Heterocycles Hot Paper

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Asymmetric Carbene-Catalyzed Oxidation of Functionalized Aldimines as 1,4-Dipoles

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Abstract: *The use of functionalized aldimines has been demonstrated as newly structural 1,4-dipole precursors under carbene catalysis. More importantly, enantiodivergent organocatalysis has been successfully developed using carbene catalysts with the same absolute configuration, leading to both (R)- and (S)- enantiomers of six-membered heterocycles with quaternary carbon centers. This strategy features a broad substrate scope, mild reaction conditions, and good enantiomeric ratio. DFT calculation results indicated that hydrogen bond C−H···F interactions between the catalyst and substrate are the key factors for controlling and even switching the enantioselectivity. These new 1,4-dipoles can also react with isatin and its imines under carbene catalysis, allowing for access to the spiro oxindoles with excellent enantiomeric ratios.*

Introduction

Asymmetric catalysis has proven to be the best method for the construction of chiral molecules from simple racemic raw materials.[1] In this field, N-heterocyclic carbene (NHC, or carbene) catalysis, one of the most powerful methods of organocatalysis, has been studied extensively with impressive advances over recent decades.[2,3] In sharp contrast to the well-developed activation of aldehydes, enals and esters promoted by carbene organocatalysis, similar activation of easily available aldimines has been largely unrecognized due to their relatively low reactivity.[4] Although considerable effort has been devoted to this field, the reactions involving NHC-activated aldimines are mainly limited to Stetter and oxidative reactions.[4] Surprisingly, only two enantioselective reactions, intramolecular cyclization and aza-Stetter reaction based on an umpolung reaction of imines with a chiral carbene, have been successfully developed to date.[4k,l] Furthermore, in all the developed reactions the in situ carbon of the imine moiety acts as the nucleophile and reacts with other electrophilic substrates; this area of research is still in its infancy. Further development of new activation modes of aldimines catalyzed by NHC, especially in an enantioselective manner, is of high importance.

As part of our ongoing interest in organocatalysis,[5] on the basis of our previous work on carbene-activated aldimines or iminiums,[4h,i,o] we planned to design a new type of aldimine containing a nucleophile moiety. We envisaged that this functionalized aldimine could be used as a new dipole via reverse polarity of the imine moiety to form an *aza*-Breslow intermediate, followed by its oxidation. Importantly, the proposed new dipole intermediate derived from the aldimine, is radically different from the well-known intermediates derived from aldehydes, and esters. Compared with the well-developed strategy of connecting a nucleophilic (or eletrophilic) moiety to the carbon atom of a carbonyl group,[3-h,i,6] connecting a nucleophilic moiety to the nitrogen atom of an imine moiety remains underdeveloped. However, the distinct difference in their structures may lead to big differences in their chemical properties. If successful, this methodology will undoubtedly greatly enhance the development of carbene chemistry.

We envisaged that aldimines **1** derived from 2-amino imidazoles and benzaldehydes, with a free amino group, might be suitable aldimines as 1,4-dipole precursors. The carbene would attack aldimines **1** to generate aza-Breslow intermediate **I** following deprotonation under basic conditions, which could be oxidized to give intermediate **II**, demonstrated by our group.[4o] Deprotonation of intermediate **II** forms 1,4-dipolar intermediate **III**, which would undergo [4+2] annulation with activated ketones **2** to deliver the products **3** and release the carbene. Some challenges must be overcome for this strategy to be successful, including (i) avoiding background reactions. Aldimines **1** could form a 1,4-dipole via deprotonation under basic condtions in absence of carbene catalyst, and this might reacted directly with activated ketones **2**. (ii) realizing good enantioselectivity. The nucleophilic nitrogen anion in intermediate **III** is not only far away from the chiral carbene moiety, but is also different from previously reported intermediates generated from aldehydes under carbene catalysis, meaning that achieving satisfactory enantioselectivity may be challenging. Herein, we present the successful development of a novel strategy for asymmetric NHC-catalyzed 1,4-dipolar cycloaddition of aldimines under mild conditions. More importantly, enantiodivergent carbene organocatalysis was realized with the same absolute configuration catalyst when trifluoromethyl ketone was used in this transformation.

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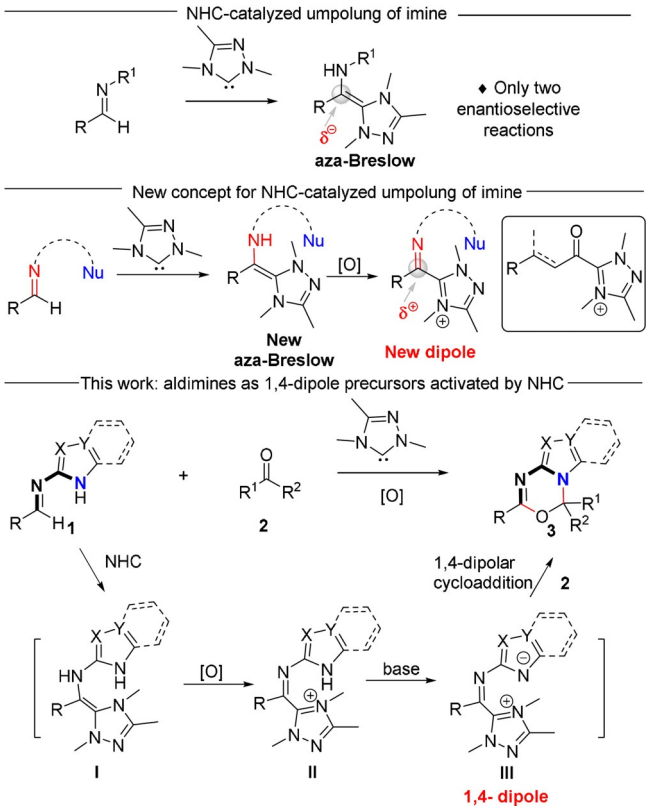


Figure 1. Activation of aldimines under carbene organocatalysis.

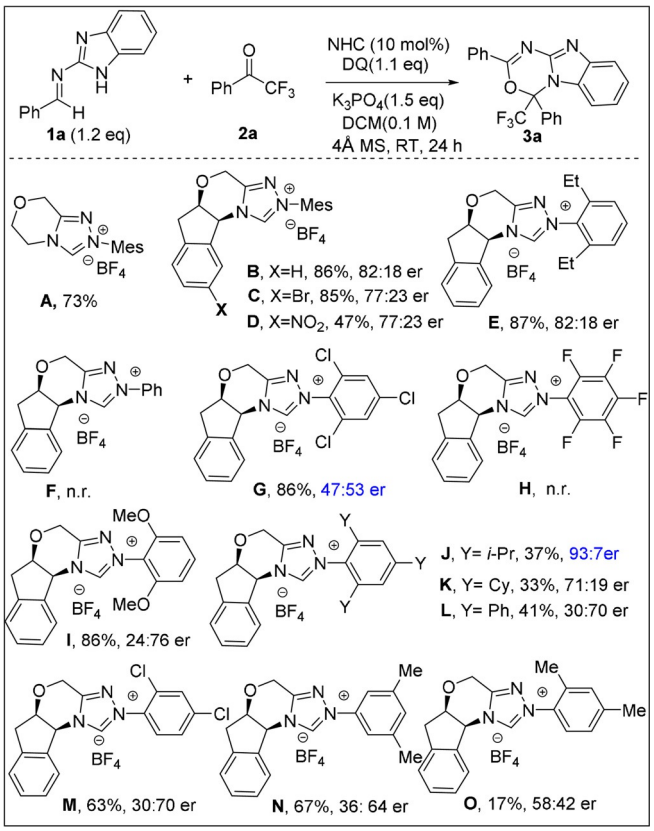


Figure 2. Catalyst Screening.

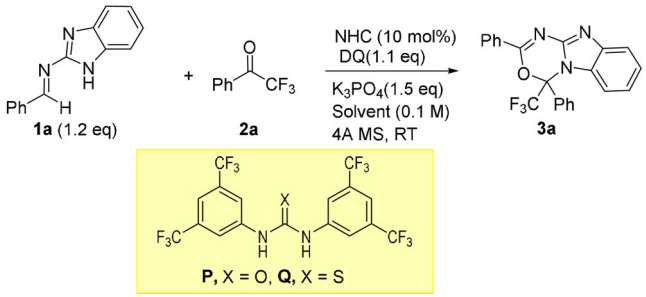
Results and Discussion

We initially tested this design with easily available aldimine **1a**, derived from 2-amino benzimidazole and benzaldehyde, and trifluoroacetophenone **2a** in presence of the racemic triazolium NHC **A** with K_2CO_3 as the base in THF at room temperature. To our delight, the desired product **3a** was obtained in 73% yield. Encouraged by this promising result, the enantioselectivity of the catalytic reaction was investigated. Base and solvent screening showed that K_3PO_4 and DCM were the most effective, respectively, affording product **3a** in 86% yield with an enantiomeric ratio (er) of 82:18 when aminoindanol-derived triazolium NHC **B** was used (for details, see Supporting Information). To further improve the enantiomeric ratio, we subsequently investigated chiral catalysts as shown in Figure 2.

Introducing a Br atom (**C**) or a nitro group (**D**) on the indane moiety did not have a positive influence, and the catalyst with an N-(2, 6-$Et_2C_6H_3$) substituent (**E**) gave similar outcomes. However, no desired product was found when catalysts with N-Ph (**F**) and N-C_6F_5 (**H**) substituents were used. Further catalyst screening indicated that NHC **J** with N-(2, 4, 6-*i*-$Pr_3C_6H_2$) substituent gives the best enantiomeric ratio (93:7 er). Surprisingly, the catalyst **G** with N-(2,4,6-$Cl_3C_6H_2$) substituent gave the opposite enantiomeric ratio (47:53 er). This indicated that it may be possible to realize an enantiodivergent organocatalytic method by slight modification of the structure of a catalyst while keeping the same absolute configuration. Besides NHC **G**, NHC **I** bearing an N-(2, 6-$MeO_2C_6H_3$) substituent and NHC **L** with an N-(2,4,6-$Ph_3C_6H_2$) substituent also gave the enantiomeric ratios to catalyst **J**. Encouraged by these unexpected results, NHCs **K**–**N**, with variation of N-substituents, were prepared and further investigated. The results indicated that this interesting enantiodivergent phenomenon still exists; however, it seems that there is no predictable pattern from looking at the current results. These surprising results prompted us to further optimize the reaction conditions; the key results are summarized in Table 1. Increasing the loading of NHC **J** to 20 mol% significantly improved the product yield (85%). Subsequently, several additives, such as $Sc(OTf)_3$, LiCl, $Mg(OTf)_2$, $Mg(O$*t*$-Bu)_2$, $Cu(OTf)_2$, HOBt, $Ti(O$*i*$-Pr)_4$, **P**, and **Q** were screened, showing that the enantiomeric ratio could not be further improved in this way. We also investigated the influence of the additives on the catalysts which gave the opposite enantiomeric ratio. Delightingly, the enantiomeric ratio could be significantly improved when the NHC **G** was used with thiourea **Q** as a co-catalyst, delivering the product **3a** in 90% yield with 10:90 er. However, co-catalyst **Q** proved to be detrimental to this transformation for other catalysts. Lowering the temperature to 0 °C improved the enantiomeric ratio considerably. Using a mixed solvent (DCM: hexane = 1:1) further improved enantiomeric ratio (6:94 er).

The above obtained results clearly indicate that these functionalized aldimines could be enantioselectively activated by NHC as 1,4-dipole precursors. More importantly, enantiodivergent organocatalysis, was successfully achieved using NHC catalysts with the same absolute configuration in

Table 1: Optimization of the reaction conditions.[a]



Entry	NHC	Additive	Solvent	Yield[%][b]	er[c]
1[d]	**J**	–	DCM	85	93:7
2	**J**	$Sc(OTf)_3$	DCM	43	91:9
3	**J**	LiCl	DCM	40	91:9
4	**J**	$Mg(OTf)_2$	DCM	35	91:9
5	**J**	$Mg(Ot\text{-}Bu)_2$	DCM	73	89:11
6	**J**	$Cu(OTf)_2$	DCM	n.r.	–
7	**J**	HOBt	DCM	55	92:8
8	**J**	$Ti(Oi\text{-}Pr)_4$	DCM	70	91:9
9	**J**	**P**	DCM	n.r.	–
10	**J**	**Q**	DCM	<10	–
11	**G**	**Q**	DCM	90	10:90
12	**I**	**Q**	DCM	<10	–
13	**L**	**Q**	DCM	32	34:66
14	**M**	**Q**	DCM	<10	–
15	**N**	**Q**	DCM	<10	-
16[e]	**G**	**Q**	DCM	91	8:92
17[e,f]	**G**	**Q**	DCM/Hex.	88	6:94

[a] **1a** (0.12 mmol), **2a** (0.1 mmol), NHC precursor (10 mol%), K_3PO_4 (1.5 equiv), DCM (0.1 M), 4 Å MS (100 mg), 30°C, 48 h. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC. [d] 20 mol% NHC precursor was used. [e] 0°C was used. [f] DCM/Hexane = (v/v = 1:1, 0. 1 M).

this transformation (entry 1 vs. entry 17). Notably, the synthesis of both enantiomers of chiral compounds catalyzed by the catalyst with the same absolute configuration represents one of the most fundamental challenges in organic chemistry.[3k,7]

With acceptable optimized conditions in hand (Table 1, entries 1 and 17), we then evaluated the scope of the enantiodivergent reaction for aldimine substrates by using trifluoroacetophenone **2a** as a model substrate (Table 2). For aldimine aldehyde moieties with aromatic rings bearing electron-donating groups (such as Me, MeO) or electron-withdrawing groups (such as F, Cl, Br, COOEt, CN, CF_3), all the reactions proceeded smoothly to generate both (*R*)- and (*S*)-enantiomers of the cycloaddition products (**3a–o**) in acceptable to excellent yields (43–91% for the (*R*)-enantiomers and 51–87% for the (*S*)-enantiomers) and enantiomeric ratios (92:8–96:4 er for the (*R*)-enantiomers and 85:15–95:5 er for the (*S*)-enantiomers). Aldimine aldehyde moieties bearing naphthalene or heteroaromatic rings (3-pyridinyl) also worked efficiently as well, affording the corresponding products **3p & 3q** with good outcomes (86%, 87% yields and 94:6, 91:9 er for the (*R*)-enantiomers, and 85%, 83% yields and 92:8, 94:6 er for the (*S*)-enantiomers, respectively). An aldimine imine moiety with a symmetric substituent on the benzoimidazole ring worked efficiently, giving the poduct **3r** with acceptable outcomes. Subsequently, the generation of trifluoromethyl ketones was evaluated. Trifluoromethyl aryl ketones bearing substituents with a variety of electronic and steric properties on the aromatic ring were well tolerated, generating the corresponding products **3s–3y** (72–86% yields and 87:13–97:3 er for the (*R*)-enantiomers, and 67–81% yields and 87:13–93:7 er for the (*S*)-enantiomers). Heteroaryls (such as pyridinyl, benzofuryl, benzothienyl, quinolyl, and carbazolyl) also worked efficiently, leading to both enantiomers of **3aa–ad** (57–93% yields and 67:33–96:4 er for the (*R*)-enantiomers, and 53–85% yields and 88:12–94:6 er for the (*S*)-enantiomers). Notably, a trifluoromethyl alkyl ketone, was also a suitable substrate for this transformation, resulting in the formation of the desired product **3ae** with an acceptable outcome. Pleasingly, CF_2H, CF_2Cl, and CF_2Br groups were all compatible with this transformation, providing access to both (*R*)- and (*S*)-enantiomers of **3af–3ah** (73–90% yields and 91:9–93:7 er for the (*R*)-enantiomers, and 45–83% yields and 83:17–90:10 er for the (*S*)-enantiomers). It should be noteworthy that the resulting products **3** bearing CF_3-containing quaternary carbon centers. Actually, trifuoromethyl (CF_3) are identified as one of most valuable functional groups and widely used in pharmaceutical chemistry, materials science, and agrochemistry.[8]

To discover the key factors for determining the enantioselectivity, we have performed DFT calculations at the M06-2X/6-31G(d, p)/IEFPCM$_{DCM/Hex}$ level as well as non-covalent interaction (NCI) and atoms in molecules (AIM) analyses for comparing the stereoselective C–N bond formation transition states. As shown in Figure 3, two C–H···F hydrogen bond interactions (2.22 and 2.40 Å) are identified in **TSS$_{Me}$**, but only

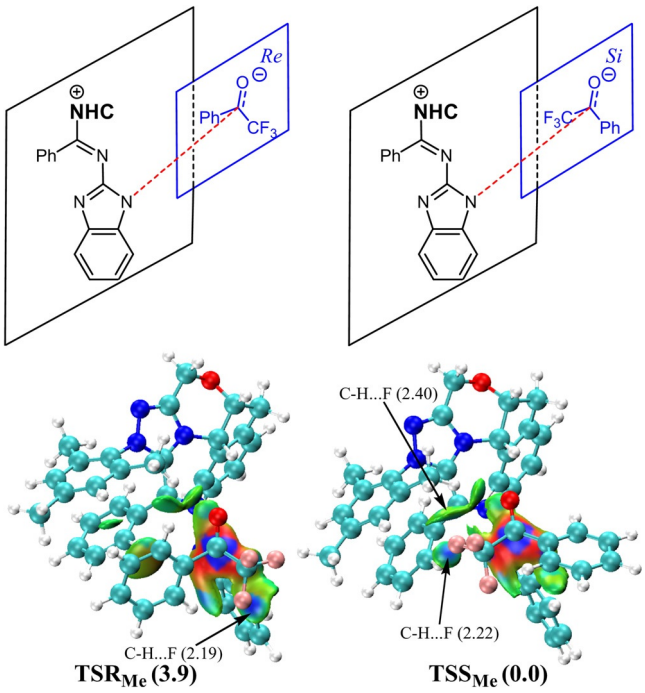
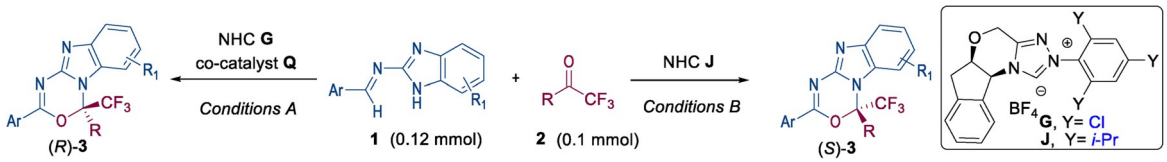
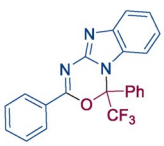


Figure 3. NCI analyses for the stereoselective C–N bond formation transition states under NHC **B** catalysis (energy in kcal mol^{-1} and distance in angstrom).

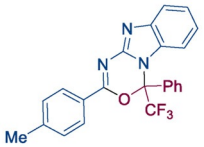
Table 2: Scope of reaction.[a,b]



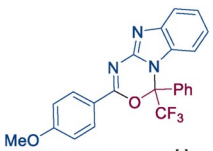
Imines scope



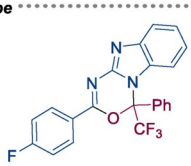
(*R*)-**3a**, 91%, 94:6 er
(*S*)-**3a**, 85%, 93:7 er



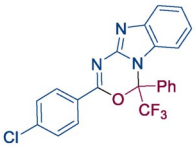
(*R*)-**3b**, 72%, 96:4 er
(*S*)-**3b**, 87%, 93:7 er



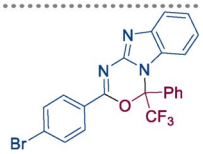
(*R*)-**3c**, 76%, 94:6 er [c]
(*S*)-**3c**, 68%, 89:11 er [e]



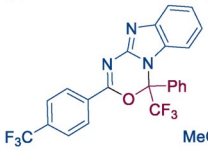
(*R*)-**3d**, 81%, 94:6 er
(*S*)-**3d**, 83%, 94:6 er



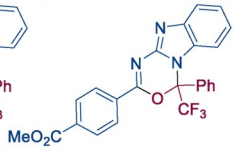
(*R*)-**3e**, 88%, 93:7 er [c]
(*S*)-**3e**, 81%, 91:9 er



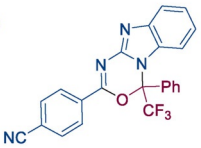
(*R*)-**3f**, 90%, 93:7 er [c]
(*S*)-**3f**, 72%, 92:8 er



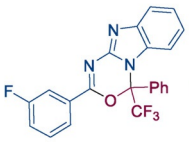
(*R*)-**3g**, 86%, 96:4 er
(*S*)-**3g**, 75%, 85:15 er



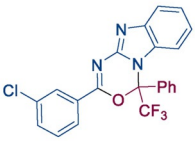
(*R*)-**3h**, 91%, 96:4 er
(*S*)-**3h**, 81%, 95:5 er



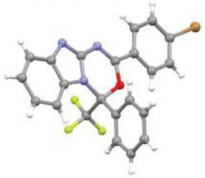
(*R*)-**3i**, 90%, 96:4 er
(*S*)-**3i**, 87%, 93:7 er



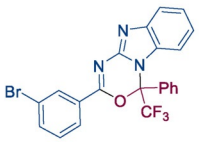
(*R*)-**3j**, 90%, 95:5 er
(*S*)-**3j**, 78%, 93:7 er



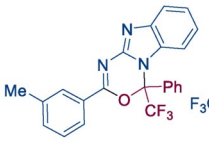
(*R*)-**3k**, 43%, 92:8 er [c]
(*S*)-**3k**, 75%, 93:7 er



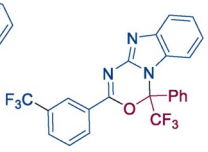
X-ray of (*R*)-**3f**



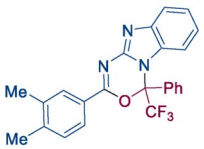
(*R*)-**3l**, 86%, 94:6 er
(*S*)-**3l**, 81%, 93:7 er



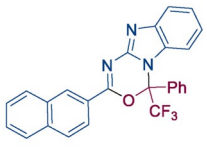
(*R*)-**3m**, 82%, 93:7 er
(*S*)-**3m**, 68%, 89:11 er [e]



(*R*)-**3n**, 81%, 95:5 er
(*S*)-**3n**, 73%, 92:8 er



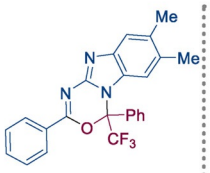
(*R*)-**3o**, 73%, 93:7 er [d]
(*S*)-**3o**, 51%, 92:8 er [e]



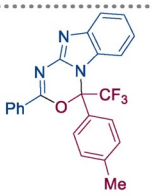
(*R*)-**3p**, 86%, 94:6 er
(*S*)-**3p**, 85%, 92:8 er

(*R*)-**3q**, 87%, 91:9 er
(*S*)-**3q**, 83%, 94:6 er

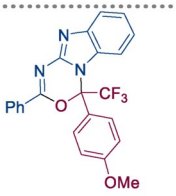
Ketones scope



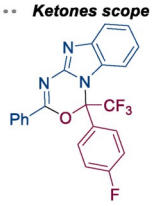
(*R*)-**3r**, 71%, 95:5 er [d]
(*S*)-**3r**, 53%, 90:10 er [e]



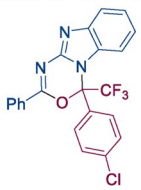
(*R*)-**3s**, 83%, 96:4 er
(*S*)-**3s**, 67%, 93:7 er [e]



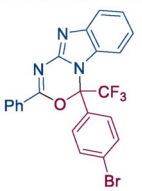
(*R*)-**3t**, 72%, 97:3 er
(*S*)-**3t**, 65%, 93:7 er [e]



(*R*)-**3u**, 86%, 92:8 er
(*S*)-**3u**, 78%, 89:11 er

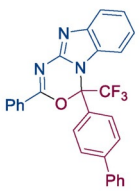


(*R*)-**3v**, 86%, 91:9 er [f]
(*S*)-**3v**, 77%, 86:14 er

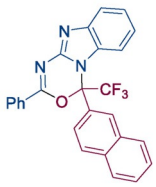


(*R*)-**3w**, 85%, 90:10 er [f]
(*S*)-**3w**, 73%, 87:13 er

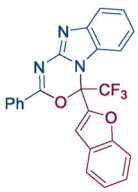
(*R*)-**3x**, 83%, 93:7 er
(*S*)-**3x**, 71%, 92:8 er



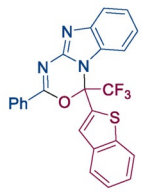
(*R*)-**3y**, 83%, 92:8 er
(*S*)-**3y**, 81%, 91:9 er



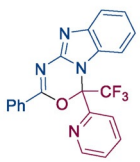
(*R*)-**3z**, 85%, 90:10 er
(*S*)-**3z**, 81%, 93:7 er



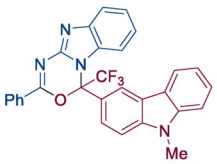
(*R*)-**3aa**, 92%, 67:33 er
(*S*)-**3aa**, 85%, 88:12 er



(*R*)-**3ab**, 78%, 75:25 er
(*S*)-**3ab**, 73%, 94:6 er

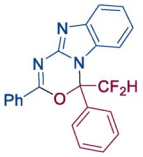


(*R*)-**3ac**, 93%, 90:10 er
(*S*)-**3ac**, 85%, 93:7 er



(*R*)-**3ad**, 57%, 96:4 er [c]
(*S*)-**3ad**, 53%, 91:9 er [e]

(*R*)-**3ae**, 87%, 95:5 er
(*S*)-**3ae**, 83%, 84:16 er [g]



(*R*)-**3af**, 90%, 91:9 er
(*S*)-**3af**, 83%, 83:17 er

(*R*)-**3ag**, 78%, 93:7 er [c]
(*S*)-**3ag**, 68%, 90:10 er [e]

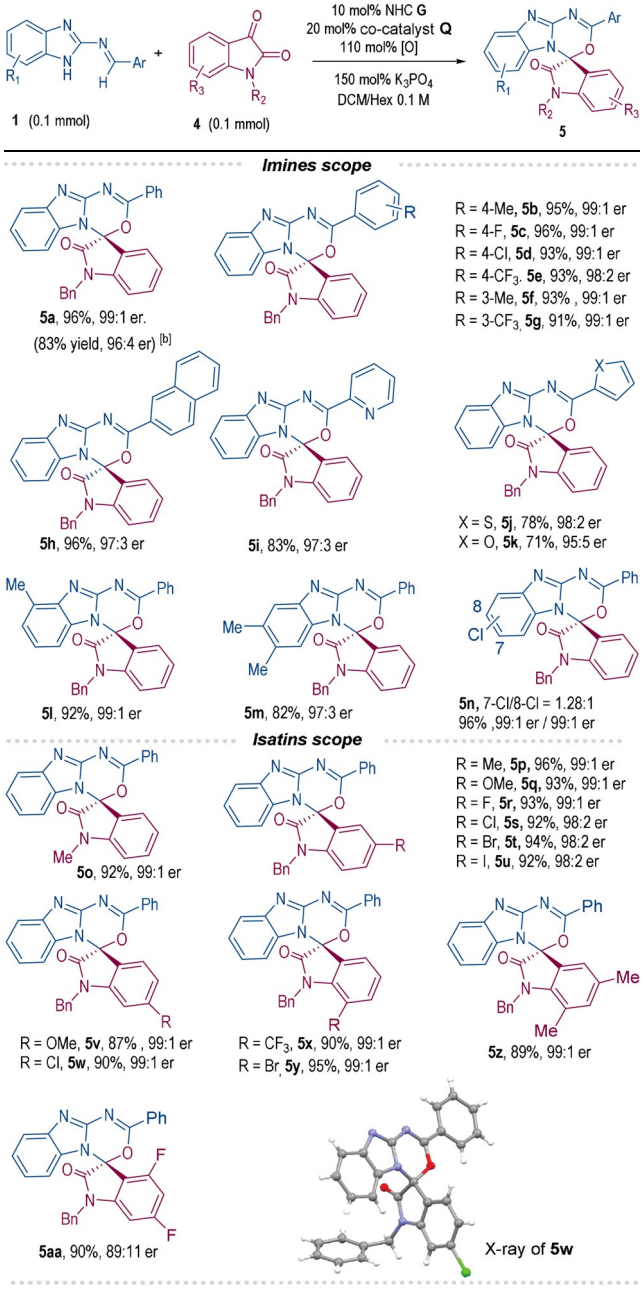
(*R*)-**3ah**, 73%, 92:8 er [c]
(*S*)-**3ah**, 45%, 86:14 er [e]

[a] Reaction conditions A: Aldimine **1** (0.12 mmol), ketones **2** (0.1 mmol), NHC precursor **G** (10 mol%), co-catalyst **Q** (20 mol%), K_3PO_4 (1.5 equiv), DCM/Hexane = (v/v = 1:1, 0. 1 M), 4 Å MS (100 mg), 0 °C, 48 h. [b] Reaction conditions B: Aldimine **1** (0.12 mmol), ketones **2** (0.1 mmol), NHC precursor **J** (20 mol%), K_3PO_4 (1.5 equiv), DCM (0.1 M), 4 Å MS (100 mg), 30 °C, 48 h. [c] Reaction was performed at rt for 48 h. [d] Reaction was performed at 0 °C for 72 h. [e] Reaction was performed at rt for 72 h. [f] Reaction was performed at −10 °C for 48 h. [g] 1.0 mL THF was used as solvent.

one C–H···F hydrogen bond interaction (2.19 Å) exists in $\mathbf{TSR_{Me}}$ according to the AIM analysis (Table S4 of SI), indicating the C–H···F hydrogen bond interaction should be responsible for the favorability of $\mathbf{TSS_{Me}}$. When the Cl groups were introduced in the catalyst (i.e. NHC **G**), all the identified C–H···F hydrogen bond interactions were significantly weakened in both transition states $\mathbf{TSS_{Cl}}$ and $\mathbf{TSR_{Cl}}$ (Table S5 of SI), and the corresponding *R*-configured isomer pathway associated with transition state $\mathbf{TSR_{Cl}}$ is slightly more energetically favorable, showing that the enantioselectivity can be switched by weakening the C–H···F hydrogen bond interactions. Inspired by this conclusion, we have assumed that the enantioselectivity would be unswitchable when the -CF_3 group is excluded in the substrate (such as isatin), which has been confirmed in both theory (Tables S6,7 of SI) and the following experiments. The additional calculations demonstrate that the enantioselectivity can be significantly improved in the presence of urea (Table S8 of SI), which is also in agreement with the experimental observation. Furthermore, we considered and compared the oxidative processes of the aldimine with or without the presence of NHC catalyst. The calculated results (Figures S1 and S2 of SI) indicate that the oxidation (i.e. the transfer of $1H^+$ and $2e^-$ to DQ oxidant) only can occur via transition state $\mathbf{TS_{Ox}}$ with an energy barrier of 14.4 kcal mol^{-1} with the presence of NHC, which is consistent with the experimental observation.

After successfully establishing functionalized aldimines as 1,4-dipole precursors under carbene catalysis, to further demonstrate the generality of the current strategy, other activated ketones (such as isatin) were investigated; the result are summarized in Table 3. Gratifyingly, the desired chiral product **5a** was obtained in 96% yield with excellent enantiomeric ratio (99:1 er) when NHC **G** was used with co-catalyst **Q** (for details, see Supporting Information). Unfortunately, enantiodivergent organocatalysis could not be realized when isatin was used as the reactant. Without the co- catalyst, both yield and enantiomeric ratio decreased considerably. With acceptable optimized conditions in hand, the generation and limitations of the aldimines and isatins for this transformation were investigated. As expected, aldimines with both aldehyde and imine moieties bearing various substituents with diverse electronic and steric properties on the aromatic ring were well tolerated, generating the corresponding spiro oxindoles **5a–5k** in excellent yields and enantiomeric ratios. Notably, For an aldimine imine moiety with a methyl group at the 4-position of the benzoimidazole ring, the nitrogen anion at the 1-position of the benzoimidazole ring regioselectively attacked the carbonyl group, generating a single product **5l** in 93% yield with 99:1 er. An aldimine imine moiety with a symmetric substituent on the benzoimidazole ring worked efficiently, giving the poduct **5m** in 82% yield with 97:3 er. For aldimines with the imine moiety bearing a Cl substituent at the 5- position of the benzoimdazole ring, the product **5n** was obtained in excellent yield and enantiomeric ratio, albeit with weak regioselectivity (1.28:1). Replacement of Bn with Me gave a similar outcome. Variation of substituents at the 4, 5, 6, 7-positions of the isatin ring did not influence the efficiency, delivering products

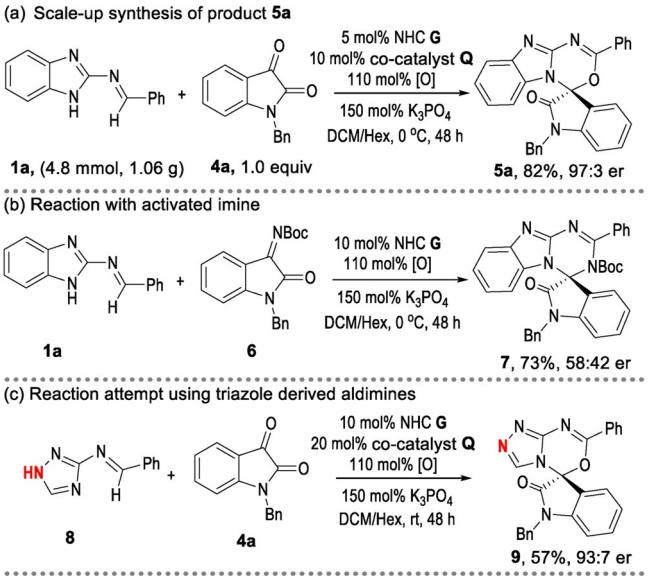
Table 3: Scope of reaction.[a]



[a] Reaction conditions: Aldimine **1** (0.1 mmol), isatins **2** (0.1 mmol), NHC precursor **G** (10 mol%), co-catalyst **Q** (20 mol%), K_3PO_4 (1.5 equiv), DCM/Hexane = (v/v = 1:1, 0. 1 M), 4 Å MS (100 mg), 0 °C, 48 h. [b] without Q.

5o–5aa in excellent yields with good to excellent enantiomeric ratios.

To demonstrate the practicality of our method, a gram-scale reaction was performed (Scheme 1). In the presence of only 5 mol% of NHC pre-catalyst **J** and 10 mol% of co catalyst thiourea **Q**, the reaction in a gram scale worked efficiently to afford spiro oxoindole **5a** in 82% yield with 97:3 er. Subsequently, further attempt showed that activated imine **6**, derived from isatin, also is suitable substrates for this transformation, generating the spiro product **7** in 73% yield,



Scheme 1. Scale-up synthesis of product **5a** and further attempts.

albiet with lower enantiomeric ratio. Interestingly, the aldimine imine mioety can be sccessfully extended to other aza-heterocyle, such as triazole, leading to the corresponding product **9** in 57% yield with 93:7 er.

Conclusion

In summary, we have addressed asymmetric NHC-catalyzed oxidative reaction of functionalized aldimines as 1,4-dipole precursors. More importantly, enantiodivergent organocatalysis has been successfully developed by using carbene catalysts with the same absolute configuration, leading to both (*R*)- and (*S*)- enantiomers of six-membered heterocycles with quaternary carbon centers. This efficient strategy features a broad substrate scope, mild reaction conditions, and good enantiomeric ratio. DFT calculation results indicated that hydrogen bond C–H···F interactions between the catalyst and substrate are the key factors for controlling and even switching the enantioselectivity. These new 1,4-dipoles can also react with isatin and its imines under carbene catalysis, allowing for access to the spiro oxindoles with excellent enantiomeric ratios. Further investigations and exploration of this catalytic process are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldimine · trifluoromethyl · dipolar cycloaddition · enantiodivergent catalysis · N-heterocyclic carbene

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