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FULL PAPER

Bifunctional N-Heterocylic Carbene-Catalyzed Highly Enantioselective Trans-Cyclopentannulation of Enals and Enones via Homoenolate

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Abstract: An efficient and flexible synthesis of a new class of chiral bifunctional NHC catalyst has been reported. These new imidazolylidene NHCs, bearing a (thio)urea function as a hydrogen bond donor promoted efficiently highly diastereoselective *trans*-cyclopentannulation of enals and enones in moderate to good yields (up to 69 % yield) along with excellent enantioselectivity (up to 96 % ee). This methodology could be applied to a large variety of substrates (30 examples).

Introduction

Nowadays, developing more sustainable chemistry seems to be essential. Various strategies have therefore been adopted in order to reduce the environmental impact of chemistry. Chemists were able to develop catalyzed transformations improving selectivity while decreasing reaction time and chemical waste.[1] Among various catalytic systems reported, organocatalysis, using a small organic molecule under mild reaction conditions, appears as a very attractive area in modern organic synthesis and is now considered the third pillar of catalysis, alongside metal catalysis and biocatalysis. The main advantages of organocatalysis lie in their tolerance towards many functional groups and therefore many types of organocatalyst have been described. For example, *N*-heterocyclic carbenes (NHCs) are a class of organocatalyst that have been studied in depth due to their efficiency in forming C-C and C-X bonds.[2] They are able to trigger non-conventional reactions thanks to the formation of reactive intermediates, such as Breslow intermediate, homoenolate intermediate, azolium enolate, acyl azolium, α,β-unsaturated acyl azolium or azolium dienenolate, generated by nucleophilic addition of the lone pair of the carbene to an aldehyde or its equivalent.[3] The first racemic reaction promoted by a thiazolium salt (precursor to NHC) is the benzoin condensation and dated since 1943 with Ukai[4] while the first umpolung reaction was described in 1832 by Wöhler and Liebig.[5] Since then, research on NHCs has intensified, and enantioselective reactions catalyzed by NHCs are now extremely efficient, thanks to the discovery of Breslow's mechanism,[6] the isolation of the first stable carbene by Bertrand[7] and Arduengo,[8] and the first example of enantioselective transformation with triazolium salt precursor.[9] Although there are manifold chiral NHC catalysts such as thiazolylidene, imidazolylidene, imidazolinylidene or triazolylidene, the latter is by far the most used in asymmetric organocatalysis. Moreover, achiral imidazolylidene derived from imidazolium salt promotes effectively racemic umpolung reactions involving homoenolate intermediate but it should be noted that only a few chiral imidazolylidene organocatalyst have been reported so far delivering poor level of enantioselectivity in most cases.[10] So, the design and synthesis of chiral imidazolium, precursor to imidazolylidene NHCs, could extend the range of reactions catalyzed by chiral NHCs. Moreover, a few triazolylidene, thiazolylidene and imidazolinylidene (saturated analogue imidazolylidene) NHC organocatalysts bearing an additional hydrogen bond donor have been reported in the literature.[11,12] For example, combination of an hydroxyl group with triazolylidene is common.[11] Amide was combined with triazolylidene[12c] or thiazolylidene.[12e-f] Furthermore, thiourea was associated with triazolylidene [12a-b] or imidazolinylidene[12d] but the results have been disappointing or still need to be enhanced to have a highly efficient chiral NHC catalyst.

To the best of our knowledge, the combination of chiral imidazolium salt precursor to imidazolylidene NHC and a thiourea function has never been reported so far. In a continuation of our research on the design and synthesis of chiral bifunctional organocatalyst[13] starting from inexpensive and commercially available precursor from the natural chiral pool, we report herein the synthesis of a new family of chiral bifunctional imidazolylidene NHC-thioureas (Figure 1) and their application in organocatalyzed asymmetric *trans*-cyclopentannulation of enals and chalcones.

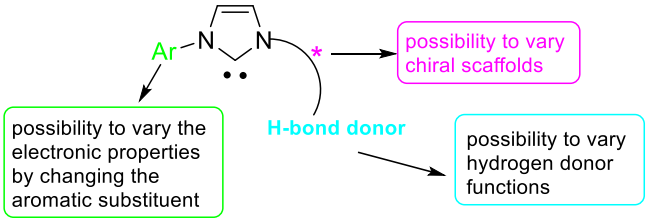
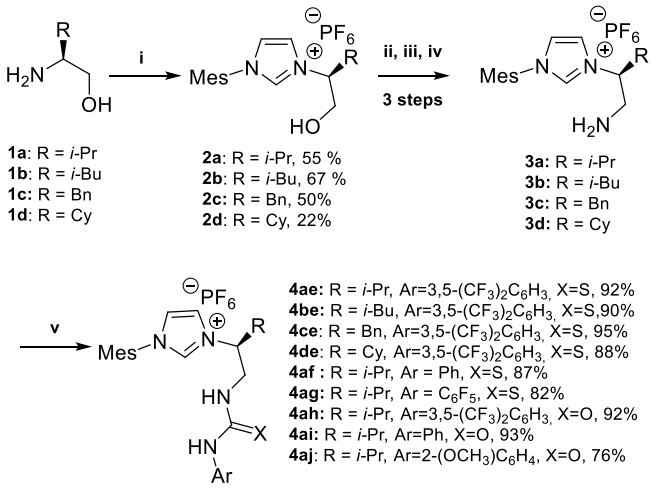


Figure 1. Design of new chiral bifunctional imidazolylidene-NHC organocatalyst.

Results and Discussion

Imidazolium scaffolds of the NHC catalyst were prepared in one step by mixing commercially available aminoalcohols, mesityl amines, formaldehyde, glyoxal and acetic acid.[14] Hydroxy-imidazolium **2a-d** were isolated in moderate yields (Scheme 1). Then amino-imidazolium **3a-d** were obtained in three steps including an activation of the hydroxyl group by a mesylate followed by a nucleophilic substitution with sodium azide and a reduction by hydrogen over Pd/C. Amino-imidazolium **3a-d** were engaged in the next step without further purification. Finally,

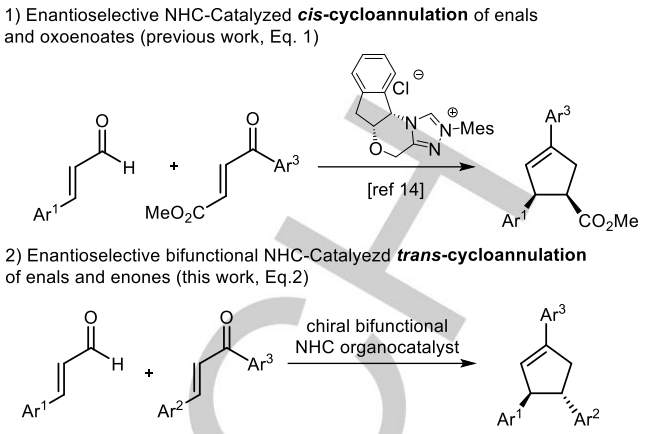
reaction with various iso(thio)cyanates afforded expected bifunctional NHC precatalyst **4** in good yields.



i) $MesNH_2$, glyoxal, formaldehyde, AcOH, 60 °C, 10 min, then KPF_6, rt, 1h ; ii) MsCl, Et_3N, DCM, rt, 2h ; iii) NaN_3, DMF, 80°C, 48 h ; iv) Pd/C, H_2, MeOH, rt, 2h; v) Ar-N=C=X, CH_3CN, rt, overnight.

Scheme 1. Synthesis of bifunctional imidazolylidene-NHC organocatalysts.

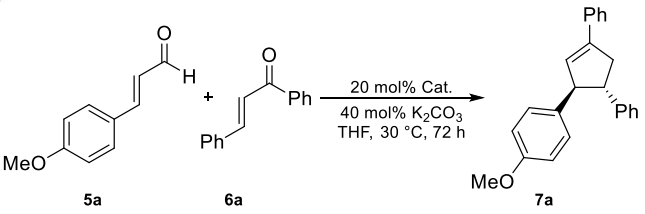
We were then interested in evaluating the potentiality of these new pre-catalysts in asymmetric transformations. In particular, we focused on a reaction for which an achiral imidazolium pre-catalyst such as 1,3-dimesityl imidazolium chloride (IMes-HCl) is an efficient pre-catalyst for racemic transformations and for which the asymmetric version still remained challenging. In 2006, Nair[10i] described a cyclopentannulation of enals and chalcones catalyzed by IMes via homoenolate intermediates, leading to the formation of racemic *trans*-disubstituted cyclopentenes in good yields. In 2007, Bode[15] reported the enantioselective *cis*-cyclopentannulation of enals and oxoenoate (scheme 2, Eq. 1) in good yields and high ee. Since these seminal studies, research groups have been interested in this transformation. For example, the use of additives (such as $Ti(OiPr)_4$)[16] gave the *cis* products in good yields and ee. In 2013, Coquerel and co-workers[12d] described the use of NHC functionalized hydrogen-bond donors to promote the formation of *trans*-cyclopentene in low yield (18%) and encouraging 78% ee compared to the previously reported enantioselectivity.[15a] Moreover, saturated carboxylic acid derivatives were efficiently used instead of enals.[17] It should be noted that an excess of DBU is needed to generate the homoenolate intermediate due to the release of nitrophenol during the reaction. Finally, various Michael acceptors such as oxindole, benzofuranones and tetrahydroquinolinone were also investigated to afford cyclopentene fused heterocycles adducts.[18] Despite these results, formation of *trans*-cyclopentene adducts in high yields and enantioselectivity starting from enals and chalcones via homoenolate intermediate was still unsolved. In light of this, we envisioned that *trans*-cyclopentannulation could be efficiently and stereoselectively promoted by our chiral bifunctional imidazolylidene-NHC organocatalysts (scheme 2, Eq. 2).



Scheme 2. Synthesis of 1,3,4-trisubstituted cyclopentenes catalyzed by NHC via homoenolate intermediate.

We began our study with the cyclopentannulation of 4-methoxy-cinnamaldehyde **5a** and chalcone **6a** in THF at 30°C using **4af** as pre-catalyst in the presence of potassium carbonate. The cyclopentene adduct was isolated in low yield and moderate ee (Table 1, entry1). It is noteworthy that only the *trans* diastereoisomer **7a** was observed (dr>25:1). Next, catalyst screening was studied. All the previously synthesized pre-catalysts were then evaluated in the same reaction conditions (Table 1). This screening revealed that thiourea function gave slightly better yield and enantiomeric excess than urea one (entries 2 and 4). Moreover 3,5-bis(trifluoromethyl)phenyl derived thiourea gave the best ee (entries 1-3). Finally, the influence of chiral scaffold of the pre-catalyst (R group) was evaluated (entries 2, 7-9), the best yield and enantioselectivity were provided by the pre-catalyst incorporating an *iso*-butyl substituent (entry 7).

Table 1. Catalyst screening.[a]



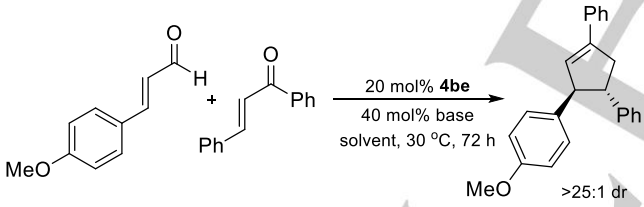
Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**4af**	28	51
2	**4ae**	32	76
3	**4ag**	36	25
4	**4ah**	28	73
5	**4ai**	21	68
6	**4aj**	45	58
7	**4be**	36	82
8	**4ce**	20	50

9	**4de**	34	81		

[a] Reaction conditions: **5a** (0.28 mmol), **6a** (0.2 mmol), cat. (0.04 mmol), K_2CO_3 (0.08 mmol), THF (2 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

With the best pre-catalyst in hand, we explored reaction conditions to increase the efficiency of this transformation. To obtain the *trans*-cyclopentene adduct in high ee, the use of K_2CO_3 as a base was crucial (Table 2, entries 1-4). Solvent was also screened. Among the solvents tested, DIPE was found to be the best to afford the expected product in 43 % yield and 89% ee. Next, different phenol derivatives were used as additives in this transformation.[19] The number of hydroxyl group on the benzene ring was crucial (Table 2, entries 8-10, see Supplementary Part, Table S3), the catechol amount could be reduced to 20 mol % (entry 11) and better yield was obtained at 40°C (entry 12). The increase in yield by using this additive might be explained by the fact that catechol could assist a proton transfer to generate homoenolate intermediate[19c] or by the activation of the enone via the formation of hydrogen bonding.[19d] In summary, using 20 mol% of catalyst **4be**, 40 mol% K_2CO_3 and 20 mol% catechol in DIPE at 40 °C afforded only the *trans*-diasteroisomer (> 25:1 dr) in 50% yield with 93% ee. Optimization of the reaction conditions allowed us to increase the yield from 36% to 50%. Generally speaking, although yields remained moderate, starting materials could be recovered and reused without difficulty. Moreover, it should be emphasized that this cyclopentannulation is an atom economy transformation since only carbone dioxide is released. Besides, the absolute configuration of the product was assigned as (*S*,*S*) in comparison with data reported in the literature.[17a]

Table 2. Optimization of the Reaction Conditions.

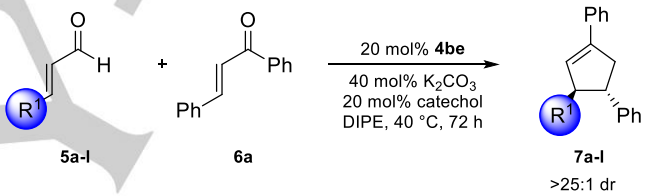


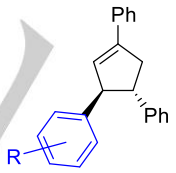
5a **6a** **7a**

Entry	Base	Solvent	Additive (1 equiv)	Yield (%)[c]	ee (%)[d]
1	K_2CO_3	THF	-	36	82
2	DBU	THF	-	58	36
3	KHMDS	THF	-	40	51
4	t-BuOK	THF	-	50	46
5	K_2CO_3	Et_2O	-	48	80
6	K_2CO_3	toluene	-	28	81
7	K_2CO_3	DIPE	-	43	89
8	K_2CO_3	DIPE	catechol	24	95
9	K_2CO_3	DIPE	pyrogallol	5	94
10	K_2CO_3	DIPE	phenol	45	89
11	K_2CO_3	DIPE	catechol[a]	42	94
12	K_2CO_3	DIPE	Catechol[a,b]	50	93

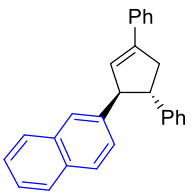
[a] 20 mol% of catechol was used. [b] The reaction was performed at 40 °C. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis.

With the optimized reaction conditions, we next evaluated the scope of cycloannulation by varying the enal substrates **5a-l**. As outlined in Scheme 3, (*Z*) or (*E*)-cinnamaldehyde afforded the same *trans*-cycloadduct **7c** with comparable yield and enantioselectivity likely due to an isomerization during the formation of the homoenolate intermediate.[20] Enals with substituents of different electronic nature on phenyl ring could be tolerated affording the cycloadduct **7a-h** in the same range of enantioselectivity (89-96%) in 41-60% yield. The best result with 60% yield and 93% ee was observed using *p*-fluorocinnamaldehyde **5f** as substrate. When the phenyl ring was changed to the naphtyl or furane ring, the reaction also worked well and the products **7i** and **7j** were isolated in 43-48% yield and 90-92% ee. The reaction was also compatible with enals bearing an alkyl chain, producing **7k** with 93% ee, albeit in lower yield (30 %). Furthermore, a styryl-substituted enal underwent the cycloannulation to yield **7l** in 54% yield and with 90% ee.

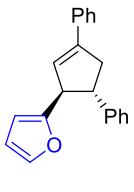




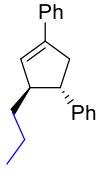
7a R = *p*-OMe 50% yield, 93% ee
7b R = *p*-Me 43% yield, 91% ee
7c R = H from *E*-cinnamaldehyde; 54% yield, 93% ee
7c R = H from *Z*-cinnamaldehyde 51% yield, 96% ee
7d R = *p*-Cl 50% yield, 92% ee
7e R = *p*-CF_3 41% yield, 91% ee
7f R = *p*-F 60% yield, 93% ee
7g R = *p*-Br 45% yield, 92% ee
7h R = *o*-OMe 46% yield, 89% ee



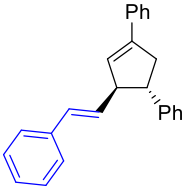
7i 43% yield, 92% ee



7j 48% yield, 90% ee



7k 30% yield, 93% ee



7l 54% yield, 90% ee

Scheme 3. Enal scope. [a] **5** (0.28 mmol), **6a** (0.2 mmol), cat. (0.04 mmol), K_2CO_3 (0.08 mmol), catechol (0.04 mmol), DIPE (2 mL). [b] Yield of isolated product. [c] ee determined by chiral HPLC analysis.

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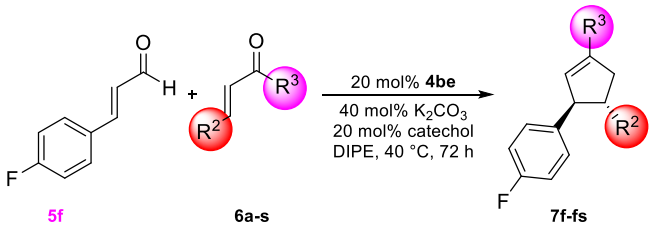
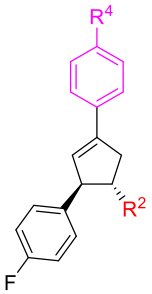
To broaden the scope of the *trans*-cycloannulation, enal **5f** was chosen to react with various unsatured ketones or esters **6a-s** (Scheme 4). First, the scope of chalcone derivatives was examined. Electron-donating and electron-withdrawing aromatic substituents at either the β-position (R^2) or the carbonyl (R^3) of the chalcone are well accommodated, *trans*-cylopentene were isolated in 41-69% yield and 86-96% ee with the exception of **7fc** (28% yield and 83% ee). This result might be explained by the presence of a nitro substituent, which could coordinate to the catalyst, thereby reducing its efficiency. Furthermore, heteroaromatic or vinylphenyl on the β-position or the carbonyl of the chalcone was also well tolerated, giving the products **7fo-fq** in moderate yield and high enantioselectivity. Finally, the reaction was conducted with 4-oxoenoate and 4-oxoenone affording respectively *trans*-cylclopentene **7fs** and **7fr** as the major diastereoisomer but in low yield and enantioselectivity along with lower diastereoselectivity. The formation of the major *trans* diastereoisomer is notable considering the result previously reported by Bode.[15]

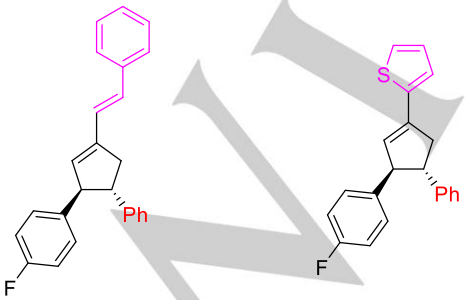


7f R^4 = H, R^2 = C_6H_5 60% yield, 93% ee
7fb R^4 = H, R^2 = *p*-ClC_6H_4 69% yield, 96% ee
7fc R^4 = H, R^2 = *p*-$NO_2C_6H_4$ 28% yield, 83% ee
7fd R^4 = H, R^2 = *p*-$OMeC_6H_4$ 57% yield, 92% ee
7fe R^4 = H, R^2 = *o*-ClC_6H_4 55% yield, 91% ee



7ff R^4 = F, R^2 = C_6H_5 63% yield, 95% ee
7fg R^4 = Cl, R^2 = C_6H_5 66% yield, 94% ee
7fh R^4 = Br, R^2 = C_6H_5 58% yield, 93% ee
7fi R^4 = CF_3, R^2 = C_6H_5 41% yield, 86% ee
7fj R^4 = OMe, R^2 = C_6H_5 43% yield, 93% ee

7fk R^4 = Me, R^2 = p-FC_6H_4 61% yield, 95% ee
7fl R^4 = Cl, R^2 = *p*-ClC_6H_4 58% yield, 93% ee
7fm R^4 = F, R^2 = *p*-$OMeC_6H_4$ 61% yield, 95% ee
7fn R^4 = F, R^2 = *p*-ClC_6H_4 65% yield, 93% ee
7fo R^4 = CH_3, R^2 = thiophen-2-yl 63% yield, 90% ee
7fr R^4 = H, R^2 = COPh 46% yield,
dr *trans*/*cis* 10/1 22% ee *(trans)*
7fs R^4 = H, R^2 = CO_2Me 32% yield,
dr *trans*/*cis* 7/1, 6% ee (*trans*)



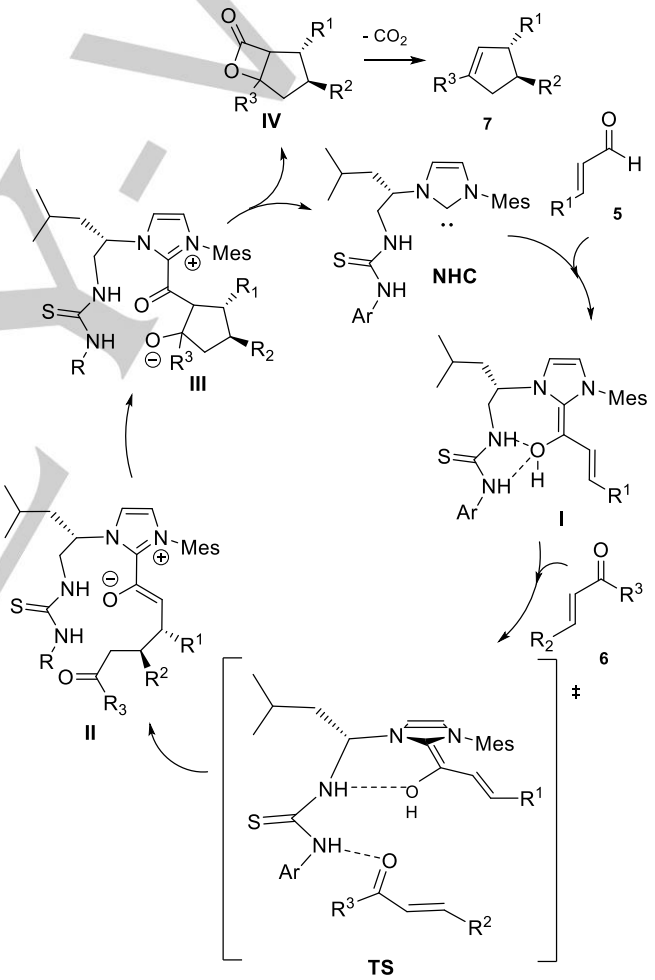
7fp 43% yield, 90% ee

7fq 49% yield, 94% ee

Scheme 4. Enone scope. [a] **5f** (0.28 mmol), **6** (0.2 mmol), cat. (0.04 mmol), K_2CO_3 (0.08 mmol), catechol (0.04 mmol), DIPE (2 mL). [b] Yield of isolated product. [c] ee determined by chiral HPLC analysis. [d] >25:1 dr except for **7fr** and **7fs**.

To evaluate the robustness of our catalytic system, the *trans*-cyclopentannulation between *p*-fluorocinnamaldehyde **5f** and chalcone **6a** was carried out at 1 mmol scale. After 4 days, only single *trans* diastereoismer **7f** was isolated in 58% yield with 93% ee. These results are comparable to those obtained at 0.2 mmol, demonstrating our catalytic transformation could be conducted at a larger scale without drop in yield and stereoselectivity.

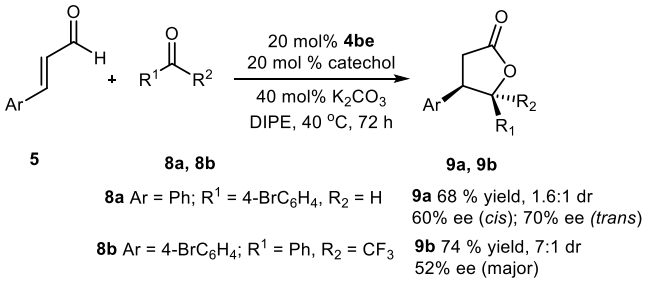
The proposed catalytic cycle[21] is depicted in Scheme 5. First NHC reacts with enal **5** to form the Breslow intermediate **I**, in which the *E*-configuration of the enol should be favored due to the formation of hydrogen bonding with the thiourea function.[12d] Then, a nucleophilic addition of the Breslow intermediate by its *Si* face to the *Si* face of the enone **6** (see **TS**) and a subsequent proton transfer occurs to afford intermediate **II**. Intramolecular aldol reaction generates intermediate **III** which is converted into lactone **IV** along with the release of NHC catalyst. Finally, retro-[2+2] process provides compound **7** with CO_2 elimination.



Scheme 5. Proposed catalytic cycle.

The applicability of our precatalyst **4be** to other transformations was then examined (Scheme 6). Thus, butyrolactones were obtained by annulation between enals and aldehyde or trifluoroketone via homoenolate intermediate in satisfactory yields and moderate enantioselectivity. These results suggest that our new family of catalyst can also be efficient in

lactonization transformations. Further optimizations on the chiral skeleton of these catalysts would be necessary to improve the enantioselectivity of these reactions.



Scheme 6. NHC-catalyzed lactonization reaction.

Conclusion

In conclusion, nine new chiral bifunctional NHC catalysts bearing imidazolylidene and a (thio)urea function could be easily prepared through an efficient synthesis from chiral amino alcohols in only five steps (13-44% overall yields). They were successfully used in enantioselective cylopentannulation processes affording *trans* diastereoisomer in moderate to good yields with excellent diasteroselectivities and enantioselectivities. In addition, *trans*-cyclopentenes were obtained starting from of enals and enones in the presence of catalytic amount of catalyst, base and catechol in DIPE and the only side product of this reaction is CO_2. Moreover, the efficiency of this methodology was proved by the large scope of this transformation and its scalability. Further investigations to expand the utilization of this new class of bifunctional NHC catalysts are currently on-going in our laboratory.

Experimental Section

General procedure for the synthesis of 7. To an oven-dried 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with enone **6** (0.2 mmol, 1.0 equiv.), enal **5** (0.28 mmol, 1.4 equiv.), K_2CO_3 (11.1 mg, 0.08 mmol, 0.4 equiv.), catechol (4.5 mg, 0.04 mmol, 0.2 equiv.) and NHC precatalyst **4be** (28.1 mg, 0.04 mmol, 0.2 equiv.). This tube was closed with a septum, evacuated, and back-filled with argon. To this mixture, at room temperature, was added freshly distilled diisopropyl ether (2 mL). The reaction mixture was warmed to 40 °C and stirred for 72 h under argon atmosphere. After removing solvent, the residue was directly subjected to silica gel column chromatography (petroleum ether/ethyl acetate as eluent, typically 100/1 to 100/1.5) to give desired single *trans*-product **7** (unless otherwise noted). All the corresponding racemic samples for the standard of chiral HPLC spectra were obtained according to the known procedure by using achiral NHC precatalyst 1,3-dimesityl imidazolium chloride.[10i]

For further experimental details including experimental procedures for preparation of organocatalyst, copies of NMR spectre and HPLC data, see Supporting Information.

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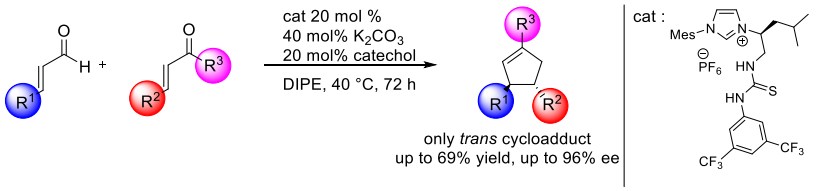

New bifunctional chiral NHC catalysts were prepared and proved their efficiency to promote highly diastereoselective trans-cyclopentannulation in moderate to good yields and excellent enantioselectivity.