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ARTICLE *in* TETRAHEDRON LETTERS · NOVEMBER 2014

Impact Factor: 2.38 · DOI: 10.1016/j.tetlet.2014.09.031

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PII: S0040-4039(14)01532-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.09.031
Reference: TETL 45125

To appear in: *Tetrahedron Letters*

Received Date: 22 July 2014
Revised Date: 19 August 2014
Accepted Date: 7 September 2014

Please cite this article as: Lin, J-H., Xiao, J-C., Recent advances in asymmetric fluorination and fluoroalkylation reactions via organocatalysis, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.09.031

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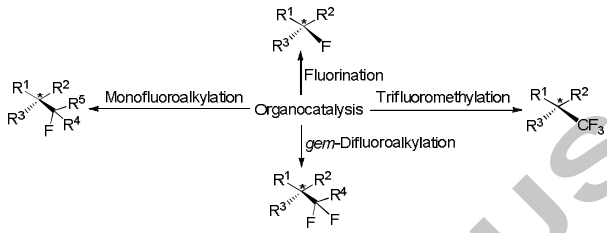

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Recent advances in asymmetric fluorination and fluoroalkylation reactions via organocatalysis

Jin-Hong Lin[a] and Ji-Chang Xiao[a,] *

[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Asymmetric
Fluorination
Monofluoroalkylation
gem-Difluoroalkylation
Trifluoromethylation
Organocatalysis

ABSTRACT

The past decade has witnessed the significant advances of asymmetric organocatalytic fluorination, monofluoroalkylation, *gem*-difluoroalkylation and trifluoromethylation. This digest summarizes the latest progress of these reactions. In the research area of asymmetric organocatalytic fluorination, a new catalysis concept, chiral anion phase-transfer catalysis strategy, has emerged and has approved to be highly efficient. Asymmetric organocatalytic monofluoroalkylation and *gem*-difluoroalkylation have been much less explored and the Lewis base/acid catalysis has been the mostly used strategy. Compared with electrophilic trifluoromethylation, nucleophilic trifluoromethylation has been intensively studied in the research field of asymmetric organocatalytic trifluoromethylation.

1. Introduction

Fluorine element has so many unique properties such as small atomic radius, extremely low polarizability and highest electronegativity among all elements that the effect of this atom has been described in various terms, including "a small atom with a big ego",[1] "fabulous fluorine",[2] "magic effect",[3] as well as "flustrates" referring to fluorine-containing substrates.[4] The incorporation of fluorine or fluoroalkyl group into a molecule usually modifies its physical and chemical properties through steric, electronic and stereoelectronic effects. The deep understanding of fluorine effects has led to the widespread application of organic fluorochemicals in a variety of research areas, such as medical and agricultural chemistry and materials science.[1, 5] Since the first F-containing drug was developed in 1957, over 150 fluorinated drugs have been approved by FDA (Food and Drug Administration) in the United States for treating different diseases.[6] A survey in 2006 showed that approximately 20% of pharmaceuticals and 30–40% of agrochemicals on the market contain a fluorine substituent.[2] These figures clearly demonstrate the exceptional importance of fluorinated compounds.

As it is well known, one enantiomer of a chiral drug may exhibit desired beneficial biological and pharmacological effects while the other may result in harmful side effects, or sometimes even beneficial but completely different effects. "In 2006, 80% of small-molecule drugs approved by FDA were chiral and 75% were single enantiomers."[7] It was estimated that around 200 chiral compounds could enter the development process each ~~year, in~~dicating the strong demand for the chiral drugs to cure diseases. To date, over 15 chiral drugs containing fluorinated or fluoroalkylated stereogenic centers are commercially available, including Fluticasone Propionate, Gemcitabine, Efavirenz and so on (Figure 1).[8] The presence of fluorine atom(s) is critical to enhance the pharmacological properties of these molecules.

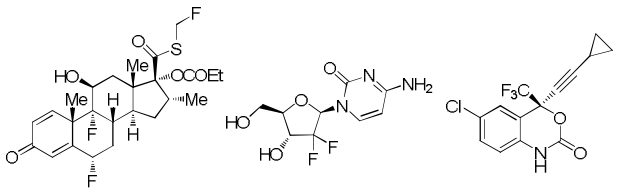


Figure 1. Chiral fluorinated drugs

The above facts serve to emphasize that the asymmetric fluorination and fluoroalkylation are fascinating research areas in organofluorine chemistry. Considerable efforts have been directed towards the development of broadly applicable catalyst system to promote asymmetric fluorination and fluoroalkylation.[9] Both asymmetric transition metal catalysis and organocatalysis have proved to be quite efficient, but the methods involving transition metal catalyst[10] are not included here. The asymmetric organocatalytic fluorination and fluoroalkylation have been intensively studied and the material appearing in the literature prior to 2011 has been reviewed.[9f, 9g] Asymmetric catalytic (including transition metal catalytic) difluoromethylation was reviewed by the group of Zhou in 2013.[9i] Very recently, Ma and

* Ji-Chang Xiao. Tel: （+86）21-5492-5340; Fax: (+86) 21-6416-6128; E-mail: jchxiao@sioc.ac.cn

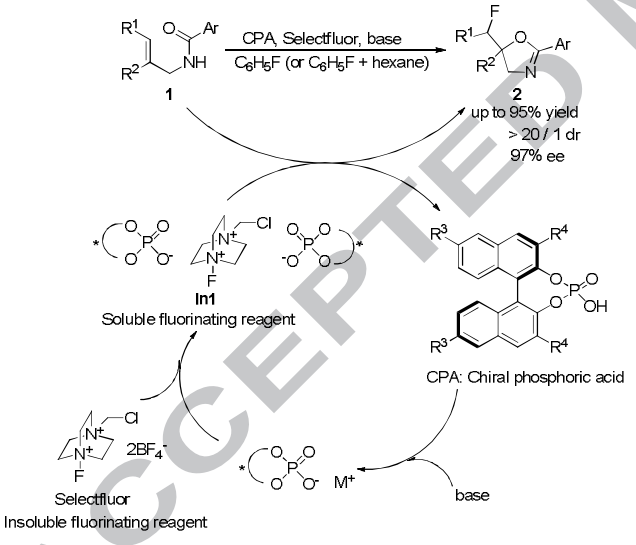
coworkers have summarized the progress in asymmetric fluorination and trifluoromethylation reactions.[9j] In this digest we only discuss the latest advances in asymmetric organocatalytic fluorination, monofluoroalkylation, *gem*-difluoroalkylation and trifluoromethylation which are not covered in the reported reviews,[9] and introduce some previous papers as background when necessary.

2. Asymmetric organocatalytic fluorination

2.1 Phase-transfer catalysis

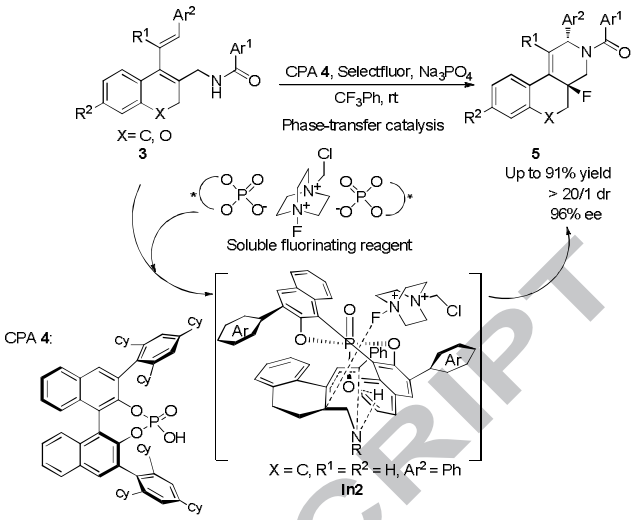
2.1.1 Chiral anion phase-transfer catalysis

In 2011, Toste and coworkers took advantage of a largely overlooked concept of phase-transfer catalysis that a chiral anionic catalyst brings a cationic specie into solution to achieve the enantioselective fluorocyclization of olefins **1** with insoluble Selectfluor in the presence of a BINOL-derived chiral phosphoric acid (CPA) catalyst (Scheme 1).[11] The important step to achieve excellent enantio- and diastereoselectivity in the catalytic cycle is the dissolution of insoluble fluorinating reagent (Selectfluor) into the nonpolar organic liquid phase by counter anion exchange from tetrafluoroborate (BF_4^-) to the chiral phosphate anion (intermediate **In1**). This strategy for catalytic enantioselective fluorination reactions is highly valuable due to the following reasons. Firstly, the two stereogenic centers generated in the desired products can't be easily constructed by alternative methods. Secondly, the approach is applicable to not only electron-rich olefins, but also un-activated olefin. Thirdly, this asymmetric organocatalytic reaction represents an efficient chiral anion phase-transfer catalysis tactic, which might find application in other asymmetric transformations involving cationic electrophiles.



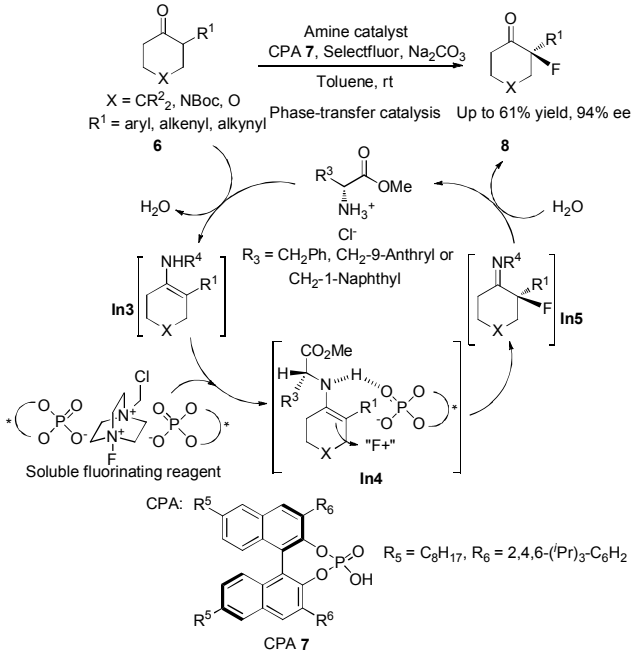
Scheme 1. Chiral anion phase-transfer catalysis

The group of Toste found this strategy could be extended to various asymmetric fluorination reactions.[12] Recently, they described an efficient method for 1,4-aminofluorocyclization of 1,3-dienes **3** with Selecfluor by utilizing phase-transfer catalysis strategy (Scheme 2).[13] Surprisingly, although far from the reactive center, substitution on the benzamide arene shows a strong influence on selectivity. 4-*tert*-Butylbenzamide group was found to be the best nucleophile after the investigation of other substituted benzamide groups. The mechanism study suggests that the observed diastereolectivity arises from a concerted *anti*-1,4-addition (**In2**).



Scheme 2. Enantioselective 1,4-aminofluorocyclization of 1,3-dienes

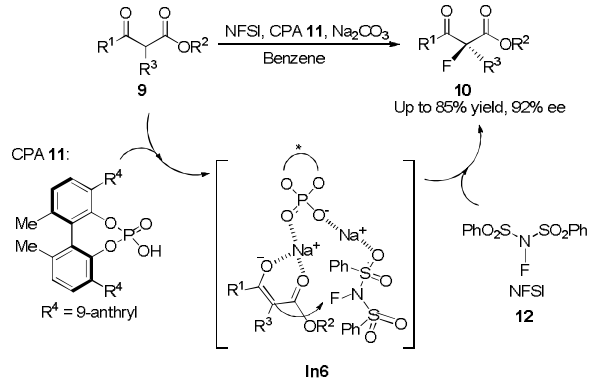
On the basis of the good results for enantioselective fluorination of enamides via phase-transfer catalysis,[12b] Toste and coworkers made further attempts at the asymmetric fluorination of α−branched cyclohexanones **6** by a combination of chiral anion phase-transfer catalysis and enamine catalysis (Scheme 3).[14] In the presence of amine catalyst, the substrate ketone would be converted to enamine intermediate **In3**, the fluorination of which and subsequent hydrolysis gives the final product. The strategy has proved to be very successful to give the desired fluorinated products with high ee. A hydrogen-bonded transition state **In4** possessing two matched elements of chirality should be able to account for the observed enantioselectivity.



Scheme 3. Asymmetric fluorination of ketones

Akiyama and coworkers reported the enantioselective fluorination of β-ketoesters **9** with NFSI (*N*-fluorobenzenesulfonimide) catalyzed by chiral sodium phosphate with a slightly different reaction mechanism (Scheme 4).[15] In

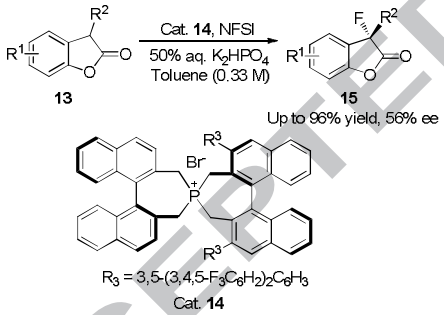
contrast to the strategy developed by the group of Toste, the utilization of Selecfluor as fluorination reagent leads to dramatic loss of enantioselectivity and decrease in reaction yield. Therefore, Akiyama and coworkers propose that the transition state of this reaction should involve NFSI. In their proposed transition state (**In6**), sodium phosphate acts as bifunctional catalyst, Lewis basic activation of sodium enolate moiety by phosphoryl oxygen and Lewis acidic activation of sulfonyl group of NFSI by sodium atom of phosphate moiety.



Scheme 4. Enantioselective fluorination of β-ketoesters

2.1.2 Chiral cation phase-transfer catalysis

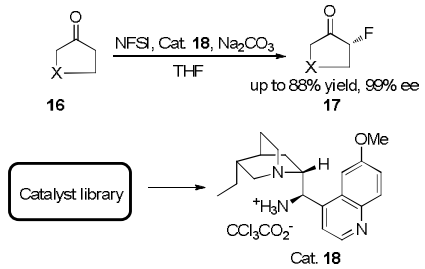
Chiral cation phase-transfer catalysis for asymmetric fluorination usually employs chiral quaternary ammonium salt as catalyst.[9f] The group of Ma employed chiral quaternary phosphonium salt as catalyst to promote fluorination of 3-substituted benzofuran-2(*3H*)-ones **13** with NFSI (Scheme 5).[16] The products were obtained with low enantioselectivity, albeit in high yields. It should be noted that low catalyst loading (2 mol%) is effective, and the initial concentration of the substrate is important to accelerate the reaction.



Scheme 5. Asymmetric fluorination of esters

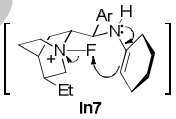
2.2 Enamine catalysis

In continuation of their efforts to realize enantioselective organocatalytic α-fluorination of carbonyl group,[17] Macmillan and coworkers recently investigated α-fluorination of cyclic ketones **16** (Scheme 6).[18] They developed a robotic platform to automate the parallel execution of ~400 small-scale reactions to determine the utility of a library of 250 novel and known organocatalysts in this reaction by utilizing NFSI as fluorinating reagent. After carefully screening the reaction conditions, they found that the primary amine catalyst **18** was quite efficient for this conversion. The reaction is applicable to a variety of ketone substrates and enables chemo-, regio- and diastereoselective fluorination of some complex substrates.



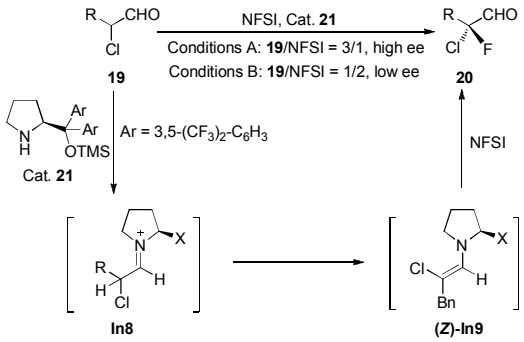
Scheme 6. Enantioselective α-fluorination of ketones

Although Macmillan suggested that the reaction may proceed by dual activation of the ketone and the fluorine source, they didn't propose a detailed mechanism (Scheme 6). Recently, the group of Houk utilized the density functional calculations to elucidate the reaction mechanism and determine the origin of selectivity (Scheme 7). [19] Simplified model catalysts were used to compute the enamine transition states (**In7**) for this reaction. It was concluded that the high facial selectivity of fluorination stems from two factors: (1) the preferred chair conformation of the fluorine transfer ring, and (2) the equatorial site of the bulky quinoline group ("Ar" in the transition state) on the organocatalyst in the seven-membered fluorine transfer ring.



Scheme 7. Transition state for α-fluorination of ketones

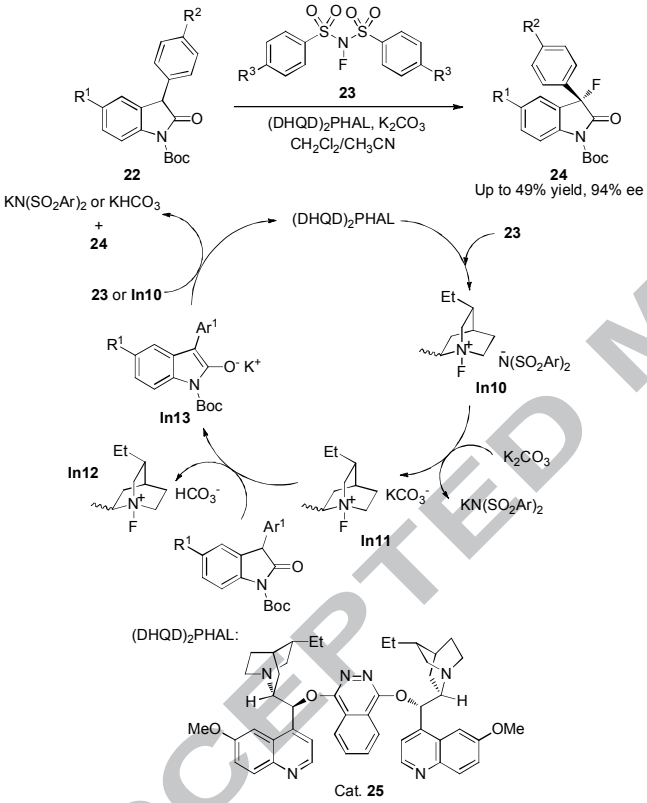
In a previous study, the group of Shibatomi found that asymmetric fluorination of chloroaldehyde *rac*-**19** with NFSI could give the fluorinated product **20** in high ee when substrate **19** was used in excess. Interestingly, the alcohol obtained from the remaining substrate by reduction with $NaBH_4$ was obtained with 37% ee. [20] If substrate **19** was used as limiting reagent and NFSI was used in excess, low ee was observed. They collect more experimental information to put forward a mechanism which could explain the phenomena (Scheme 8).[21] They propose that (*R*)-**19** could be converted to intermediate (*Z*)-**In9** faster than to the thermodynamically unfavorable intermediate (*E*)-**In9**, suggesting that fluorination of (*R*)-**19** would give the desired product in high ee. The conversion of (*S*)-**19** to intermediate (*Z*)- or (*E*)-**In9** is kinetically and thermodynamically unfavorable respectively. Thus, fluorination of (*S*)-**19** goes slower than fluorination of (*R*)-**19**, and it is difficult to control the enantioselectivity of the fluorination of (*S*)-**19**, indicating that if NFSI is used as limiting reagent in the reaction of *rac*-**19** with NFSI, kinetic resolution of the aldehyde *rac*-**19** would be observed and the fluorination reaction would afford the product **20** with high enantioselectivity.



Scheme 8. Asymmetric fluorination of chloroaldehyde

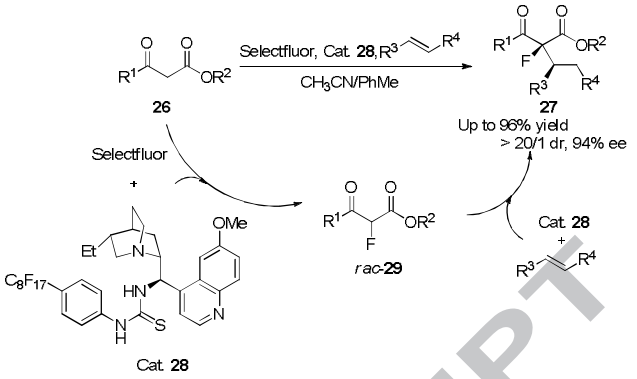
2.3 Brønsted base/acid catalysis

On the basis of the results of a previous study that the combination of $(DHQD)_2PHAL$ and NFSI is effective for enantioselective fluorination,[22] Yang and coworkers investigated the $(DHQD)_2PHAL$-catalyzed fluorination of oxindoles **22** with modified NFSI **23** (Scheme 9).[23] The modified NFSI are benzenesulfonimides bearing different substituents such as F, *t*-Bu, OMe, CF_3, and OCF_3 on the *para*-position of the symmetric phenyl ring. The fluorinating efficiency of these reagents was compared with that of NFSI in the context of the enantioselective fluorination of various oxindole substrates. It was found that the *p*-*t*-Bu substituted NFSI can considerably increase the enantioselectivity in most cases, albeit exhibiting lower fluorinating reactivity. In their proposed mechanism, the anion metathesis of K_2CO_3 with intermediate **In10** generated from the reaction of catalyst and NFSI gives intermediate **In11**. The deprotonation of substrate by **In11** produces intermediate **In12** and **In13**. The fluorination of **In13** with modified NFSI or intermediate **In10** affords the final product.



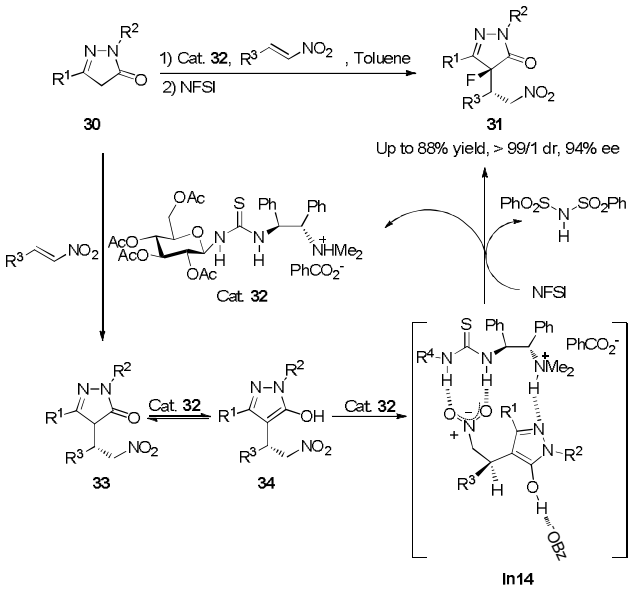
Scheme 9. Asymmetric fluorination of β-ketoesters

Recently, Yi and coworkers described a one-pot approach for the construction of fluorinated stereogenic center via fluorination of β-ketoesters **26**, followed by Michael addition (Scheme 10).[24] The mechanism study suggested that fluorination of β-ketoesters gives racemic product **29**, and the Michael addition constructs two stereogenic centers in the final product **27**. The bifunctional fluoroalkylated catalyst **28** could be recycled by fluorous solid-phase extraction in high purity and without significant loss of mass. The reused catalyst can catalyze the reaction almost without change of product yield and selectivity.



Scheme 10. One-pot fluorination and Michael addition

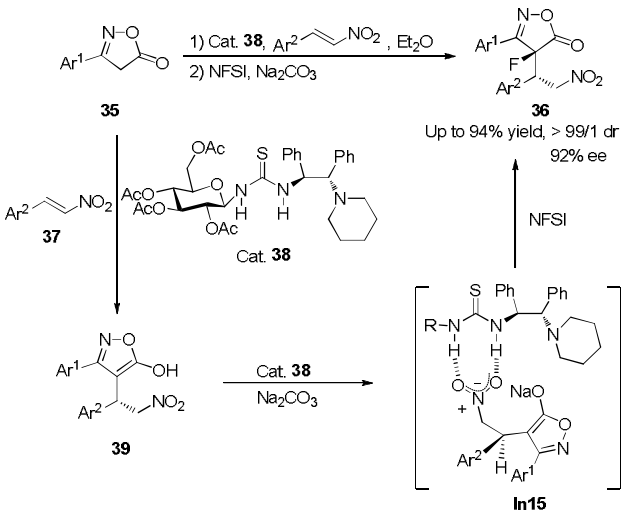
The group of Ma developed a one-pot sequential 1,4-addition/dearomative-fluorination transformation of pyrazolones **30** with nitroolefins and NFSI (Scheme 11).[25] The reaction could be applied to aromatic, hetero-aromatic and alkylated nitroolefins. All of these products could be obtained with excellent levels of enantioselectivity, albeit with lower diastereoselectivity for hetero-aromatic olefin and in lower yields for alkylated olefins. In order to elucidate the reaction mechanism, they collected much experimental information. They proved that the keto substrate **30** could readily tautomerize to enol form and the hydroxyl group in the enol form is important to promote the reaction, suggesting that tautomerization of both substrate **30** and Michael addition product **33** to their corresponding enol forms is very important for this conversion. Interestingly, fluorination of some isolated Michael addition products **33** can give the desired products in high ee with the use of Et_3N instead of the catalyst **32**, but lower diastereoselectivity was observed, indicating that the chiral catalyst controls the stereoselectivity of both steps, Michael addition and fluorination.



Scheme 11. One-pot 1,4-addition/dearomative-fluorination

Soon afterwards, the group of Ma further extended their strategy to one-pot sequential conjugate addition/dearomative fluorination transformation of isoxazol-5(*4H*)-ones **35** with nitroolefins and NFSI (Scheme 12).[26] This conversion could only be applied to aromatic and hetero-aromatic nitroolefins. No product was observed for the cases of alkylated nitroolefins. They made an attempt at the fluorination of one Michael addition product **39** with NFSI and Na_2CO_3 without the presence of the

catalyst **38**. It was found that this reaction can afford the final product **36** in excellent yield, but with lower ee, suggesting that the chiral catalyst controls the stereoselectivity of both steps.

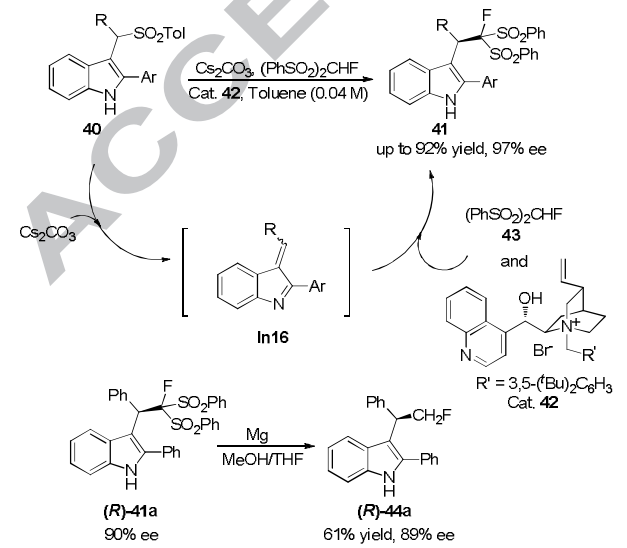


Scheme12. One-pot sequential conjugate addition/dearomative fluorination

3 Asymmetric organocatalytic monofluoroalkylation

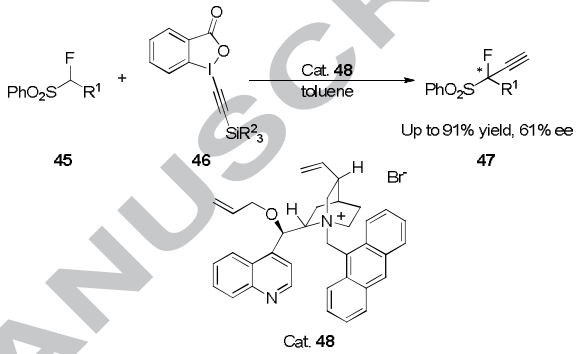
3.1 Chiral phase-transfer catalysis

In the examination of asymmetric catalytic monofluoromethylation of C2-arylindoles **40** with FBSM (1-fluoro-1,1-bis(phenylsulfonyl)methane) **43**, Shibata and coworkers found that a chiral quaternary ammonium salt (**42**) was very efficient to convert the substrates into desired products in high yields and high ee (Scheme 13).[27] The initial concentration of substrate shows an important effect on ee value, and excellent enantioselectivity was observed in toluene with the concentration at 0.04 M. The C2-aryl group of indoles also plays an important role for the asymmetric induction. The reactions of substrates possessing either methyl or hydrogen at the C2 position afforded an almost racemic mixture of **41,** albeit in high yields. A simple one-step reduction of the two phenylsulfonyl groups in substrate **40a** can be realized under conventional Mg/MeOH conditions to furnish the corresponding monofluoromethylated product **44a** with only slightly loss of enantioselectivity.



Scheme 13. Asymmetric monofluoromethylation of indoles

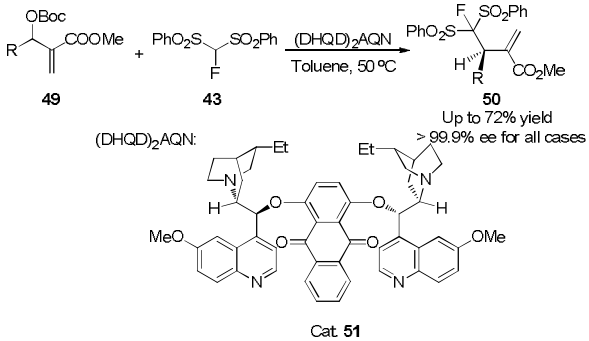
The group of Veselý demonstrated the monofluoromethyaltion of hypervalent iodine substituted silyl alkynes **46** with monofluorosubstituted compound **45** catalyzed by cinchona-based ammonium salt **48** to give fluoro-propargyl compounds **47** (Scheme 14).[28] The R^1 group in the substrate **45** can be different electron-withdrawing groups, including nitro, nitrile and carbonyl groups. In contrast to the results obtained by Shibata,[27] FBSM (R^1 = $PhSO_2$) isn't a suitable monofluoromethylation reagent. The reaction of alkyne with FBSM afforded the desired product in moderate yield without any enantioselectivity. Best enantioselectivity was observed when R^1 was nitro group. The silyl group in substrate **46** was found to be important for both the reaction yield and ee value. Bulky silyl group such as *tert*-butyldiphenylsilyl or *tri*-isopropylsilyl group results in no reaction. A smaller silyl group such as TMS or TES is favor for the reaction.



Scheme 14. Asymmetric monofluoromethylation of alkynes

3.2 Brønsted base/acid catalysis

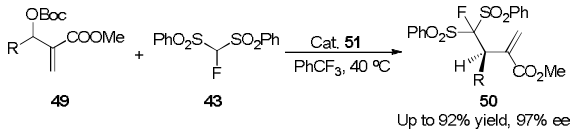
In 2011, Huang and coworkers achieved the monofluoromethyaltion of Morita–Baylis–Hillman carbonates (MBH carbonates) **49** with FBSM **43** catalyzed by $(DHQD)_2AQN$ (Scheme 15).[29] Interestingly, a convenient work-up procedure can give the desired product as a pure enantiomer. A simple filtration and the subsequent washing of the residue with cold toluene/petroleum ether give the product with > 99.9% ee. They compared the reactivity of BSM [bis(phenylsulfonyl)methane, $(PhSO_2)_2CH_2$] with FBSM and found that the reactivity of FBSM was lower than BSM in this conversion.



Scheme 15. Asymmetric monofluoromethylation of MBH carbonates using Huang's procedure

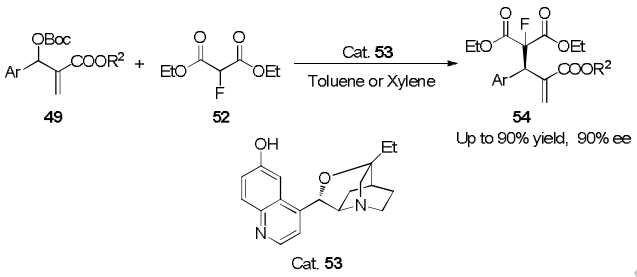
Almost at the same time, the group of Shibata reported the same reaction with the utilization of the same catalyst (Scheme 16).[30] The slightly different reaction conditions include reaction solvent and temperature. Shibata and coworkers used a different work-up procedure, resulting in higher yields and lower ee. After the reaction was completed, the reaction mixture was subjected to

flash column chromatography to give the desired product. But in Huang's case,[29] the crude product was washed with cold solvent so that the minor enantiomer was washed away, meaning that the reaction yield would be lowered and the ee value would be increased.



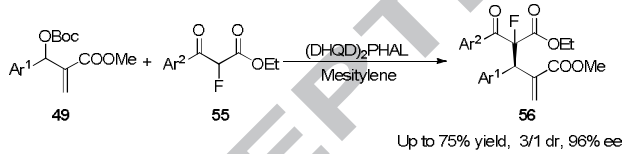
Scheme 16. Asymmetric monofluoromethylation of MBH carbonates using Shibata's procedure

Rios and coworkers described the monofluoroalkylation of MBH carbonates **49** with 2-fluoromalonate **52** catalyzed by β-isocupreidine (Cat. **53**) (Scheme 17).[31] The electronic effect of the substituent on phenyl group (Ar group) in the substrates **49** shows an important effect on the enantioselectivity. The electron-donating group results in good yield and good ee, but electron-withdrawing group leads to lower ee.



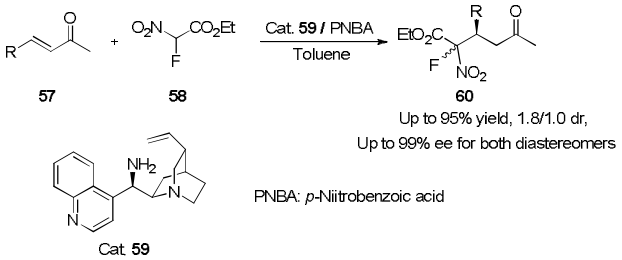
Scheme 17. Asymmetric monofluoromethylation of MBH carbonates

Monofluoroalkylation of MBH carbonates **49** with α-fluoro-β-keto esters **55** catalyzed by $(DHQD)_2PHAL$ was recently reported by Tan and coworkers (Scheme 18).[32] Even though the diastereoselectivity was low (3/1 to 4/1 dr), the enantioselectivity was excellent in many cases.



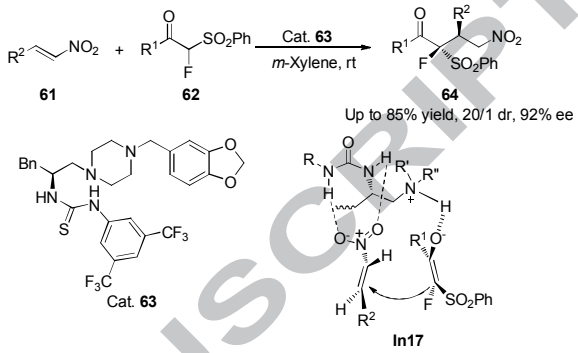
Scheme 18. Asymmetric monofluoromethylation of MBH carbonates

Zhao and coworkers demonstrated the monofluoroalkylation of α,β-unsaturated ketones **57** with α-fluoro-α-nitro esters **58** via Michael addition (Scheme 19).[33] The reaction can construct two stereogenic centers, but the diastereoselectivity was quite low. The two diasteromers in each reaction could be separated by flash column chromatography and both of them were obtained in excellent enantioselectivity.



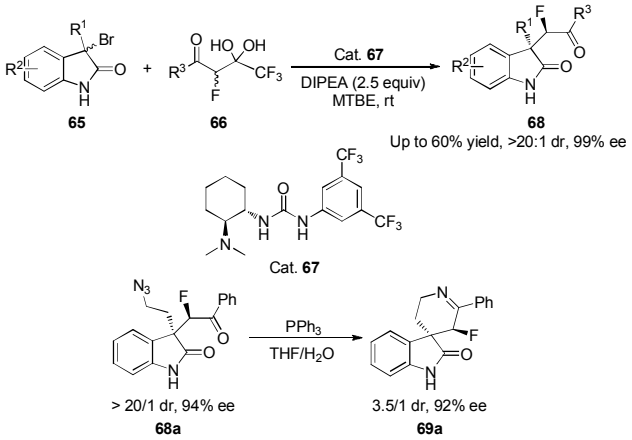
Scheme 19. Asymmetric monofluoroalkylation of α,β-unsaturated ketones

Soon afterwards, the group of Zhao further extended the Michael addition strategy to achieve the monofluoroalkylation of nitroolefins **61** with α-fluoro-α-phenylsulfonyl ketones **62** (Scheme 20).[34] In this conversion, the diastereoselectivity and enantioselectivity were excellent in most cases. On the basis of the absolute configuration of one of major product determined by X-ray crystallographic analysis, they propose a possible transition state **In17** to account for the stereochemical results.



Scheme 20. Asymmetric monofluoroalkylation of nitroolefins

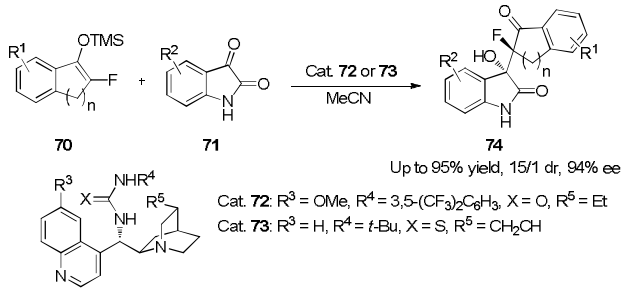
Trifluoromethyl α-fluorinated β-keto *gem*-diol (**66**) can be used as an efficient monofluoroalkylating reagent to achieve asymmetric monofluoroalkylation of 3-bromooxindoles (**65**) catalyzed by Takemono's catalyst (Cat. **67**) (Scheme 21).[35] This conversion affords the desired products in excellent diastereoselectivity and excellent enantioselectivity starting from two racemic substrates under mild conditions. The synthetic utility of this methodology was further illustrated by the conversion of one of the monofluoroalkylation products (**68a**) into 5'-fluorinated 3,4'-piperidyl spirooxindole (**69a**), a derivative which shows potential in clinical efficiency in nervous system diseases.



Scheme 21. Asymmetric monofluoroalkylation of 3-bromooxindoles

Very recently, Zhou et al. disclosed the monofluoroalkylation of isatins **71** with monofluorinated silyl enol ethers **70** via an organocatalytic Mukaiyama-Aldol reaction (Scheme 22).[36] The reactions proceeded slowly to afford the expected products in moderate to high yields and with good to high stereoselectivity. Both the yield and stereoselectivity were dramatically decreased for the case of *N*-methyl protected substrate, suggesting that the free N-H in substrate **71** is essential for good results. The acyclic fluorinated silyl enol ether is not suitable for this reaction under

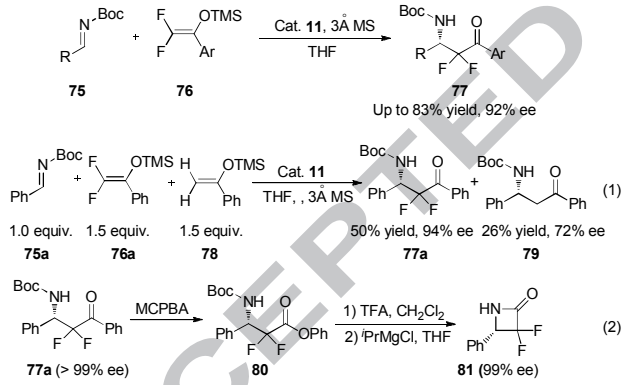
standard conditions, as the corresponding product was obtained in much lower yield and diastereoselectivity.



Scheme 22. Asymmetric monofluoroalkylation of isatins

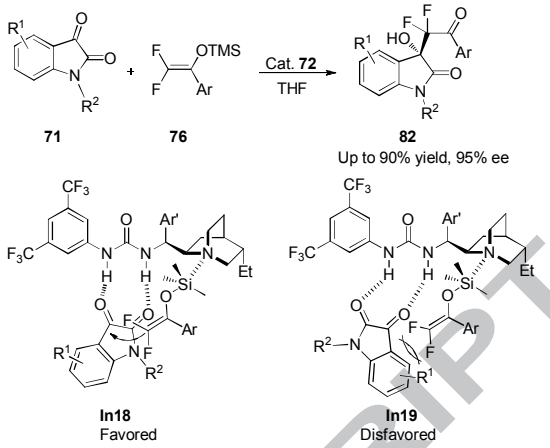
4 Asymmetric organocatalytic *gem*-difluoroalkylation

The studies on asymmetric organocatalytic *gem*-difluoroalkylation remained largely unexplored. In 2011, Akiyama and coworkers reported the chiral phosphoric acid catalyzed *gem*-difluoroalkylation of *N*-Boc imine **75** with difluoroenol silyl ethers **76** via Mannich-type reaction (Scheme 23).[37] The reaction is applicable to aromatic and heteroaromatic aldimines (**75**), but not suitable for aliphatic aldimine. The effect of fluorine substituent was disclosed by comparing the reactivity of **76a** with non-fluorinated analogue **78**. Although it was expected that **76a** would be less reactive than **78** due to the –I effect and +Iπ effect of fluorine, competitive experiments with **76a** and **78** revealed that **76a** is much more reactive than **78** (eq. 1, Scheme 23). The synthetic utility of this *gem*-difluoroalkylation reaction was demonstrated by converting one of the products **77a** into 3,3-difluoroazetidin-2-one **81**, a derivative which might be used as a pharmaceutically important target as well as a synthetic building block (eq.2, Scheme 23).



Scheme 23. Asymmetric *gem*-difluoroalkylation of *N*-Boc imine

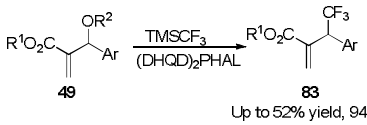
Zhou et al. also used difluoroenol silyl ethers **76** as *gem*-difluoroalkylating reagent to achieve *gem*-difluoroalkylation of isatins **71** catalyzed by Brønsted base **72** (Scheme 24).[38] The reaction is quite effective for α-aromatic group substituted difluoroenol silyl ethers (**76**), but not suitable for α-aliphatic group substituted difluoroenol silyl ethers because aliphatic ether can't be prepared as pure compounds and can only be isolated as mixture with DMF, a solvent which was found to have negative effect on both the reactivity and enantioselectivity of the *gem*-difluoroalkylation reaction. In contrast to their results for monofluoroalkylation of isatines **71** (Scheme 22),[36] the free N-H in substrate **71** is not essential in this work. *N*-Methyl protected isatines **71** can also be converted into the desired products in good yields with high enantioselectivity. They propose a possible transition state **In18** to account for the absolute configuration of products. Transition state **In19** is disfavored due to steric effect.



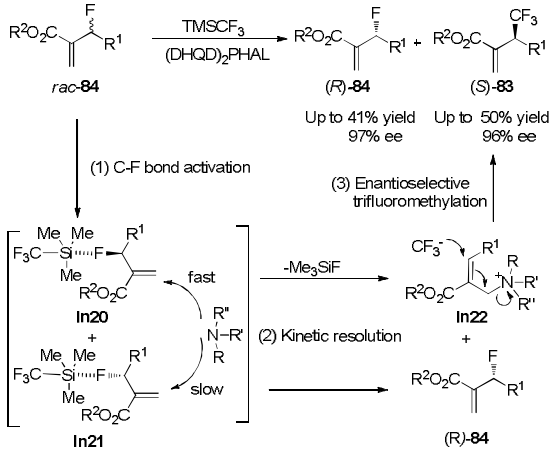
Scheme 24. Asymmetric *gem*-Difluoroalkylation of isatins

5 Asymmetric organocatalytic trifluoromethylation

In 2011, the groups of Shibata and Jiang independently disclosed the trifluoromethylation of MBH carbonates **49** with Ruppert-Prakash reagent $TMSCF_3$ catalyzed by $(DHQD)_2PHAL$ with high enantioselectivity (Scheme 25).[39] On the basis of these results, Shibata and coworkers further developed a "kill two birds by one stone" strategy to realize kinetic resolution of allyl fluorides by an enantioselective allylic trifluoromethylation of racemic MBH-type allyl fluorides **84** via organocatalysis (Scheme 26).[40] They propose that the kinetic resolution/trifluoromethylation proceeds via three steps, starting from C-F bond activation of *rac*-**84** by coordination to the silicon atom of $TMSCF_3$. The subsequent S_N2' process through the addition of $(DHQD)_2PHAL$ to the alkene moiety of **In20** or **In21** is the rate-determining step. Kinetic resolution of *rac*-**84** occurs because the catalyst $(DHQD)_2PHAL$ prefers to attack **In20** to release Me_3SiF and produce intermediate **In22** while **In21** remains intact. A second S_N2' substitution of **In22** with CF_3^- affords the final trifluoromethylation product (*S*)-**83**.

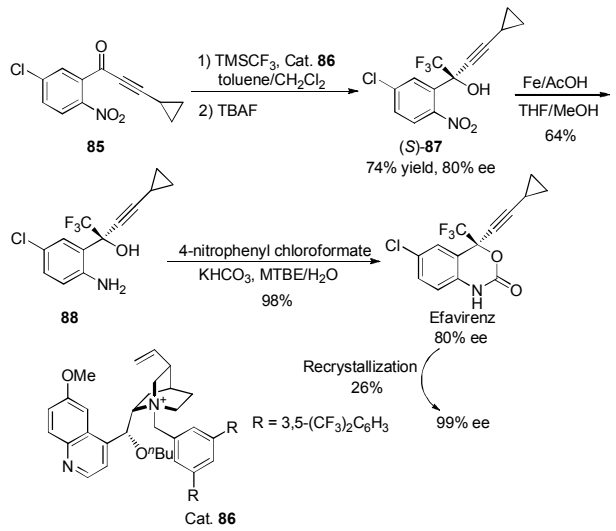


Scheme 25. Asymmetric trifluoromethylation of MBH carbonates



Scheme 26. Kinetic resolution of allyl fluorides by an enantioselective allylic trifluoromethylation

Recently, the group of Shibata reported the asymmetric synthesis of Efavirenz, which was approved by the FDA in 1998 to be used as a potent non-nucleoside reverse transcriptase inhibitor of HIV-1 and has been used in combination with other antiretrovirals for the treatment of HIV infection, beginning with the organocatalyzed enantioselective trifluoromethylation of ketone **85** (Scheme 27).[41] The following reduction of nitro group in trifluoromethylation product (*S*)-**87** and cyclization reaction give Efavirenz with 80% ee. A single recrystallization easily increased the ee value from 80% ee to 99% ee.



Scheme 27. The asymmetric synthesis of Efavirenz

6 Conclusions and perspectives

The past decade has witnessed the significant advances of asymmetric organocatalytic fluorination and fluoroalkylation. Among these reactions, fluorination and trifluoromethylation have been intensively studied, whereas monofluoroalkylation and *gem*-difluoroalkylation have been much less explored and remained challenging. Even though a variety of electrophilic and nucleophilic fluorinating reagents are commercially available, electrophilic fluorination, usually employing Selecfluor or NFSI as fluorine source, has been the mostly used methods for asymmetric organocatalytic fluorination. In contrast, asymmetric organocatalytic trifluoromethylation usually utilizes nucleophilic trifluoromethylating reagents. Asymmetric trifluoromethyaltion of carbonyl compounds, imines and MBH carbonates have been the subject of intense research.[9j] The development of efficient and generally applicable monofluoroalkylating and *gem*-difluoroalkylating reagents, especially monofluoromethylating and difluoromethylating reagents, are the main issues that remain to be addressed for the asymmetric organocatalytic monofluoroalkylation and *gem*-difluoroalkylation.

So far, the asymmetric organocatalytic fluorination and fluoroalkylation usually construct only one or two stereogenic centers. More efforts should be directed towards the construction of multi-stereogenic centers and multi-membered ring(s) via tandem reactions. More importantly, the exploration of new organocatalysis concepts is also highly desirable.

Acknowledgements

We thank the National Natural Science Foundation (21032006, 21172240), the 973 Program of China (2012CBA01200), the Chinese Academy of Sciences, Science and Technology Commission of Shanghai Municipality (14ZR1448800).

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