Organocatalyzed direct asymmetric α-halogenation of carbonyl compounds

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The formation of carbon–halogen bonds in an enantioselective manner is an important reaction because it leads to optically active halogen compounds, which are useful intermediates for further elaboration to other valuable compounds. Within the past few years various enantioselective α-halogenations of carbonyl compounds by asymmetric organocatalysis have been reported. Most importantly, these recent developments have greatly enhanced the synthetic utility of α-halogenations and opened up a promising new frontier in organic synthesis.

1 Introduction

Asymmetric halogenations are among the most practical and significant reactions due to the usefulness of the halogenation products as versatile synthetic intermediates in medicinal chemistry and materials science.[1] Indeed, they can serve as chiral precursors in the formation of carbon–carbon bonds as well as various carbon–heteroatom bonds.[2]

Among the halogen-containing compounds, optically active α-halocarbonyls are easily converted to various chiral building blocks,[2] and catalytic enantioselective α-halogenations of carbonyl compounds have been investigated by many research groups.[3–5] In 2000, the first enantioselective α-fluorination of β-keto esters catalyzed by chiral Lewis acid catalyst was reported by Togni and Hintermann.[3] Since then, asymmetric α-halogenations (α-fluorination, α-chlorination and α-bromination) of various substrates have been developed.[4,5] However, there has been no example of the asymmetric α-iodination of carbonyl compounds by using chiral Lewis acid catalysts.

In the past several years, various transformations promoted by organocatalysts have been reported.[4,6,7] Organocatalysis represents one of the most important synthetic methods in organic chemistry today. The advantages of this approach include its simple experimental procedures, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations. Recently, these chiral organocatalysts have been successfully applied to the field of α-halogenation of carbonyl compounds. In this article, we present recent advances in the field of organocatalyzed asymmetric α-halogenations of carbonyl compounds.

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2 Asymmetric fluorination

2.1 Asymmetric fluorination by enamine-forming chiral amines

In 2005, Enders and Hüttl reported the organocatalytic enantioselective α-fluorination of aldehydes and ketones using various chiral secondary amines as catalysts and Selectfluor as the fluorinating agent.[8] The use of L-proline derivative **1** (catalyst loading of 30 mol%) gave the mono α-fluorocyclohexanone in 43% conversion and 34% enantiomeric excess (Scheme 1). They also showed that L-proline is an effective catalyst for the α-fluorination of aldehydes, although the enantiomeric excesses were not reported.

Soon after the report of Enders and Hüttl, the highly enantioselective α-fluorination of aldehydes was independently reported by

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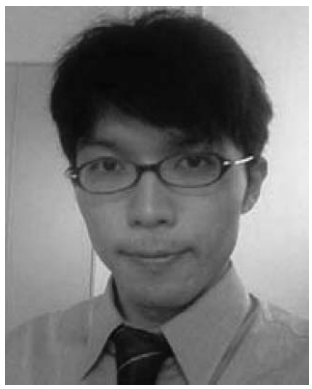

Taichi Kano

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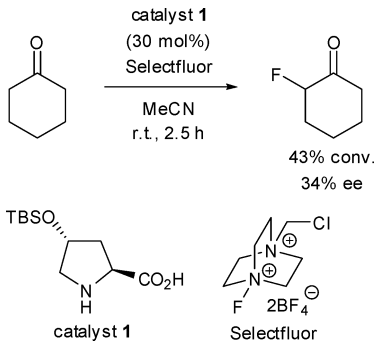

Scheme 1

three research groups (Barbas, MacMillan, and Jørgensen).[9] All these groups applied *N*-fluorodibenzenesulfonimide (NFSI) as the best fluorinating agent (Scheme 2).

Barbas *et al.* reported that the chiral imidazolidinone **2a** (stoichiometric amounts) promoted the α-fluorination of aldehydes. In this reaction, the choice of solvent is important to suppress the formation of α,α-difluorinated aldehyde. Screening of various solvents revealed that the difluorination of the aldehyde was found to be suppressed by DMF. Under these conditions, the reaction of aldehydes with NFSI proceeded smoothly to give α-fluorinated aldehydes in moderate to good yields with excellent enantioselectivities (up to 96% ee) (Scheme 2).[9a]

On the other hand, MacMillan and Beeson reported that the dichloroacetic acid (DCA) salt of chiral imidazolidinone **2b** (catalyst loading of 20 mol%) can catalyze the α-fluorination of aldehydes in THF/*i*-PrOH (9/1). While the use of *i*-PrOH as a solvent was not effective, the addition of *i*-PrOH as a cosolvent gave improved enantioselectivities and yields. Under these conditions, catalyst **2b** gave the α-fluorinated aldehydes in moderate to good yields with excellent enantioselectivities (up to 99% ee) (Scheme 2). They also showed that a wide range of functional groups (including olefins, esters, amines, carbamates, and aryl rings) can be tolerated. Furthermore, the catalyst loading

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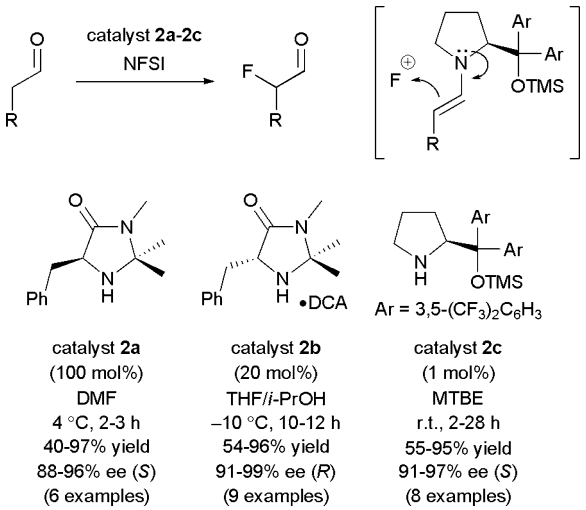


Scheme 2

can be decreased to 2.5 mol% without any loss of enantioselectivity (98% ee).[9b]

Jørgensen *et al.* successfully applied the diarylprolinol silyl ether **2c** as a catalyst for the α-fluorination of aldehydes. In their initial study, this catalyst **2c** was desilylated by the fluorinating agent in CH_2Cl_2, and hence gave a low conversion caused by inactivation of the catalyst. On the other hand, the reaction using catalyst **2c** (catalyst loading of 20 mol%) in methyl *tert*-butyl ether (MTBE) gave a significant amount of the difluorinated product. The difluorination problem was suppressed by decreasing the amount of catalyst, and the use of only 1 mol% of catalyst **2c** and an excess of the aldehydes resulted in good yields of the monofluorinated products with excellent enantioselectivities (up to 97% ee) (Scheme 2).[9c] The proposed transition state model for the reaction using **2c** is included in Scheme 2.

The α-fluorinated aldehydes are generally unstable under column purification or distillation conditions, and more volatile than the starting aldehydes. Therefore, the α-fluoroaldehydes were directly reduced by $NaBH_4$, and isolated as the β-fluoroalcohols without any loss of enantioselectivity.

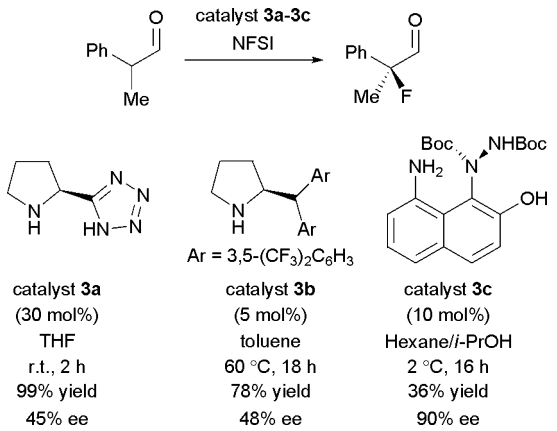
Barbas *et al.* also showed that proline-derived tetrazole **3a** (catalyst loading of 30 mol%) can catalyze the α-fluorination of an α-branched aldehyde. The reaction of 2-phenylpropanal with NFSI proceeded smoothly to give 2-fluoro-2-phenylpropanal in 99% yield with 45% ee (Scheme 3).[9a]

Jørgensen *et al.* reported that the combined use of catalyst **3b** (catalyst loading of 5 mol%) and NFSI in toluene at 60 °C afforded the 2-fluoro-2-phenylpropanal in 78% yield with 48% ee (Scheme 3).[9c]

Furthermore, Jørgensen *et al.* synthesized a new non-biaryl atropisomeric amine **3c**, which was successfully applied to the enantioselective α-fluorination of α-branched aldehydes as the catalyst (Scheme 3). In the presence of 10 mol% of catalyst **3c** (with 96% ee), 2-phenylpropanal was α-fluorinated in hexane/*i*-PrOH (9/1) with good enantioselectivity (90% ee) (Scheme 3).[10]

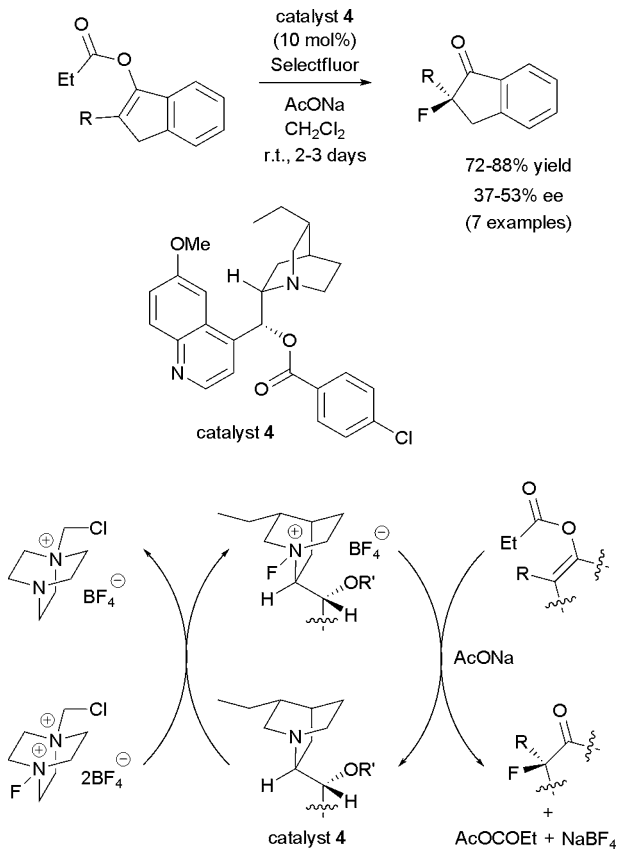
2.2 Asymmetric fluorination by chiral *tert*-amine

In 2005, Shibata and Toru *et al.* developed the α-fluorination of acyl enol ethers of ketones by using a *Cinchona* alkaloid derivative



Scheme 3

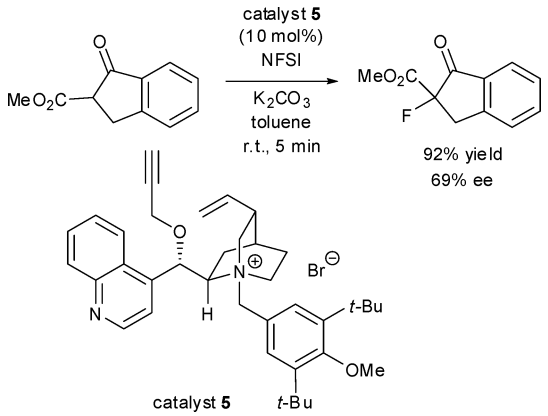
4 (catalyst loading of 10 mol%) and Selectfluor as the fluorinating agent in the presence of sodium acetate. In this reaction, Selectfluor fluorinates catalyst **4** to generate the actual chiral fluorinating agent, and sodium acetate traps the acetyl cation and BF_4^-. Under these conditions, α-fluorinated ketones were obtained in good yields with moderate enantioselectivities (up to 53% ee) (Scheme 4).[11]



Scheme 4

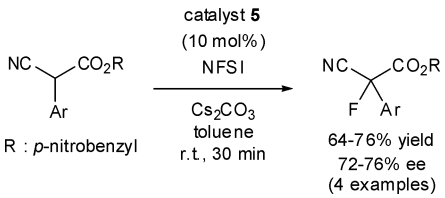
2.3 Asymmetric fluorination by chiral PTCs

In 2002, Kim and Park reported the α-fluorination of β-keto ester under phase-transfer conditions. The combined use of quaternary ammonium salt **5** (catalyst loading of 10 mol%) derived from cinchonine as the catalyst and NFSI in toluene with base (K_2CO_3) afforded the α-fluorinated β-keto ester in 92% yield with 69% ee (Scheme 5).[12]



Scheme 5

Furthermore, they reported catalyst **5** effectively catalyzed the α-fluorination of α-cyano esters to give the fluorination products in good yields and enantioselectivities (up to 76% ee). In this case, Cs_2CO_3 was best used as the base (Scheme 6).[13]



Scheme 6

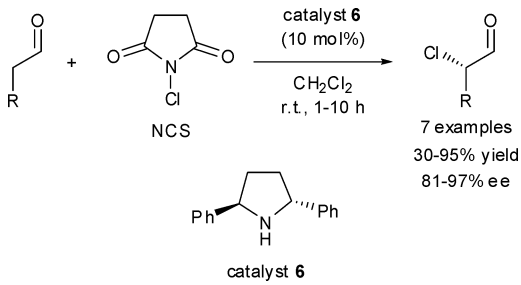
3 Asymmetric chlorination

3.1 Asymmetric chlorination by enamine-forming chiral amines

In 2004, the enantioselective α-chlorination of unbranched aldehydes was independently reported by Jørgensen *et al.* and MacMillan *et al*.

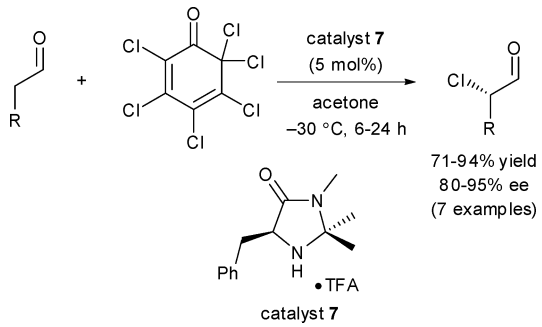
Jørgensen *et al.* reported that the C_2-symmetric (2*R*,5*R*)-diphenylpyrrolidine **6** (catalyst loading of 10 mol%) can catalyze the α-chlorination of aldehydes using simple and inexpensive *N*-chlorosuccinimide (NCS) as the chlorinating agent. Both the yield and enantioselectivity of the α-chlorinated product were dependent on the solvent used. Screening of various solvents revealed that use of dichloroethane (DCE) gave the best result, and the reaction of aldehydes with NCS proceeded smoothly to give α-chlorinated aldehydes in moderate to good yields with good to excellent enantioselectivities (up to 97% ee) (Scheme 7).[14a,b] It should be noted that in the reaction using this catalyst **6** the formation of homo-aldol product and α,α-dichlorinated aldehyde were not observed at ambient temperature. In contrast to α-fluorinated aldehydes, α-chlorinated aldehydes are stable to neutral pH silica purification.

MacMillan *et al.* reported that the trifluoroacetic acid (TFA) salt of chiral imidazolidinone **7** (catalyst loading of 5 mol%)



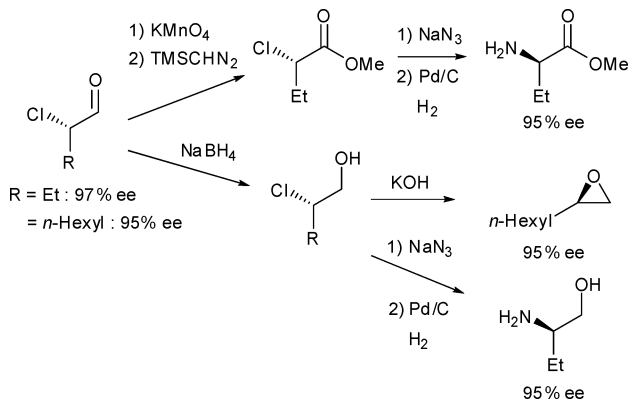
Scheme 7

can catalyze the α-chlorination of aldehydes using perchlorinated quinone as the chlorinating agent. In this reaction, a variety of solvents can be employed without significant loss of enantioselectivity. The use of acetone provided the best result in terms of reaction rate, yield and enantioselectivity (up to 95% ee), and also suppressed the formation of homo-aldol product and α,α-dichlorinated aldehyde (Scheme 8).[14c]



Scheme 8

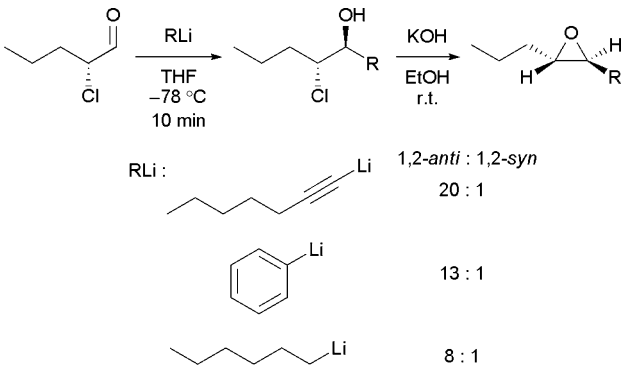
Jørgensen *et al.* also showed that α-chlorinated aldehydes can be easily transformed into useful chiral building blocks, such as α-amino ester, epoxide and α-amino alcohol. All these transformations took place without any loss of enantioselectivity (Scheme 9).[14a,b]



Scheme 9

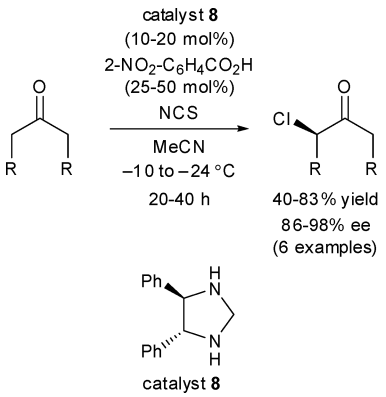
More recently, Britton and Kang succeeded in obtaining *trans*-epoxides from α-chlorinated aldehydes (Scheme 10).[14d]

Jørgensen *et al.* synthesized imidazolidine **8**, which was successfully applied to the α-chlorination of ketones as the catalyst



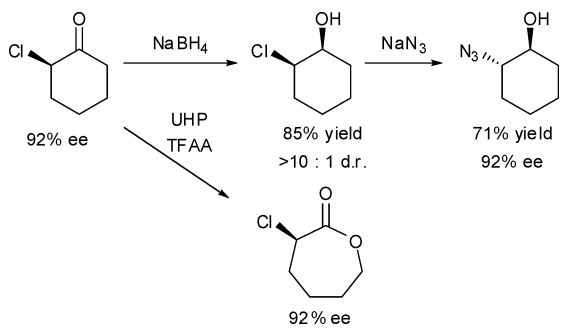
Scheme 10

(10–20 mol%) with NCS as the chlorinating agent (Scheme 11). Screening of various solvents revealed that the formation of polychlorination was suppressed dramatically in acetonitrile. The use of benzoic acids as additives also increased the reaction rate and enantioselectivity. The best result was given by the use of 2-nitrobenzoic acid. Under these conditions, various ketones were mono α-chlorinated in moderate to good yields with excellent enantioselectivities (up to 98% ee).[15]



Scheme 11

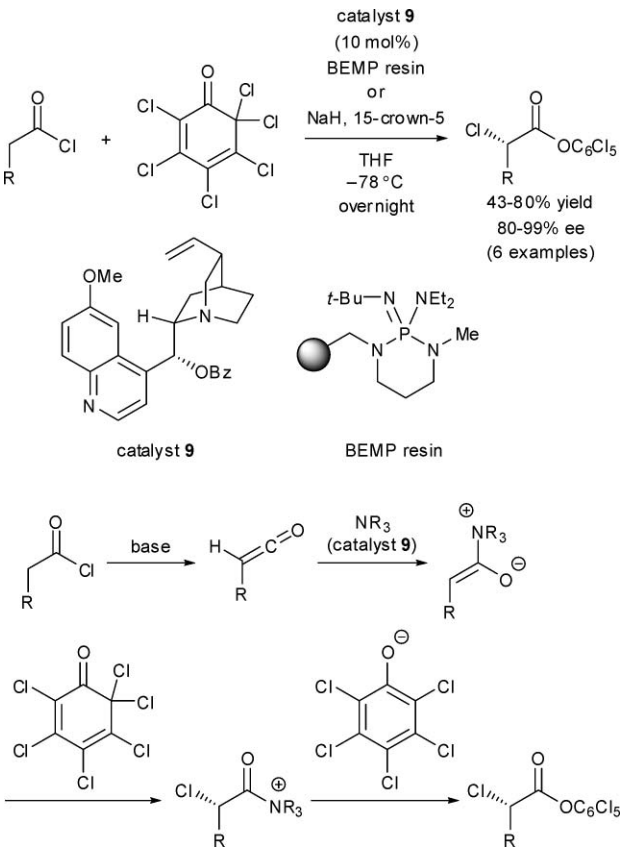
Jørgensen *et al.* also showed that the α-chlorinated ketone could be easily transformed into the azide alcohol after reduction with $NaBH_4$ and sodium azide treatment, and also the α-chlorinated lactone by Baeyer–Villiger oxidation. These transformations took place without decreasing the initial enantiomeric excess (Scheme 12).[15]



Scheme 12

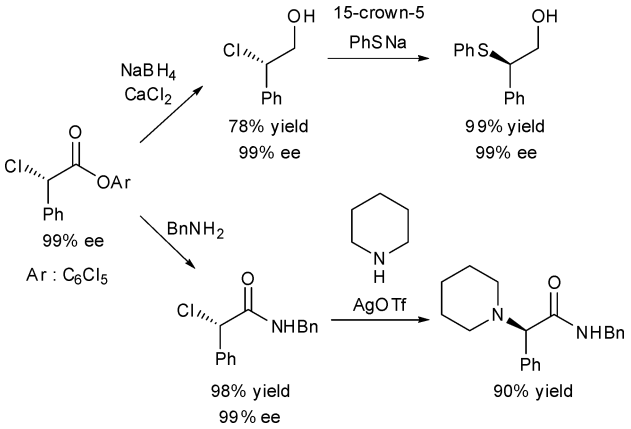
3.2 Asymmetric chlorination by chiral *tert*-amines

The first organocatalytic asymmetric α-chlorination of carbonyl compounds was developed by Lectka *et al.* They discovered that inexpensive benzoylquinine **9** (catalyst loading of 10 mol%) can catalyze the reaction of acid chlorides and perchlorinated quinone as the chlorinating agent to form the α-chlorinated esters. In this reaction, the chiral ketene enolates generated from the acid chlorides and catalyst **9** are chlorinated by perchlorinated quinone in an enantioselective fashion. The choice of base is most important for the efficient formation of the α-chlorinated esters, and satisfactory results were obtained using BEMP resin. In the presence of this organic base, catalyst **9** gave the α-chlorinated esters in moderate to good yields with good to excellent enantioselectivities (up to 99% ee) (Scheme 13).[16a] Furthermore, they recently developed an easier and more cost-effective method, in which the combined use of NaH or $NaHCO_3$ as a base with 15-crown-5 as a phase transfer cocatalyst can be applied instead of BEMP resin.[16b]



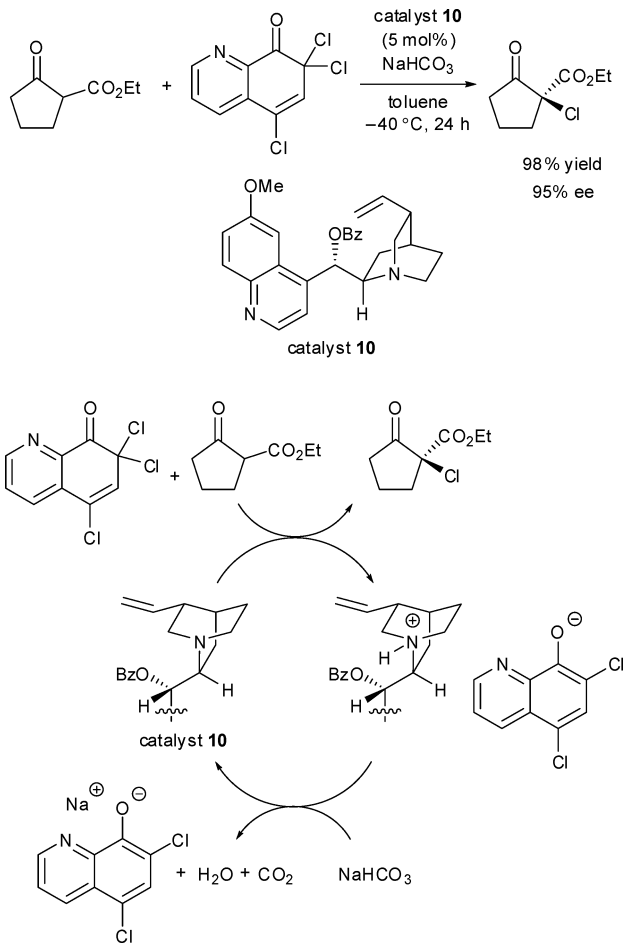
Scheme 13

Lectka *et al.* also showed that the optically enriched α-chlorinated ester can be easily transformed into the β-hydroxy sulfide with $NaBH_4$ and sodium thiophenoxide treatment without decreasing the initial enantiomeric excess. In the presence of AgOTf, amination of the optically enriched α-chloroamide, which was prepared by amidation of the α-chlorinated ester with benzylamine, proceeded to give the α-amino amide in good yield, although about 10% of the optical purity was lost (Scheme 14).[16]



Scheme 14

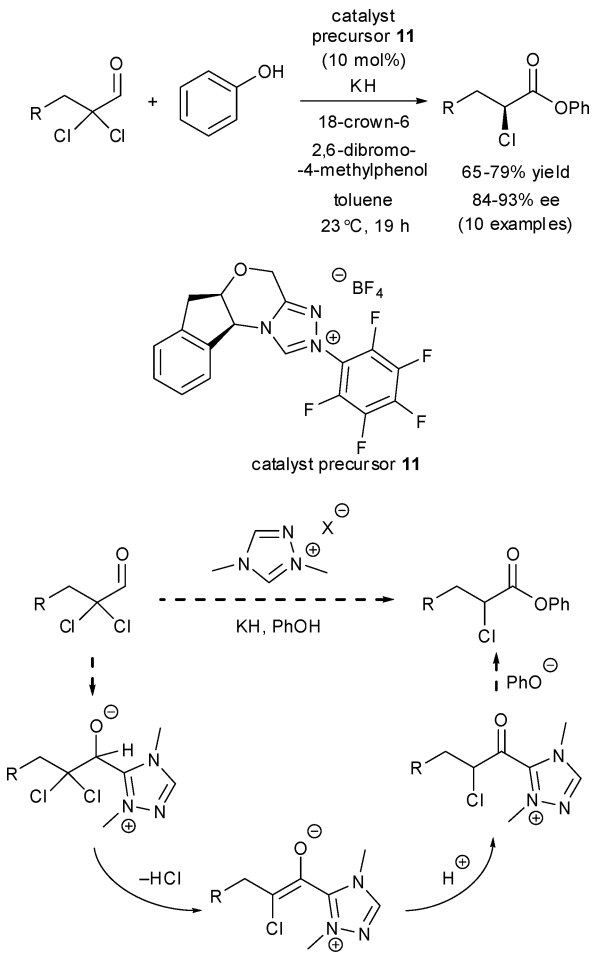
In 2005, Bartoli and Melchiorre *et al.* reported the α-chlorination of 1,3-dicarbonyl compounds using a *Cinchona* alkaloid derivative, benzoylquinidine **10** as a chiral base catalyst (catalyst loading of 5 mol%) with a trichloroquinolinone as the chlorinating agent.[17] They also discovered that the addition of $NaHCO_3$ (1 equiv.) could accelerate the turnover of catalyst **10**. Under these conditions, the reaction of the β-keto ester gave the α-chlorinated β-keto ester in 98% yield with 95% ee (Scheme 15). The proposed reaction mechanism is included in Scheme 15.



Scheme 15

3.3 Synthesis of α-chloroesters by chiral carbene catalyst

Rovis and Reynolds have developed another powerful method for the formation of the chiral α-chloroesters.[18] They discovered that the chiral triazolinylidene carbene generated from azolium salt **11** (catalyst loading of 10 mol%) can catalyze the reaction of 2,2-dichloroaldehydes with phenols to form the corresponding α-chloro esters. In this catalytic asymmetric reaction, the enantioselective step is the protonation of the chiral enolates generated from α,α-dichloroaldehydes and the carbene catalyst. Buffering the solution by adding 2,6-dibromo-4-methylphenol resulted in an increase of enantioselectivity, due to the suppression of background racemization under basic conditions. Under these conditions, the α-chloro esters were obtained in good yields and enantioselectivities (up to 93% ee) (Scheme 16).



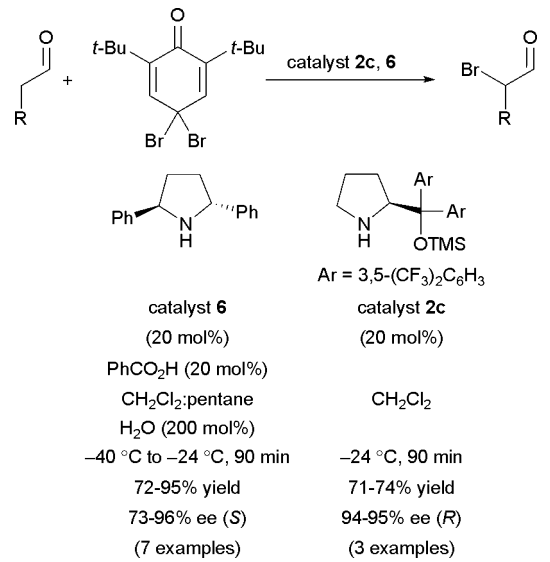
Scheme 16

The dichloroaldehydes as the starting substrates are benchstable compounds, easily accessed by treatment of various aldehydes with *tert*-butylamine and NCS.

4 Asymmetric bromination

4.1 Asymmetric bromination by enamine-forming chiral amines

In 2005, the enantioselective α-bromination of aldehydes was reported by Jørgensen *et al.* They showed that secondary amine **6** (catalyst loading of 20 mol%), which is an effective catalyst for the α-chlorination of aldehydes, can also catalyze the α-bromination of aldehydes. The reaction of aldehydes with 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone as the brominating agent proceeded smoothly to give the α-brominated aldehydes in high yields with high to excellent enantioselectivities (up to 96% ee) (Scheme 17).[19a]

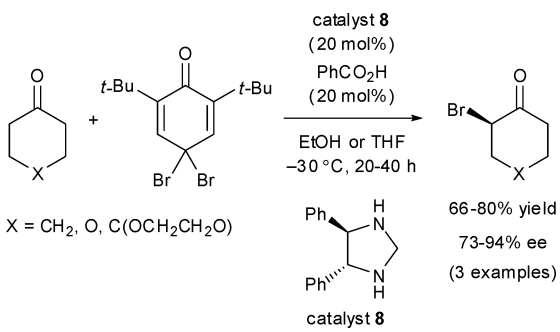


Scheme 17

The observed results seem to be strongly dependent upon the chosen solvent, with a 1:1 mixture of CH_2Cl_2 and pentane giving optimal results. Moreover, the addition of benzoic acid and water was found to be necessary to obtain high yields and high enantioselectivities.

They showed that the application of catalyst **2c** (catalyst loading of 20 mol%) to the α-bromination of unbranched aldehydes also gave similar results (Scheme 17). In this case, the addition of pentane, benzoic acid and water was not necessary.[19b]

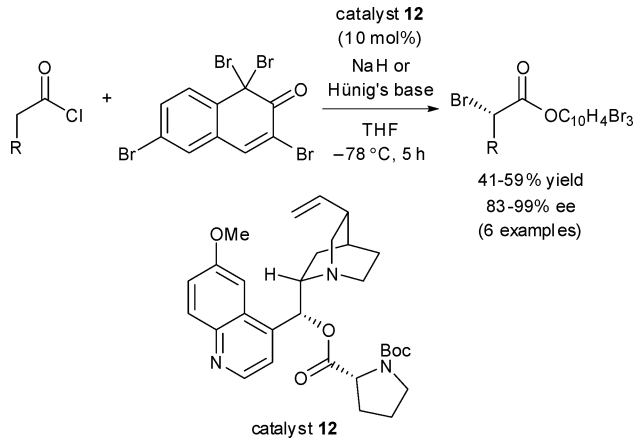
Cyclic ketones were also α-brominated by using a C_2-symmetric imidazolidine catalyst **8** (catalyst loading of 20 mol%) with good to high enantioselectivities (up to 94% ee) (Scheme 18). In this reaction, the use of 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone as the brominating agent and EtOH or THF as the solvent gave the best results.[19a] All the α-brominated carbonyl compounds described above were isolated as β-bromoalcohols after reduction with $NaBH_4$.



Scheme 18

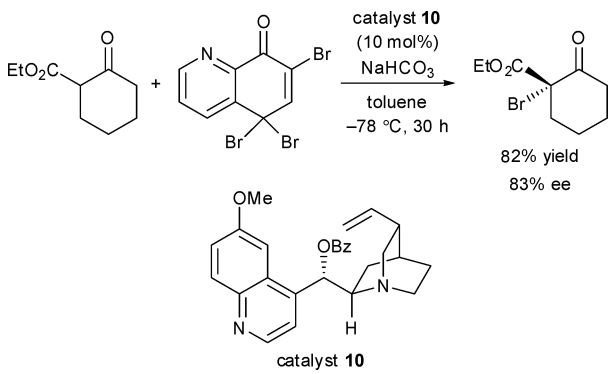
4.2 Asymmetric bromination by chiral *tert*-amines

In 2001, Lectka *et al.* developed the catalytic, enantioselective α-bromination of acid chlorides (up to 98% ee). In this reaction, the chiral ketene enolates generated from acid chlorides, amine **12** and K_2CO_3 were brominated by 4,4-dibromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone.[20a] Recently, they discovered the combined use of tetrabromonaphthalenone as the brominating agent and NaH or Hünig's base gave high enantioselectivities (up to 99% ee) (Scheme 19).[20b,c]



Scheme 19

Bartoli and Melchiorre *et al.* showed that catalyst **10** was effective for the α-bromination of 1,3-dicarbonyl compounds. In the presence of $NaHCO_3$ as the base, the reaction of β-keto ester with tribromoquinolinone as the brominating agent proceeded to give the α-bromo-β-keto ester in 82% yield with 83% ee (Scheme 20).[17]

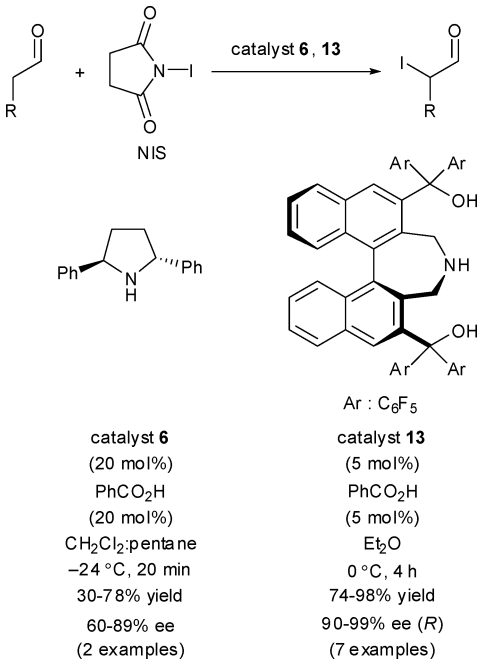


Scheme 20

5 Asymmetric iodination

5.1 Asymmetric iodination by enamine-forming chiral amines

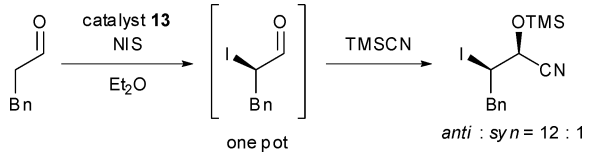
In 2005, Jørgensen *et al.* demonstrated that the secondary amine **6** (catalyst loading of 20 mol%), an effective catalyst for α-chlorination and α-bromination of aldehydes, can also catalyze the α-iodination of aldehydes with simple and inexpensive *N*-iodosuccinimide (NIS) as the iodinating agent and benzoic acid (20 mol%). Under these conditions, the reaction of isovaleraldehyde gave the α-iodinated product in 78% yield with 89% ee, while butyraldehyde gave a lower yield and enantioselectivity (30% yield, 60% ee) (Scheme 21).[19a,21]



Scheme 21

Recently, Maruoka *et al.* designed the chiral bifunctional binaphthyl-based amine **13**, and successfully applied it to the α-iodination of aldehydes with NIS. In the presence of catalyst **13** (catalyst loading of 5 mol%) and benzoic acid (5 mol%), the reaction of various aldehydes gave the α-iodinated products in high yields with excellent enantioselectivities (up to 99% ee) (Scheme 21). Since catalyst **13** is less nucleophilic and basic than pyrrolidine-type catalysts, racemization of α-iodinated aldehydes by the catalyst used may be suppressed.[22]

Maruoka *et al.* also demonstrated the one pot silylcyanation of the in-situ generated α-iodinated aldehyde with TMSCN in the presence of I_2 generated from a slight excess of NIS. The in-situ generated α-iodinated aldehyde was smoothly converted to the corresponding silylcyanation product with high diastereoselectivity, probably due to the steric bulk of the iodo group (Scheme 22).[22]



Scheme 22

Conclusions

The development of enantioselective α-halogenation of carbonyl compounds is among the topical areas of asymmetric synthesis. In this area, organocatalytic halogenation has been applied as the most successful approach to obtaining optically active

α-halocarbonyls. Especially, the catalytic asymmetric α-iodination of carbonyl compounds has been achieved only by organocatalysis.

We believe that continuous effort should be devoted to the development of α-halogenations of carbonyl compounds by using organocatalysis and their applications to synthetically useful transformations. Also, we are certain that these methodologies are able to give solutions to many problems in total synthesis and medicinal chemistry.

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