Recent Developments in Catalytic, Asymmetric α-Halogenation: A New Frontier in Asymmetric Catalysis

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The development of milder and more sophisticated halogenating reagents that offer significantly greater chemoselectivity and stereocontrol than diatomic halides has been critical to the realization of asymmetric α-halogenation. Within the past few years several groups have reported catalytic, enantioselective methods for α-halogenation achieved by utilizing the catalytic generation of either enolates (zwitterionic or metal-based charge delocalized) or enamines. Most importantly, this recent work has greatly enhanced the synthetic utility of organic halogenations and, in doing so, opened up a promising new frontier in organic synthesis. This microreview presents recent advances in the area of catalytic, asymmetric α-halogenations of carbonyl compounds.

Introduction

Halogenation reactions are among the most practical and historically significant processes in organic chemistry. The products of these halogenations have long been valued as useful synthetic intermediates.[1] For example, every year novel metabolites containing chiral halogens are isolated from various biological sources.[2] Also, halogenated (particularly fluorinated) analogues of amino acids[3] or pharmaceutically-active drugs have been shown to enhance cytotoxicity as compared with their parent compounds.[4] In addition, alkyl halides can serve as precursors or branch points in the synthesis of carbon–carbon bonds, ethers, amines, sulfides, and epoxides.[5] When the halogen atom is attached to a chiral center, stereospecific S_N2 displacement may be used to preserve chirality, potentially affording a wealth of optically enriched products.

Historically, the most commonly used halogenating reagents for this purpose have been the diatomic halides,

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

which, frankly, are too reactive for asymmetric catalysis. It has only been in the past few years that significant strides have been made in the development of catalytic, asymmetric halogenation reactions. To date, the most notable advances have been made in the area of α-halogenation − processes in which the new chiral center attached to the halogen is adjacent to either one or two carbonyl groups. It has been a century since the appearance of the classic report demonstrating the autocatalytic role of protic acids in these α-halogenation reactions.[6] The intermediacy of enol tautomers as the crucial intermediates in α-halogenations was also elucidated at this time.[7] Realization that the reaction is also electrophilic in nature has had a lasting impact on the way organic chemists conduct these reactions, and, ultimately, has led to the intense development of mild sources of electrophilic halogen (Figure 1).

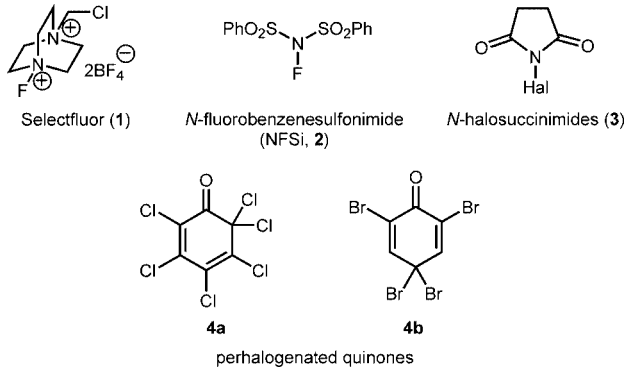
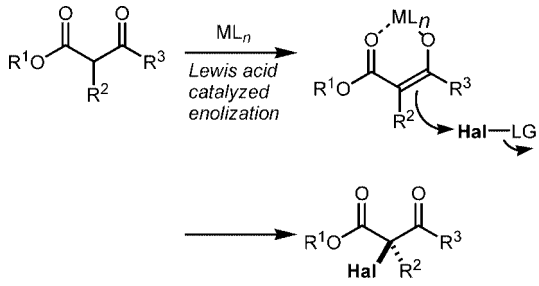


Figure 1. Some commerically available electrophilic halogenating agents

The preceding observations would suggest an obvious strategy for catalytic α-halogenation involving the transient formation of an enolate (or enol) that can be halogenated to generate the desired product. The catalyst may serve to form the enolate, either through 1) coordination of a Lewis acid and simultaneous action of a base; 2) the formation of an enamine derived from the reaction of a ketone or aldehyde (containing an α-hydrogen) with a chiral secondary amine; 3) ionic association of a phase-transfer catalyst with the enolate oxygen; or 4) the attack of a chiral nucleophile on a ketene intermediate to give rise to zwitterionic enolates. All four of these strategies have been successfully employed in the past few years. As with classic α-halogenations of carbonyl compounds, the cases reported to date have presumably involved the transfer of an electropositive halogen, either concertedly or through a stepwise process facilitated by electron transfer.

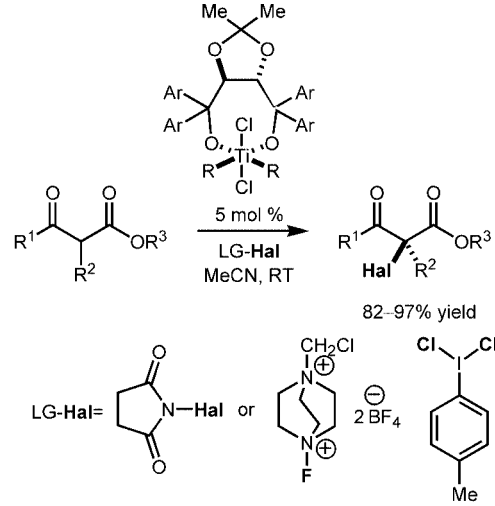
A. Lewis Acid Catalyzed Enolization of β-Keto Esters

β-Keto esters, which are ideal candidates for halogenation reactions due to the relatively high acidity of their α-protons ($pK_a \approx 12$), can form six-membered chelates with oxophilic Lewis acids at their carbonyl groups, thus promoting enolization of the β-ketone [Equation (1)]. In the presence of a chiral Lewis acid, an enantioselective reaction may occur to afford optically enriched products. Lewis acid–dicarbonyl complexes have the Lewis acid bound in a rigid fashion and can be expected to provide the best opportunity for facial selectivity.



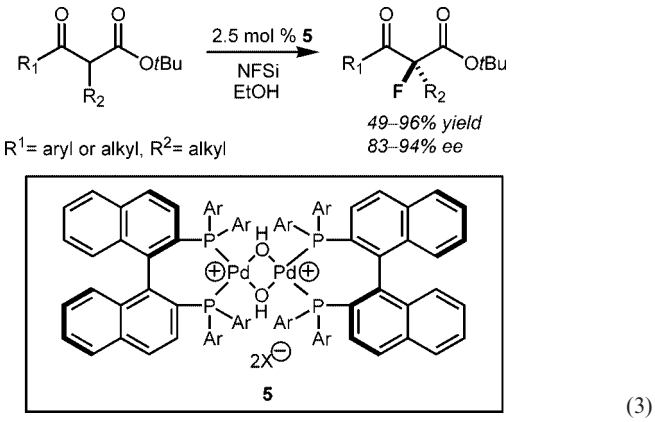
(1)

The first catalytic, asymmetric halogenation, involving the action of a chiral Lewis acid, was reported in the pioneering work of Togni on α-alkyl-β-keto esters [Equation (2)]. The key step in his methodology involves the formation of a Ti-based cyclic enolate that can react with mild halogenating agents such as Selectfluor®, to afford fluorinated products,[8] or *N*-chlorosuccinimide (NCS), to afford chlorinated products.[9] He reports enantioselectivities (*ee*'s) ranging from 62 to 90%. He has proposed that electron transfer from the enolate to Selectfluor® occurs first, thus leading to the formation of a radical species prior to fluorine transfer.[10] This proposed mechanism is supported by a number of interesting experimental observations. For example, when any source of chloride is present, including the catalyst itself, chlorinated side-products can be isolated. When a radical scavenger is added to the reaction mixture, chlorinated byproducts are no longer observed. Recently, Togni has expanded his Ti(TADDOL) method to employ the hypervalent iodine compound (dichloroiodo)toluene[11] as a chlorinating agent, albeit with limited success (67–83% yield and 10–71% *ee*). He has also been successful in achieving geminal heterodihalogenations[12] of unsubstituted β-keto esters (up to 65% *ee*).



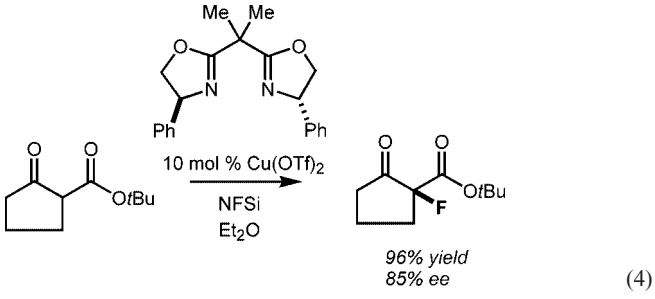
for R^1 = Me, R^2 = Me, R^3 = 2,4,6-triisopropylbenzyl, Hal = F; *ee* = 90%
for R^1 = Et, R^2 = Me, R^3 = benzyl, Hal = Cl; *ee* = 88% (2)

Encouraged by results obtained in the Michael addition of β-keto esters to enones,[13] Sodeoka et al. have reported a similar process employing Pd-based bis(phosphane) complexes **5** to afford fluorinated products in high *ee* (83–94%) and good chemical yields for both acyclic (49–96%) and cyclic (85–91%) β-keto esters [Equation (3)].[14] The catalysts are water-tolerant and have been shown to catalyze the reaction with equal facility in ionic liquids.[15] The authors have also demonstrated the utility of their method by reduction of the product ketones to α-fluoro-β-hydroxy esters, then subsequent conversion to α-fluoro-β-amino esters.



(3)

As a complement to Sodeoka's findings, Cahard evaluated chiral bis(oxazoline)copper complexes as catalysts for the formation of α-fluoro-β-keto esters [Equation (4)].[16] The *ee*'s ranged from 35–85% for the cyclic esters, whereas lower *ee*'s were observed for acyclic ones (40–52%).

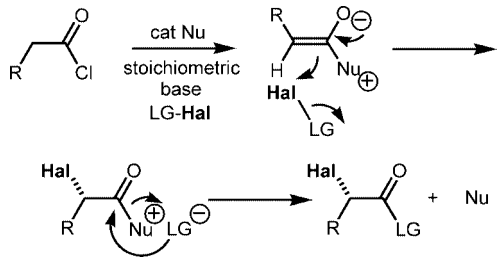


(4)

Similarly, Jørgensen has employed chiral bis(oxazoline)-copper(II) complexes and *N*-halosuccinimides to obtain optically active α-bromo- and α-chloro-β-keto esters in high yields (80–99%) and *ee*'s ranging from 32–82%.[17] An attempt was made to chlorinate a β-diketone, but only 32% *ee* was recorded.

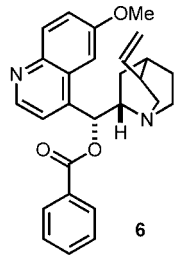
Chiral Zwitterionic Enolates from Ketenes

Our group has explored an approach to asymmetric chlorination and bromination using simple acid halides as practical starting materials (over 500 acid chlorides are available commercially). In the presence of a chiral nucleophilic catalyst (such as benzoylquinine, BQ **6**) and an adventitious base, a chiral zwitterionic enolate is generated in situ that subsequently reacts with an electrophilic halogen source. Depending on the conditions and the nature of the base, ketenes may form as intermediates to the enolates. After halogen transfer, the leaving group counterattacks the acylammonium salt, thereby regenerating the catalyst and affording configurationally stable, optically enriched α-halogenated activated esters possessing two convenient sites of functionalization [Equation (5)]. After extensive initial screening of halogenating reagents, we were particularly attracted to perhalogenated quinones **4a** and **4b**, since a nucleophilic phenolate would be formed as an intermediate upon halogen transfer.

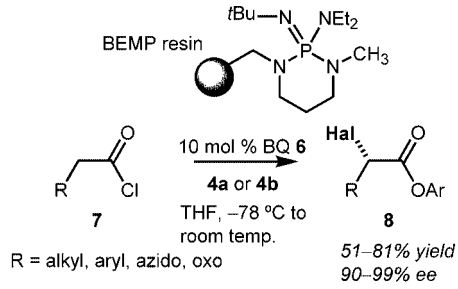


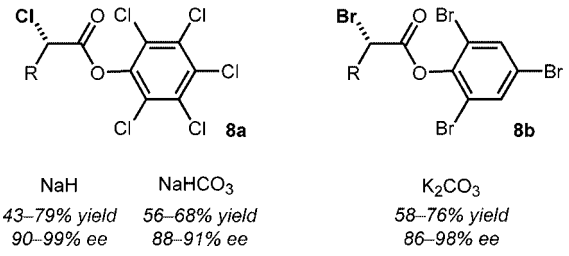
(5)

Initially, we formed clean ketene solutions using the phosphazine base 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) on a polymer support. When we applied this methodology to the halogenations, we were successful in forming activated α-haloesters **8a** and **8b** in yields ranging from 51 to 80% with *ee*'s ranging from 90–99% [Equation (6)].[18] A wide range of substrates, including aliphatic and aromatic acid chlorides **7**, can be halogenated asymmetrically.[19] It is possible to obtain one enantiomer or the other as desired, with similar stereochemical fidelity, by employing either benzoylquinine or benzoylquinidine, the "pseudo-enantiomer" of **6**.



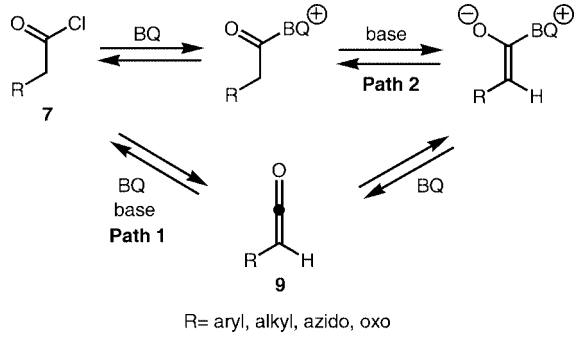
Due to the high price of BEMP resin we were determined to find a more cost-effective method of ketene generation. Based on our previous success in the catalytic, asymmetric synthesis of β-lactams from ketenes and imines, we developed what we call the "shuttle deprotonation" method to form the ketene and/or the zwitterionic enolate in situ.[20] Two plausible mechanisms exist depending on the base used: path 1, a kinetically active catalytic base, such as benzoylquinine, effects dehydrohalogenation of the acid chloride to form ketene **9**, followed by proton transfer to a stoichiometric thermodynamic base, and subsequent acylation of the catalyst to form the enolate; or path 2, one





(6)

molecule of the catalyst is acylated while a second catalyst molecule acts as the kinetic base, followed by proton transfer (Scheme 1). We have published examples of this method using sodium hydride[21] and sodium hydrogencarbonate[22] for our chlorination protocol, and potassium carbonate[23] for our bromination methodology.

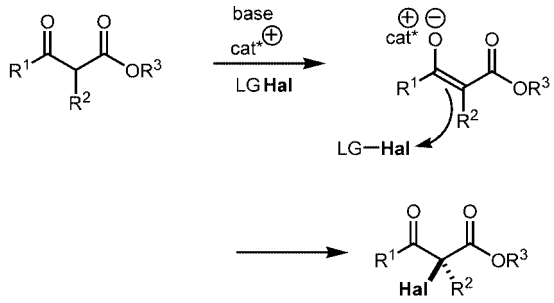


Scheme 1. Shuttle deprotonation mechanism for the generation of zwitterionic enolates

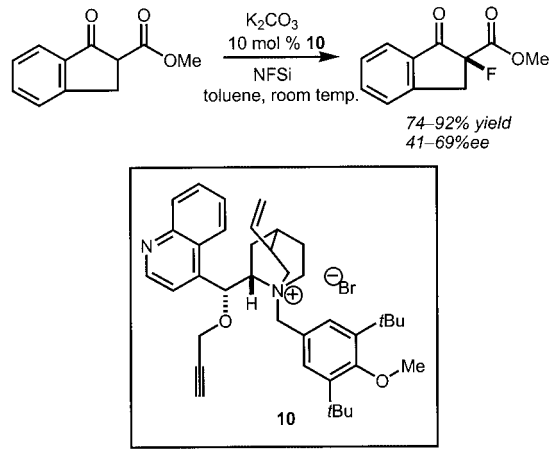
Phase-Transfer Catalysis

Given the acidity of the α-proton of the keto ester, another plausible reaction design would involve a salt comprised of a negatively charged, achiral base coupled with a positively charged, chiral counterion to promote phase-transfer catalysis [Equation (7)]. The requirements for the base include low solubility and mild basicity such that, upon deprotonation and isomerization of the substrate to the enolate form, the positively charged chiral catalyst will be tightly associated with the negatively charged enolate oxygen and provide significant facial discrimination.[24]

Kim and Park have achieved an enantioselective fluorination of β-keto esters using chiral quaternary ammonium salts as phase-transfer catalysts [Equation (8)].[25] The cinchonidinium salt **10** was paired with K_2CO_3 in the presence of *N*-fluorobenzenesulfonimide (NFSi) to afford α-fluorinated ketones in good yields (74–92%) and moderate enantioselectivity (40–69% *ee*). This result offers the possibility that, given the right base and chiral catalyst, these results can be improved dramatically.



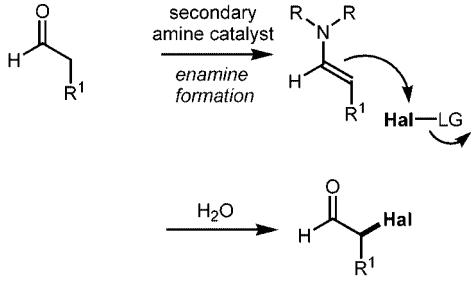
(7)



(8)

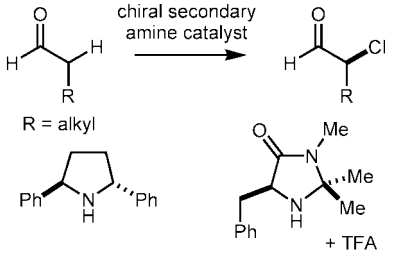
Chiral Enamine Catalysis

Another important method for selectively installing halogens, which is undergoing development at this time, employs enamine catalysis. Secondary amines react with aldehydes and ketones in the presence of an acid catalyst to generate highly nucleophilic enamines [Equation (9)]. Therefore, when a chiral amine is employed, attack on an electrophilic halogen source will be limited to one face, thus resulting in optically enriched α-haloaldehydes or ketones. L-Proline, the most common chiral enamine catalyst, and its derivatives, have been used successfully for many years in a variety of asymmetric reactions.[26]



(9)

Both Jørgensen[27] and MacMillan[28] have developed similar approaches to the asymmetric α-chlorination of aldehydes employing chiral secondary amines as catalysts. For example, Jørgensen has reported the use of *N*-chlorosuccinimide (NCS) as the halogen source, whereas MacMillan has employed the perchlorinated quinone **4a** to produce products in high chemical and optical yields [Equation (10)]. The configurational stability of these products is quite remarkable; given the tendency for aldehydes to possess a high enol content, one would expect the presence of an electron-withdrawing α-chlorine to tip the equilibrium even further towards the enol. In these instances, this prediction would seem to be turned on its head, at least as long as the products remain in solution. Jørgensen has demonstrated the utility of these asymmetric products through both their oxidation and reduction in situ to obtain optically active α-chloroacids and chloroalcohols, respectively. MacMillan has further expanded the scope of these reactions by demonstrating that catalyst-enforced induction overrides substrate-directed stereocontrol when halogenating β-chiral aldehydes. This methodology should prove to be very useful for the synthesis of enantiopure α-chloroaldehydes, although the configurational instability of the products when subjected to common purification methods suggests that the α-chlorinated products obtained are best used immediately, not isolated.



10 mol % cat
NCS
CH_2Cl_2, room temp.
82–99% yield
81 97% ee
(Jørgensen)

5 mol % cat
4a
acetone, –30 °C
71–94% yield
80 95% ee
(MacMillan)

(10)

Conclusions

To date, the most successful approaches to asymmetric halogenation have employed carbonyl compounds as precursors to obtain efficient α-halogenations. The future will undoubtedly see these new methodologies applied to many problems in areas such as total synthesis and pharmaceutical chemistry. Further work on this new frontier of asymmetric catalysis will hopefully also witness an expansion of scope both to more challenging substrates, such as alkenes (both activated and unactivated), and alternate routes, such as asymmetric halogenation through C–H bond activation.

Acknowledgments

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