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Dihydrooxazine *N*-Oxide Intermediates as Resting States in Organocatalytic Kinetic Resolution of Functionalized Nitroallylic Amines with Aldehydes

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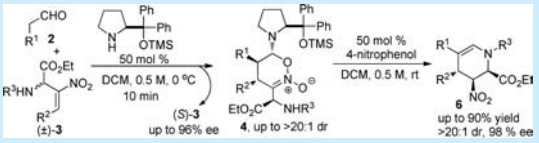
Supporting Information

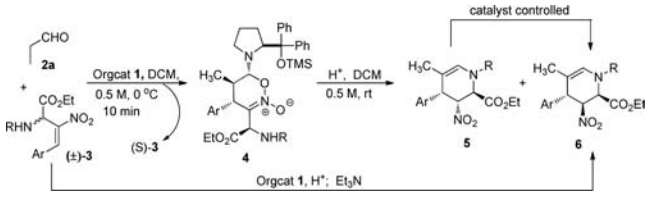
ABSTRACT: Kinetic resolution of nitroallylic amines was established using chiral α,α-L-diphenylprolinol silyl ether auxiliary through isolation of the dihydrooxazine *N*-oxide intermediates. Further hydrolyzing the resting states provided tetrahydropyridines in high chemical yields and high to excellent stereoselectivities (up to >20:1 dr and 98% ee). A detailed mechanistic explanation for stereoselective protonation in the dihydrooxazine was probed computationally. In addition, the probable intermediates in α-halogenation of aldehydes (masked with enamines) were isolated to provide crystallographic evidence.



The development of the organocatalytic domino/cascade reaction[1] has proven effective in developing complex structural skeletons that have multistereogenic centers.[2] Among the various reaction sequences, the reaction of aldehyde with nitroolefins through enamine catalysis is one of the most well-studied transformations. The revelation of the mechanism intermediates and rate-determining step (rds) will provide new understanding in organocascade reactions. In 2011, Blackmond and Seebach-Hayashi identified the cyclobutane species as an essential intermediate in the Michael addition of aldehydes to β-nitrostyrenes.[3] These pioneering studies disclosed that the addition of aldehyde to nitrostyrenes is not as simple as the original mechanism proposed, rather it proceeds through a complex mechanism.[4] Seebach, Pihko, Pápai and their co-workers later noticed a six-membered dihydrooxazine *N*-oxide intermediate species in the Michael addition of aldehydes to α,β-disubstituted nitroolefins.[5] Mechanistically, one of the noteworthy features of this Michael reaction is the virtual role of the acid additive in protonating either the cyclobutane or oxazine *N*-oxide species, which is the rate-determining step.[3,5] The intrinsic information in these mechanisms attracted several groups to further study the prominent α,α-L-diphenylprolinol silyl ether catalyst **1**[6] and other organocatalysts with multiple hydrogen bond donors.[7] Herein, we present an interesting kinetic resolution (KR) of racemic nitroallylic amines **3** by aldehydes through the isolation of dihydrooxazine *N*-oxide intermediates **4** as resting states in the Michael reaction. Computational studies were used to determine the site of protonation in dihydrooxazine species.

Recently, various organocatalytic kinetic resolution (OCKR) methods were developed to provide densely functionalized and malleable enantioenriched substances.[8] Previously, we reported the KR of densely functionalized nitroallylic acetates and alcohols through chiral enamine/iminium catalysis.[9] We envisaged that the KR of nitroallylic amines **3** would afford the enantioenriched functionalized tetrahydropyridines (THP) (Scheme 1). The six-membered nitrogen heterocycles are of high importance as these

Scheme 1. KR of Nitroallylic Amines with Aldehydes



are ubiquitous in numerous natural products and biologically active pharmaceutical skeletons.[10] Considering this, various organocatalytic methods have been developed for synthesizing enantioenriched six-membered nitrogen heterocycles under enamine/iminium and/or hydrogen bonding catalysis.[11]

After extensive studies on the KR of nitroallylic amines **3a**,[12] an organocatalyst **1** (50 mol %) was used to produce a dihydrooxazine *N*-oxide intermediate **4a** with a 47% yield and excellent stereoselectivity (20:1 dr) (Table 1, entry 1). The kinetically less reactive (*S*)-**3a** was recovered with a 51% yield with 80% ee. The stable dihydrooxazine intermediate **4a** acts as a catalyst trap in the catalytic reaction. Subjection of various aldehyde and nitroallylic amines under the same reaction conditions resulted in stable heterocyclic nitronates **4** (Table 1, entries 2−11). The absolute stereochemistry of the oxazine was assigned unambiguously from the single crystal X-ray structural analysis of **4b**, and the stereochemistry of the nitroallylic amine component was found to be *R* in the intermediate.[13,14] The

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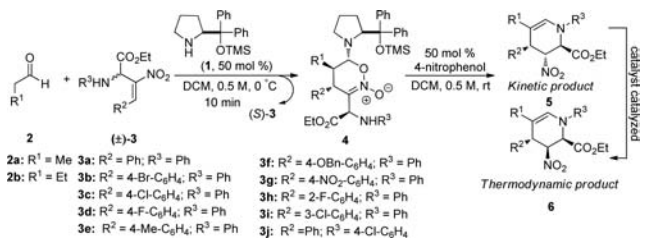
Table 1. KR of Nitroallylic Amines, Isolation and Hydrolysis of Oxazine Intermedites[a]



entry	2; 3	(*S*)-3	4	6[e]
		yield[b]/% ee[c]	yield[b]/dr[d]	yield[b]/dr[d]/% ee[c]
1	**2a**;**3a**	51/80	**4a**;47/20:1	**6a**;83/>20:1/98
2	**2a**;**3b**	49/96	**4b**;48/>20:1	**6b**;90/>20:1/92
3	**2a**;**3c**	49/60	**4c**;46/16:1	**6c**;86/20:1/92
4	**2a**;**3d**	55/66	**4d**;33/10:1	**6d**;88/20:1/84
5	**2a**;**3e**	42/66	**4e**;48/9:1	**6e**;89/19:1/90
6	**2a**;**3f**	50/70	**4f**;48/>20:1	**6f**;72/17:1/94
7	**2a**;**3g**	50/70	**4g**;43/12:1	**6g**;89/>20:1/84
8	**2a**;**3h**	54/70	**4h**;43/20:1	**6h**;84/>20:1/96
9	**2a**;**3i**	49/56	**4i**;39/20:1	**6i**;84/20:1/86
10	**2a**;**3j**	49/85	**4j**;46/14:1	**6j**;89/>20:1/88
11	**2b**;**3a**	48/64	**4k**;50/8:1	**6k**;88/20:1/98

[a]The reactions were carried out with **3** (0.2 mmol), **2** (0.12 mmol) using **1** (0.1 mmol) at 0 °C in DCM. [b]Isolated yield. [c]Determined from chiral HPLC analysis. [d]Determined by ^{1}H NMR crude analysis. [e]The reactions were carried out with isolated oxazine **4** using 4-nitrophenol (50 mol %) in DCM at 25 °C.

absolute stereochemistry of the antipodal recovered nitroallylic amines was tentatively assigned an *S* configuration.

NMR studies revealed that the formation of the oxazine *N*-oxide intermediate is spontaneous and the concentration of these species reaches saturation within 10 min (Figure 1a).[13] Next, the

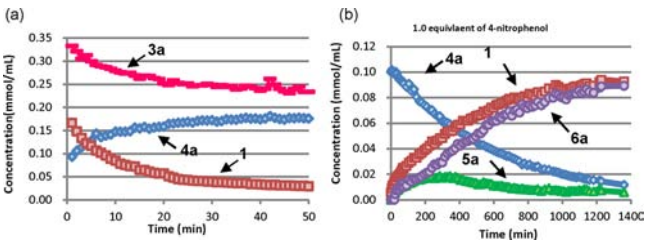


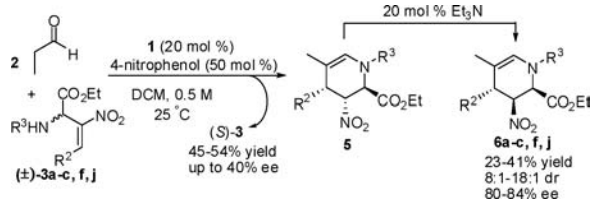
Figure 1. (a) NMR profile of the reaction progress for KR process; (b) progress of the oxazine hydrolysis and isomerization from kinetic (**5a**) to thermodynamic (**6a**) product.

hydrolytic ring opening reaction was studied. After vigorous optimization of the hydrolysis conditions, we found that 4-nitrophenol (50 mol %) was suitable for diastereoselective protonation of nitronate in the oxazine **4a** to provide enantioenriched THP. The thermodynamic product **6a** and the regenerated catalyst **1** were formed steadily with the hydrolysis of the oxazine **4a** (Figure 1b). The concentration of the initially formed kinetic product **5a** diminished with time as it was epimerized to the thermodynamic product **6a** the transformation of which was promoted by a base or even in situ generated auxiliary alone. The oxazine hydrolysis is dependent on the amount of 4-nitrophenol and the rate of protonation is proportional to the acid loading up to 4.0 equiv (see Supporting Information (SI)). In addition, we have observed deuterium incorporation in **6a** at C3 when we carried out the experiment in a mixture of 4-nitrophenol and D_2O.

The optimized conditions were successfully employed for diastereoselective protonation of other isolated oxazine intermediates **4** to furnish corresponding THPs **6** with excellent diastereo- and enantioselectivities (>20:1 dr and up to 98% ee) (Table 1). The relative stereochemistry of the thermodynamic products was established unequivocally from the X-ray structural analysis of **6a**, whereas the relative stereochemistry of kinetic product **5a** was assigned based on NOESY analysis (see SI).

Next, the enantioselective approach was attempted for synthesizing THP **6** in a one-pot fashion through sequential addition (see SI). The presence of the starting substrates, reactive reagents, intermediates, and additives complicated the reaction. The optimized reaction conditions provided the recovered nitroallylic amine (*S*)-**3a** with 40% ee (45% yield) and product **6a** with 13:1 dr and 84% ee (40% yield), employing 4-nitrophenol (50 mol %) and Et_3N (20 mol %) (Scheme 2).[13] The acid

Scheme 2. KR of Nitroallylic Amines in a One-Pot Operation



additive facilitates diastereoselective protonation (followed by oxazine hydrolysis) and the base additive maintains good diastereoselectivities in products (**5** vs **6**). The eroded enantioselectivity of the recovered (*S*)-**3** was ascribed to the base catalyzed racemization.

To elucidate the details of the mechanism, we used density functional theory (DFT) to explore several protonation pathways for acid addition to species **4a**. Pihko revealed that the *Si*-face protonation proceeds preferentially on the C3 carbon of the intermediate species with asynchronous ring opening.[5b] In the present study, direct protonation of C3 in **4a** by acids from the *Re*-face and *Si*-face using 4-nitrophenol, acetic acid, and hydronium ion was simulated. The corresponding energy barriers were tabulated in Table 2. Substantial differences in the energy barriers for protonation were identified using 4-nitrophenol, where *Si*-face protonation was more than 20 kcal/mol lower than that from the opposite face. Steric hindrance introduced by -OTMS and -NHPh groups is believed to block the incoming acid. Protonation by acetic acid and hydronium

Table 2. Calculated $\Delta G^{\ddagger}_{TS}$ (kcal/mol) for Protonation to 4a Using 4-Nitrophenol, Acetic Acid, and Hydronium

entry	acid (face of protonation)	$\Delta G^{\ddagger}_{TS}$[a]
1	4-nitrophenol (*Re*-)	55.18
2	4-nitrophenol (*Si*-)	24.48
3	acetic acid (*Re*-)	30.82
4	acetic acid (*Si*-)	26.60
5	hydronium (*Re*-)	51.87
6	hydronium (*Si*-)	22.09
7	hydronium (*Si*-)[b]	11.02
8	hydronium (*Re*-)[b]	5.57

[a]$\Delta G^{\ddagger}_{TS}$ was estimated in respect to hydrogen bonded **4a**. [b]Using intermediate of Seebach et al.[5a]

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also showed such face selectivity as listed in Table 2. The hydrogen bonded 4-nitrophenol-**4a** complex and transition state geometries of *Re*- and *Si*-face protonation are shown in Figure 2,

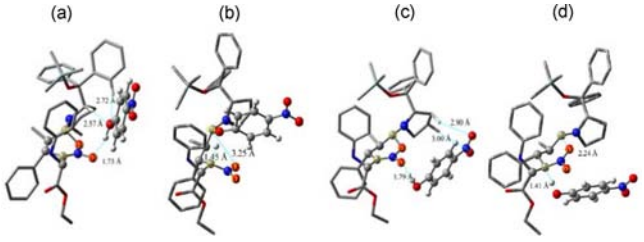


Figure 2. Hydrogen bonded 4-nitrophenol and transition state geometries of **4a** from *Re*- (a and b) and *Si*- (c and d) face protonation.

in which the C4−O3 distance was substantially more elongated for the *Re*-face conditions than the *Si*-face counterpart. For comparison, Seebach's intermediate in which C3 was connected with a methyl group and was significantly accessible to external incoming acids was calculated using H_3O^+ for protonation. The corresponding predicted energy barriers for *Re*- and *Si*-face were only 5.57 and 11.02 kcal/mol, respectively (Table 2, entries 7 and 8).

The electrostatic potential of the dihydrooxazine *N*-oxide intermediate (**4a**) using its crystal structure showed the *N*-oxide group to be the most nucleophilic region. Protonation at *N*-oxide was determined to be more energetically favorable and structurally accessible to the incoming acids (see SI). The stable geometries of hydrogen-bonded **4a** and incoming acid was identified for 4-nitrophenol and acetic acid where hydronium was found to protonate dihydroxazine *N*-oxide without any barrier. Trace amounts of water could be attracted to the hydrophilic groups, for example, *N*-oxide and CO_2Et, near the C3 moiety. Thus, a possible C3 protonation pathway from the protonated *N*-oxide to C3 via a hydrogen-bond network was investigated. The intermediates using two explicit water molecules along the proposed reaction coordinate was shown (Figure 3). The barrier

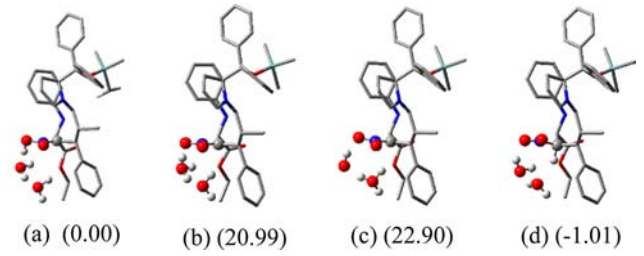


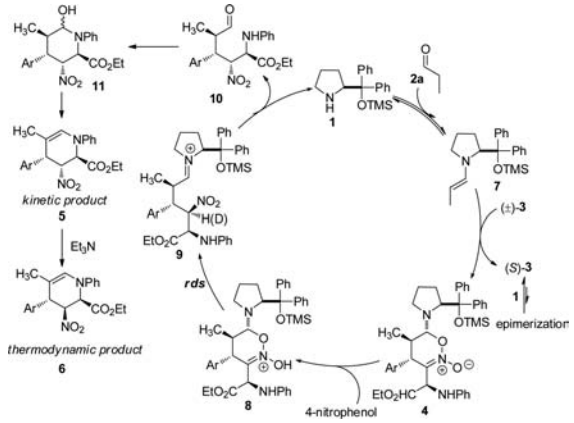
Figure 3. Schematic representation for H^+ transferring from the protonated *N*-oxide via hydrogen bond network to C3 is shown (from a → d). The relative energetics (kcal/mol) is listed in parentheses.

of such a pathway was predicted to be greater than 22.90 kcal/mol, and the thermodynamically favored C3 protonation state is lower than that of protonated *N*-oxide state (−1.01 kcal/mol). Moreover, C3 protonation by 4-nitrophenol with the protonated *N*-oxide (a two-proton transfer pathway) was also calculated, and the corresponding barrier was predicted to be 36.09 kcal/mol (see SI). These studies indicate that substantial energy barriers (>20 kcal/mol) were found for the above protonation pathways and this suggests the protonation process is the rds.

Vibrational analysis of this constrained-optimized geometry identified the ring-opening vibration at 467 cm^{-1} in which C3 attempted to break the planar ring structure and reversibly moved toward incoming acids. Charge analysis of such a flipping mode suggested more negative charge accumulated at C3 as C3 moved away from the equilibrium position (see SI) and that enhanced basicity would attract protons.

Under the acidic conditions, the stable intermediate **8** can be converted to the substituted THP by sequential processes (Scheme 3). The rds was believed to be the *Si*-face

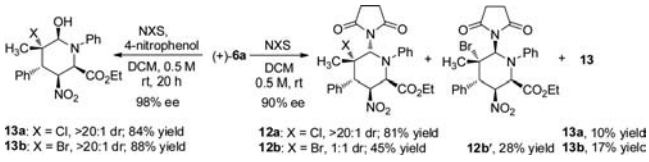
Scheme 3. Mechanistic Investigation of the Reaction



diastereoselective protonation and the heterocyclic ring opening by enlarging the C−O bond. These two events occurred asynchronously. Further hydrolyzing the iminium ion and cyclization/dehydration afforded the final THPs and regenerated catalyst **1**.

Next, we investigated the applications of (+)-**6a**, and to our delight, this chiral enamine reacts in a highly diastereoselective (>20:1 dr) path with *N*-chlorosuccinimide to furnish adduct **12a** in 81% yield, along with minor hydrolyzed product **13a** (Scheme 4). This adduct **12a** has a significance in mechanism perspectives,

Scheme 4. Synthesis of Fully Substituted Pipecolic Ester Derivatives



as these adducts could be the probable intermediate species involved in chiral enamine catalyzed α-chlorination of aldehydes.[3c,15] This kind of species cannot be isolated with the linear aldehydes due to facile dissociation of the succinimide. For the first instance, the probable intermediate species that were involved in α-halogenation of aldehydes are isolated and characterized with X-ray structural analysis.[14] This is an additional piece of evidence for the mechanism proposed by Blackmond and co-workers on α-chlorination of linear aldehydes.[3c]

The pipecolic acid derivatives prevail in numerous biological and pharmaceutical molecules.[16] In view of this, we found that 4-nitrophenol is an appropriate acid additive for intermediate **12a** hydrolysis to afford five contiguous asymmetric centered pipecolic ester motifs **13a** including one quaternary halide center in good yield (84%) with excellent stereoselectivities (>20:1 dr and 98% ee) (Scheme 4). The relative stereochemistry

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of the hydrolyzed product **13** was assigned from X-ray structural analysis of **13a**.[14] Surprisingly, *N*-bromosuccinimide furnished corresponding adduct **12b** and **12b′** in 1:1 dr with (+)-**6a** under the same reaction conditions. Albeit, we obtained the hydrolyzed product **13b** in excellent diastereoselectivity (>20:1) after hydrolysis.

In conclusion, we demonstrated a KR of densely functionalized nitroallylic amines through isolation of the resting states intermediates with excellent chemical yields and diastereo- and enantioselectivities via the Michael reaction of aldehydes. These isolated intermediates provided enantioenriched THPs upon *N*-oxide protonation and subsequent diastereoselective protonation/ring opening, followed by hydrolysis and dehydration. For the first instance, computational studies have provided evidence for nitronate oxygen atom protonation. The rds of diastereoselective protonation and asynchronous ring opening is compelling. Finally, we have provided an additional support over the mechanism on α-chlorination of chiral enamines derived from aldehydes and amines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00493.

Experimental procedures, X-ray data (PDF)
HPLC analysis; characterizations (PDF)
NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006;. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, *2007*, 1477. (d) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (e) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (f) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (g) Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866.

(2) (a) Jones, S. P.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (b) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774.

(3) (a) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822. (b) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719. Also see: (c) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741. (d) Moberg, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2160.

(4) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(5) (a) Seebach, D.; Sun, X.; Sparr, C.; Ebert, M.-O.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2012**, *95*, 1064. (b) Sahoo, G.; Rahaman, H.; Madarász, A.; Pápai, I.; Melarto, M.; Valkonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13144. Also see: (c) Seebach, D.; Sun, X.; Ebert, M.-O.; Schweizer, W. B.; Purkayastha, N.; Beck, A. K.; Duschmalé, J.; Wennemers, H.; Mukaiyama, T.; Benohoud, M.; Hayashi, Y.; Reiher, M. *Helv. Chim. Acta* **2013**, *96*, 799.

(6) For representative works, see: (a) Hayashi, Y.; Okamura, D.; Yamazaki, T.; Ameda, Y.; Gotoh, H.; Tsuzuki, S.; Uchimaru, T.; Seebach, D. *Chem. - Eur. J.* **2014**, *20*, 17077. (b) Mukaiyama, T.; Ishikawa, H.; Koshino, H.; Hayashi, Y. *Chem. - Eur. J.* **2013**, *19*, 17789. (c) Rahaman, H.; Madarász, U.; Pápai, I.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6123.

(7) For selected examples, see: (a) Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 12619. (b) Duschmalé, J.; Wiest, J.; Wiesner, M.; Wennemers, H. *Chem. Sci.* **2013**, *4*, 1312. (c) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366.

(8) Gurubrahamam, R.; Cheng, Y.-S.; Huang, W.-Y.; Chen, K. *ChemCatChem* **2016**, *8*, 86 and the references cited therein..

(9) For the KR reaction of using racemic nitroallylic acetates/alcohols, see: (a) Reddy, R. J.; Chen, K. *Org. Lett.* **2011**, *13*, 1458. (b) Jannapu Reddy, R.; Lee, P.-H.; Magar, D. R.; Chen, J.-H.; Chen, K. *Eur. J. Org. Chem.* **2012**, *2012*, 353. (c) Roy, S.; Chen, K. *Org. Lett.* **2012**, *14*, 2496. (e) Roy, S.; Chen, K.-F.; Gurubrahamam, R.; Chen, K. *J. Org. Chem.* **2014**, *79*, 8955. (f) Gurubrahamam, R.; Cheng, Y.-S.; Chen, K. *Org. Lett.* **2015**, *17*, 430. From Cheng's group, see: (g) Han, B.; Xie, X.; Huang, W.; Li, X.; Yang, L.; Peng, C. *Adv. Synth. Catal.* **2014**, *356*, 3676.

(10) (a) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives*; Elsevier: Amsterdam, 1991. (b) Cuthbertson, J. D.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 1490.

(11) For selected organocatalytic methods, see: (a) Blümel, M.; Chauhan, P.; Hahn, R.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 6012. (b) Lin, H.; Tan, Y.; Liu, W.-J.; Zhang, Z.-C.; Sun, X.-W.; Lin, G.-Q. *Chem. Commun.* **2013**, *49*, 4024. (c) Li, X.; Zhao, Y.; Qu, H.; Mao, Z.; Lin, X. *Chem. Commun.* **2013**, *49*, 1401. (d) Shi, F.; Tan, W.; Zhu, R.-Y.; Xing, G.-J.; Tu, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 1605. (e) Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7825. (f) Huo, L.; Ma, A.; Zhang, Y.; Ma, D. *Adv. Synth. Catal.* **2012**, *354*, 991. (g) Wang, Y.; Zhu, S.; Ma, D. *Org. Lett.* **2011**, *13*, 1602. (h) Imashiro, R.; Uehara, H.; Barbas, C. F. *Org. Lett.* **2010**, *12*, 5250. (i) Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 4588. (j) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem. - Eur. J.* **2010**, *16*, 3922.

(12) *rac*-**3** were synthesized from their Morita-Baylis-Hillman alcohols. Also, see: Rastogi, N.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Biomol. Chem.* **2006**, *4*, 3211. For the use of primary nitroallylic amine in organocatalytic reaction, see: Wang, Y.; Zhu, S.; Ma, D. *Org. Lett.* **2011**, *13*, 1602.

(13) See Supporting Information.

(14) CCDC 1434063 (**4b**), CCDC 1434068 (**6a**), CCDC 1453775 (**12a**), CCDC 1453874 (**12b**) and CCDC 1453873 (**13a**) contains the supplementary crystallographic data.

(15) For mechanistic studies, see: (a) Halland, N.; Alstrup Lie, M.; Kjaersgaard, A.; Marigo, M.; Schiøtt, B.; Jørgensen, K. A. *Chem. - Eur. J.* **2005**, *11*, 7083. Also, see: (b) Jimeno, C.; Cao, L.; Renaud, P. *J. Org. Chem.* **2016**, *81*, 1251.

(16) (a) Smith, A. B, III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 962. (b) Boger, D. L.; Chen, J.-H.; Saionz, K. W. *J. Am. Chem. Soc.* **1996**, *118*, 1629.

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