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Organocatalytic asymmetric α–functionalizations of β–ketoesters with hypervalent iodine-based reagents and catalysts

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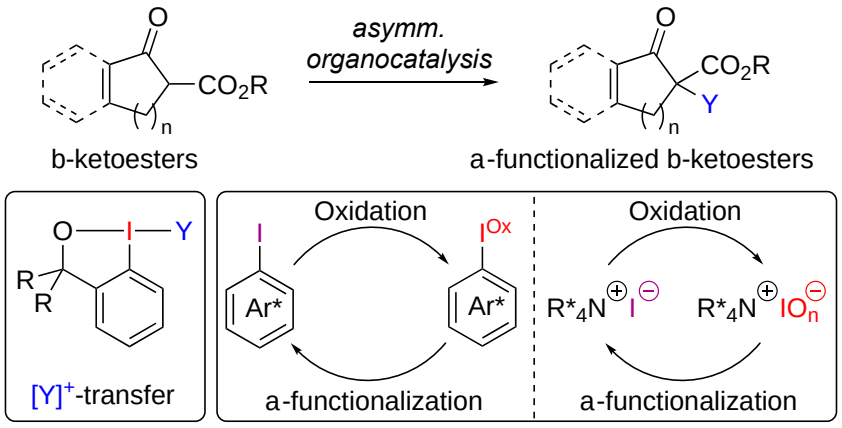
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Abstract

The introduction of hypervalent iodine-based electrophilic functional group transfer reagents and the development of catalysis concepts making use of *in situ* generated hypervalent iodine species has significantly contributed to the advancement of organic synthesis. Especially asymmetric α-functionalizations of prochiral pronucleophiles have been very successfully introduced by utilizing hypervalent iodine chemistry recently. Among the different classes of commonly used pronucleophiles, prochiral β-ketoesters emerged as compounds of particular interest. Inspired by impressive recent reports, this short review therefore discusses different concepts using hypervalent iodine chemistry in asymmetric organocatalytic α-functionalization reactions of prochiral β-ketoesters.



Keywords: Asymmetric catalysis, hypervalent iodine reagents, organocatalysis, α-functionalization, oxidative transformations

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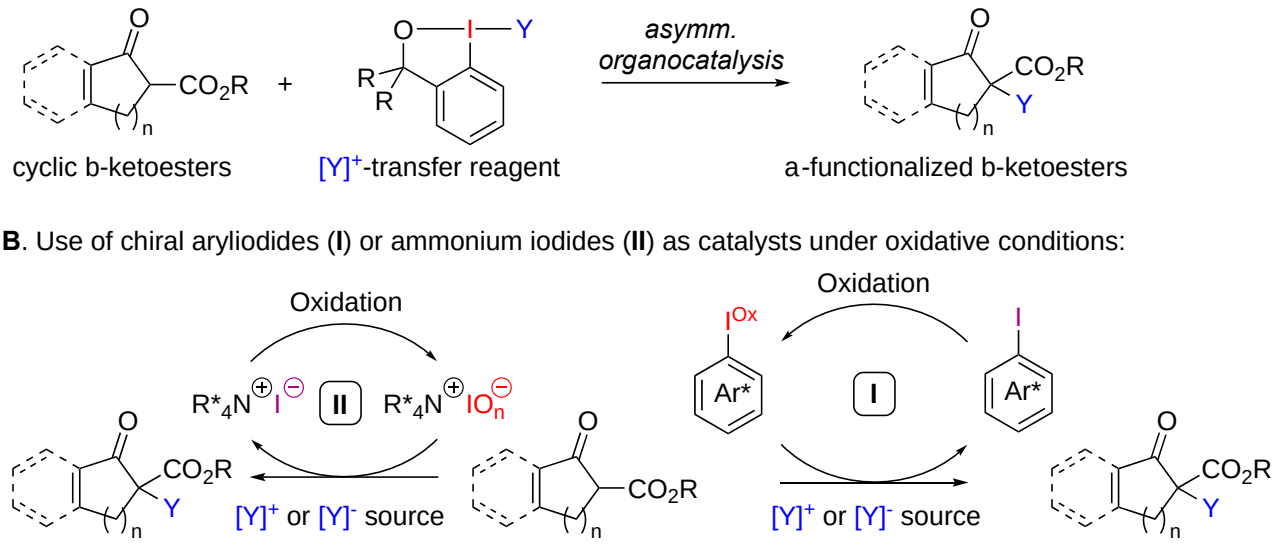
1. Introduction

Among the broad variety of different prochiral (pro)-nucleophiles that are commonly employed to access molecules of potential biological interest or which may serve as a platform for the development of novel (catalytic) methods, β-ketoesters, i.e. cyclic ones, stand out.[1,2] Their high popularity and value can mainly be attributed to their high reactivity[3] and C-H acidity,[4] which allows for the controlled formation of the prochiral reactive enolate intermediates under mild conditions. The stereoselective addition of these *in situ* formed species to different electrophilic reagents can then be controlled by numerous catalysis strategies and especially the use of chiral non-covalent organocatalysis[5-7] has proven its potential for numerous highly enantio- and/or diastereoselective β-ketoester applications to access chiral α-functionalized products.[2]

The use of hypervalent iodine-based compounds has become an increasingly important strategy to facilitate organic transformations and the unique reactivity as well as the catalytic properties of these species have contributed significantly to the development of novel asymmetric synthesis and catalysis methods over the course of the last two decades.[8-25] Noteworthy, hypervalent iodine-based compounds can be employed for a variety of conceptually different approaches. On the one hand, their use as easy to handle and metal-free oxidants has for decades been a heavily investigated field of application.[11,12] In addition, the last two decades have seen an increasing interest in the utilization of hypervalent iodine-based electrophilic functional group transfer reagents which allow for a reactivity Umpolung of the classical inherent nucleophilicity of e.g. alkynes, cyanides, CF_3-groups, ….[15-19] Furthermore, more recently novel concepts making use of *in situ* generated chiral hypervalent iodine-based catalytically active species have been introduced, leading to remarkable highly versatile catalytic methods.[20-22]

Based on several inspiring recent developments, we now wish to discuss selected examples about the use of asymmetric organocatalysis to control the addition of β-ketoesters to electrophilic hypervalent iodine-based $[Y]^+$-transfer reagents (Scheme 1A) as well as examples about the use of chiral aryliodides and ammonium iodides as organocatalysts under oxidative conditions (leading to the *in situ* formation of the catalytically competent hypervalent iodine-based species, Scheme 1B) within this short review.

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Scheme 1. Different strategies employing hypervalent iodine-based reagents and catalysts for the asymmetric organocatalytic α-functionalization of β-ketoesters.

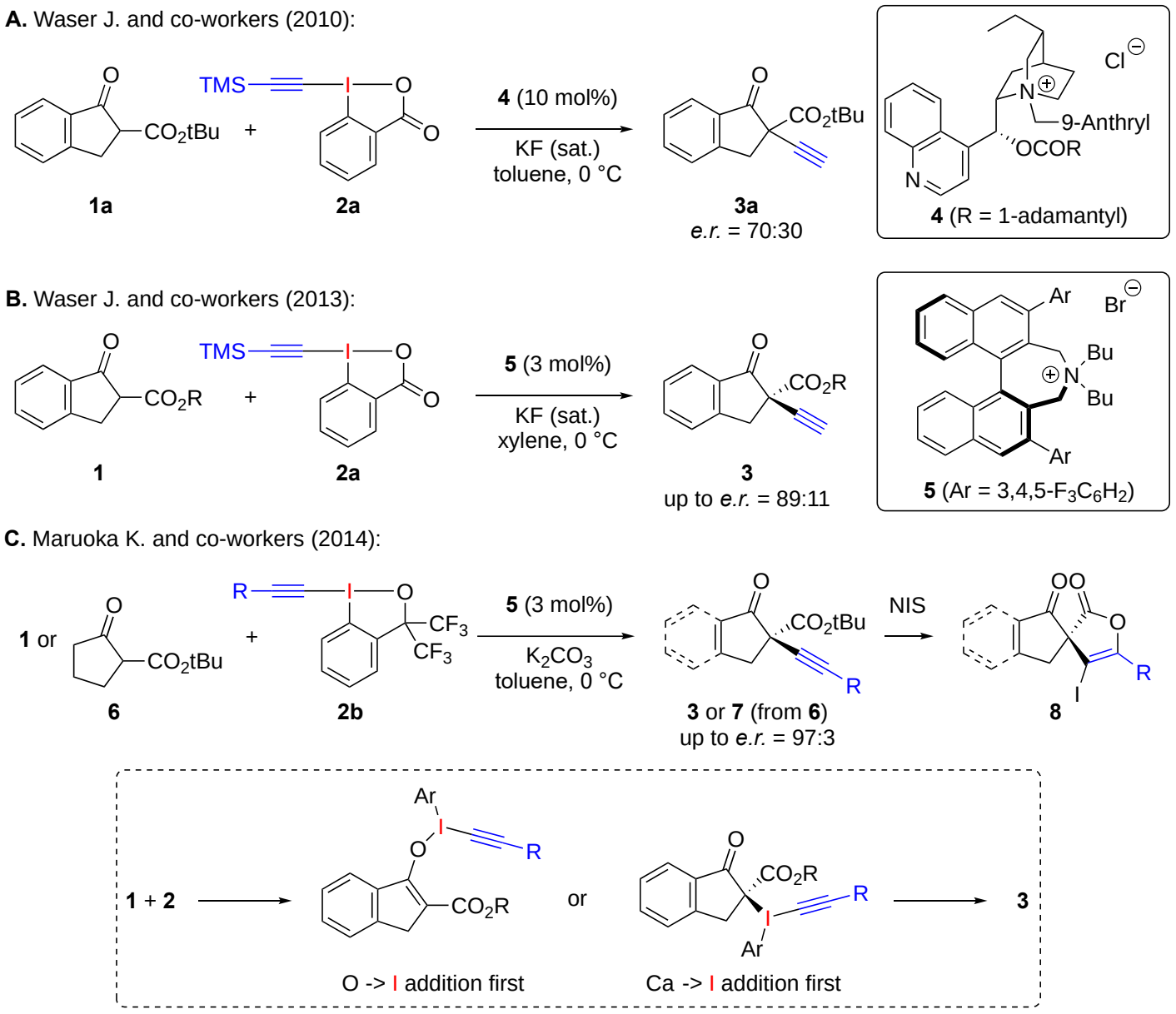
2. Hypervalent Iodine-Based Electrophilic Reagents

As stated above, the use of hypervalent iodine-based electrophilic functional group transfer reagents has established itself as a powerful and frequently used "Umpolung" strategy which allows for disconnection approaches where classical methods fail.[15-19] As a consequence, numerous versatile transformations accessing achiral or chiral target molecules have been developed and also the successful combination of such reagents with asymmetric organocatalysis has been very commonly reported.[23,24]

One class of electrophilic functional group transfer reagents that stands out are the alkyne-transfer reagents **2**, i.e. the TMS-protected **2a**, which have been very impressively developed mainly by Jerome Waser's group over the last decade.[19,26-28] This group was also the first who investigated the asymmetric α-alkynylation of cyclic β-ketoesters **1** in 2010 already. In their seminal study, they demonstrated the potential of asymmetric ammonium salt ion pairing catalysis[29,30] to control such reactions, although the initially used Cinchona alkaloid-derived ammonium salt **4** allowed for only moderate enantioselectivity in the synthesis of the target **3a** (Scheme 2A).[27] While some improvement with reagent **2a** was possible[28] by using the simplified Maruoka ammonium salt catalyst **5**,[31] it required a change of the alkyne-transfer reagent, as demonstrated by Maruoka's group in 2014,[32] to achieve significantly higher levels of enantioselectivities (Scheme 2C). By using the alternative hypervalent iodine-based reagents **2b** in combination with catalyst **5** again, it was possible to access a broad variety of differently functionalized targets **3** or **7** with very satisfactory levels of enantioselectivities under classical phase-transfer conditions. Noteworthy, in this report they also demonstrated some interesting further functionalizations of the alkynylated products **3** and **7**, like the direct NIS-trigged deprotection – electrophilic cyclization cascade towards the highly functionalized spirocycles **8**.[32] With respect to the mode of catalyst control in these applications it should be pointed out that, based on the studies by Waser[27,28] and supported by Maruoka's results,[32] it seems most plausible that the transient β-ketoester-derived enolate species first undergoes addition to the iodine of reagent **2** (either with the enolate

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oxygen or the α-carbon; both scenarios have been postulated, also for reactions with stoichiometric amounts of chiral hypervalent iodine-based alkyne-transfer reagents[33]). This leads to I-O-bond cleavage within reagent **2**, resulting in either a free carboxylate group (in case of reagent **2a**) or an alcoholate (reagent **2b**) which both can form an ion pair with the chiral ammonium salt catalyst. The stereoselective transfer of the alkyne group to the α-position of the β-ketoesters then proceeds in an intramolecular face-selective fashion on these chiral ion pairs.

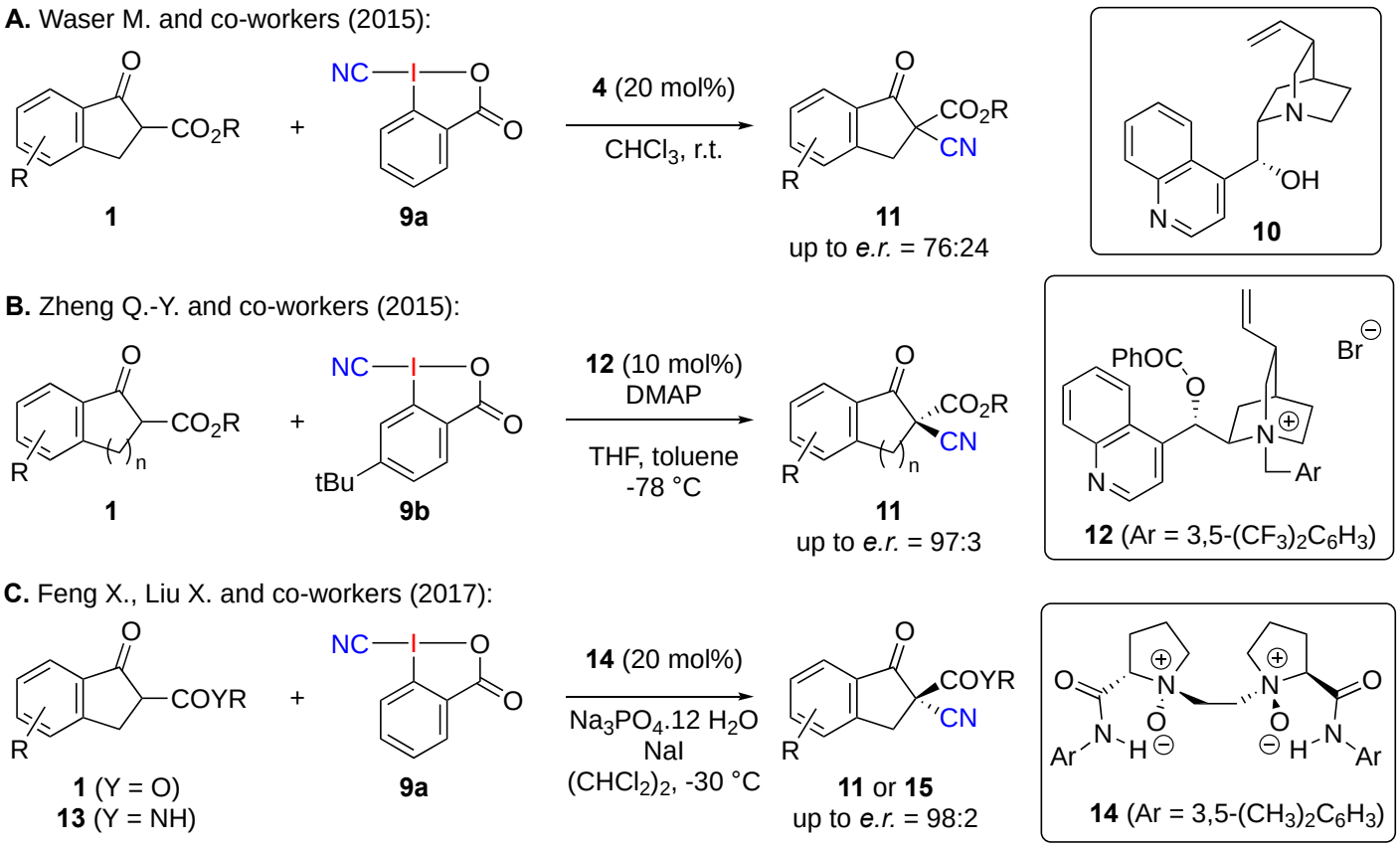


Scheme 2. Asymmetric organocatalytic α-alkynylations of β-ketoesters.

Another class of hypervalent iodine-based functional group transfer agents that has received increasing interest over the last years are the cyano-containing compounds **9**.[34-40] These easily accessible and long-known reagents[34,35] can serve as valuable electrophilic CN-transfer agents,[36-40] thus allowing for complementary "Umpolung" reactivities compared to textbook nucleophilic (inorganic) cyanide-based approaches. This potential can either be exploited to carry out highly valuable heteroatom cyanations[36] or, with more relevance

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to the context of this review, for (asymmetric) enolate α-cyanations.[37-40] In 2015, our group achieved the first proof-of-concept for an asymmetric α-cyanation of the cyclic β-ketoesters **1** by using the benziodoxole-based CN-transfer reagent **9a**.[38] This transformation could be rendered enantioselective by using Cinchonidine (**10**) as a readily available naturally occurring organocatalyst but unfortunately the selectivities were only moderate (Scheme 3A). A remarkable improvement was reported shortly after by the group of Zheng, who developed a highly enantioselective protocol by using the chiral ammonium salt catalyst **12** in combination with DMAP as an organic base.[38] The use of this base is especially noteworthy as usually asymmetric ammonium salt catalysis makes use of inorganic bases mainly,[29,30] while in this application the presence of DMAP was absolutely crucial to warrant high levels of enantioselectivities (Scheme 3B). Besides these two earlier approaches, which relied on Cinchona alkaloid-based organocatalysts, it was also demonstrated by Feng and Liu that chiral N-oxide-based organocatalysts like compound **14** can serve as powerful catalysts for such hypervalent iodine-mediated α-cyanations as well, allowing for the use of β-ketoesters **1** as well as the analogous amides **13** straightforwardly (Scheme 3C).[40]

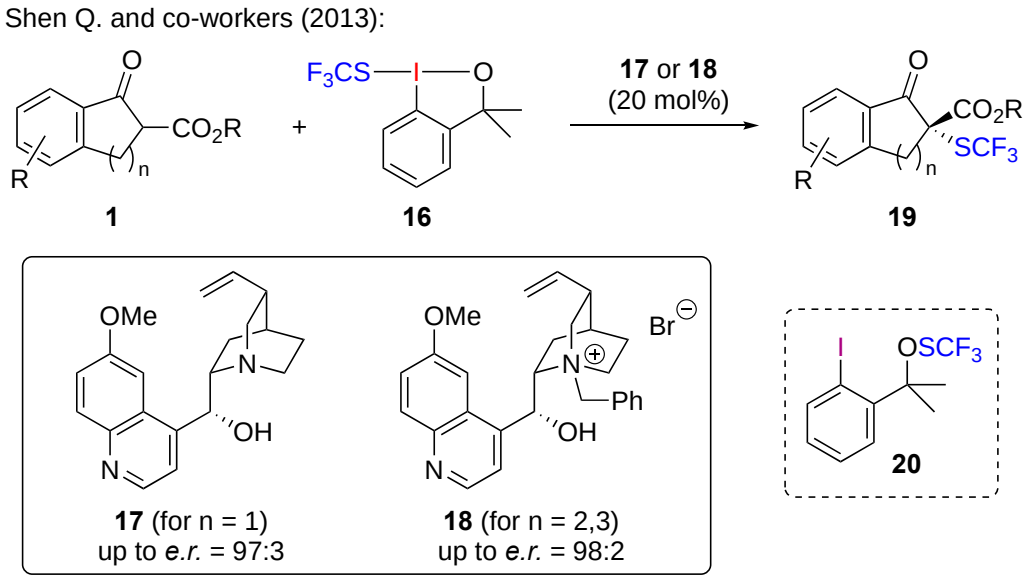


Scheme 3. Asymmetric organocatalytic α-cyanations of β-ketoesters.

Asymmetric trifluoromethylthiolations have attracted increasing interest by the synthesis and target-oriented community recently,[41] and hypervalent iodine-based reagents have contributed to the advance of this field as well. In 2013, Shen's group described the asymmetric organocatalytic α-trifluoromethylthiolation of β-ketoesters **1** employing reagent **16** (Scheme 4).[42] By using either classical Cinchona alkaloids, like compound **17** as organobase catalysts (superior for 5-ring β-ketoesters **1**) or Cinchona alkaloid-based ammonium salts like derivative **18** as an ion pairing catalyst (more selective for 6- or 7-ring ketoesters **1**), they were able to introduce highly enantioselective organocatalytic protocols for these valuable transformations.

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Interestingly however, it was shortly after shown by Buchwald and co-workers that the real structure of the postulated reagent **16** is actually the O-SCF_3-containing aryliodide **20**.[43] Thus, conceptually this protocol may not be considered as a hypervalent iodine-based transformation in a closer context, but nevertheless it represents a very powerful approach to access these interesting chiral targets in an enantioselective fashion straightforwardly.

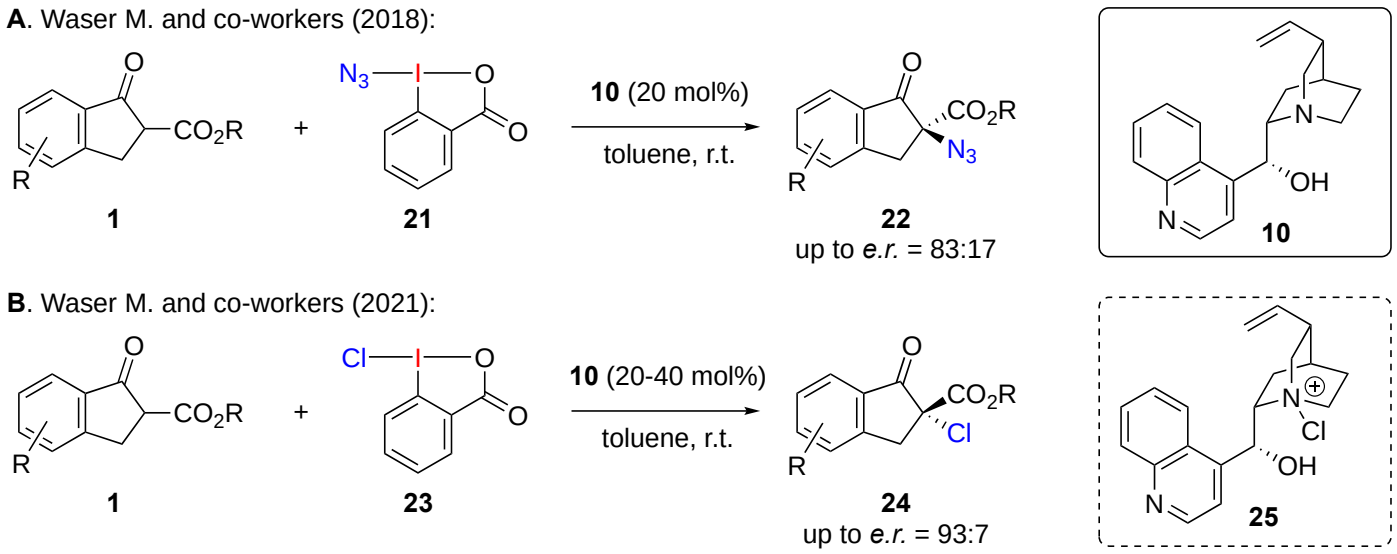


Scheme 4. Asymmetric organocatalytic α-trifluoromethylthiolation using reagent **16**, respectively **20**.

Besides the above discussed α-trifluoromethylthiolation, surprisingly little progress in asymmetric α-heterofunctionalizations of β-ketoesters with electrophilic hypervalent iodine-based reagents have been reported so far (conceptually complementary approaches using catalytically active hypervalent iodine species will be discussed in sections 3 and 4). Two synthetically easily accessible reagents are the azide-containing compound **21**[44] and the chloride-containing **23**[45,46] (which classically represents a useful intermediate in the synthesis of other more advanced hypervalent iodine reagents like e.g. Togni's powerful CF_3-transfer reagent[46]). Pioneering reports by the groups of J. Waser[47] and Gade[48] underscored the value of compound **21** to achieve direct electrophilic α-azidations of β-ketoesters and other pronucleophiles in a highly enantioselective manner by using asymmetric transition metal catalysis.[48] In 2018, our group demonstrated that Cinchonidine (**10**) can also serve as a suited organocatalyst to render the azidation of compounds **1** asymmetric (Scheme 5A),[49] although it has to be admitted that the obtained levels of enantiocontrol were significantly lower compared to Gade's powerful transition metal-catalyzed protocol.[48]

With respect to the use of electrophilic hypervalent iodine-based reagents for direct α-halogenations[50,51] of prochiral pronucleophiles like compounds **1**, only very few racemic[52] and asymmetric approaches[53] utilizing reagent **23** have been reported so far. Very recently, we reported the Cinchona alkaloid-catalyzed enantioselective α-chlorination of compounds **1** (Scheme 5B).[53] Very interestingly, careful monitoring of the reaction with NMR and HRMS revealed the formation of the chiral N-chlorinated intermediate **25** hereby (obtained by reaction of **10** with **23**). This species most presumably serves as the asymmetric electrophilic Cl-transfer reagent herein and the need for relatively high amounts of organocatalysts to warrant reasonable enantioselectivities can be rationalized by an otherwise relatively fast, uncatalyzed racemic direct background reaction between **1** and **23**.

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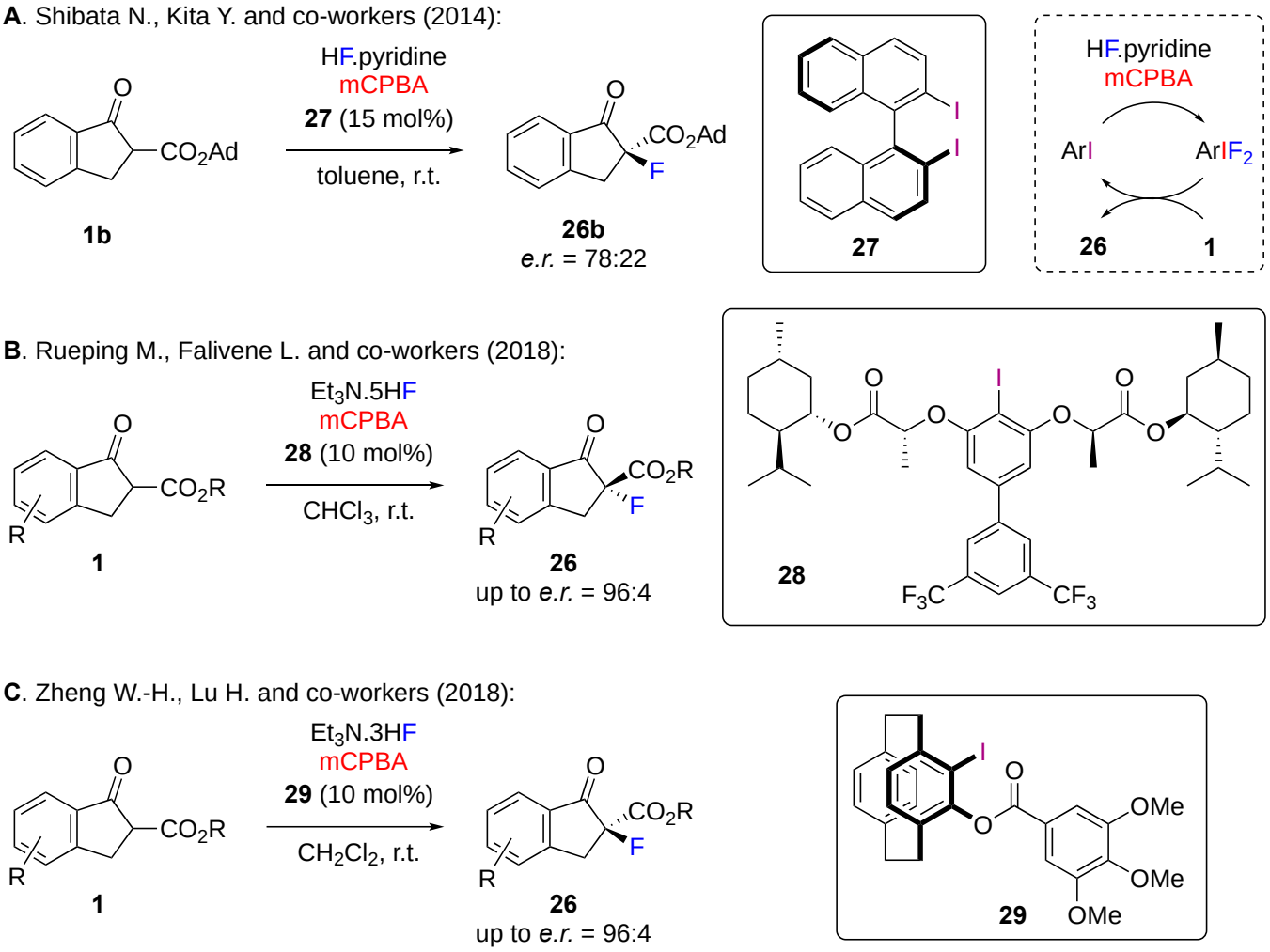


Scheme 5. Asymmetric Cinchona alkaloid-catalyzed α-azidation and α-chlorination.

3. Chiral Aryliodine Species as Catalysts Under Oxidative Conditions

Besides the very popular and versatile use of preformed hypervalent iodine-based reagents for electrophilic functional group transfer reactions (as discussed above), hypervalent iodine species can also be formed *in situ* under oxidative conditions starting from suited organic iodides, especially aryliodides. This unique and reversible redox behaviour has very impressively been utilized for different catalytic functional group transfer reactions, where a suited aryl iodide (ArI) catalyst first undergoes oxidation to an I(III) species. The latter then reacts with a suited nucleophile (X^-) *in situ* to form a reactive electrophilic hypervalent iodine species ($ArIX_2$), representing an *in situ* Umpolung of the inherent nucleophilicity of the employed X^-.[21,22] By utilizing chiral aryliodides, this concept then allows for asymmetric transformations in a unique catalysis manner, which was also very successfully applied to asymmetric α-heterofunctionalizations of β-ketoesters recently.[54-57] One of the seminal contributions in this field came from the groups of Shibata and Kita in 2014, who introduced a very appealing aryl iodide-catalyzed protocol for electrophilic fluorinations of pronucleophiles like β-ketoesters **1** by using HF.pyridine as a cheap and easily available F^--source under oxidative conditions.[54] While the primary focus in this early report was on the development of catalytic racemic protocols, they also succeeded in obtaining an impressive first proof-of-concept for an asymmetric variant by employing the binaphthyl-based diiodide **27** as a catalyst for the α-fluorination of the ketoester **1b** (Scheme 6A). Catalytic turnover could be achieved in the presence of mCPBA as an oxidant, combined with promising early levels of enantioselectivities already, thus paving the way for future developments. In 2018, the groups of Falivene and Rueping[55] and Lu and Zheng[56] came up with novel carefully designed catalyst scaffolds to achieve higher levels of enantioselectivities for this appealing α-fluorination. While Falivene and Rueping introduced the novel centrochiral aryliodide **28** (Scheme 6B),[55] Lu and Zheng developed the new planarchiral paracyclophane-based iodide **29** (Scheme 6C)[56] as efficient organocatalysts for this oxidative application. By using easily available $Et_3N.nHF$ as F^- sources hereby, high enantioselectivities up to e.r. = 96:4 could be achieved with both catalyst classes for a variety of differently decorated starting materials **1**.

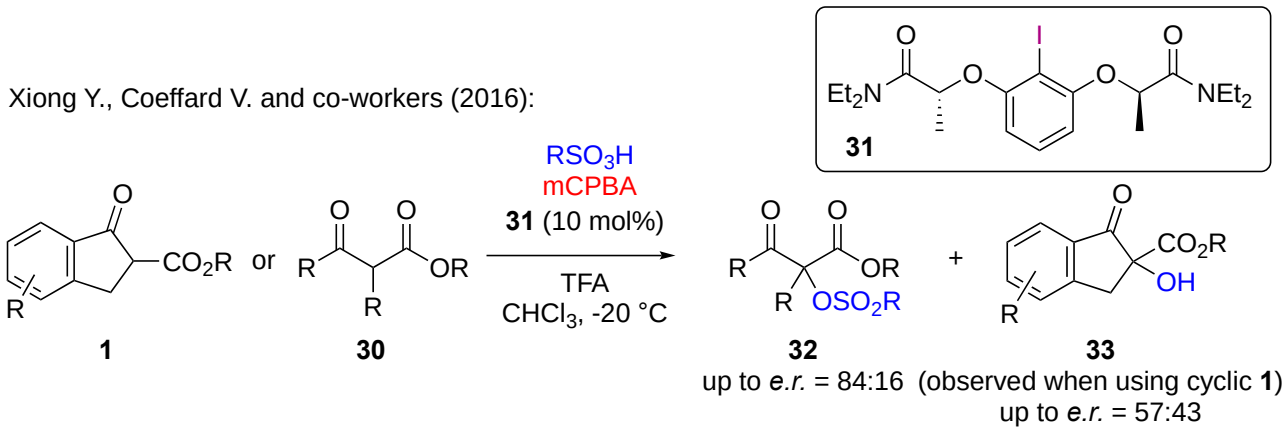
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Scheme 6. Asymmetric α-fluorination using chiral aryliodide catalysts under oxidative conditions.

This oxidative aryliodide-catalysis concept is also applicable to other α-heterofunctionalization reactions when using alternative nucleophilic sources.[21,22] However, surprisingly few reports with respect to the asymmetric α-functionalization of β-ketoesters utilizing this strategy have been reported so far. In 2016, the groups of Xiong and Coeffard investigated α-oxygenations of cyclic (compounds **1**) and acyclic (derivatives **30**) β-ketoesters under oxidative aryliodide-catalysis (Scheme 7).[57] By using catalyst **31** in combination with mCPBA as an oxidant and different sulfonic acids (RSO_3H) as the nucleophilic species, they were able to access products **32** and **33** with low to good levels of enantioselectivities. Interestingly, while the use of acyclic starting materials **30** resulted in formation of **32** only (with reasonable enantioselectivities), the cyclic ketoesters **1** were found to be more problematic, resulting in mixtures of compounds **32** and **33** and with lower enantioselectivities, especially for the α-hydroxylated products **33**. Nevertheless, despite of these limitations, this report represents a nice proof-of-concept demonstrating that this general oxidative aryliodide-catalysis strategy can be expanded beyond the so far more systematically addressed α-fluorinations of β-ketoesters (please refer to more general reviews[21,22] for further inspiring α-heterofunctionalization reports utilizing alternative pronucleophiles).

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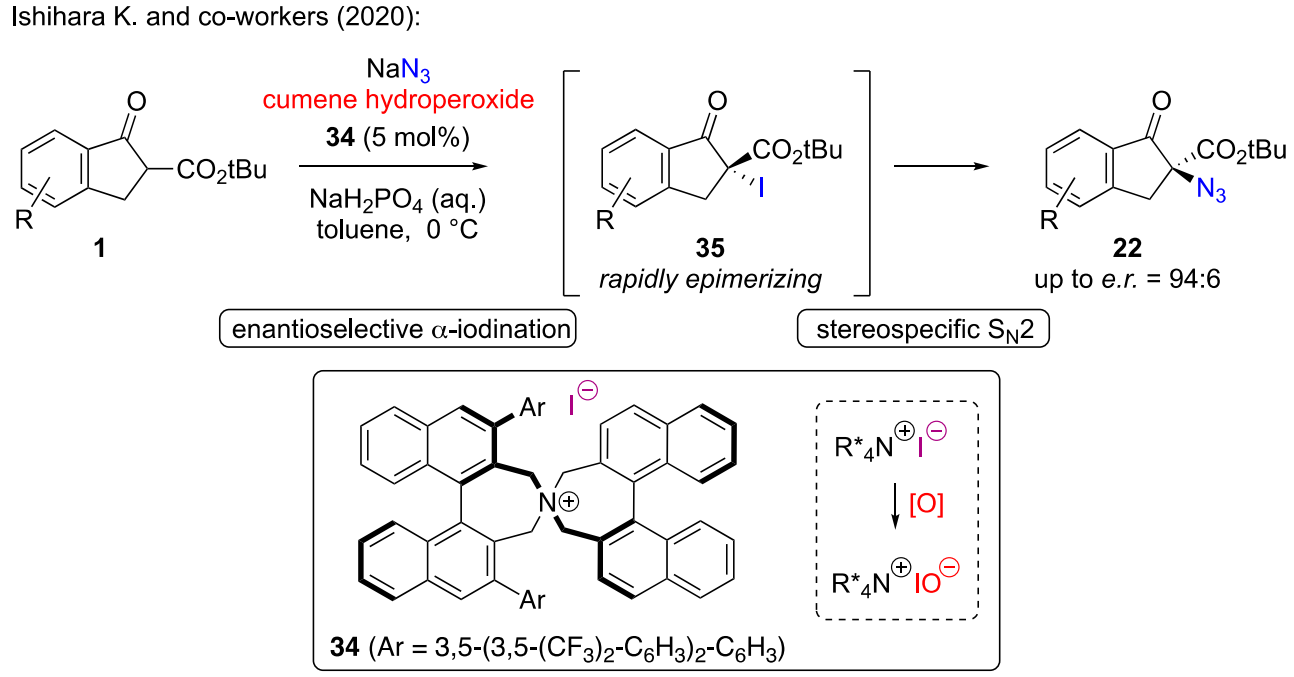


Scheme 7. Asymmetric α-oxygenation using chiral aryliodide catalysis under oxidative conditions.

4. Chiral Ammonium Iodides as Catalysts Under Oxidative Conditions

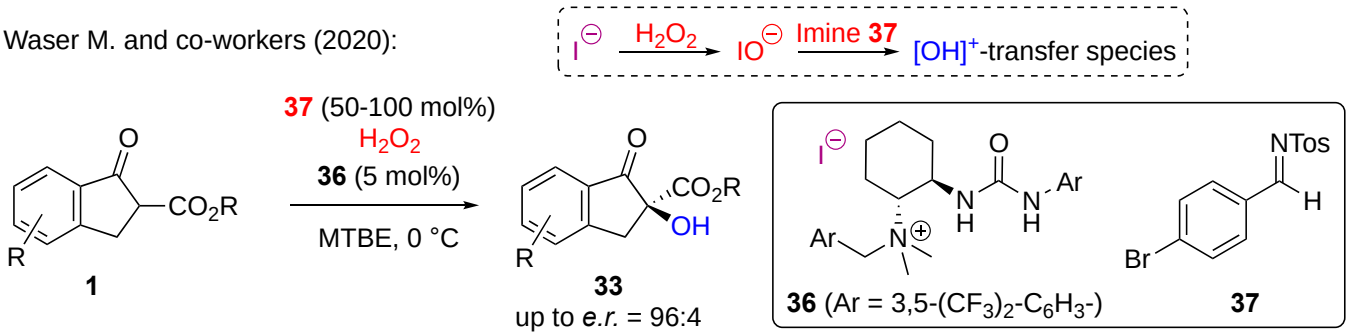
Besides the afore discussed use of (chiral) aryliodides as catalysts under oxidative conditions, the last years have also witnessed increasing interest in the use of (chiral) quaternary ammonium iodides under oxidative conditions.[20,58] This concept can be utilized for interesting racemic as well as asymmetric transformations (when chiral quaternary ammonium iodides are utilized) and, depending on the oxidant and the overall conditions, oxidation of the iodide counter anion to different catalytically active higher oxidation state species (I_3^-, IO_n^-) can be achieved. Among them, ammonium hypoiodite derivatives $R_4N^+IO^-$ have been the most commonly postulated and/or detected catalytically relevant species (which can easily be accessed with simple oxidants like e.g. H_2O_2 or organic hydroperoxides).[59-64] Pioneering work in this field came from the Ishihara group, who has introduced several conceptually unique asymmetric ammonium hypoiodite applications over the last years.[59-63] Mechanistically the exact role of the hypervalent iodine-based anion very much depends on the investigated transformation and the utilized substrates.[59,60,63] For example, very recently Ishihara and co-workers developed a straightforward protocol to achieve the direct enantioselective α-azidation of β-ketoesters **1** with NaN_3 as a simple inorganic nucleophilic azide-source.[63] By utilizing the Maruoka-type ammonium iodide catalyst **34** in combination with cumene hydroperoxide as an oxidant, the targets **22** could be accessed with high enantioselectivities (Scheme 8). Careful mechanistic studies revealed, that for this specific target transformation the *in situ* formed chiral ammonium hypoiodite catalyst species first facilitates the enantioselective formation of the α-iodinated ketoester **35** (which was detected and characterized). This configurationally labile compound then immediately undergoes a fast stereospecific S_N2 displacement with the azide, leading to product **22** directly (and liberating the iodide which can then reenter the catalytic cycle).[63] The detection of this α-iodinated intermediate **35** is a mechanistically remarkable fact hereby, as analogous α-I intermediates have not been observed for other enolate α-heterofunctionalizations under similar ammonium hypoiodite-catalyzed conditions before[59,60] or after,[64] illustrating the high mechanistic complexity of these catalytic applications and the fact that different mechanistic scenarios are likely, depending on the investigated target transformation.

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Scheme 8. Asymmetric α-azidation using chiral ammonium hypoiodite catalysis.

Our group recently introduced a protocol for the asymmetric α-hydroxylation of β-ketoesters **1** catalyzed by the chiral bifunctional ammonium iodide **36** (Scheme 9).[64] As a simple source of oxygen we used aqueous H_2O_2. Interestingly however, during the optimization of this reaction we realized that the presence of simple aromatic aldimines, i.e. derivative **37**, is absolutely crucial to achieve high levels of enantioselectivities and good catalytic turnover. While we initially speculated that H_2O_2 and imine **37** result in the formation of the corresponding oxaziridine, which then serves as the actual electrophilic O-transfer agent,[65] detailed control studies showed that oxaziridines are actually not involved in this process at all.[64] We could however demonstrate that the imine can be used in catalytic quantities and that the *in situ* formed IO^- species somehow reacts with imine **37** to form the, so far not further elucidated, electrophilic O-transfer agent, thus resulting in a synergistic catalytic scenario consisting of an ammonium hypoiodite-catalyzed process combined with an aldimine as the actually oxygenation-shuttle.



Scheme 9. Asymmetric α-hydroxylation using chiral ammonium hypoiodite/aldimine catalysis.

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5. Conclusions

The development of hypervalent iodine-based reagents and catalysts has contributed significantly to the advancement of organic synthesis and one particularly appealing field of application is the use of such reagents to facilitate (asymmetric) α-functionalizations of prochiral pronucleophiles. (A)cyclic β-ketoesters have emerged as versatile and frequently used pronucleophiles over the last decades. Thus, it comes as no surprise that the potential of hypervalent iodine chemistry has also been very successfully applied to asymmetric α-functionalizations of prochiral β-ketoesters. As discussed in this short review, both, electrophilic hypervalent iodine-based functional group transfer agents and the use of catalysis principles making use of (*in situ* generated) hypervalent iodine-species, have been very successfully utilized hereby, resulting in a broad variety of powerful novel transformations and catalysis modes. In addition, several of these methods that have initially been developed for β-ketoester functionalizations have in the meantime also been utilized for alternative scaffolds, thus demonstrating the more general potential and value of carrying out further research in this field.

Acknowledgements

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Authors' Biographies



Christopher Mairhofer obtained his M.Sc. from the Johannes Kepler University (Linz, Austria) in 2019. He is currently pursuing his Ph.D. with Prof. Mario Waser funded through the Linz Institute of Technology (LIT). His current research interests are focused on the asymmetric α-heterofunctionalization of pronucleophiles and the development of novel synergistic catalysis principles under oxidative conditions.

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Mario Waser was born in Steyr, Austria in 1977 and studied chemistry at JKU Linz, Austria where he obtained his Ph.D. in 2005 in the group of Prof. Heinz Falk. After a postdoctoral stay with Prof. Alois Fürstner (Max-Planck Institut für Kohlenforschung, Mülheim, Germany), he spent two years as an R&D chemist working for DSM. In 2009 he started his independent career at JKU Linz. In 2014 he obtained his habilitation (venia docendi) and became Associate Professor and in 2020 he became Full Professor for Organic Stereochemistry. His main research interests are on the design and application of asymmetric organocatalysts (i.e. quat. ammonium salt-based ion pairing catalysts) and on the development of asymmetric organocatalytic synthesis methods.

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