Asymmetric Organocatalysis

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Designing N-Heterocyclic Carbenes: Simultaneous Enhancement of Reactivity and Enantioselectivity in the Asymmetric Hydroacylation of Cyclopropenes**

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Since their initial use in benzoin condensation,[1] N-heterocyclic carbenes (NHCs) have become widely utilized as organocatalysts in forging challenging C–C bonds.[2] Our laboratory has dedicated efforts to utilize electron-neutral multiple bonds as unconventional reaction partners in organocatalysis.[3,4] We recently reported the first NHC-catalyzed intermolecular hydroacylation reaction of electron-neutral olefins using cyclopropenes as the coupling partner.[5,6] Because acyl cyclopropanes are versatile structural motifs present in valuable natural products,[7] their asymmetric synthesis is highly desirable.[8] Additionally, utilizing electron-neutral olefins as synthetic building blocks remains a considerable challenge in enantioselective organocatalysis.[9]

Chiral NHCs were shown to be powerful organocatalysts in effecting asymmetric reactions, although certain transformations remain challenging[10] and limited in scope.[11] Consequently, designing of new catalysts with improved reactivity profiles continues to represent one of the greatest challenges in NHC organocatalysts. Shortly after their introduction, triazolium-derived NHCs[12] established themselves as the most efficient carbenes in exerting stereocontrol (Figure 1).[13] Their advantage arises from wide tunability: modification of the carbene backbone creates different chiral environments around the NHC;[13,14] although poorly understood, fine-tuning of the electronic and steric environment around the N1 nitrogen atom greatly affects both the reactivity and selectivity.[15]

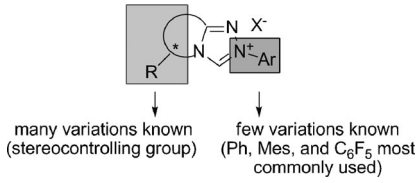

Figure 1. Chiral triazolium salts.

An aromatic group is most often attached to N1, with phenyl, mesityl, and pentafluorophenyl groups being the most common. Rovis et al. have demonstrated that pentafluorophenyl-substituted NHCs, of lower basicity, are beneficial in reactions that create easily epimerizable stereogenic centers.[15a,b] Intriguingly, Ye and co-workers showed that modification of the achiral N1 substituent could alter the absolute stereochemical outcome of the reaction.[15c] Recently, the Bode group provided an elegant study on the origin of the exceptional efficiency of N-mesityl-substituted NHCs in homoenolate chemistry.[15d,e] Herein we report the preparation of the first triazolium salt with a highly electron-donating 2,6-dimethoxyphenyl N1 substituent and demonstrate its superiority over known catalysts in the asymmetric hydroacylation of cyclopropenes.

We commenced our study on the desymmetrization of cyclopropenes with triazolium salt **4a**, which showed both excellent reactivity and enantioselectivity in our previous study on the intramolecular hydroacylation reaction.[3d,16] To our delight, catalyst **4a** furnished the desired product **3a** in 77% yield, greater than 20:1 diastereoselectivity, and 83% *ee* (Table 1, entry 1). Attempts to enhance the enantioselectivity by tuning the reaction conditions proved futile: the choice of base, solvent, concentration, temperature, and reaction time greatly affected the yield of the desired product but exerted little influence on the enantioselective outcome.[17,18] Other known triazolium salts provided product **3a** in variable yields and lower enantioselectivity.[17]

Several factors dictate the stereochemical outcome of hydroacylation via our proposed concerted five-membered transition state:[5] enantioselectivity is controlled by the geometry and facial selectivity of the Breslow intermediate, as well as the approach (*Re* versus *Si*) of the alkene; the facial selectivity of the cyclopropene is manifested in the diastereomeric ratio of the resulting product.[19] As calculated by the groups of Houk[13c] and Yates,[20] the *E* geometry of the Breslow intermediate likely dominates (Scheme 1, top). With the facial selectivity of the Breslow intermediate controlled by the benzyl group on the chiral NHC catalyst, four of the eight possible diastereomeric transition states are shown in Scheme 1. By comparison with a related compound,[8,17] the experimentally obtained *R*,*R* configuration of the major enantiomer is in agreement with the cyclopropene approaching an *E*-configured Breslow intermediate in a *Re*-selective fashion.

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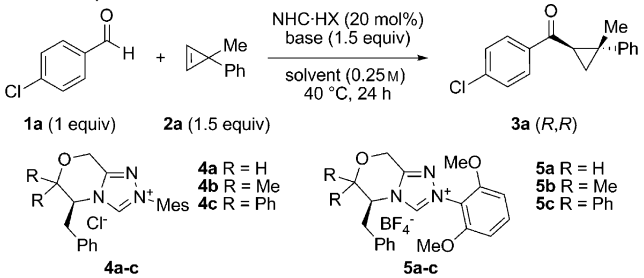
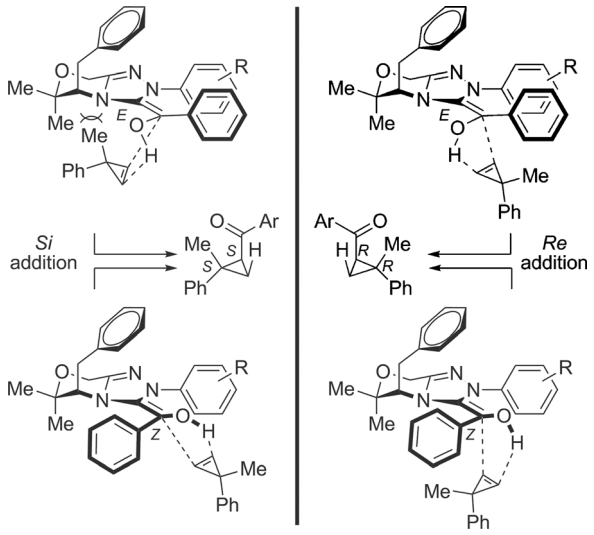
Table 1: Optimization of reaction conditions.[a]



Entry	NHC·HX	Base	Solvent	Yield [%][b]	*ee* [%][c]
1	**4a**	K_2CO_3	THF	77	83
2	**4b**	K_2CO_3	THF	33	86
3	**4c**	K_2CO_3	THF	<5	–
4	**5a**	K_2CO_3	THF	81	90
5	**5b**	K_2CO_3	THF	83	92
6	**5c**	K_2CO_3	THF	32	60
7	**5b**	K_3PO_4	THF	97 (91[d])	92
8	**5b**	K_3PO_4	dioxane	98 (86[d])	94

[a] General reaction conditions: **1a** (0.1 or 0.2 mmol, 1 equiv), **2a** (1.5 equiv), NHC·HX (20 mol%), base (1.5 equiv), solvent (0.25 M), 40°C, 24 h. [b] Yield determined by ^{1}H NMR spectroscopy of the crude product using CH_2Br_2 as the internal standard. Diastereoisomeric ratio as determined by ^{1}H NMR spectroscopy was consistently >20:1 for all entries shown. [c] Enantiomeric excess determined by HPLC on a chiral stationary phase. [d] Yield after purification.

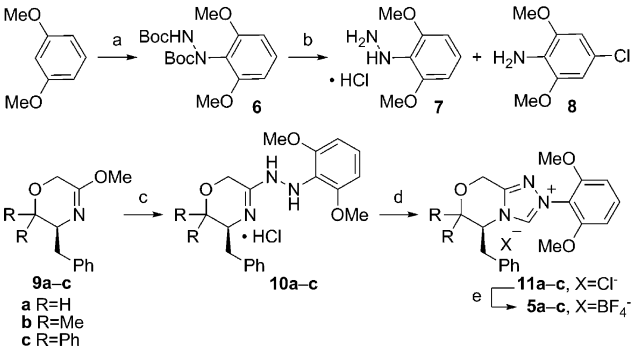


Scheme 1. Proposed mode of enantioinduction in the asymmetric hydroacylation of cyclopropenes.

Based on our proposed stereochemical model, the modest enantioselectivity likely stems from low selectivity in the approach of the cyclopropene and/or the geometry of the Breslow intermediate. To address the first issue, we believed that additional steric interactions with the morpholine backbone of the catalyst could further disfavor the *Si* approach.[21] The *gem*-dimethyl substituents were thus introduced. Consistent with our hypothesis, the enantioselectivity increased to 86% (Table 1, entry 2), but at the cost of lower reactivity. Further increasing the steric demand led to little formation of the desired product (Table 1, entry 3). This apparent trade-off between reactivity and selectivity attests to the challenges of the present transformation: because of its relatively small size, the cyclopropene reaction partner offers few opportunities for substrate recognition.[22] Achieving high enantioselectivity may therefore require a substantially more crowded NHC. At the same time, a bulky catalyst could be detrimental to the reactivity, as the same catalyst is required for addition to the sterically hindered benzoin.[23] For these reasons, the development of a new catalyst that would simultaneously enhance both the reactivity and enantioselectivity is highly important.

During the course of our study on the racemic variant of this reaction, we observed that an N1-mesityl-substituted NHC catalyst provided the hydroacylation products in excellent yields, whereas the corresponding Ph- and C_6F_5-substituted NHCs did not catalyze the desired hydroacylation.[5,15e] This observation suggests that for steric and/or electronic reasons, electron-donating *ortho* substituents are crucial to productivity.[24] Quantum chemical calculations have suggested that a more electron-rich N1-substituted triazolium salt should increase the E to Z ratio of the Breslow intermediate, thereby improving the enantioselectivity of the process.[20] We therefore embarked on the preparation of NHC catalysts **5a–c**, which could increase the selectivity and enhance reactivity towards the productive hydroacylation pathway.

Retrosynthetically, triazolium salt **5a** could be accessed from the convergent union of imidate **9a** (Scheme 2) and 2,6-dimethoxyphenylhydrazine.[25] To date, these triazolium salts have eluded the field of organocatalysis, most likely because of redox instability of the corresponding hydrazine starting material.[26] Our synthetic efforts began with the preparation of the Boc-protected hydrazine precursor **6** by directed lithiation (Scheme 2).[27] Mild deprotection at room temperature with HCl led to an 85:15 mixture of the desired hydrazine hydrochloride salt **7**[28] and its corresponding 4-chloroaniline **8**.[29] Treatment of **7** with imidates **9a–c** provided amidrazones **10a–c**, which furnished **11a–c** after cyclization using triethylorthoformate. Because of their



Scheme 2. Preparation of NHC precursors **5a–c**. Conditions: a) *n*BuLi, TMEDA, THF, 0°C; then BocN=NBoc, −78°C, 89%. b) HCl, MeOH, RT, 4 h; c) **7**, cat. HCl, MeOH, RT; d) $HC(OEt)_3$, PhCl, HCl, 120°C; e) $NaBF_4$, CH_2Cl_2, RT, 45% (3 steps, **5a**), 55% (3 steps, **5b**), 21% (3 steps, **5c**). TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-ethylene-diamine, Boc = *tert*-butoxycarbonyl.

highly hygroscopic nature, **11a–c** were subjected to ion exchange to afford tetrafluoroborate salts **5a–c** as air-stable white solids,[30] which represent the first triazolium salts bearing two highly electron-donating *ortho* substituents. The structures of **5a–c** were verified by NMR spectroscopy and were unambiguously confirmed by X-ray crystallography (Figure 2).[17]

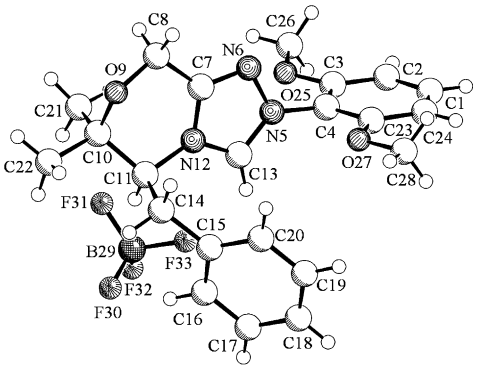


Figure 2. Crystal structure of triazolium salt **5b**.

Gratifyingly, the new NHC catalyst **5a** allowed complete conversion to the desired product and led to an increased enantiomeric excess of 90% (Table 1, entry 4). The *gem*-dimethyl-substituted catalyst **5b** provided the desired product in 83% yield and 92% *ee* (Table 1, entry 5). Further increasing the steric demand to *gem*-diphenyl substituents (triazolium salt **5c**) not only led to a more sluggish reaction but also to lower enantioselectivity (Table 1, entry 6).[31] Screening of bases and solvents showed that dioxane was optimal and that potassium phosphate was unique in suppressing undesired side reactions (Table 1, entries 6 and 7).[32] Under the optimized conditions, the desired product was isolated in 86% yield and 94% *ee*.

We then undertook a preliminary kinetic study to determine the relative reactivities of the four productive catalysts in the reaction of **1a** with cyclopropene **2a** under the optimized conditions. In all cases, the aldehyde starting material was rapidly converted to its corresponding benzoin at the beginning of the reaction, with subsequent exponential growth of the amount of the hydroacylation product.[17] Comparing the kinetic profiles of catalysts **4a**, **4b**, **5b**, and **11a**[30] clearly demonstrates the superiority of the 2,6-dimethoxyphenyl-substituted catalysts over their mesityl-substituted counterparts (Figure 3). As evident from the turnover frequencies calculated at 20% conversion,[17] replacement of the mesityl group by the 2,6-dimethoxyphenyl unit provided an approximate five-fold increase in reactivity while simultaneously enlarging the energetic difference among the diastereomeric transition states. This effect is particularly manifested in the catalysts bearing a *gem*-dimethyl motif on the morpholine backbone. This concurrent gain in both reactivity and enantioselectivity is solely attributed to the electron-donating *ortho* substituents, which stabilized the *E*-configured Breslow intermediate and accelerated the turn-over-limiting process.

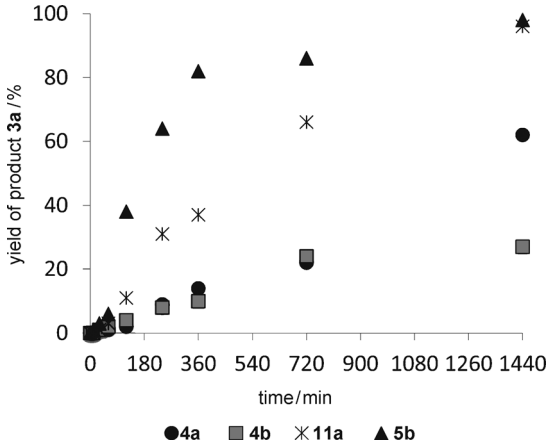


Figure 3. Kinetic studies. Comparison of catalysts **4a**, **4b**, **11a**, and **5b** in with respect to the yield of product **3a**.

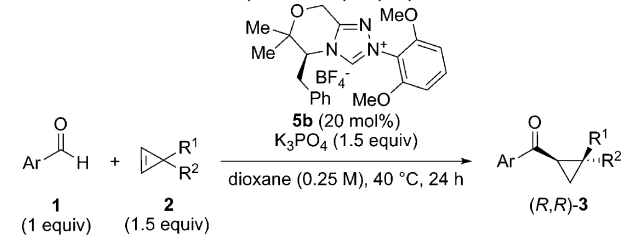
The generality of the new NHC catalyst **5b** in the asymmetric hydroacylation was then examined through a variety of substrates (Table 2). Aromatic and heteroaromatic aldehydes of various electronic characters underwent the desired transformation in good yields (50–93%) and with the exceptions of **1f** (Ar = benzoic acid methylester) and **1l** (Ar = furan) in outstanding diastereo- and enantioselectivities (d.r ≥ 12:1, 86–96% *ee*). Similarly, electronically different cyclopropenes uniformly exhibited excellent reactivity and superb selectivity in the hydroacylation reaction (91–94% *ee*). Moreover, cyclopropenes identically substituted at C3 are shown to be suitable reaction partners, and the resulting acyl cyclopropanes **3s**,**t** were obtained in a highly selective fashion, albeit with reduced yield for the diphenyl-substituted **3t**.

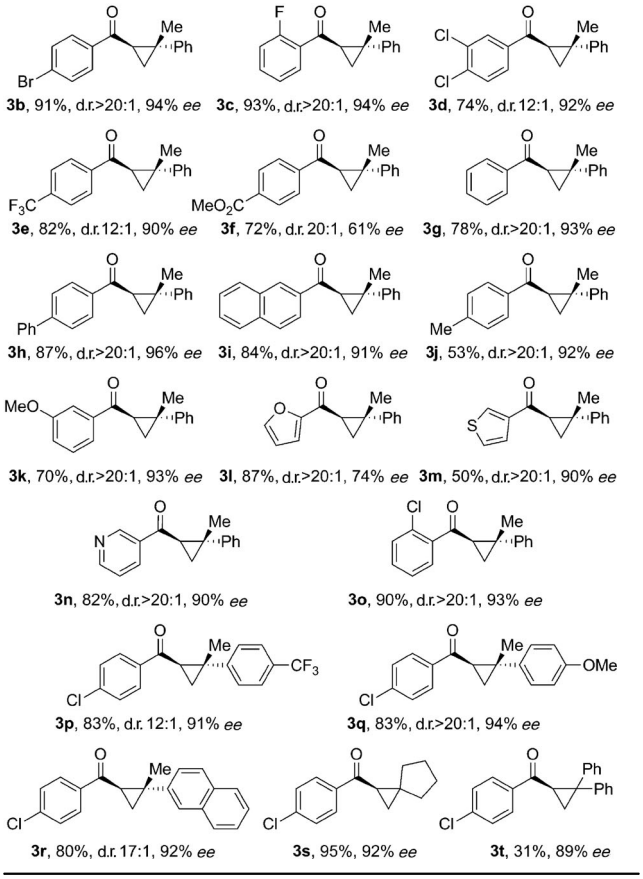
We have described the first syntheses of *ortho*,*ortho*′-disubstituted electron-rich triazolium salts **5a–c** and demonstrated their synthetic utility in the preparation of enantiomerically enriched acyl cyclopropanes. Preliminary kinetic studies showed that the newly designed catalysts allowed for a simultaneous enhancement of reactivity and selectivity, which is in accordance with previous calculations. We believe that this new 2,6-dimethoxyphenyl unit is an effective addition to the current spectrum of NHC aryl substituents and has the potential to become a widely employed motif in carbene catalysts. This dramatic effect on reactivity and enantioselectivity is further evidence for the power and potential of NHCs and should find further applications in unexplored territories of organocatalysis.

Experimental Section

A Schlenk tube was charged with aldehyde (0.500 mmol, 1.00 equiv), K_3PO_4 (159 mg, 0.750 mmol, 1.50 equiv), and triazolium salt **5b** (46.7 mg, 0.100 mmol, 20.0 mol%) and equipped with a Teflon screw cap inside a glovebox. Cyclopropene (0.750 mmol, 1.50 equiv) was then added with a syringe outside the glovebox under a positive pressure of argon. Anhydrous 1,4-dioxane (2.0 mL, 0.25 M) was then introduced into the flask, and the reaction mixture was heated to 40 °C. After 24 h, the solution was diluted with CH_2Cl_2, filtered over a short pad of silica gel, and concentrated under reduced pressure. The

Table 2: Variations of aldehydes and cyclopropenes.





resulting yellow oil was purified by flash column chromatography on silica gel to provide the *R*,*R*-acyl cyclopropane.

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[17] See the Supporting Information for details. CCDC 842105, 842106, 842107 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[18] The fact that external parameters, such as solvent, exert limited influence on the stereochemical outcome of the transformation is consistent with our proposed concerted transition state for the enantiodetermining hydroacylation step.
[19] The Breslow intermediate preferentially approaches from the side of the methyl group for steric and stereoelectronic reasons. See reference [5] for a discussion on the diastereoselectivity of the present transformation.
[20] K. J. Hawkes, B. F. Yates, *Eur. J. Org. Chem.* **2008**, 5563.
[21] a) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, *9*, 371; b) B. E. Maki, A. Chan, K. A. Scheidt, *Synthesis* **2008**, 1306.
[22] a) For an excellent review on the mode of action and stereoinduction of organocatalysts, see: P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. For a review on hydrogen bonding in asymmetric organocatalysis, see: A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.
[23] The aldehyde starting material is rapidly converted to its corresponding benzoin at the beginning of the reaction.
[24] For an example of improved reactivity imparted by an electron-donating substituent on the NHC catalyst, see: C. Fischer, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 1472.
[25] For a general method for the synthesis of triazolium salts, see: J. R. Struble, J. W. Bode, *Org. Synth.* **2010**, *87*, 362.
[26] Mesityl hydrazine is stable as its hydrogen chloride salt and is most often prepared by a strenuous, low-yielding process (see reference [25]). The same method, however, is ineffective for more sensitive hydrazine substrates.
[27] a) J. P. Demers, D. H. Klaubert, *Tetrahedron Lett.* **1987**, *28*, 4933; b) for an application of this strategy in the preparation of mesitylhydrazine hydrogen chloride, see: K. B. Ling, A. D. Smith, *Chem. Commun.* **2011**, *47*, 373.
[28] 2,6-Dimethoxyphenylhydrazine hydrochloride (**7**) exhibits a unique fragmentation pattern in the ESI mass spectrum; see the Supporting Information for details. Deprotection at 90 °C led to exclusive formation of the chlorinated aniline **8**. Attempts to suppress the formation of **8** by further decreasing the temperature and/or the amount of acid led to diminished conversion of the starting material. Trifluoroacetic acid and $ZnBr_2$ led to partial deprotection of the primary Boc group.
[29] Formation of chlorinated aniline byproduct **8** likely arises from expulsion of ammonia upon cleavage of the primary Boc group and subsequent addition of chloride to the resulting azaquinone. In the subsequent synthetic operations, **8** was unreactive and could later be easily removed.
[30] During the reaction optimization, we observed that the triazolium-salt counterion exerted minimal influence on the yield and enantioselectivity. See the Supporting Information for details. Chloride and tetrafluoroborate triazolium salts were thus directly compared in this study.
[31] The pseudo-axially disposed phenyl group may block the bottom face of the Breslow intermediate and lead to lower facial selectivity. It is also possible that additional non-bonding interactions between the phenyl substituents of the chiral catalyst and of the cyclopropene make the *Si*-side approach more favorable and thereby contribute to diminished stereocontrol.
[32] 4,4′-Dichlorodeoxybenzoin was formed as a byproduct; the mechanism of this transformation is currently unknown. See the Supporting Information for details.

