A.; Stanley, L. M., *Org. Chem. Front.* **2016,** *3*, 639-644.

of the C–H bond using copper catalyst in the presence of hydroperoxide, effecting an oxidative coupling of aldehydes and olefins (**Figure 44b**).[87]

I envisioned that it could be possible to directly olefinate aldehydes employing organocatalysis with *N*–heterocyclic carbenes to activate the formyl C–H bond by the formation of Breslow intermediate.[76d, 88] This nucleophilic species may then undergo a reaction with vinyl(aryl)iodonium salts, which would serve as the donor of the vinyl group (**Figure 44c**). An similar reactivity of the Breslow intermediate toward aryliodonium salts has been previously described by Gaunt.[32]

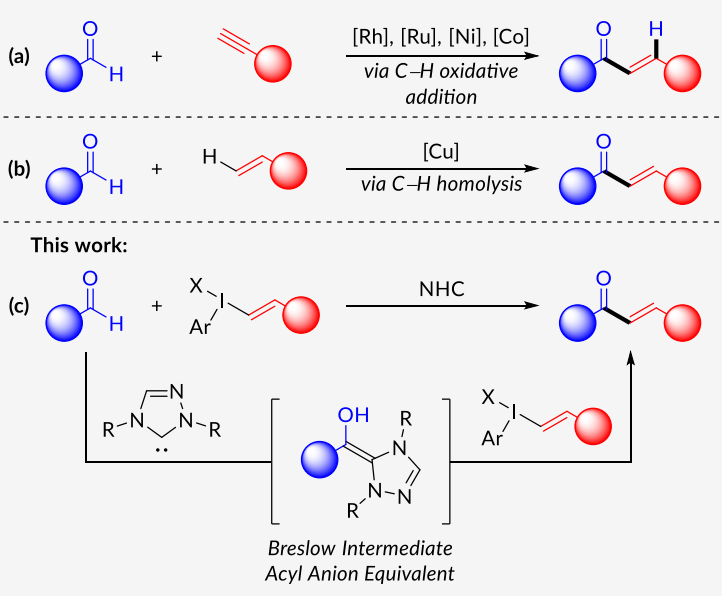

Figure 44. Examples of direct olefination of the C–H bond of aldehydes leading to enones.

Vinyl(aryl)iodonium salts are an important class of electrophilic vinyl transfer reagents.[10c, 10d, 89] Under non-catalytic conditions, they have been mostly used for the olefination of heteroatom nucleophiles,[90] and only a few examples of vinyl-transfer processes to carbon nucleophiles exist.[91] The majority these rely on transition metal

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[87] Wang, J.; Liu, C.; Yuan, J.; Lei, A., *Angew. Chem. Int. Ed.* **2013**, *52*, 2256-2259.

[88] Menon, R. S.; Biju, A. T.; Nair, V., *Beilstein J. Org. Chem.* **2016**, *12*, 444-461.

[89] (a) Pirkuliev, N. S.; Brel, V. K.; Zefirov, N. S., *Russ. Chem. Rev.* **2000**, *69*, 105-120; (b) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V., *Arkivoc* **2011**, *i*, 370–409.

[90] (a) Ochiai, M.; Yamamoto, S.; Suefuji, T.; Chen, D.-W., *Org. Lett.* **2001**, *3*, 2753-2756; (b) Chen, J.-M.; Huang, X., *Synlett* **2004**, *2004*, 552-554; (c) Hara, S.; Guan, T.; Yoshida, M., *Org. Lett.* **2006**, *8*, 2639-2641; (d) Guan, T.; Yoshida, M.; Hara, S., *J. Org. Chem.* **2007**, *72*, 9617-9621; (e) Yan, J.; Jin, H.; Chen, Z., *J. Chem. Res.* **2007**, *2007*, 233-235; (f) Zawia, E.; Moran, W. J., *Molecules* **2016**, *21*, 1073.

[91] (a) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E., *Tetrahedron* **1988**, *44*, 4095-4112; (b) Ochiai, M.; Shu, T.; Nagaoka, T.; Kitagawa, Y., *J. Org. Chem.* **1997**, *62*, 2130-2138; (c) Stridfeldt, E.; Seemann, A.; Bouma, M. J.; Dey, C.; Ertan, A.; Olofsson, B., *Chem. Eur. J.* **2016**, *22*, 16066-16070.

catalysis, typically with Cu or Pd.[29b, 92] Thus, the NHC organocatalysis would create a metal-free alternative for the vinyl transfer using vinyliodonium salts, resulting in a C–C bond formation.

2. Optimization of the Reaction Conditions

The investigations were started by examining the reaction between model aldehyde **44a** and phenyl(styryl)iodonium triflate **45a**, under the conditions described previously for the coupling of diaryliodonium salts,[32] i.e. using *N*–pentafluorophenyl–triazolium carbene precursor **9** and 4–dimethylaminopyridine (DMAP) as the base in DCM/*i*–PrOH solvent mixture at –40 °C. Already this initial attempt resulted in the formation of the desired ketone **46a**, however, accompanied by approximately equal amount of aryl-transfer product **46a'** (**Table 1**, *entry 1*). To address this selectivity issue, we synthesized[93] and evaluated several aryl(styryl)iodonium salts, bearing variously substituted aryl moieties (**Table 1**). The presence of sterically hindered and electron-rich aryl groups was found to secure a highly selective vinyl transfer (*entries 2–5*), whereas electron-poor aryl ligands lead to poor selectivity (*entries 6–8*). Vinylbenziodoxolone **47a** did not provide any of the desired product under these conditions (*entry 9*). 2-Methoxyphenyl has been identified as the most efficient auxiliary aryl, leading to the formation of product **46a** in 81% yield (*entry 4)*, which was not that surprising, because this substituent has been established before to be a superior auxiliary group promoting alkynyl transfer from alkynyl(aryl)iodonium salts.[94] Importantly, all the reactions in **Table 1** proceeded with a complete retention of the double bond configuration, no trace of the (*Z*)-configured product was detected in any case. It is a rather extraordinary behavior, because in many reported cases, the vinyl transfer from vinyliodonium salts lead to either retention or inversion of the double

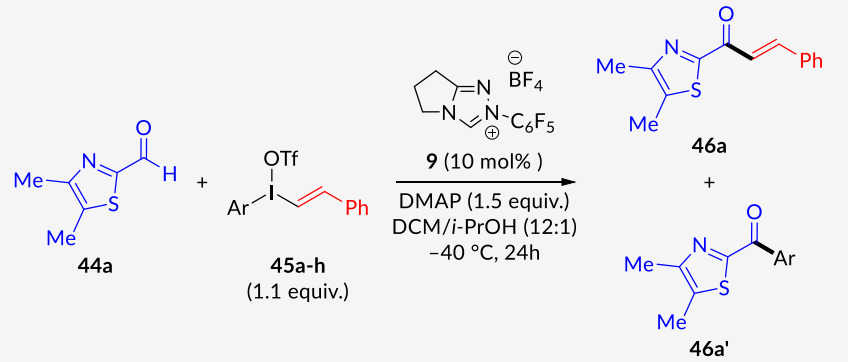
[92] (a) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K., *J. Am. Chem. Soc.* **1991,** *113*, 6315-6317; (b) Pirguliyev, N. S.; Brel, V. K.; Zefirov, N. S.; Stang, P. J., *Tetrahedron* **1999,** *55*, 12377-12386; (c) Yoshida, M.; Komata, A.; Hara, S., *J. Fluor. Chem.* **2004,** *125*, 527-529; (d) Thielges, S.; Bisseret, P.; Eustache, J., *Org. Lett.* **2005,** *7*, 681-684; (e) Liu, C.; Zhang, W.; Dai, L.-X.; You, S.-L., *Org. Lett.* **2012,** *14*, 4525-4527; (f) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J., *J. Am. Chem. Soc.* **2013,** *135*, 5332-5335; (g) Cahard, E.; Bremeyer, N.; Gaunt, M. J., *Angew. Chem. Int. Ed.* **2013,** *52*, 9284-9288; (h) Holt, D.; Gaunt, M. J., *Angew. Chem. Int. Ed.* **2015,** *54*, 7857-7861; (i) Liu, C.; Wang, Q., *Org. Lett.* **2016,** *18*, 5118-5121.

[93] Ochiai, M.; Toyonari, M.; Nagaoka, T.; Chen, D.-W.; Kida, M., *Tetrahedron Lett.* **1997,** *38*, 6709-6712.

[94] Hamnett, D. J.; Moran, W. J., *Org. Biomol. Chem.* **2014,** *12*, 4156-4162.

bond geometry, or a rearrangement.[95]

Table 1. Evaluation of auxiliary aryl groups.[a]



entry	*Ar*	*yield (%)*[b] **37a**	**37a'**	*entry*	*Ar*	*yield (%)*[b] **37a**	**37a'**
1	**45a**	**33**	**37**	*5*	**45e**	**66**	**<1**
2	**45b**	**70**	**<1**	*6*	**45f**	**24**	**50**
3	**45c**	**68**	**<1**	*7*	**45g**	**24**	**36**
4	**45d**	**81**	**<1**	*8*	**45h**	**18**	**76**
				9	**47a**	**<1**	**<1**

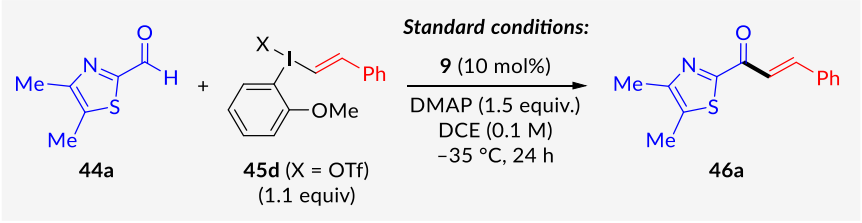
[a] All data are the average of two experiments; [b] Determined through analysis by ^{1}H NMR spectroscopy.

[95] (a) Ochiai, M.; Kitagawa, Y.; Yamamoto, S., *J. Am. Chem. Soc.* **1997**, *119*, 11598-11604; (b) Fujita, M.; Sakanishi, Y.; Nishii, M.; Okuyama, T., *J. Org. Chem.* **2002**, *67*, 8138-8146; (c) Okuyama, T., *Acc. Chem. Res.* **2002**, *35*, 12-18; (d) Fujita, M.; Kim, W. H.; Sakanishi, Y.; Fujiwara, K.; Hirayama, S.; Okuyama, T.; Ohki, Y.; Tatsumi, K.; Yoshioka, Y., *J. Am. Chem. Soc.* **2004**, *126*, 7548-7558; (e) Fujita, M.; Kim, W. H.; Fujiwara, K.; Okuyama, T., *J. Org. Chem.* **2005**, *70*, 480-488; (f) Slegt, M.; Gronheid, R.; van der Vlugt, D.; Ochiai, M.; Okuyama, T.; Zuilhof, H.; Overkleeft, H. S.; Lodder, G., *J. Org. Chem.* **2006**, *71*, 2227-2235; (g) Miyamoto, K.; Suzuki, M.; Suefuji, T.; Ochiai, M., *Eur. J. Org. Chem.* **2013**, *2013*, 3662-3666.

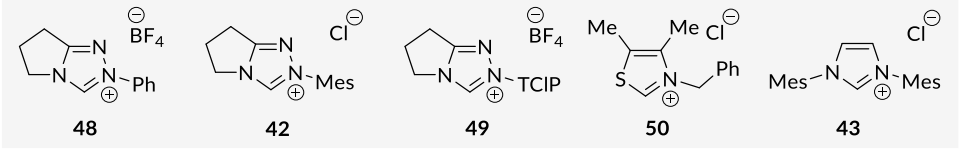
The refinement of other reactions parameters has been carried out on the model coupling between aldehyde **44a** and vinyliodonium salt **45d**. Application of 10 mol% of **9**, DMAP, and DCE solvent at –35 °C was found to be the optimal conditions (**Table 2**, *entry 1*). Related NHC precatalysts **42**, **43** and **48**–**50** did not furnish satisfactory results (*entries 2–6*). Also, no reaction was observed in the absence of the carbene precursor (*entry 7*). Decreased loading of precatalyst results in lower yield, while increasing the amount of catalyst to 15 mol% has only minor impact on the product yield (*entries 8–9*). Elevation of the temperature to 0 °C or to an ambient temperature has a detrimental effect on the efficiency of the coupling resulting in the decrease of yield (*entries 10–11*). Solvent screening showed that the addition of a small amount of *i*–PrOH is beneficial when using DCM (*entries 13* vs *12*), however, if the reaction is performed in DCE alone a slightly better yield is obtained (*entries 14* vs *1*). Employment of other organic solvents delivers the product in moderate yields (*entries 15–17*). Application of bases other than DMAP leads to a decrease in the amount of product and the emergence of ketone **46a'** (*entries 18–20*). The amount of DMAP was settled on 1.5 equiv., which was found to be optimal (*entries 21–23*). Finally, the effect of counter-ion present in the iodonium salt was evaluated. It was found that tetrafluoroborate salt **45i** is completely ineffective in the vinyl transfer process (*entry 24*). The more strongly coordinating ions, such as trifluoroacetate (**45j**), tosylate (**45k**), and fluoride (**45l**) give moderately to slightly lower yields compared to triflate (*entries 25–27*).[96] Importantly, the reaction seems to be insensitive to the presence of oxygen and traces of water (*entries 28–29*). Finally, shorter reaction time resulted in a slightly decreased yield, thus the optimal reaction time is 24 hours (*entries 30* vs *1*).

[96] Chan, L.; McNally, A.; Toh, Q. Y.; Mendoza, A.; Gaunt, M. J., *Chem. Sci.* **2015**, *6*, 1277-1281.

Table 2. Effect of reaction parameters.[a]



entry	*change from the standard conditions*	*yield (%)*[b]
1	none	85
2	**48**, instead of **9**	13
3	**42**, instead of **9**	5
4	**49**, instead of **9**	71
5	**50**, instead of **9**	<1
6	**43**, instead of **9**	<1
7	no **9**	<1
8	5 mol% **9**, instead of 10 mol%	53
9	15 mol% **9**, instead of 10 mol%	88
10	0 °C, instead of –35 °C	48
11	rt, instead of –35 °C	42
12	CH_2Cl_2, instead of DCE	73
13	CH_2Cl_2/*i*–PrOH (12:1), instead of DCE	81
14	DCE/*i*–PrOH (12:1), instead of DCE	77
15	MeCN, instead of DCE	71
16	*n*-hexane, instead of DCE	65
17	THF, instead of DCE	47
18	DABCO, instead of DMAP	43[c]
19	DIPEA, instead of DMAP	54[c]
20	Cs_2CO_3, instead of DMAP	26[c]
21	1.2 equiv. DMAP, instead of 1.5 equiv.	66
22	2.0 equiv. DMAP, instead of 1.5 equiv.	87
23	3.0 equiv. DMAP, instead of 1.5 equiv.	57
24	X = BF_4 (**45i**), instead of X = TfO	<1
25	X = CF_3CO_2 (**45j**), instead of X = TfO	47
26	X = TsO (**45k**), instead of X = TfO	52
27	X = F (**45l**), instead of X = TfO	77
28	under air in capped vial	81
29	20 mol % H_2O added	74
30	8 h, instead of 24 h	80



[a] All data are the average of two experiments; [b] Determined through analysis by ^{1}H NMR spectroscopy; [c] Minor amount of side product **46a'** was observed; Mes = 2,4,6–trimethylphen–1–yl, TClP = 2,4,6–trichlorophen–1–yl.

3. Scope and Limitations of the Method

After optimization of the reaction conditions, the exploration of scope was commenced (**Figure 45**). A variety of heteroaromatic aldehydes, containing both five- and six-membered rings (such as: thiazole, benzoxazole, pyrazole, pyridine, and quinoxaline) were olefinated, leading to heteroaryl-vinyl ketones in good yields (**46a–46f**). Benzaldehyde-derived aldehydes were found to be more challenging substrates, requiring the presence of an electron-withdrawing group (*e.g.*, $-CF_3$, $-NO_2$, or $-CO_2Me$) for the yields to be acceptable (**46g–46i**). Under these conditions, benzaldehyde and 4-methoxybenzaldehyde gave 33% and 7% ^1H NMR yield of product, respectively. However, propargyl aldehyde is a suitable starting material, delivering an interesting and synthetically versatile enynone scaffold **46j**. Finally, the developed protocol was applied to the preparation of a pharmaceutically relevant ketone[97] **46k** in 39% yield. Further exploration disclosed that aliphatic aldehydes are not efficient substrates for the olefination under the developed conditions.

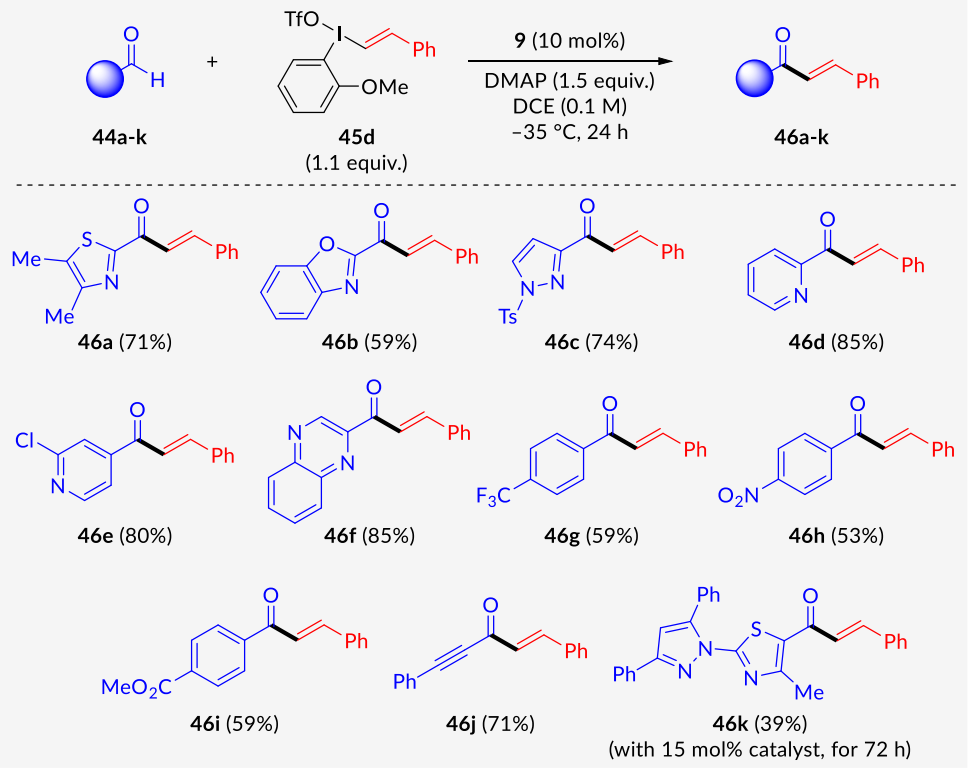


Figure 45. Scope with regard to the aldehyde.

The scope with regard to vinyliodonium salt was also examined (**Figure 46**). The method allows for an introduction of an array of variously substituted β-styryl groups (**46l–46q**), including sterically hindered 2,6-dimethylphenyl (**46m**), as well as fluorinated

[97] Li, Z.; Khaliq, M.; Zhou, Z.; Post, C. B.; Kuhn, R. J.; Cushman, M., *J. Med. Chem.* **2008**, *51*, 4660-4671.

moieties (**46p–46q**). The electronic properties of aryl substituent in structure of vinyl group seem to have an impact on the efficiency of group transfer process. Specifically, the electron-deficient groups are transferred more effectively than the electron-rich ones. A thiophene unit in the β-position of the double bond is also well tolerated (**46r**). Noteworthy, β,β–disubstituted vinyliodonium salts undergo transfer under the developed conditions, however in somewhat lower yields (**46s–46t**).

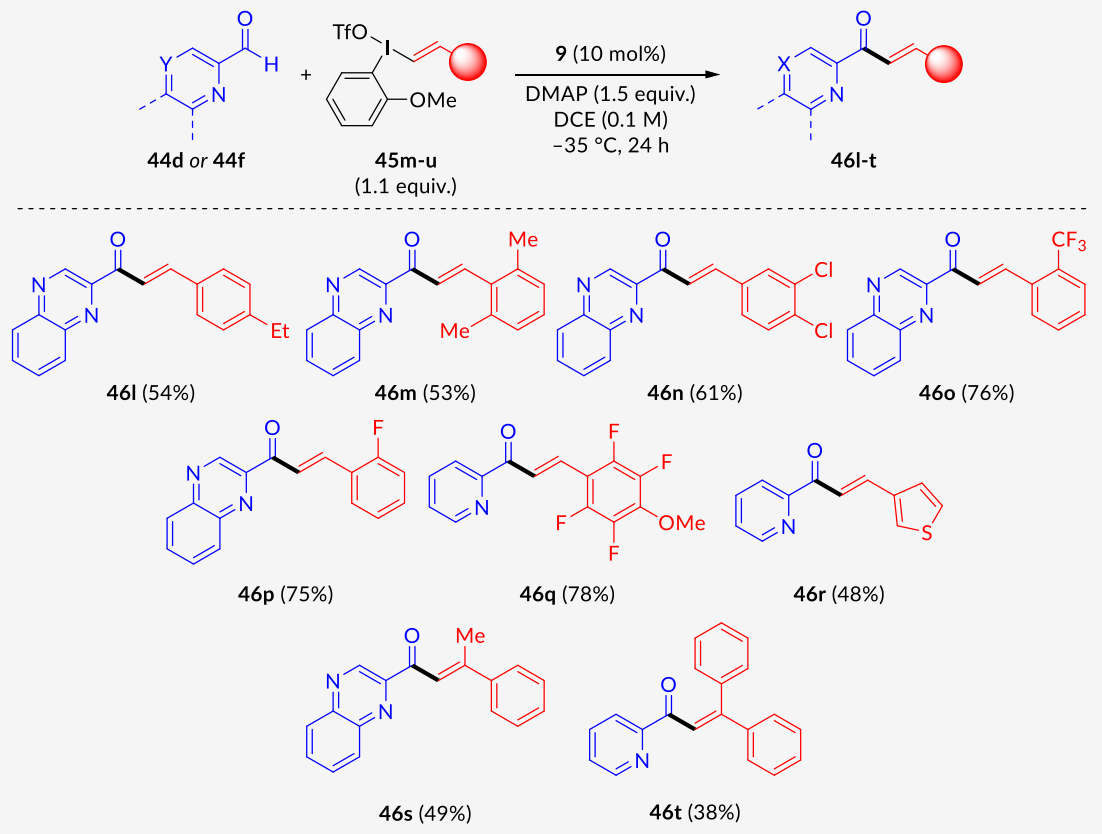
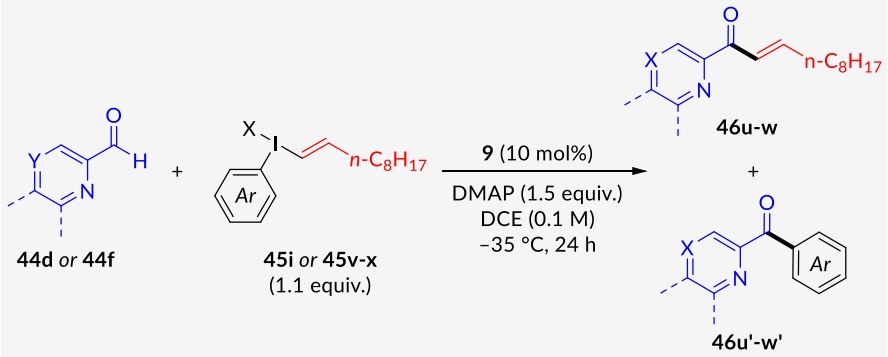


Figure 46. Scope with regard to the vinyliodonium salt.

All the presented reactions employ β–arylvinyliodonium salts, thus I endeavored to extend the scope of functionalities in β–position. Unfortunately, for vinyliodonium salts bearing β–alkyl groups, regardless of the choice of the auxiliary aryl group and the salt counterion, the olefination was inefficient and outcompeted by the undesired aryl transfer products (**Table 3**).

Table 3. Reaction with β–alkyl-substituted vinyliodonium salts.



entry	*substrate*	*Ar*	*X*	*yield (%)*[a] **46u** *or* **46w**	*yield (%)*[a] **46u'** *or* **46u'**
1	**44f**	**45i**	TfO	**13**	**56**
2	**44d**	**45i**	TfO	**7**	**18**
3	**44f**	**45v**	BF_4	**10**	**48**
4	**44d**	**45v**	BF_4	**6**	**13**
5	**35d**	**45w**	BF_4	**7**	**14**
6	**44d**	**45x**	BF_4	**6**	**53**

[a] Determined through analysis by ^{1}H NMR spectroscopy.

4. Mechanistic Investigations

To gain some insight into the mechanism of the developed transformation the kinetic investigations have been performed. The reaction was found to be very rapid at the outset, achieving over 30% yield within the first 5 min (**Figure 47**, black squares). This shows a very high susceptibility of nucleophilic Breslow intermediate for reacting with vinyliodonium salt. Interestingly, at this point the reaction unexpectedly decelerates, and it takes several hours to reach high conversion of the substrate. To probe for a possible inhibition of the reaction by its products, the NHC-catalyzed olefination was carried out with either product **46f** or DMAP·TfOH added from the outset. The obtained time-course profiles (**Figure 47**, red circles and blue triangles, respectively) are very similar, within the experimental error, to the one obtained under the standard conditions, thus presumably the decrease in the rate is rather due to an unidentified catalyst decomposition pathway.

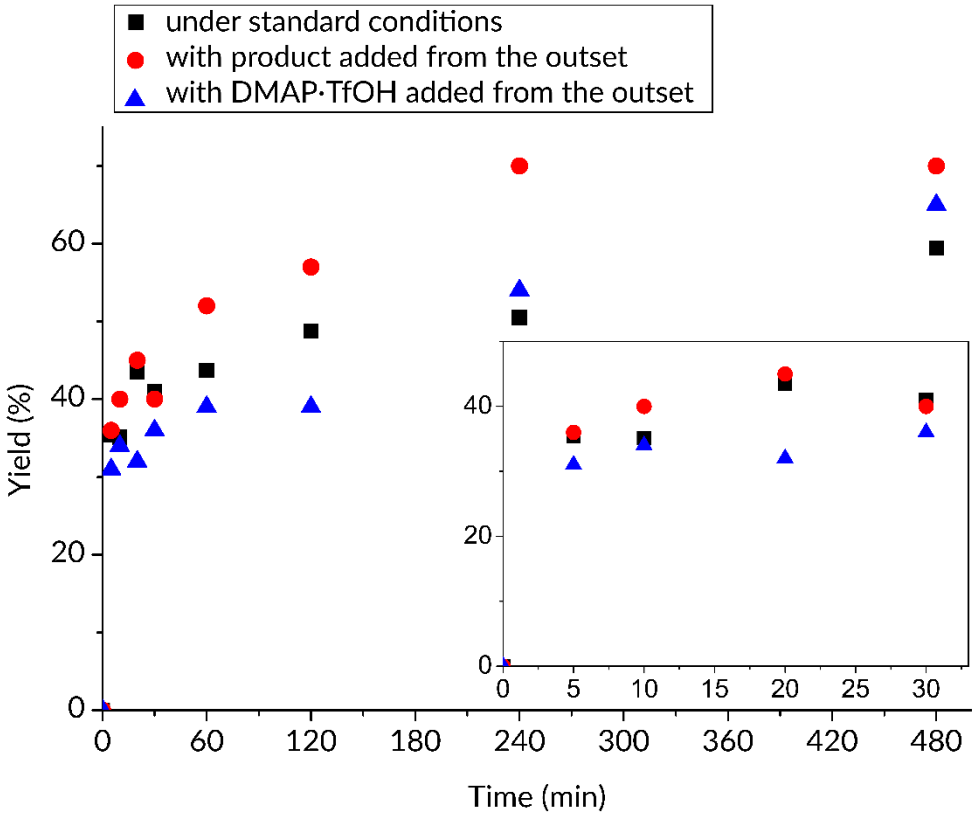


Figure 47. Time-course of the NHC-Catalyzed Olefination of Aldehyde **44f** with Salt **45d**.

5. Summary

In conclusion, the NHC-catalyzed direct olefination of aldehydes using vinyliodonium salts has been developed. The reaction proceeds under mild conditions and yields an array of α,β–vinyl ketones, notably, those containing pharmacophoric heteroaryl moieties. A careful optimization of the auxiliary aryl substituent of the vinyliodonium salt has allowed for a selective and efficient vinyl transfer to a carbon-based nucleophile.

Chapter III. N–Heterocyclic Carbene-Catalyzed Synthesis of Ynones via C–H Alkynylation of Aldehydes with Alkynyliodonium Salts — Synthetic and Mechanistic Studies (Paper III)

1. Background

The ynone motif is present in several biologically active molecules.[98] Moreover, ynones are important precursors for the preparation of a variety of molecular scaffolds,[99] which makes them key intermediates in multiple total syntheses.[100]

Traditionally, ynones have been synthesized by one of the three methods: (1) the reaction of metal acetylides (such as magnesium or lithium reagents) with acyl chlorides or other carboxylic derivatives; (2) the C–H oxidation of propargylic position in alkynes or of propargylic alcohols; and (3) a carbonylative cross-coupling reactions.[101]

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[98] (a) Fawcett, C. H.; Firn, R. D.; Spencer, D. M., *Physiol. Plant Pathol.* **1971,** *1*, 163-166; (b) Kundu, N. G.; Das, B.; Spears, C. P.; Majumdar, A.; Kang, S. I., *J. Med. Chem.* **1990,** *33*, 1975-1979; (c) Kundu, N. G.; Mahanty, J. S.; Spears, C. P., *Bioorg. Med. Chem. Lett.* **1996,** *6*, 1497-1502; (d) Quesnelle, C. A.; Gill, P.; Dodier, M.; St. Laurent, D.; Serrano-Wu, M.; Marinier, A.; Martel, A.; Mazzucco, C. E.; Stickle, T. M.; Barrett, J. F.; Vyas, D. M.; Balasubramanian, B. N., *Bioorg. Med. Chem. Lett.* **2003,** *13*, 519-524; (e) Kuklev, D. V.; Domb, A. J.; Dembitsky, V. M., *Phytomedicine* **2013,** *20*, 1145-1159.

[99] For reviews on the synthetic utility of ynones, see: (a) Bagley, M. C.; Glover, C.; Merritt, E. A., *Synlett* **2007,** *2007*, 2459-2482; (b) Arai, T.; Ikematsu, Y.; Suemitsu, Y., *Pure Appl. Chem.* **2010,** *82*, 1485; (c) Sengee, M.; Sydnes, L. K., *Pure Appl. Chem.* **2011,** *83*, 587; (d) Fraile, A.; Parra, A.; Tortosa, M.; Alemán, J., *Tetrahedron* **2014,** *70*, 9145-9173; (e) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E., *Synthesis* **2014,** *46*, 687-721; (f) Whittaker, R. E.; Dermenci, A.; Dong, G., *Synthesis* **2016,** *48*, 161-183.

[100] (a) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A., *Angew. Chem. Int. Ed.* **2004,** *43*, 3947-3951; (b) Forsyth, C. J.; Xu, J.; Nguyen, S. T.; Samdal, I. A.; Briggs, L. R.; Rundberget, T.; Sandvik, M.; Miles, C. O., *J. Am. Chem. Soc.* **2006,** *128*, 15114-15116; (c) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M., *Angew. Chem. Int. Ed.* **2007,** *46*, 4708-4711; (d) Tietze, L. F.; Singidi, R. R.; Gericke, K. M.; Böckemeier, H.; Laatsch, H., *Eur. J. Org. Chem.* **2007,** *2007*, 5875-5878.

[101] Chinchilla, R.; Nájera, C., *Chem. Rev.* **2014,** *114*, 1783-1826.

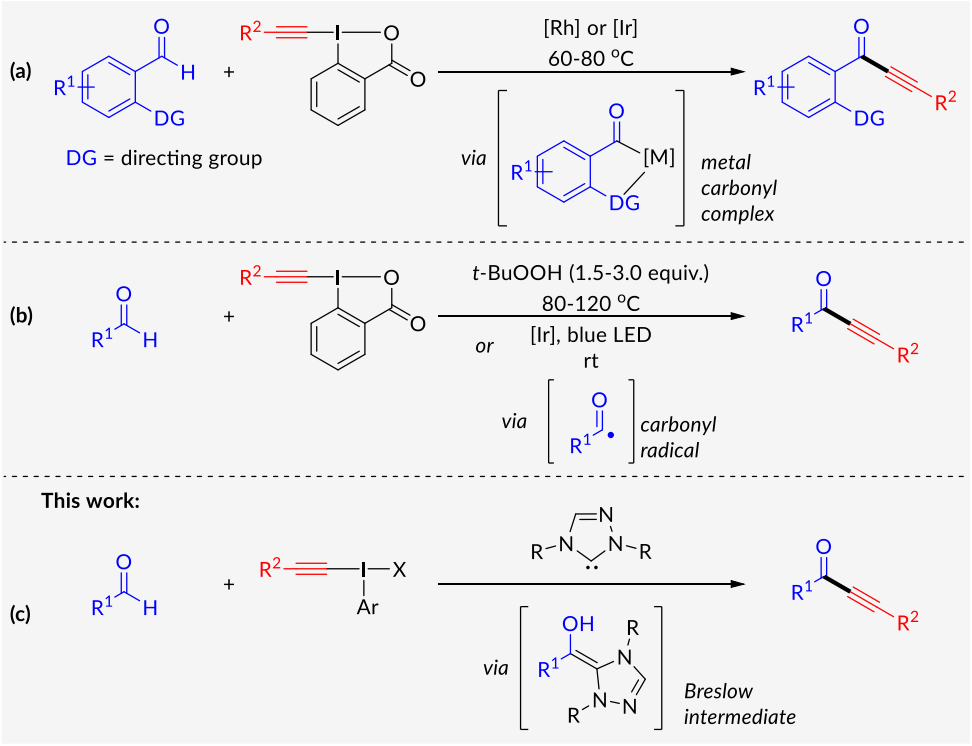

Figure 48. Synthesis of ynones via direct C–H alkynylation of aldehydes employing hypervalent iodine compounds.

An interesting alternative to these standard approaches that have recently gained attention is the direct alkynylation of the C–H bond in aldehydes. This strategy brings the advantage of delivering propargyl ketones in a single synthetic step from abundant and stable starting materials. Interestingly, all the existing methods based on this approach employ hypervalent iodine group transfer reagents. The first example was reported by Zhou in 2015, who described rhodium- and iridium-catalyzed alkynyl transfer from ethynylbenziodoxolone (EBX) to aromatic aldehydes (**Figure 48a**).[102] The reaction proceeds *via* a directing group-assisted activation of the formyl C–H to form a metal carbonyl complex. The second existing methodology for aldehydes alkynylation is based on the homolytic cleavage of the formyl C–H bond. The groups of Wei, Yu, and Li described independently the synthesis of ynones in the presence of *tert*–butyl hydroperoxide as a radical initiator (**Figure 48b**).[103] Regardless to the robustness and simplicity of these approaches, their substantial disadvantage is the high reaction temperature required, resulting in a limited scope. In 2017, Glorius and co-workers employed photoredox catalysis to generate radicals from aldehydes (**Figure 48b**). By the application of an iridium complex, the alkynylation of a variety of aldehydes with EBX

[102] Ai, W.; Wu, Y.; Tang, H.; Yang, X.; Yang, Y.; Li, Y.; Zhou, B., *Chem. Commun.* **2015**, *51*, 7871-7874.
[103] (a) Zhang, R.-Y.; Xi, L.-Y.; Zhang, L.; Chen, S.-Y.; Yu, X.-Q., *Tetrahedron* **2015**, *71*, 6176-6182; (b) Ouyang, X.-H.; Song, R.-J.; Wang, C.-Y.; Yang, Y.; Li, J.-H., *Chem. Commun.* **2015**, *51*, 14497-14500; (c) Liu, X.; Yu, L.; Luo, M.; Zhu, J.; Wei, W., *Chem. Eur. J.* **2015**, *21*, 8745-8749.

could be carried out at room temperature, overcoming the limited scope of the previously-mentioned radical reactions.

On the basis of the seminal work by Gaunt on the NHC-catalyzed arylation of aldehydes,[32] as well as on my own studies on the vinylation of aldehydes (see **Chapter II**),[104] I anticipated that the formation of a Breslow intermediate by reaction between NHC catalyst and aldehyde substrate may constitute an alternative mean to activate the formyl C–H bond for the subsequent alkynyl group transfer to produce propargyl ketones (**Figure 48c**). Based on my previous experience with the vinylation of aldehydes (see **Chapter II**) I expected that alkynyliodonium salts will be optimal reagents, unlike in the other methods that employ EBX (**Figure 48a-b**). Alkynyl(aryl)iodonium salts are widely used for the direct alkynylation of heteroatom nucleophiles and enolates of 1,3–dicarbonyl compounds,[105,106] and their utilization as a alkynyl group transfer reagents to less trivial carbon nucleophiles often requires transition metal catalysis.[107]

2. Synthetic Studies

First, the effect of a number of reaction parameters on a model coupling between 2-quinoxalinecarbaldehyde **44f** and phenylethynyl(aryl)iodonium salts was examined. The application of carbene precursor **9**, tetramethylethylenediamine (TMEDA) as the base, and toluene at −40 °C, were found as optimal conditions, affording product **52a** in 86% yield (**Table 4**, *entry 1*). Not surprisingly, the structure of the alkynyliodonium salt is crucial for the selective and efficient transfer of the alkynyl group.[108] Mesityl was found as the superior auxiliary aryl group, securing selective formation of ynone in high yield

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[104] Rajkiewicz, A. A.; Kalek, M., *Org. Lett.* **2018,** *20*, 1906-1909.

[105] Reviews: (a) Zhdankin, V. V.; Stang, P. J., *Tetrahedron* **1998,** *54*, 10927-10966; (b) Brand, J. P.; Waser, J., *Chem. Soc. Rev.* **2012,** *41*, 4165-4179.

[106] Selected examples: (a) Beringer, F. M.; Galton, S. A., *J. Org. Chem.* **1965,** *30*, 1930-1934; (b) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y.; Kunishima, M.; Tani, S.; Nagao, Y., *J. Chem. Soc., Chem. Commun.* **1990**, 118-119; (c) Tykwinski, R. R.; Williamson, B. L.; Fischer, D. R.; Stang, P. J.; Arif, A. M., *J. Org. Chem.* **1993,** *58*, 5235-5237; (d) Liu, Z.; Chen, Z., *J. Org. Chem.* **1993,** *58*, 1924-1925; (e) Tsugio, K.; Takahiro, F.; Lei, Z.; Takeshi, F.; Hiroshi, T.; Yuzo, F., *Bull. Chem. Soc. Jpn.* **1996,** *69*, 2649-2654; (f) Kitamura, T.; Tashi, N.; Tsuda, K.; Chen, H.; Fujiwara, Y., *Heterocycles* **2000,** *52*, 303-312; (g) Witulski, B.; Alayrac, C., *Angew. Chem. Int. Ed.* **2002,** *41*, 3281-3284; (h) Finkbeiner, P.; Weckenmann, N. M.; Nachtsheim, B. J., *Org. Lett.* **2014,** *16*, 1326-1329; (i) Dhara, A.; Weinmann, J.; Krause, A.-M.; Beuerle, F., *Chem. Eur. J.* **2016,** *22*, 12473-12478; (j) Companys, S.; Peixoto, P. A.; Bosset, C.; Chassaing, S.; Miqueu, K.; Sotiropoulos, J.-M.; Pouységu, L.; Quideau, S., *Chem. Eur. J.* **2017,** *23*, 13309-13313.

[107] (a) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S., *Chem. Commun.* **1996**, 835-836; (b) Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Yoon, S.-K.; Son, H.-J., *Synth. Commun.* **1998,** *28*, 1481-1489; (c) Yu, C.-M.; Kweon, J.-H.; Ho, P.-S.; Kang, S.-C.; Lee, G. Y., *Synlett* **2005,** *2005*, 2631-2634; (d) Zhu, M.; Song, Y.; Cao, Y., *Synthesis* **2007,** *2007*, 853-856; (e) Guo, J.; Lin, L.; Liu, Y.; Li, X.; Liu, X.; Feng, X., *Org. Lett.* **2016,** *18*, 5540-5543.

[108] Stuart, D. R., *Chem. Eur. J.* **2017,** *23*, 15852-15863.

(*entry 1*). Less sterically hindered aryls lead to a significant loss of the transfer selectivity and the formation of a bisaryl ketone side-product (*entries 2–4*). The presence of two *ortho* substituents in 2,6-dimethylphen-1-yl auxiliary suppresses the side aryl transfer, however, it delivers the product in lower yield (*entry 5* vs *1*). The effect of the counterion was also examined. The best result was obtained with a tosylate salt (*entry 1*), whereas iodonium trifluoromethanesulfonate and trifluoroacetate exhibit only a moderate reactivity (*entries 6–7*), while tetrafluoroborate salt is rather ineffective (*entry 8*). Finally, cyclic hypervalent iodine reagent EBX **53** was tested, but only traces of the product were obtained (*entry 9*).

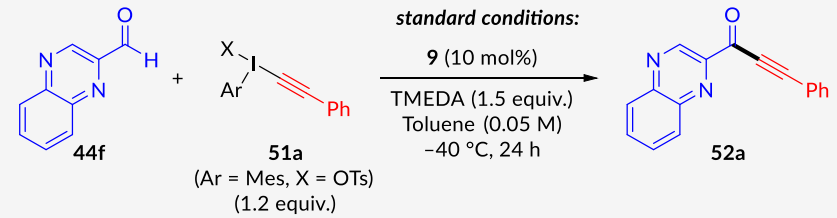
It is worth to mention, that the optimal alkynyl(mesityl)iodonium tosylates of type **44a** are well-described, stable and easy to handle reagents, which can be very conveniently prepared by the method reported by Stang.[109]

Naturally, different types of NHCs commonly used in organocatalysis have been tested (*entries 10–15*), however they are inferior to the commercially available **9**, bearing an electron-deficient pentafluorophenyl group. Decrease of the catalyst loading from 10 to 5 mol% lowers the yield to a moderate level (*entry 16*), and no product formation was observed in the absence of a catalyst (*entry 17*).

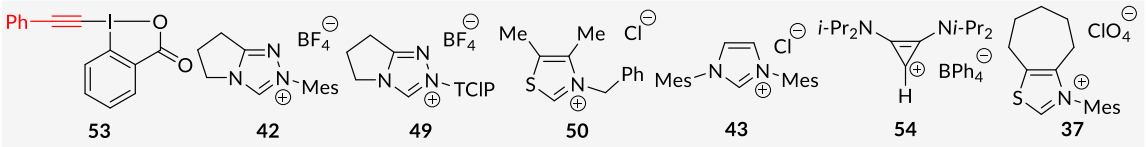
Elevation of the temperature has a negative effect on the reaction outcome (*entries 18–19*). Application of other organic amine bases results in moderate to good yields (*entries 20–23*), while inorganic bases are unproductive in this transformation (*e.g., entry 24*). Good performance of TMEDA cannot be associated with just a doubled number of amine group equivalents, as an increased amount of Et_3N did not lead to improved yield, quite the contrary (*entry 21*). Interestingly, more polar solvents (*entries 25–27*) that almost completely solubilize the reactants are not as efficient as toluene, which affords a heterogenous reaction mixture.

[109] Kitamura, T.; Stang, P. J., *J. Org. Chem.* **1988**, *53*, 4105-4106.

Table 4. Effect of reaction parameters.[a]



entry	*deviation from the standard conditions*	*yield (%)*[b]
1	-	**86**
2	Ar = Ph (**51b**), instead of Ar = Mes	**38 (16)**[c]
3	Ar = *o*–anisyl (**51c**), instead of Ar = Mes	**17 (11)**[c]
4	Ar = *o*–tolyl (**51d**), instead of Ar = Mes	**73 (20)**[c]
5	Ar = 2,6–dimethylphen–1–yl (**51e**), instead Ar = Mes	**67**
6	X = OTf (**51f**), instead of X = OTs	**64**
7	X = CF_3COO (**51g**), instead of X = OTs	**66**
8	X = BF_4 (**51h**), instead of X = OTs	**24**
9	Ph-EBX (**53**), instead of **51a**	**4**
10	**42**, instead of **9**	**50**
11	**49**, instead of **9**	**58**
12	**50**, instead of **9**	**11**
13	**43**, instead of **9**	**<1**
14	**54**, instead of **9**	**<1**
15	**37**, instead of **9**	**19**
16	5 mol% of **9**	**64**
17	no **9**	**<1**
18	0 °C, instead of –40 °C	**66**
19	r.t., instead of –40 °C	**47**
20	Et_3N, instead of TMEDA	**66**
21	Et_3N (3.0 equiv.), instead of TMEDA	**50**
22	DMAP, instead of TMEDA	**32**
23	DABCO, instead of TMEDA	**80**
24	K_3PO_4, instead of TMEDA	**8**
25	DCE, instead of toluene	**62**[d]
26	CH_2Cl_2, instead of toluene	**51**
27	MeCN, instead of toluene	**50**



[a] All data are the average of two experiments; [b] Determined through analysis by ^{1}H NMR spectroscopy; [c] The formation of bisaryl ketone side-product was observed, its yield is given in parenthesis; [d] At –35 °C. Mes = 2,4,6–trimethylphen–1–yl; OTs = *p*–tolenesulfonate; OTf = trifluoromethanesulfonate; TClP = 2,4,6–trichlorophen–1–yl; DCE = 1,2–dichloroethane.

With the established optimal conditions in the hand, the scope of the reaction was examined. Successfully, a wide range of heteroaromatic aldehydes could be efficiently alkynylated (**Figure 49**). Arylpropargyl ketones containing heterocyclic six-membered rings with nitrogen, such as quinoxaline (**52a**), quinoline (**52b**), and pyridine (**52g–l**), as well as five-membered rings, *e.g.*, pyrazole (**52c–d**) and thiazole (**52e–f**), were synthesized in good to excellent yields. The ability to incorporate these moieties is highly valuable, as they are ubiquitous in therapeutically important molecules.[110] Notably, several functional groups are well tolerated under the reaction conditions, including aryl bromide (**52i**), double (**52k**) and triple (**52l**) bonds, providing building blocks useful for further functionalization and building the molecular complexity. The method is also compatible with fluorinated substituents (**52h** and **52j**), which adds to its value for the synthesis of pharmaceutically important strcutures.[111] On the downside, benzaldehydes are poor substrates and only the one containing a strong electron-withdrawing nitro group delivered the desired product in a satisfactory yield (**52m**). While heterocyclic aldehydes are remarkably reactive in the transformation, several of them, such as nicotinaldehyde derivative (**52n**), as well as uracil- aldehyde (**52o**), imidazole- (**52p**), indole- (**52q**) and finally thiophene-based aldehydes (**52r–s**) did not undergo the reaction under these conditions. The lack of activity can be explained by the electron-donating properties of the 5-membered heterocyclic rings. The electron-rich ferrocenecarboxaldehyde (**52t**) was also not reactive, so was benzaldehyde with a moderately electron withdrawing $–CO_2Me$ group (**52u**). Aliphatic aldehydes (**52v–x**), as well as enals (**46j**, **52y**) also exhibit poor reactivity.

[110] (a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G., *J. Med. Chem.* **2014**, *57*, 5845-5859; (b) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O., *Org. Biomol. Chem.* **2016**, *14*, 6611-6637.

[111] (a) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K., *J. Med. Chem.* **2015**, *58*, 9041-9060; (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., *J. Med. Chem.* **2015**, *58*, 8315-8359; (c) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H., *Chem. Rev.* **2016**, *116*, 422-518.

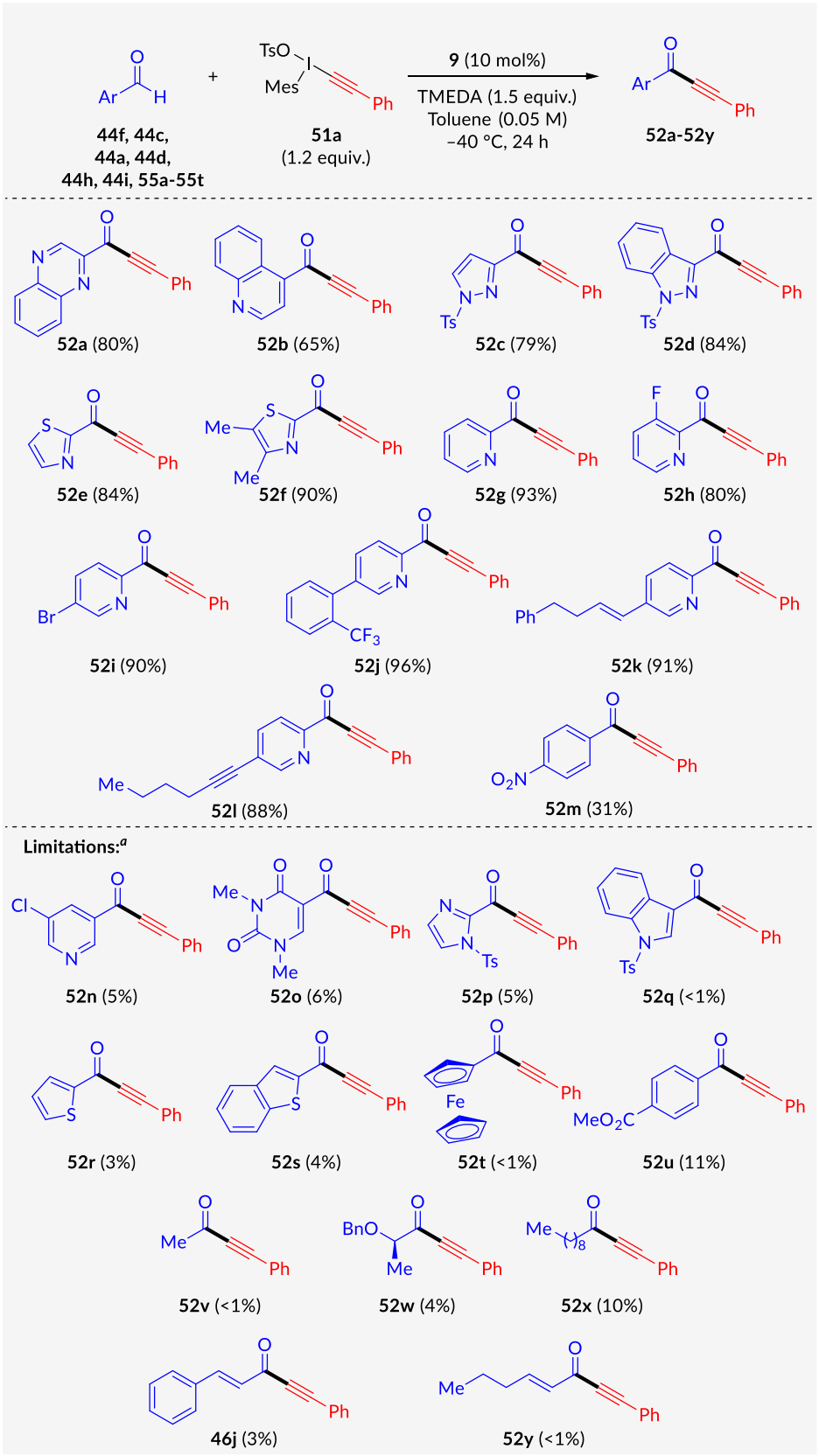


Figure 49. Scope with regard to the aldehyde; [a] Yield determined through analysis by ^{1}H NMR spectroscopy.

Next, the scope with regard to the alkynyliodonium salt was examined. The method could be applied to transfer a range of arylethynyl groups, containing a multitude of substituents (**Figure 50**). All the alkyl-substituted (**52z–52ab**), aryl-substituted (**52ac–52ad**), as well as extended (**52e**) aryl systems can be incorporated into the product. The reaction proceeds equally well for arylethynyl moieties bearing both electron-withdrawing and electron-donating groups. Thus, regardless of the substituent position, ynones containing halogens (**52af-ag** and **52ai**), trifluromethyl (**52ah**), cyano (**52aj**), ketone (**52ak**), ester (**52ap**), and ether (**52aq–ar**) functionalities were synthesized in good to excellent yields. Unfortunately, several groups lead to a decreased reactivity in the transformation, such as trifluoromethyl ketone (**52al**), cyclic indanone (**52am**), fluorenone (**52an**) moieties, and a formyl group (**52ao**). Notably, the method allows to obtain propargyl ketone with a phtalamide-masked amine (**52at**) in the *meta*–position, opposite to low-yielding *para*–substituted counterpart (**52as**). Moreover, sulfur-containing functional groups was tested and *N*–morpholinesulfonamide (**52au**) was isolated in good yield, demonstrating a broad functional group tolerance of the developed methodology. The other sulfur-based substituents such as sulfoxide (**52au**), sulfone (**52av**) and *N*,*N*–dimethylsulfonamide (**52ax**) gave unsatisfactory yields. Unfortunately, when iodonium salts containing alkylethynyl and silylethynyl groups were tested, the desired products (**52ay** and **52az**, respectively) were formed in low yields under these conditions.

Finally, to demonstrate the synthetic utility of the developed procedure, I have applied it to synthesize compound **52ar** on a gram scale, which was obtained without any loss in the yield (80%, 1.64 g of product).

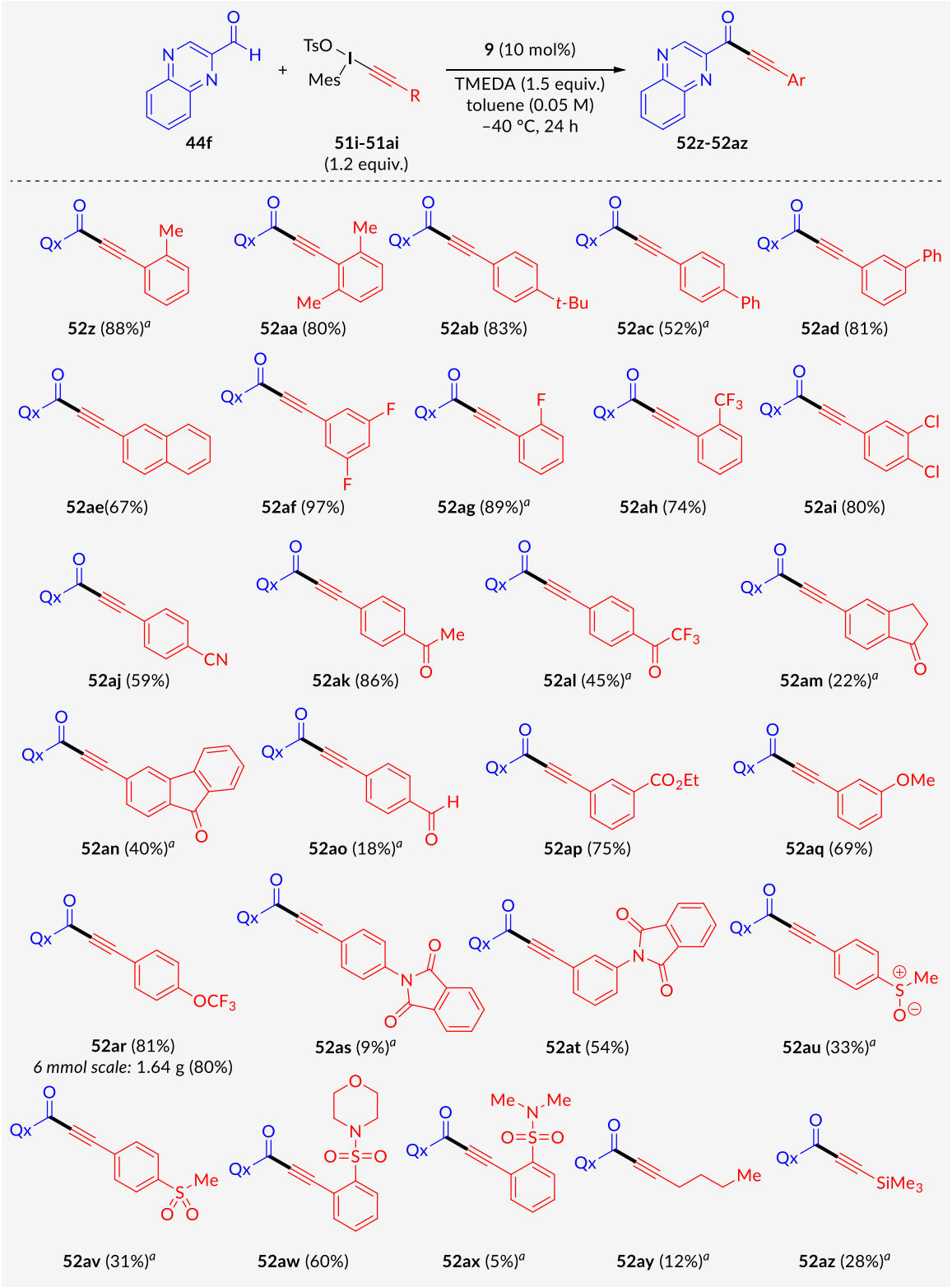


Figure 50. Scope with regard to the alkynyliodonium Salt (Qx = quinoxalin–2–yl); [a] Yield determined through analysis by ^{1}H NMR spectroscopy.

3. Experimental Mechanistic Studies

The alkynyliodonium salts contain three electrophilic centers: the iodine atom, the α–carbon of the triple bond, and the β–carbon of the triple bond. Therefore, their reactions may follow three general mechanistic pathways (**Figure 51**).

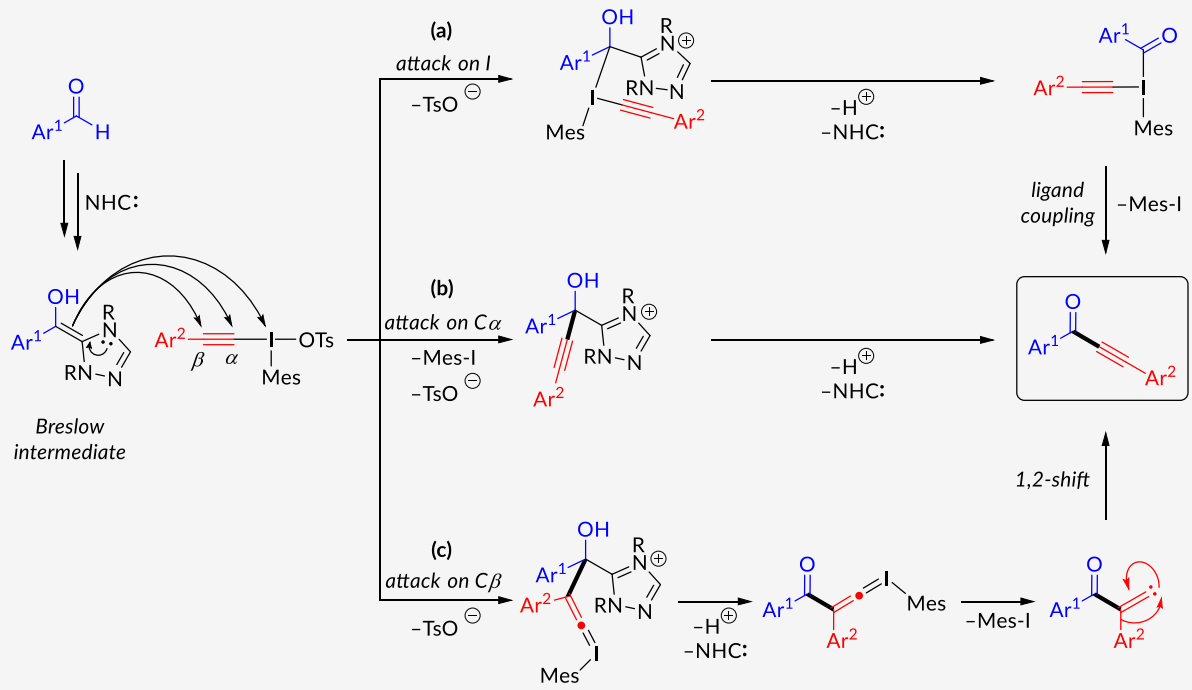


Figure 51. Outline of possible general mechanisms.

In the first pathway, the nucleophilic Breslow intermediate incorporates into the coordination sphere of iodine (**Figure 51a**). After the exclusion of NHC catalyst, the C–C bond formation occurs *via* a reductive elimination, leading to the ynone product. This particular mechanism is very common for related aryl transfer reactions with diaryliodonium salts, as it has been demonstrated by several computational studies, but it has never been shown to operate for an alkynylation with hypervalent iodine reagents.[112]

The second possibility is a direct substitution at the α–acetylenic carbon, by dissociation of iodine acting as a leaving group with a parallel attack of the nucleophile (**Figure 51b**). Such a mechanistic route has so far been shown in only one case of alkynyl transfer from hypervalent iodine species, namely for the alkynylation of thiols with EBX

[112] (a) Norrby, P.-O.; Petersen, T. B.; Bielawski, M.; Olofsson, B., *Chem. Eur. J.* **2010**, *16*, 8251-8254; (b) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B., *Chem. Eur. J.* **2013**, *19*, 10334-10342; (c) Stridfeldt, E.; Lindstedt, E.; Reitti, M.; Blid, J.; Norrby, P.-O.; Olofsson, B., *Chem. Eur. J.* **2017**, *23*, 13249-13258; (d) Ghosh, M. K.; Rzymkowski, J.; Kalek, M., *Chem. Eur. J.* **2019**, *25*, 9619-9623.

reagents.[20b, 20c, 113] Nonetheless, it was demonstrated that this pathway is not the privileged mechanism in that case, and depending on the structure of the starting materials it may contribute more or less to the formation of the product.[20c]

The final alternative involves the nucleophilic attack of Breslow intermediate on the β–carbon of the triple bond *via* a Michael-type conjugate addition (**Figure 51c**). Formed iodonium ylide, after a prior extrusion of NHC, undergoes a fragmentation to a vinylidene carbene intermediate. The intermediate rearranges to the final product *via* 1,2–shift of the aryl substituent. It is broadly accepted that the majority of alkynylations with hypervalent iodine reagents follow this mechanism, as there is strong experimental evidence supporting it. First, many reports describe cases of iodonium ylide trapping by protonation, which yields isolable vinyliodonium derivatives.[95a, 114] Secondly, in the absence of any groups prone to migration, the emergence of products originating from the insertion of the vinylidene carbene into C–H bond occurs.[106h, 115] Finally, the acetylenic carbons have been shown to switch their positions during the reactions with ^{13}C–labeled alkynyliodonium starting materials, in line with the 1,2-shift step.[20c, 36a, 115a]

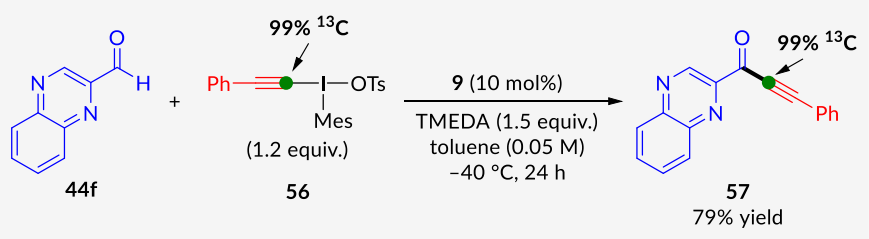


Figure 52. NHC-Catalyzed alkynylation of aldehyde **44f** with alkynyliodonium salt **56** labelled with ^{13}C at the α–carbon.

In order to distinguish between the different possible mechanisms, the alkynylation of aldehyde **44f** using iodonium salt **56**, labeled with ^{13}C at the α–carbon, was carried out (**Figure 52**). The resulting product **57** was obtained in a consistent yield compared to the unlabeled case (see **52a** in **Figure 49**) and it contained the ^{13}C label exclusively incorporated at the acetylenic carbon adjacent to the carbonyl group. It allows to doubtlessly eliminate the attack of Breslow intermediate on the β–carbon of the alkynyliodonium salt (**Figure 51c**) as the pathway of the investigated reaction.

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[113] Le Vaillant, F.; Wodrich, M. D.; Waser, J., *Chem. Sci.* **2017**, *8*, 1790-1800.

[114] (a) Kitamura, T.; Stang, P. J., *Tetrahedron Lett.* **1988**, *29*, 1887-1889; (b) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y., *J. Am. Chem. Soc.* **1991**, *113*, 3135-3142; (c) Ochiai, M.; Oshima, K.; Masaki, Y., *Tetrahedron Lett.* **1991**, *32*, 7711-7714.

[115] (a) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E., *J. Am. Chem. Soc.* **1986**, *108*, 8281-8283; (b) Tykwinski, R. R.; Whiteford, J. A.; Stang, P. J., *J. Chem. Soc., Chem. Commun.* **1993**, 1800-1801; (c) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J., *J. Am. Chem. Soc.* **1994**, *116*, 93-98; (d) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L., *J. Org. Chem.* **2002**, *67*, 7096-7109.

To obtain deeper insight into the course of the reaction, I carried out kinetic investigations. First, the progress of the reaction under the optimized conditions was monitored over time (**Figure 53a**). After that, I analyzed the decay of the starting material to determine the overall order of the reaction. The obtained data clearly exhibit the linear fit for the second order rate law (**Figure 53c**), what leads to the conclusion that the process follows a **second order** kinetics.

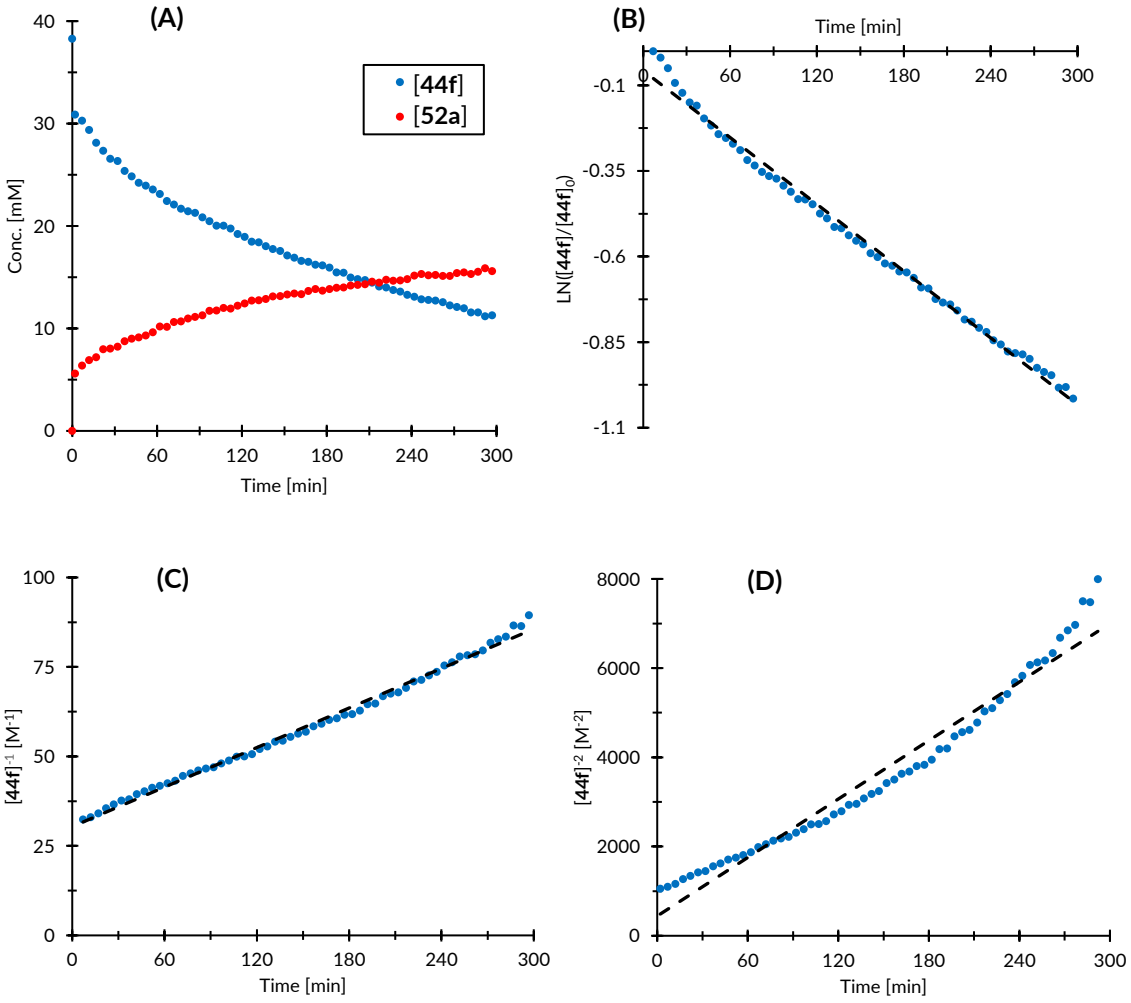

Figure 53. (A) Time-course of the NHC-catalyzed alkynylation of aldehyde **44f** with alkynyliodonium salt **51a** in d_8-Toluene at –40 °C. The concentrations were determined by ^{1}H NMR spectroscopy relative to internal standard. The initial leap in the concentrations is due to a temporary heating of the sample during the addition of the initiating reagent (TMEDA). (B) Plot of $ln\frac{[\mathbf{44f}]}{[\mathbf{44f}]_0}$ vs time. (C) Plot of $[\mathbf{44f}]^{-1}$ vs time. (D) Plot of $[\mathbf{44f}]^{-2}$ vs time.

In order to ascribe the orders to the concentrations of specific reagents, initial rate studies were conducted. The first attempts to follow the initial rates under the optimized conditions were unsuccessful, as highly erratic and irreproducible time curves were being obtained, which may originate from the heterogeneity of the reaction mixture. Thus, the switch of the solvent from d_8-toluene to $CDCl_3$, which solubilizes all the substances at the reaction temperature of –40 °C, allowed to acquire a far better

quality of data. Nevertheless, technical difficulties in measuring the reaction kinetics at so low temperature using NMR technique caused the data points to be still far from perfect. Anyhow, the obtained data is sufficient to grasp the general kinetic characteristics of the transformation.

The initial rates were measured with varied concentrations of the corresponding reagents (aldehyde **44f**, iodonium salt **51a**, TMEDA) and the catalyst precursor **9** (**Figure 54**). Analysis of this data (**Figure 55**) results in an experimental rate law, wherein the reaction is first order in the concentrations of **44f**, TMEDA, and NHC **9**, whereas zeroth order in the concentration of **51a**:

$$rate = k[\mathbf{44f}][\text{TMEDA}][\mathbf{9}]$$

This is in agreement with the overall **second order** in the substrates, *i.e.* aldehyde **44f** and TMEDA, determined from the reaction monitored over a longer period (**Figure 53**; the concentration of NHC **9** is constant with conversion, hence its influence on the rate does not present in that experiment).

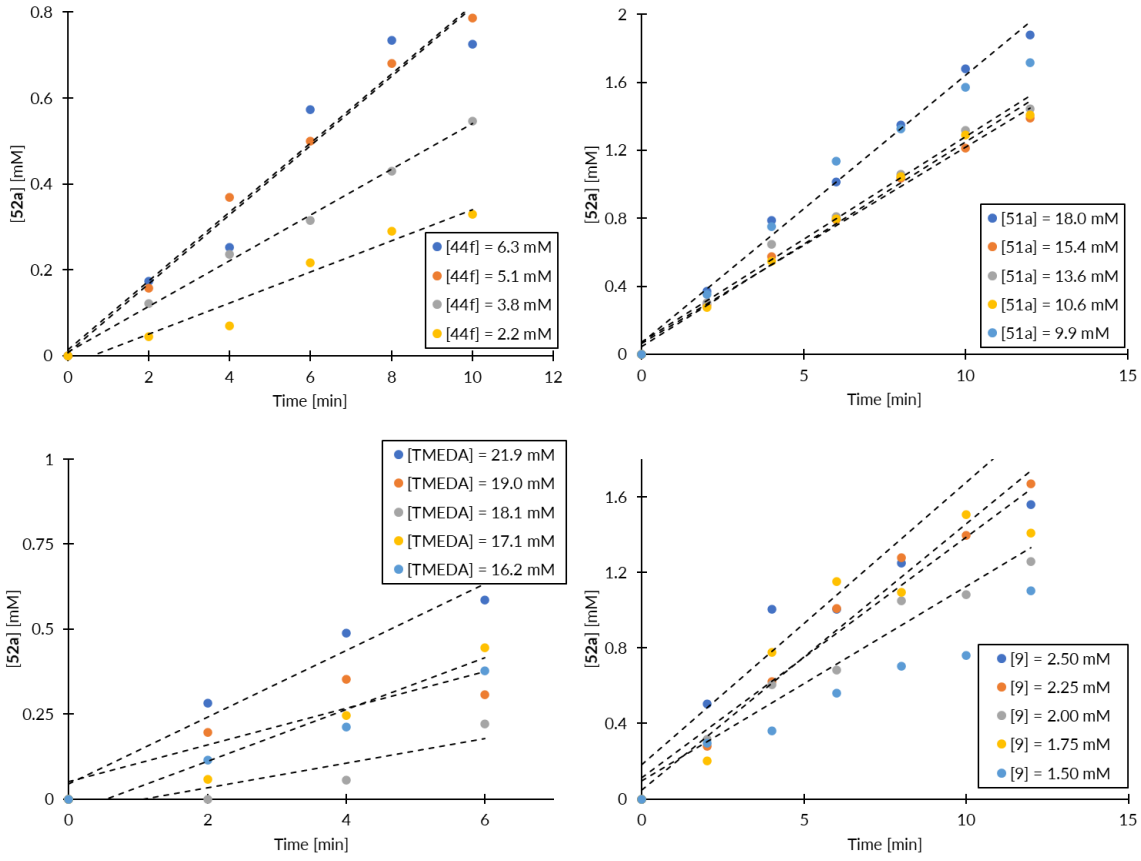

Figure 54. Initial rate measurements for the NHC-catalyzed alkynylation of aldehyde **44f** with alkynyliodonium salt **51a** in $CDCl_3$ at –40 °C, with varied concentration of (A) **44f**, (B) **51a**, (C) TMEDA, and (D) **9**. Product concentration was determined by ^{1}H NMR spectroscopy relative to internal standard.

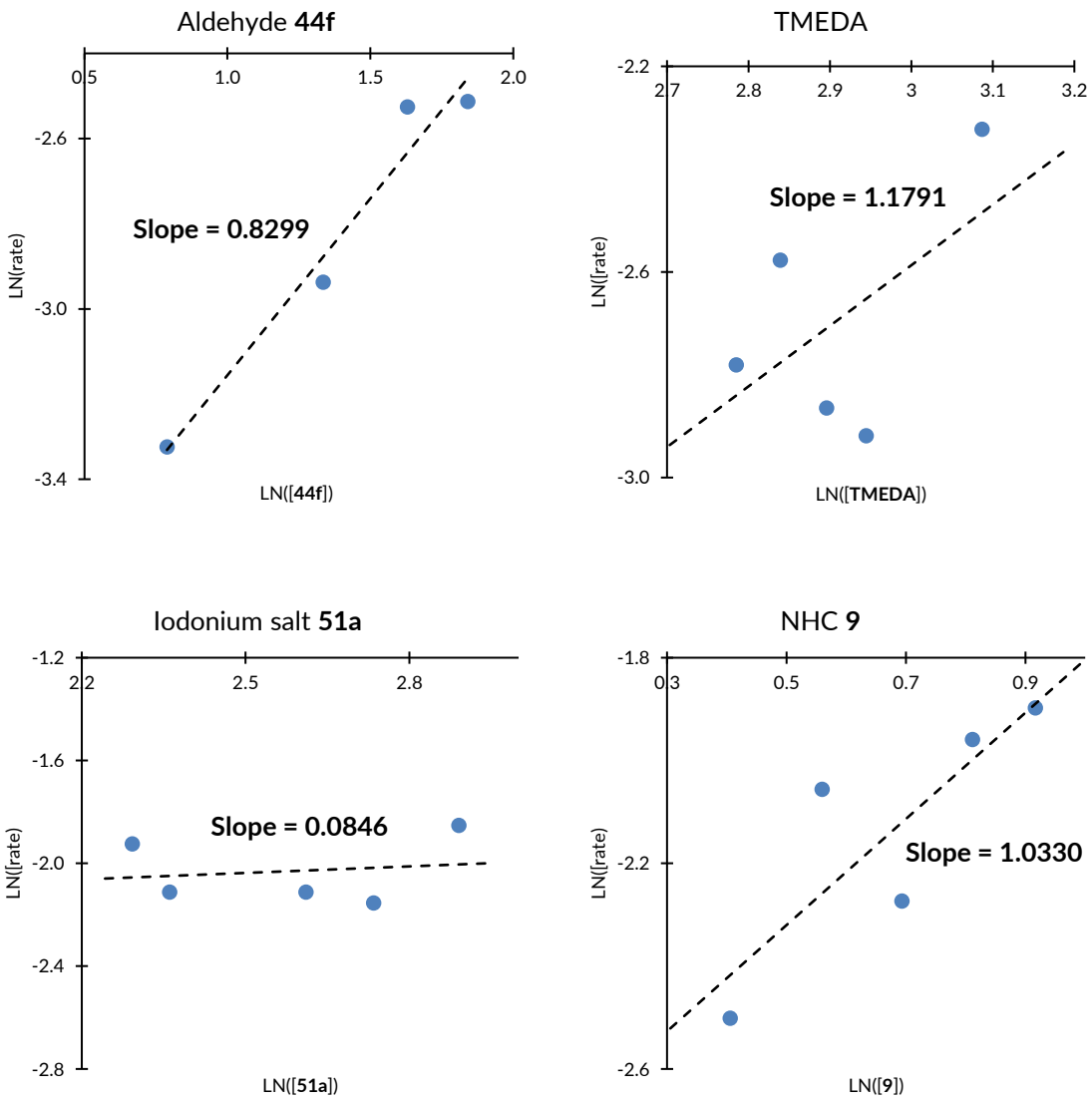

Figure 55. Initial rate LN/LN plots for the NHC-catalyzed alkynylation of aldehyde **44f** with alkynyliodonium salt **51a**.

The presence of the aldehyde and the NHC precatalyst concentrations in the rate law implies that the turnover-limiting step of the catalytic cycle is the formation of the Breslow intermediate. It is also in accordance with the presence of TMEDA concentration in the rate equation, due to the fact that the base is responsible for the deprotonation of precatalyst 9 and the generation of a free NHC. In addition, since the concentration of the alkynyliodonium salt does not impact the rate, the following C–C bond formation must be a fast step, demonstrating a very high reactivity of the alkynyliodonium salt toward the Breslow intermediate.

4. Computational Studies

To gain insight into the details of the catalytic cycle and complement the mechanistic picture obtained in the above investigations, a computational density functional theory (DFT) study was performed. The alkynylation of 2–pyridinecarboxaldehyde (**44d**) with (mesityl)(phenylethynyl)iodonium tosylate (**51a**) using NHC precatalyst **9** was employed as a model reaction in the calculations. The computations were carried out at B3LYP-D3BJ/Def2-QZVP//B3LYP-D3BJ/6-31+G(d,p)[116] (LANL2DZ(d) for I atom)[117] level of theory with the modelling of toluene and chloroform solvation using SMD method[118] for both the geometry optimizations and the final energy calculations. The free energy profile for the mechanism established by the calculations is shown in on **Figure 56**.

The mechanism starts the deprotonation of catalyst precursor **9** with TMEDA *via* transition state **TS1**, resulting in free carbene **A**, which has 2.4 $^{kcal}/_{mol}$ higher energy compared to its protonated form **9**. In the next step, the NHC attacks aldehyde **44d**, furnishing alkoxide species **B**. The overall barrier for this transformation is calculated to be 16.7 $^{kcal}/_{mol}$ relative to **9**. In the next step, **B** undergoes a barrierless protonation at oxygen by the protonated TMEDA, yielding intermediate **C**. Finally, Breslow intermediate **D** is delivered upon the abstraction of proton of **C** at the carbon atom by TMEDA *via* a low-barrier **TS3**. Overall, the formation of the Breslow intermediate is exergonic by 2.1 $^{kcal}/_{mol}$ relative to the catalyst precursor. The highest energy span along the way, amounting to 16.7 $^{kcal}/_{mol}$, is located between **9** and **TS2**. Importantly, this part of the energy diagram involves all three species, whose concentrations are present in the experimental rate-law, that is: the catalyst precursor, the aldehyde substrate, and TMEDA. The subsequent stepwise proton-shuttling (**B** → **D**) is facile and does not contribute to the reaction rate.

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[116] **B3LYP functional:** (a) Lee, C.; Yang, W.; Parr, R. G., *Phys. Rev. B* **1988,** *37*, 785-789; (b) Becke, A. D., *Phys. Rev. A* **1988,** *38*, 3098-3100; **D3 dispersion correction with BJ dumping:** (c) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H., *J. Chem. Phys.* **2010,** *132*, 154104; (d) Grimme, S.; Ehrlich, S.; Goerigk, L., *J. Comput. Chem.* **2011,** *32*, 1456-1465; **Def2-QZVP basis set:** (e) Weigend, F.; Furche, F.; Ahlrichs, R., *J. Chem. Phys.* **2003,** *119*, 12753-12762; (f) Weigend, F.; Ahlrichs, R., *Phys. Chem. Chem. Phys.* **2005,** *7*, 3297-3305; **quasi-harmonic approximation:** (g) Grimme, S., *Chem. Eur. J.* **2012,** *18*, 9955-9964.

[117] (a) Wadt, W. R.; Hay, P. J., *J. Chem. Phys.* **1985,** *82*, 284-298; (b) Check, C. E.; Faust, T. O.; Bailey, J. M.; Wright, B. J.; Gilbert, T. M.; Sunderlin, L. S., *J. Phys. Chem. A* **2001,** *105*, 8111-8116; (c) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M., *J. Chem. Phys.* **2003,** *119*, 11113-11123.

[118] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., *J. Phys. Chem. B* **2009,** *113*, 6378-6396.

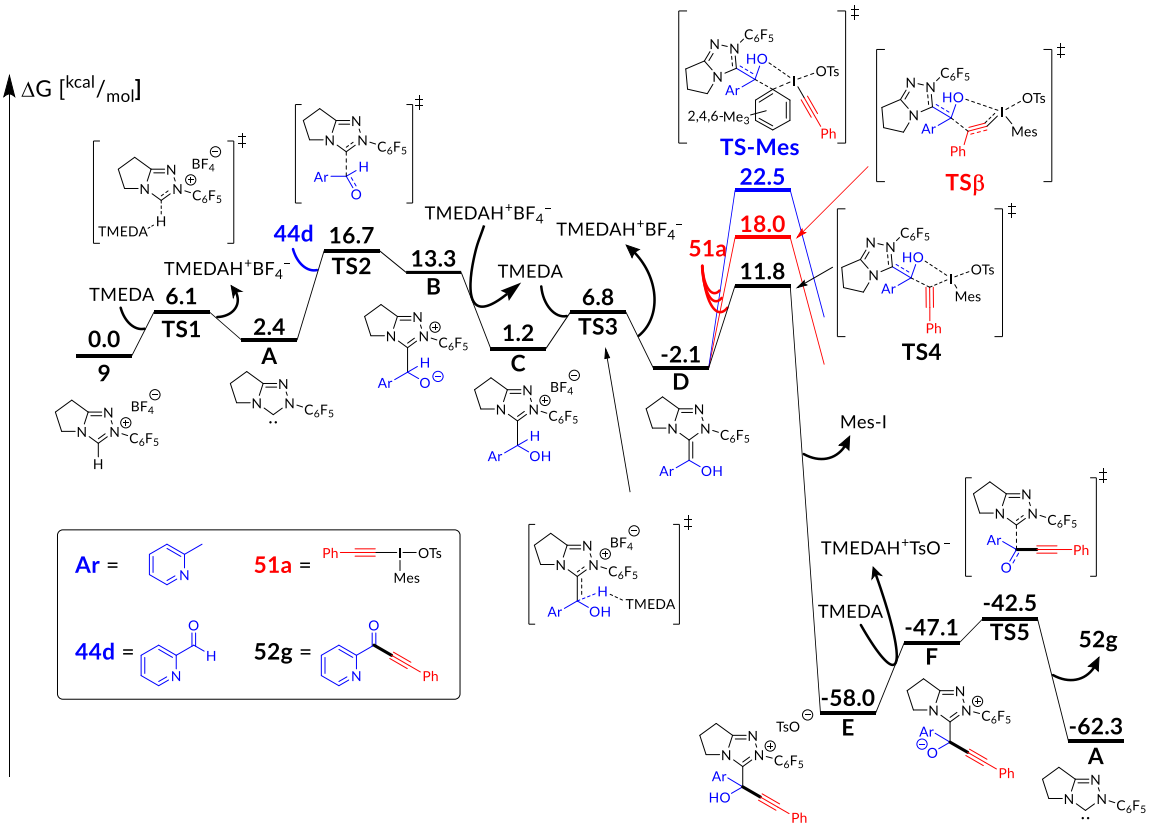


Figure 56. Free energy profile for the alkynylation of aldehyde **44d** with alkynyliodonium salt **51a** using precatalyst **9** in toluene, calculated at B3LYP-D3BJ/Def2-QZVP(SMD)//B3LYP-D3BJ/6-31+G(d,p)(SMD) level of theory.

Next, the possible options for the reaction of Breslow intermediate **D** with alkynyliodonium salt **51a** were examined. It was quickly established that the direct coordination of **D** to the iodine center is not feasible, as it does not result in a stable structure that is a minimum on the potential energy surface. Thus, the inner-sphere mechanism, involving the reductive elimination (**Figure 51a**) can be eliminated. However, I was able to find the plausible transition states, **TS4** and **TSβ**, for the other two alternative pathways, *i.e.*, the direct substitution at the α–carbon (**Figure 51b**) and the Michael-type addition to the β–carbon (**Figure 51c**), respectively. The first one is clearly energetically favored over the latter (by 6.2 $^{kcal}/_{mol}$), thus, it constitutes the true pathway of the C–C bond formation. The alkynyl group transfer *via* **TS4** was found to be a very exergonic irreversible process, by 55.9 $^{kcal}/_{mol}$. This is due to the superior effect of the reduction of iodine from +III to +I oxidation state and the loss of its hypervalent character.

To complete the picture, the transition state for the transfer of the mesityl group in **51a** (**TS-Mes**) was calculated. This course of the reaction requires crossing a very high barrier of 24.6 $^{kcal}/_{mol}$, which explains the excellent performance of the mesityl substituent acting as an auxiliary non-transferable aryl group in the alkynyl(aryl)iodonium salts. The catalytic cycle closes with a barrierless deprotonation

of intermediate **E**, followed by the release of the final product **52g** and regeneration of free NHC **A** *via* **TS5**. Overall, the total thermodynamics of the reaction is calculated to –59.9 $^{kcal}/_{mol}$.

To have a full agreement between the computational and kinetic investigation I re-calculated the whole catalytic cycle with chloroform as a solvent, which was a used for the kinetics measurements. The energy differences are not significant and all of the trends and overall characteristic of catalytic cycle remain the same as for toluene (**Figure 57**).

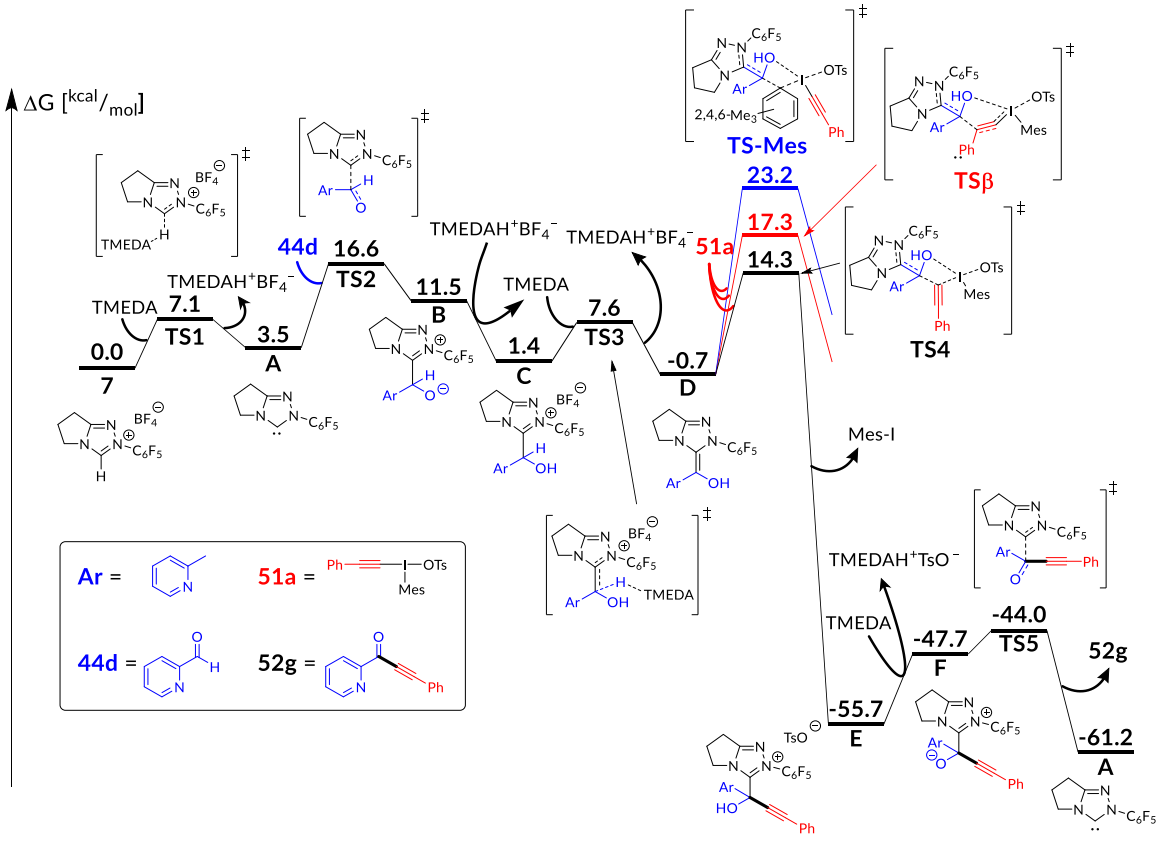


Figure 57. Free energy profile for the alkynylation of aldehyde **44d** with alkynyliodonium salt **51a** using precatalyst **9** in chloroform, calculated at B3LYP-D3BJ/Def2-QZVP(SMD)//B3LYP-D3BJ/ 6-31+G(d,p)(SMD) level of theory.

The optimized structures of transition states **TS4**, **TSβ**, and **TS-Mes**, as well as of alkynyliodonium salt **51a**, are depicted in **Figure 58**. In all three transition states the alkynyl ligand participating in the creation of new C–C bond occupies the hypervalent position. Hence, in the case of **TS4** and **TSβ** (**Figure 58b** and **Figure 58c**, respectively), the arrangement of ligands around the iodine center is the same as in the parent iodonium salt (**Figure 58a**), while in **TS-Mes** the phenylethynyl and mesityl groups are swapped (**Figure 58d**). The opposite orientation of the ligands contributes significantly to the high barrier associated with **TS-Mes**, as the calculated energy of the isomer of **51a** bearing the mesityl group in the hypervalent position and the alkynyl group in the

equatorial one is higher by 10.0 $^{kcal}/_{mol}$ compared to **51a**. The energy difference between **TS4** and **TSβ** most likely originates from the distortion of the conjugation between the forming double C–C bond and the phenyl substituent, which due to steric reasons must rotate nearly perpendicularly. On the other hand, in **TS4**, the phenyl ring is aligned is a way allowing for a complete π-conjugation over the triple bond to both the breaking C–I bond and the parallelly forming C–C bond, providing stabilization. Noticeably, in all the transition states, the hydroxyl group of Breslow intermediate is interacting with the iodine center, which is somewhat similar to the case of alkynylation of thiols with EBX, wherein the thiolate nucleophile interacts with the alkynyl group and iodine in a three-center transition state structure.[20b, 20c]

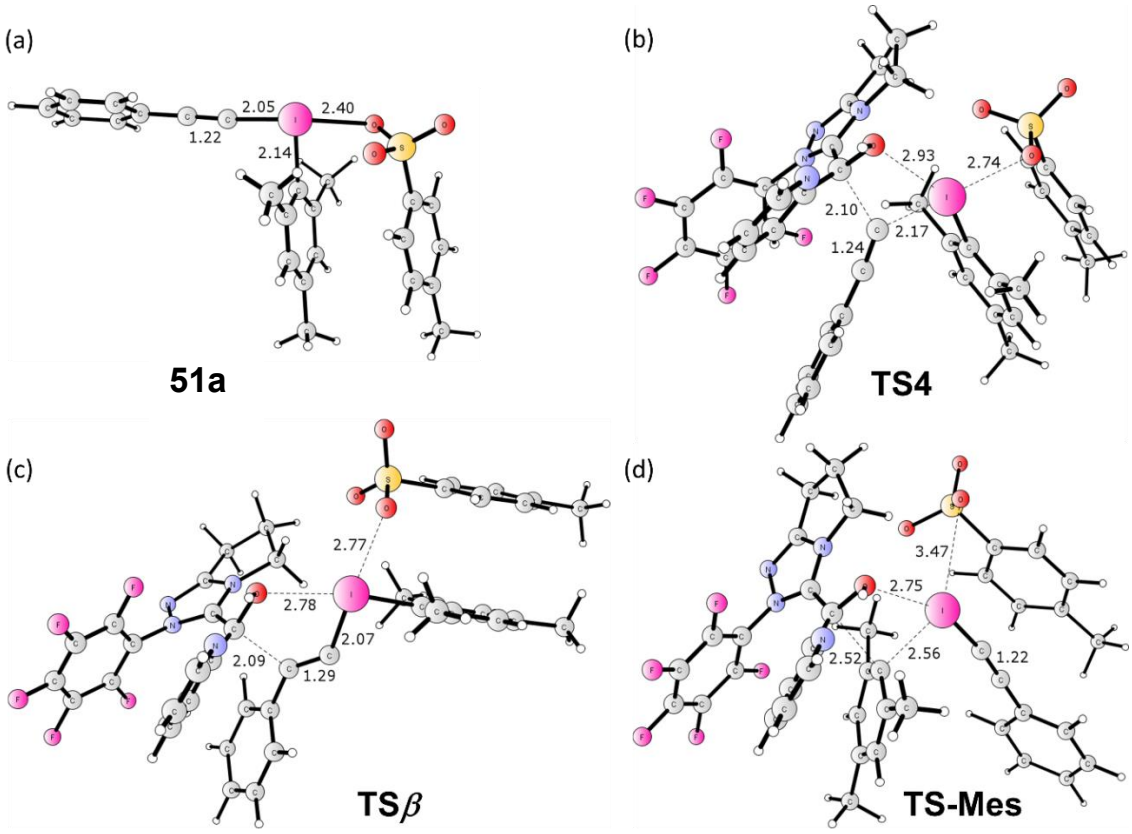


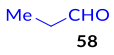
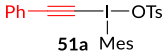
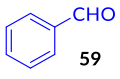
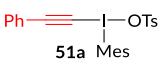
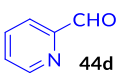
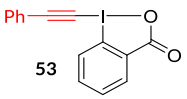
Figure 58. Optimized structures of (a) alkynyliodonium salt **51a**, (b) **TS4**, (c) **TSβ**, and (d) **TS-Mes** (distances are given in Å).

The mechanistic picture gathered from the calculations is in a full agreement with the results of the experiment with ^{13}C–labeled iodonium salt and the experimental kinetic studies. First, the lowest energy pathway established for the C–C bond formation, namely, the direct substitution at α-acetylenic carbon *via* **TS4**, explains the direct transfer of the ^{13}C-labeled carbon between iodonium salt **56** and product **57** without swapping (**Figure 52**). Secondly, the calculated free energy profile is in line with the experimentally determined rate-law. It correctly predicts that only the NHC precatalyst, the aldehyde, and TMEDA are involved in the rate determining sequence, corresponding

to the largest energy span between **9** and **TS2** (overall 16.7 $^{kcal}/_{mol}$). This result implies also that the protonated form of TMEDA should inhibit the reaction, as it is within the largest energy span. This should lead to the lower than the observed second order during the time-course experiment (**Figure 53**). However, under the experimental conditions (toluene, –40 °C) the salts of TMEDA are almost insoluble, so their concentrations remain constant, not affecting the kinetics of the reaction. The height of the turnover-limiting barrier is also quantitatively consistent with the experimental rate of the reaction at –40 °C. Conversely, the iodonium salt enters the free energy profile within a lower barrier, later in the catalytic cycle (13.9 kcal/mol, **D** to **TS4**), thus, its concentration does not influence the overall rate.

To better understand the limitations of the developed transformation, I recalculated the key stationary points in the free-energy profile for other substrates, in particular these that did not provide satisfactory results (**Table 5**). The Breslow intermediates derived from propionaldehyde (**58**) and benzaldehyde (**59**) (*entries 1* and *2*) are feasible to react with iodonium salt **51a** (**D→TS4**: 8.9 $^{kcal}/_{mol}$ and 14.9 $^{kcal}/_{mol}$ barriers, respectively). However, the barriers for their formation (**TS2**: 20.3 $^{kcal}/_{mol}$ and 19.3 $^{kcal}/_{mol}$, respectively) are considerably higher than that calculated for 2-pyridinecarboxaldehyde **44d** (16.7 $^{kcal}/_{mol}$). The barrier for the alkynyl group transfer for Ph-EBX reagent **53** (*entry 3*) was also evaluated. It was found to be far higher compared to the one obtained in the case of the iodonium salt **51a** (23.3 $^{kcal}/_{mol}$ vs 13.9 $^{kcal}/_{mol}$, respectively). This is most likely due to the considerable basicity of the carboxylate group in benziodoxolone compound, which decreases the leaving group ability of iodine, causing the alkynyl transfer more challenging.

Table 5. Relative free-energies of key stationary points for the reactions involving other substrates, calculated at B3LYP-D3BJ/Def2-QZVP(SMD)//B3LYP-D3BJ/6-31+G(d,p)(SMD) level of theory.

Entry	*Aldehyde*	*Alkynyliodonium Reagent*	***NHC 9** (initial state)*	***TS2***	***D***	***TS4***
1	 **58**	 **51a**	**0.0**	**20.3**	**6.2**	**15.1**
2	 **59**	 **51a**	**0.0**	**19.3**	**3.3**	**18.2**
3	 **44d**	 **53**	**0.0**	**16.7**	**–2.1**	**21.2**

5. Summary

In summary, NHC-catalyzed direct C–H alkynylation of aldehydes using alkynyliodonium salts as alkynyl donors has been developed, extending the scope of the NHC organocatalysis. The appropriate choice the auxiliary aryl substituent secured the selective transfer of the alkynyl group from iodine, facilitating the access to a variety of ynones in good to excellent yields. In particular, the method seems to be tailored for the synthesis of compounds containing pharmaceutically relevant heterocyclic scaffolds. Notably, a range of fragile functional groups is well tolerated, as the reaction proceeds under mild reaction conditions, in terms of both low temperature and the use of a weak amine base. Specifically, alkenes, alkynes, nitriles, ketones, esters, and amides can be incorporated into the products.

The mechanism of the reaction has been thoroughly studied by both experimental and computational methods. The ^{13}C-labeling and DFT calculations have shown that the alkynyl group transfer occurs *via* a direct substitution of iodine by the Breslow intermediate taking place at α-acetylenic carbon, and not by the ubiquitous pathway involving the initial attack of nucleophile at the β-position. It establishes the second reported example of such a course of the alkynylation reaction with a hypervalent iodine reagent and the first wherein it is the distinctly an exclusive mechanistic pathway. It may therefore implicate that related mechanisms can be more frequent than previously thought. In addition, the kinetic studies, validated and confirmed by the computed free energy profile, have identified that the formation of the Breslow intermediate is the rate-determining step of the catalytic cycle. The following C–C coupling between the Breslow intermediate and the alkynyliodonium salt is a facile, low-barrier process. Above result opens opportunities for the wider application of alkynyliodonium salts as efficient alkynyl-transfer reagents for other non-trivial nucleophilic species, including catalytically generated ones.

Chapter IV. Transition Metal-Free and Regioselective Vinylation of Phosphine Oxides and H–Phosphinates with VBX Reagents (Paper IV)

1. Background

Among the variety of iodine(III) reagents,[10e, 22] cyclic benziodoxolone moiety has been introduced as an alternative to acyclic iodonium salts in processes such as alkynylation and trifluoromethylation.[23g, 23h, 119] Notably, novel cyclic hypervalent iodine compounds, namely vinylbenziodoxolones (VBX) were recently introduced as efficient vinylating agents[91c] utilized in metal-catalyzed cross coupling reactions and C–H vinylations,[120] as well as in metal-free reactions.[121] The clear advantage of VBX reagents is their simple and straightforward synthesis, performed in a one-pot fashion from 2–iodobenzoic acid[91c] or *via* iodine(III) species, which are reacted with a suitable vinylboronic acid.[120c, 120e] Another convenient method is based on the addition of heteroatom nucleophiles to EBX reagents leading to β,β–disubstituted cyclic iodine(III) compounds,[120d, 120e, 121c, 122] allowing to obtain a plentiful of highly functionalized vinylbenziodoxolones. Olofsson and co-workers demonstrated an unique β–reactivity of VBXs in the vinylation of nitrocyclohexane, selectively delivering a terminal alkene (**Figure 59a**), compared to standard vinyliodonium salts affording internal olefin.[91c] Interestingly, the vinylation of thiols and mercaptothiazoles with VBX results in the

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[119] Hari, D. P.; Caramenti, P.; Waser, J., *Acc. Chem. Res.* **2018,** *51*, 3212-3225.

[120] (a) Wu, J.; Deng, X.; Hirao, H.; Yoshikai, N., *J. Am. Chem. Soc.* **2016,** *138*, 9105-9108; (b) Wu, J.; Xu, K.; Hirao, H.; Yoshikai, N., *Chem. Eur. J.* **2017,** *23*, 1521-1525; (c) Boelke, A.; Caspers, L. D.; Nachtsheim, B. J., *Org. Lett.* **2017,** *19*, 5344-5347; (d) Tessier, R.; Ceballos, J.; Guidotti, N.; Simonet-Davin, R.; Fierz, B.; Waser, J., *Chem* **2019,** *5*, 2243-2263; (e) Pisella, G.; Gagnebin, A.; Waser, J., *Org. Lett.* **2020,** *22*, 3884-3889.

[121] (a) Davies, J.; Sheikh, N. S.; Leonori, D., *Angew. Chem. Int. Ed.* **2017,** *56*, 13361-13365; (b) Liu, B.; Lim, C.-H.; Miyake, G. M., *J. Am. Chem. Soc.* **2018,** *140*, 12829-12835; (c) Caramenti, P.; Declas, N.; Tessier, R.; Wodrich, M. D.; Waser, J., *Chem. Sci.* **2019,** *10*, 3223-3230; (d) Amos, S. G. E.; Nicolai, S.; Gagnebin, A.; Le Vaillant, F.; Waser, J., *J. Org. Chem.* **2019,** *84*, 3687-3701; (e) Liu, B.; Alegre-Requena, J. V.; Paton, R. S.; Miyake, G. M., *Chem. Eur. J.* **2020,** *26*, 2386-2394.

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internal alkene products with a very high (*E*)–selectivity (**Figure 59a**),[123] while vinyliodonium salts give exclusively the (*Z*)–isomer *via* a vinylic S_N2 pathway.[90a]

The alkenylphosphorus compounds are essential building blocks in a series of transformations, including reduction,[124] epoxidation,[125] Michael addition,[126] and cycloaddition.[127] Moreover, a number vinylphosphorus species constitute pharmacologically important and biologically active compounds, such as antibiotics and enzyme inhibitors.[128] In addition, alkenylphosphine oxides and phosphonates are also valuable monomers in polymer and material chemistry.[129] The most common approach to the synthesis of alkenyl phosphorus compounds relies on the transition metal-catalyzed cross coupling methodologies[130] and the metal-catalyzed hydrophosphonylation of alkynes, leading to terminal vinyl-phosphorus derivatives.[131] However, these methods exhibit common drawbacks, including the need to remove the transition metal residues from the final product, the toxicity and cost of the catalysts, and often, the need for the preparation of non-commercial ligands.[132] Therefore, the metal-free methodologies for C–P bond formation are highly desirable. Recently, several

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[129] (a) Schmider, M.; Müh, E.; Klee, J. E.; Mülhaupt, R., *Macromolecules* **2005**, *38*, 9548-9555; (b) Parvole, J.; Jannasch, P., *Macromolecules* **2008**, *41*, 3893-3903; (c) Sato, T.; Hasegawa, M.; Seno, M.; Hirano, T., *J. Appl. Polym. Sci.* **2008**, *109*, 3746-3752; (d) Levchik, S. V.; Weil, E. D., *Polym. Int.* **2005**, *54*, 11-35.

[130] (a) Niu, M.; Fu, H.; Jiang, Y.; Zhao, Y., *Chem. Commun.* **2007**, 272-274; (b) Kalek, M.; Ziadi, A.; Stawinski, J., *Org. Lett.* **2008**, *10*, 4637-4640; (c) Kalek, M.; Johansson, T.; Jezowska, M.; Stawinski, J., *Org. Lett.* **2010**, *12*, 4702-4704; (d) Evano, G.; Tadiparthi, K.; Couty, F., *Chem. Commun.* **2011**, *47*, 179-181; (e) Hu, J.; Zhao, N.; Yang, B.; Wang, G.; Guo, L.-N.; Liang, Y.-M.; Yang, S.-D., *Chem. Eur. J.* **2011**, *17*, 5516-5521; (f) Kalek, M.; Stawinski, J., *Adv. Synth. Catal.* **2011**, *353*, 1741-1755; (g) Liu, L.; Wang, Y.; Zeng, Z.; Xu, P.; Gao, Y.; Yin, Y.; Zhao, Y., *Adv. Synth. Catal.* **2013**, *355*, 659-666; (h) Wu, Y.; Liu, L.; Yan, K.; Xu, P.; Gao, Y.; Zhao, Y., *J. Org. Chem.* **2014**, *79*, 8118-8127; (i) Hu, G.; Gao, Y.; Zhao, Y., *Org. Lett.* **2014**, *16*, 4464-4467.

[131] (a) Han, L.-B.; Tanaka, M., *J. Am. Chem. Soc.* **1996**, *118*, 1571-1572; (b) Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S., *J. Am. Chem. Soc.* **2004**, *126*, 5080-5081; (c) Dobashi, N.; Fuse, K.; Hoshino, T.; Kanada, J.; Kashiwabara, T.; Kobata, C.; Nune, S. K.; Tanaka, M., *Tetrahedron Lett.* **2007**, *48*, 4669-4673; (d) Xu, Q.; Shen, R.; Ono, Y.; Nagahata, R.; Shimada, S.; Goto, M.; Han, L.-B., *Chem. Commun.* **2011**, *47*, 2333-2335; (e) Li-Biao, H.; Yutaka, O.; Qing, X.; Shigeru, S., *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1086-1099.

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such methods have been developed, *e.g.*, an addition of secondary phosphine oxides to alkynes *via* photoredox catalysis,[133] a decarboxylative phosphorylation of cinnamic acids,[134] and a phosphonocarboxylation of alkenes with carbon dioxide *via* visible-light photoredox catalysis.[135] These methods allow only to obtain internal P–olefines, and so far the only known metal-free β–vinylations of phosphorus nucleophiles are: the vinylation of secondary phosphine oxides by vinyl sulfones, developed by Xiao in 2017,[136] and the olefination of H–phosphonates utilizing nitroolefines reported in 1997 by Ogawa,[137] refined in 2014 by Weng and Lu (**Figure 59b**).[138] However the authors demonstrated a very limited scope of these reactions.

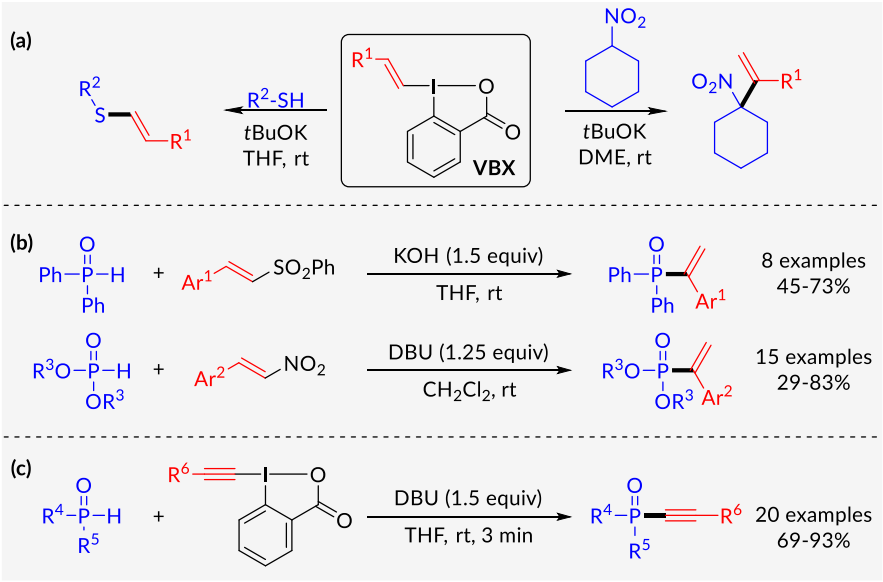

Figure 59. Examples of transition metal-free examples of vinylation and alkynylation.

In 2014, ethynylbenziodoxolone reagent (EBX) was employed by Waser as an efficient alkynylation reagent of H–phosphites, H–phosphinates, and secondary phosphine oxides under mild conditions and in short reaction times (**Figure 59c**).[139] This report provides a very auspicious perspective for the application of the novel VBX reagent to the construction of C–P bonds.

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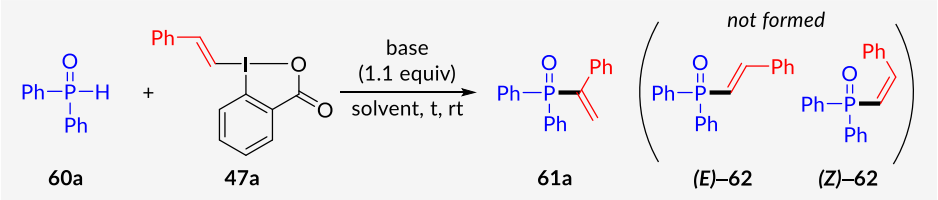
[139] Chen, C. C.; Waser, J., *Chem. Commun.* **2014**, *50*, 12923-12926.

2. Optimization of the Reaction Conditions

Table 6. Optimization for phosphine oxides.[a]



Entry	*Base*	*Solvent*	*Conc. [mol/L]*	*Time [h]*	*Yield 61a [%]*[b]
1	Et_3N	THF	0.1	20	**5**
2	DMAP	THF	0.1	20	**<5**
3[c]	Cs_2CO_3	THF	0.1	20	**62**
4	-	THF	0.1	20	**0**
5	DBU	THF	0.1	20	**88**
6	BTMG	THF	0.1	20	**90**
7	DBU	Et_2O	0.1	20	**40**
8	DBU	Toluene	0.1	20	**64**
9	DBU	EtOAc	0.1	20	**76**
10	DBU	THF	0.1	1	**84**
11[d]	DBU	THF	0.1	1	**80**
12	DBU	THF	0.25	1	**78**
13	DBU	THF	0.05	1	**93 (94)**

[a] Reaction conditions: **60a** (0.05 mmol) and base were stirred in solvent for 5 min before addition of **47a** (1.2 equiv); [b] Determined through analysis by ^{1}H NMR spectroscopy, isolated yield in brackets; [c] At 60 °C; [d] 1.0 equiv of **47a**; DBU = 1,8–diazabicyclo[5.4.0]undec–7–ene; BTMG = 2–*tert*–butyl–1,1,3,3–tetramethylguanidine; DMAP = 4–(dimethylamino)pyridine.

I started the investigation of the vinylation of phosphorous compounds on a model reaction between diphenylphosphine oxide **60a** and phenyl VBX **47a**. The vinylation proceeds with a complete regioselectivity in the favor of the terminal alkene **61a**, without any detectable traces of internal alkenes **62** (**Table 6**). Several organic and inorganic bases were tested in the reaction with THF as a solvent at room temperature for 20 hours (*entries 1-6*). DBU and BTMG were found to be superior compared to other bases (*entries 5-6*), and no reactivity was detected in the absence of the base (*entry 4*). Due to the economy and sustainability issues, DBU was selected over BTMG for further investigations. A number of solvents were tested furnishing the product in moderate yields, and THF was chosen as the best one (*entry 5* vs *entries 7-9*). Shortening the reaction time to 1 hour and reducing the amount of VBX to 1.0 equiv. resulted in a slight decrease of the yield (*entries 10-11*). Finally, **61a** was obtained in 94% isolated yield by lowering the concentration of the reaction to 0.05 M (*entry 13*).

3. Scope and Limitations of the Method

With the established optimized conditions, the substrate scope was examined with symmetric and unsymmetric diarylphosphine oxides (**Figure 60a** and **60b**, respectively). The method allows for the synthesis of a variety of β–vinyl tertiary phosphine oxides. Diarylphosphine oxides are suitable substrates furnishing functionalized products bearing alkyl (**61b-c**), ether (**61g**), and fluorine (**61h**) substituents. Moreover, sterically demanding phosphine oxides containing naphthyl and 2–tolyl substituents were obtained in good yield (**61d-f**). The presence of electron withdrawing groups drastically reduces the reactivity of the nucleophile, and a modest yield of **61i** was obtained under the standard conditions, however, this was improved to 27% yield by increasing the temperature to 60° C and prolonging the reaction time to 20 hours. The use of dialkylphopshine oxides is strongly limited, even under the improved conditions, as only 30% yield was obtained for product **61j**. Next, the unsymmetrical phosphines oxides were evaluated. Products containing methyl (**61k**) and trifluoromethyl (**61l**) substituents in one of the aryl rings were successfully synthetized. Notably, heteroaromatic substituents are also well tolerated, *e.g.*, phenylthienylphosphine oxide **60m** furnishes the desired product **61m** in 64% yield. Due to the unsatisfactory reactivity of dialkylphosphine oxides, I decided to test unsymmetrical alkylarylphosphine oxides, however, the yields were still not acceptable. Fortunately, increasing of the reaction temperature to 60 °C and prolonged reaction time (2 hours) allowed to obtain the desired products. Phosphine oxides bearing ethyl (**61n**), benzyl (**61o-p**), and also allyl (**61q**) substituents were synthetized in very good yields, demonstrating functional group tolerance towards aromatic bromides and double bounds. Moreover, the product containing cyclopropyl (**61r**) and sterically demanding *tert*–butyl group (**61s**) were tolerated and synthetized in good yield.

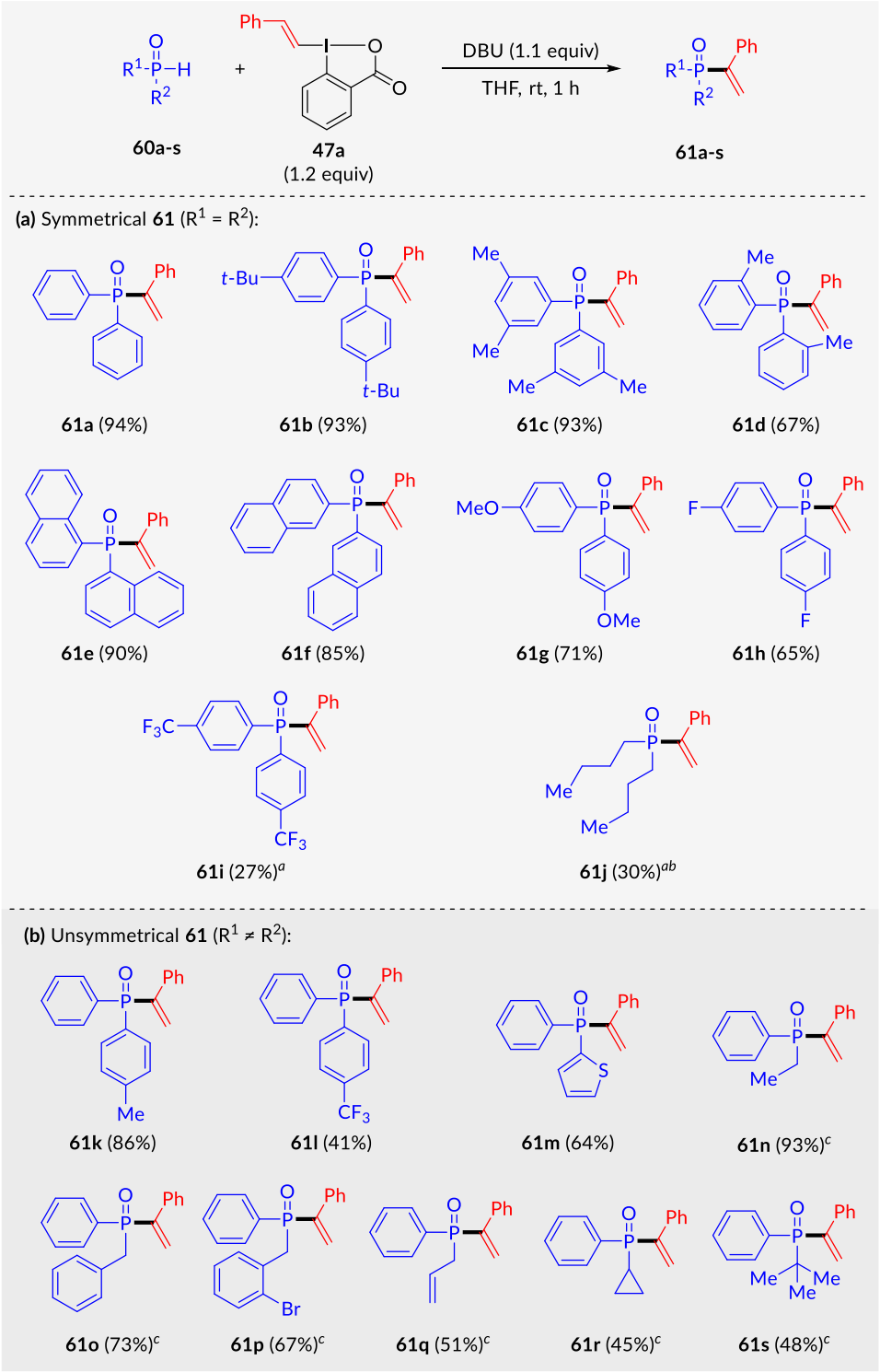


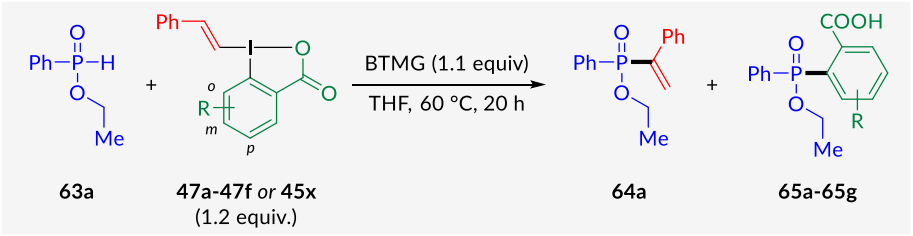
Figure 60. Scope with regard to the secondary phosphine oxides; [a] At 60 °C, 20 h; [b] Yield determined through analysis by ^{1}H NMR spectroscopy; [c] At 60 °C, 2 h.

As a further step in expanding the reaction scope, H–phosphinates and H–phosphonates were tested. It was quickly established that these types of substrates require more harsh conditions to furnish the products in satisfactory yields. The first attempts with ethyl phenylphosphinate **63a** lead to a conclusion that it requires elevated

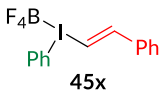
temperature (60 °C), longer reaction time (20 h), and also the change of the base from DBU to BTMG (**Table 7**, *entry 1*).

At this point, I envisioned that except for the reaction conditions and the character of the nucleophile, the substituents at the aromatic core of VBX may have an effect on the reaction outcome. In 2012, Legault described the influence of steric hindrance in the *ortho* position on the reactivity of iodonium(III) species in the catalytic iodane-based α–tosyloxylation of ketones.[140] One year later Waser and co-workers developed an asymmetric alkynylation of stabilized enolates using ethynylbenziodoxolone (EBX) reagents.[36b] The authors found that 2,3–dimethoxy-substituted benziodoxolone core secures efficient and more selective ethynyl group transfer. Recently, Olofsson described an enhanced reactivity of 2,3–dimethyl substituted VBX towards demanding substrates in the vinylation of sulfur nucleophiles.[123] Encouraged by these discoveries, I attempted to investigate the effect of several core-substituted VBX reagents (**Table 7**).

Table 7. Influence of core substituents on VBX.[a]



63a **47a-47f** *or* **45x** (1.2 equiv.) **64a** **65a-65g**

Entry	*I(III)*	***R***	*Yield 64a (%)*	*Yield 65 (%)*	*Recovered 63a (%)*
1	**47a**	H	**79**	**0**	**0**
2	**47b**	*p*–Br	**45**	**0**	**30**
3	**47c**	*p*–OMe	**44**	**0**	**34**
4	**47d**	*o*–Me	**0**	**0**	**92**
5	**47e**	*o*–NO_2	**0**	**60**	**0**
6	**47f**	*m,p*–Me_2	**75**	**0**	**0**
7	**45x**	 **45x**	**10**	**0**	**0**

[a] Determined through analysis by ^{1}H NMR spectroscopy.

[140] Guilbault, A.-A.; Legault, C. Y., *ACS Catal.* **2012**, *2*, 219-222.

In a model reaction, phosphinate **63a** was reacted with substituted VBX reagents **47b-f** to investigate electronic and steric influences. Surprisingly, the presence of both electron-withdrawing (**47b**) and electron-donating (**47c**) groups in the *para* position had a negative effect on the reactivity (*entries 2-3*), as lowered yield of product and also significant amount of unreacted substrate were obtained. Moreover, the steric effect was evaluated with two electronically different, *o*–methyl– and *o*–nitro–substituted VBX reagents (**47d** and **47e**, respectively). The methyl substitution close to iodine(III) center entirely hinders the reactivity of the corresponding VBX reagent (*entry 4*), while NO_2 substituent causes swapped regioselectivity toward the aryl VBX core transfer, instead of the vinyl group transfer (*entry 5*). The 2,3–dimethyl substitution pattern does not improve the activity of the reagent, providing comparable yield of product **47a** (*entry 6* vs *entry 1*). Finally, a simple acyclic phenyl(styryl)iodonium tetrafluoroborate **45x** was identified as an ineffective for the transformation (*entry 7*).

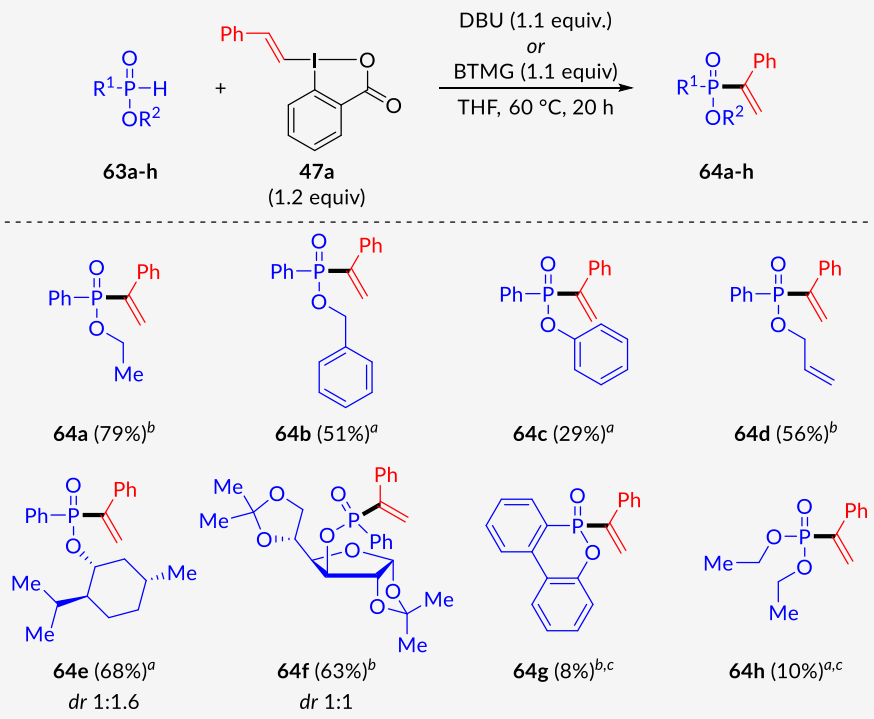


Figure 61. Scope with regard to the H–phosphinates and H–phosphonates; [a] DBU used as a base; [b] BTMG used as a base; [c] Yield determined through analysis by ^{1}H NMR spectroscopy.

As the standard non-substituted VBX reagent was found to be the most efficient, the scope with regard to the H–phosphinates was subsequently examined using this compound. The method delivers a range of β–styryl phosphinates with a variety of alkoxy functionalities (**Figure 61**). Ethyl phenylphosphinate and benzyl phenylphosphinate give corresponding products in good yields (**64a** and **64b**, respectively), while phenoxy moiety is not well-tolerated and it slowly decomposes during the reaction, however, the product **64c** was still obtained in 29% of yield. Allyl

alcohol derivative is well-tolerated, delivering the desired product in good yield (**64d**). Notably, the methodology allows for the synthesis of structurally complex phosphinates with biologically relevant scaffolds, such as menthyl (**64e**) and glucose diacetonide (**64f**). The vinylation leading to products **64g** and **64h** demonstrates the limitation of the method.

Next, the scope with regard to the vinylbenziodoxolone reagent was examined (**Figure 62**). The developed method allows for an efficient transfer of styryl groups containing a number of substituents, such as aryl (**61t**), trifluoromethyl (**61u**), and chloride (**61v**). Interestingly, alkyl-substituted vinyl moieties are transferred efficiently, furnishing vinylated phosphine oxides bearing cycloalkyl (**61w**) and a very reactive allyl chloride (**61x**) functionality. Unfortunately, β–*N*–sulfonamide substituted VBX exhibited a lack of activity and did not afford the desired product (**61y**).

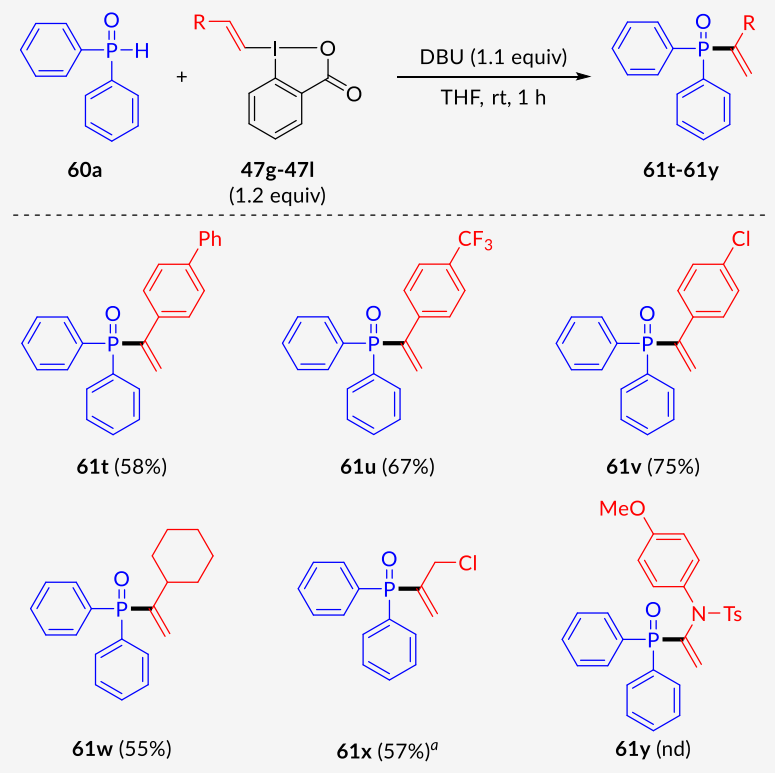


Figure 62. Scope with regard to the vinylbenziodoxolone; [a] At –10 °C, 2 h; nd – not detected.

4. Preliminary Mechanistic Investigations

The exclusive β–regioselectivity displayed by the vinylations of phosphorus nucleophiles with VBX is somehow intriguing, thus, preliminary tests with radical scavengers were conducted to investigate whether any radical pathway could be operating (**Figure 63**). The reactions of diphenylphosphine oxide (**60a**) under the standard conditions in the presence of 1 equiv. of TEMPO (**66**) or diphenylethylene (DPE, **67**) afforded the desired product with yields comparable to the one without additive, indicating that a radical pathway is not likely.

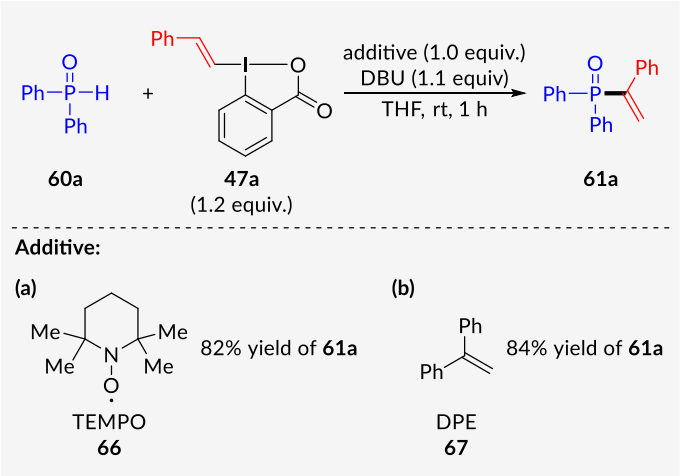


Figure 63. Test reactions with radical scavengers: TEMPO and DPE.

The scope and limitation studies revealed also a number of interesting features, hinting on the plausible mechanism. First, the standard non-substituted VBX exhibits the best reactivity and performance toward phosphorous-based nucleophiles, which means that the electronic properties of the VBX core do not affect the process of C–P bond formation (except the strongly EWG nitro group, which inverses the selectivity of the transfer). Secondly, the lack of reactivity of *o*–methyl-substituted VBX reagent suggests that the methyl substituent distorts the geometry of transition state of C–P bond formation making it energetically unfavorable.

These observations allow to propose the plausible mechanistic pathway to be a phospha-Michal-type[141] addition/elimination process (**Figure 64**). This picture is supported by a previous mechanistic investigation on the thiourea–catalyzed phospha–Michael additions.[142]

[141] Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A., *Eur. J. Org. Chem.* **2006**, *2006*, 29-49.

[142] (a) Alcaine, A.; Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P., *Org. Biomol. Chem.* **2011**, *9*, 2777-2783; (b) Huang, H.; Palmas, J.; Kang, J. Y., *J. Org. Chem.* **2016**, *81*, 11932-11939.

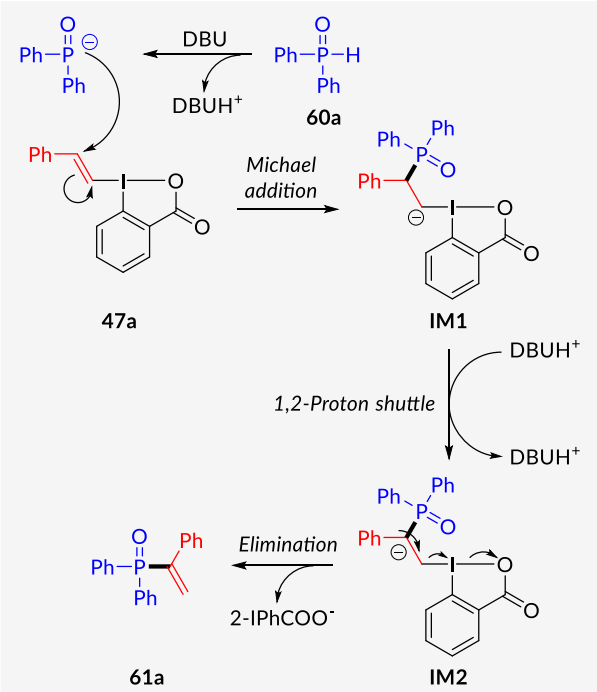


Figure 64. Proposed mechanism of the vinylation of P-based nucleophiles with VBX reagents.

The deprotonated form of phosphorus substrate attacks β–carbon of vinylbenziodoxolone reagent *via* Michael-type addition furnishing **IM1**. Next, upon a 1,2-proton shift, which is likely assisted by $DBUH^+$, **IM2** is generated. Finally, due to the high leaving-group ability of iodine(III), the elimination with an accompanying reduction to +1 oxidation state occurs, delivering product **61a** and 2–iodobenzoate.

5. Summary

To conclude, vinylbenziodoxolone reagent was employed in an efficient olefination of a wide range of phosphine oxides and H–phosphinates. The reaction proceeds under mild and transition metal-free conditions, furnishing a variety of vinylphosphorus derivatives, bearing an array of functional groups, including pharmaceutically relevant ones. Exclusive β–regioselectivity was observed. The plausible mechanism involves a phospha-Michal-type addition followed by a proton shift and an elimination.

Concluding Remarks

In this thesis, the process of a functional group transfer from hypervalent iodine compounds to a number of nucleophiles has been explored. The investigations have led to the development of two new *N*–heterocyclic carbene-catalyzed strategies for the functionalization of aldehydes with iodonium salts, namely vinylation and alkynylation, and a metal-free selective β–vinylation of phosphorus-based nucleophiles using vinylbenziodoxolone reagent.

The first and the second project focused on the reaction between iodonium salts and a catalytically generated Breslow intermediate, whose only a single example existed at the start of my PhD studies – the arylation of aldehydes devised by Gaunt. Thus, my work has expanded the scope of this methodology to two additional synthetically useful processes, namely the vinylation and the alkynylation. I carefully optimized the reaction conditions, including the key auxiliary aryl moiety in the structure of vinyl- and alkynyliodonium salt, which allowed to secure selective and high yielding formation of the products. The scope of the reactions has been investigated extensively, showing a superior performance of heteroaromatic aldehydes in these transformations, which also proceeded smoothly for propargyl aldehydes and aromatic aldehydes bearing strongly electron-withdrawing groups. On the side of the moieties transferred from iodine(III), they can contain a plethora of functional groups, such as halides, ethers, ketones, as well as phthalimides and sulfonamides. In general, very mild reaction conditions resulted in a good functional group tolerance.

To fully understand the underlying nature of the developed processes, I investigated the mechanism of the alkynylation reaction using both experimental and computational methods. First, the experiment with ^{13}C–labeled alkynyliodonium salt showed that the substitution occurs at the α-acetylenic carbon. Secondly, the kinetic investigation using the initial rate approach, led to a rate equation, which depends on the concentrations of aldehyde, carbene, and the base, identifying the formation of Breslow intermediate as the rate-determining step. Finally, using DFT computations, I calculated the free energy profile of the reaction, which is in a full agreement with the experimental observations.

In the final part, I investigated a metal-free vinylation of phosphorus nucleophiles with vinylbenziodoxolone reagent. This novel compound has been previously found to be an efficient vinylation reagent exhibiting an extraordinary β–regioselectivity during the group transfer to carboanion nucleophiles. I explored how VBX behaves toward nucleophilic phosphorus compounds and found that this the process followed also the

unique β–vinylation pathway. The successful optimization of the reaction conditions allowed to efficiently prepare various β–vinylphosphine oxides bearing number of aromatic and aliphatic moieties. Moreover, under slightly modified conditions the vinylation of H–phosphinates could also be performed, delivering several products, including such containing fragile pharmaceutically-relevant groups. A brief mechanistic investigation enabled to tentatively dismiss the radical pathway, and supported the mechanism involving a phospha–Michael addition/elimination sequence.

To conclude, the thesis describes the successful development of a number of methods employing hypervalent iodine compounds to transfer functional groups under organocatalytic and metal-free conditions. The former approach seems to be an excellent match not only because of its robustness but also because both hypervalent iodine compounds and organocatalysts are inherently environmentally benign. The in-depth understanding of the newly discovered processes is very important and valuable for future developments in the area of hypervalent iodine chemistry. I strongly believe that scientific results described in this thesis will support other researchers to discover other outstanding applications for this class of compounds.

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Appendix A

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Introduction

Appendix B

24.09.2020

Contribution report for the doctoral thesis of Adam Rajkiewicz

Adam A. Rajkiewicz

My contribution to the publications listed below:

Ghosh, M. K.; Rajkiewicz, A. A.; Kalek, M.

„Organocatalytic Group-Transfer Reactions with Hypervalent Iodine Reagents"

Synthesis **2019**, *51*, 359-370.

I found the literature references for and wrote the first draft of 3 subsections (Chapter 2) of the review text.

Rajkiewicz, A. A.; Kalek, M.

„N–Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts To Generate α,β-Unsaturated Ketones"

Org. Lett. **2018**, *20*, 1906–1909.

I participated in the planning of the research, conducted all of the experimental work, and I wrote the first draft of the manuscript and the supporting information.

Rajkiewicz, A. A.; Wojciechowska, N.; Kalek, M.

„N–Heterocyclic Carbene-Catalyzed Synthesis of Ynones via C–H Alkynylation of Aldehydes with Alkynyliodonium Salts — Evidence for Alkynyl Transfer via Direct Substitution at Acetylenic Carbon"

ACS Catal. **2020**, *10*, 831–841.

I participated in the planning of the research, conducted the majority of the experiments in the publication (optimization, scope and limitations, and mechanistic investigations), performed all the computations, and wrote the first draft of manuscript and the supporting information.

Castoldi, L.; Rajkiewicz, A. A.; Olofsson, B.

„Transition Metal-Free and Regioselective Vinylation of Phosphine Oxides and H-Phosphinates with VBX Reagents"

Submitted

During the internship in Stockholm University under the supervision of Berit Olofsson, I participated in the planning of the research, carried out a part of the experimental work (optimization, and part of the scope and limitation studies) and took a part in the editing of the manuscript and the supporting information.

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Warsaw, 29-09-2020

Contribution report for the doctoral thesis of Adam Rajkiewicz

Ghosh, M. K.; Rajkiewicz, A. A.; Kalek, M.
„Organocatalytic Group-Transfer Reactions with Hypervalent Iodine Reagents"
Synthesis **2019**, *51*, 359-370.
I proposed the subject and scope of the review. I wrote the introduction and summary sections, and edited the manuscript.

Rajkiewicz, A. A.; Kalek, M.
„*N*–Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts To Generate α,β-Unsaturated Ketones"
Org. Lett. **2018**, *20*, 1906–1909.
I proposed the subject of the research, participated in the planning of the experiments, and I oversaw the ongoing work. I edited the manuscript and the supporting information.

Rajkiewicz, A. A.; Wojciechowska, N.; Kalek, M.
„*N*–Heterocyclic Carbene-Catalyzed Synthesis of Ynones via C–H Alkynylation of Aldehydes with Alkynyliodonium Salts — Evidence for Alkynyl Transfer via Direct Substitution at Acetylenic Carbon"
ACS Catal. **2020**, *10*, 831–841.
I proposed the subject of the research, participated in the planning of the experiments, and I oversaw the ongoing work. I edited the manuscript and the supporting information.

Sincerly Yours

Marcin Kalek

24.09.2020

Contribution report for the doctoral thesis of Adam Rajkiewicz

Manoj K. Ghosh

Ghosh, M. K.; Rajkiewicz, A. A.; Kalek, M.

"Organocatalytic Group-Transfer Reactions with Hypervalent Iodine Reagents"

Synthesis **2019**, *51*, 359-370.

I found the literature references for and wrote the first draft of 3 subsections (Chapter 3) of the review text.

Manoj Kumar Ghosh
29/09/2020

28.09.2020

Contribution report for the doctoral thesis of Adam Rajkiewicz

Natalia Wojciechowska

My contribution to the publications listed below:

Rajkiewicz, A. A.; Wojciechowska, N.; Kalek, M.

„N–Heterocyclic Carbene-Catalyzed Synthesis of Ynones via C–H Alkynylation of Aldehydes with Alkynyliodonium Salts — Evidence for Alkynyl Transfer via Direct Substitution at Acetylenic Carbon"

ACS Catal. **2020**, *10*, 831–841.

I took part in synthesis of substrates (alkynyliodonium salts) for the reaction described in the publication.

Natalia Wojciechowska

21.10.2020

Contribution report for the doctoral thesis of Adam Rajkiewicz

Berit Olofsson

My contribution to the publications listed below:

Castoldi, L.; Rajkiewicz, A. A.; Olofsson, B.

„Transition Metal-Free and Regioselective Vinylation of Phosphine Oxides and H-Phosphinates with VBX reagents"

Submitted

I conceived the concept of research, participated in the planning of the experiments, supervised the project, and edited the manuscript and the supporting information.

Berit Olofsson
Professor of Organic chemistry
Stockholm University

24.09.2020

Contribution report for the doctoral thesis of Adam Rajkiewicz

Laura Castoldi

My contribution to the publications listed below:

Castoldi, L.; Rajkiewicz, A. A.; Olofsson, B.

„Transition Metal-Free and Regioselective Vinylation of Phosphine Oxides and H-Phosphinates with VBX reagents"

Submitted

I participated in the planning of the research, conducted a part of the experimental work (part of the scope and limitation studies), wrote the first draft of the manuscript, and participated in the editing of the manuscript and the supporting information.