Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

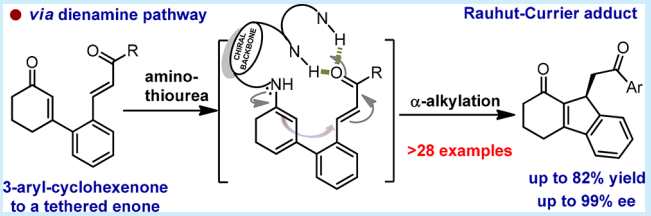
Primary Aminothiourea-Catalyzed Enantioselective Synthesis of Rauhut−Currier Adducts of 3-Arylcyclohexenone with a Tethered Enone on the Aryl Moiety at the *Ortho*-Position

Sanjay Maity, Suman Sar, and Prasanta Ghorai*

Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal By-pass Road, Bhauri, Bhopal-462066, India

Supporting Information

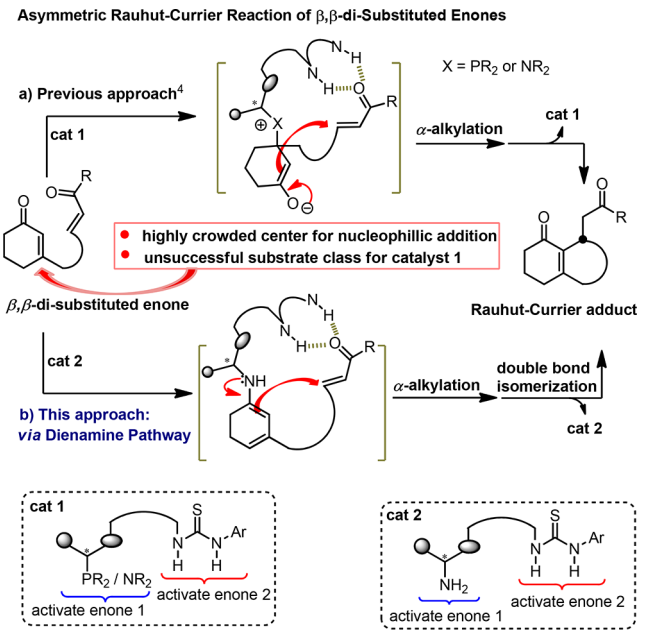
ABSTRACT: An enantioselective synthesis of Rauhut−Currier (RC) adducts from 3-aryl cyclohexenone with a tethered enone moiety at the *ortho*-position on the aryl group is accomplished. This method provides a wide range of valuable synthetic building blocks having a unique [6−5−6] all-carbon-fused tricyclic skeleton. A primary amine-containing thiourea, a bifunctional organocatalyst, was found to be an efficient catalyst for this transformation. The primary amine counterpart of the catalyst possibly activates the aliphatic enone via dienamine formation (HOMO activation), whereas the thiourea counterpart activates the tethered enone (LUMO activation). Considering the difficulty in achieving an RC reaction of *β*,*β*-disubstituted (alkyl and aryl) enones, this method would be significantly rewarding.



The development of methods for the construction of the chiral C−C bond is an exciting and fascinating area of research in organic chemistry. In this context, Morita−Baylis−Hillman (MBH)[1] and Rauhut−Currier (RC)[2] reactions are used for the synthesis of structurally complex natural products and bioactive molecules.[3] Traditionally, the reaction involves an organocatalytic nucleophilic (e.g., PR_3 or NR_3) addition to an enone (Scheme 1a) followed by enolate addition to another carbonyl or enone moiety. Despite advances, the major limitation in MBH and RC reactions is the substrates with *β*,*β*-disubstituted enones. The steric crowding of such substrates at the *β*-position makes the above nucleophilic addition impossible, which is the bottleneck for this reaction. Very recently, Ramasastry et al. disclosed the first asymmetric MBH reaction of *β*,*β*-substituted enones with high enantioselectivities using thiourea containing phosphine catalyst (Scheme 1a),[4] whereas the corresponding RC reactions are not explored. Therefore, finding an alternative reaction pathway to access such adducts with excellent enantio- and regioselectivities would be significantly rewarding.

Over the past few decades, asymmetric amino catalysis has become one of the most widespread and emerging areas of research in organic chemistry. It activates the carbonyls (HOMO) through enamine formation.[5] Recently, this amino catalysis has been further extended to activate the *α*,*β*-unsaturated ketones via formation of a dienamine intermediate that leads to a diverse range of chemical reactions to construct a variety of complex chiral molecules. This dienamine provides two reacting nucleophilic sites: the *α*- and *γ*-position of the enone. The dienamine chemistry has been utilized in many chemoselective reactions including MBH and RC reactions.[6] The enantioselective intra- and intermolecular *α*-selective[7] as well as *γ*-selective[8] functionalizations of *α*,*β*-unsaturated ketone were well developed in MBH and RC reactions. However, as mentioned above, such reactions on *β*,*β*-disubstituted enones as nucleophiles remain a significant challenge.[9,10] Moreover, in

Scheme 1. Alternative Reaction Pathway for Enantioselective and Regiospecific Rauhut−Currier Adduct



Received: January 3, 2018

DOI: 10.1021/acs.orglett.7b03959
Org. Lett. XXXX, XXX, XXX−XXX

almost all of the previous reports for dienamine formation,[9,10] a secondary amine such as a proline or proline derivative is used as the catalyst in the presence of additives.

Here, we investigate a primary aminothiourea/squaramide as a bifunctional organocatalyst. The primary amine counterpart of the catalyst would activate the aliphatic enone via the formation of dienamine (HOMO); on the other hand, the thiourea counterpart would activate the tethered enone (LUMO) to provide a highly rigid platform for the generation of the enantioselective Rauhut–Currier adduct (Scheme 1b).

Notably, [6–5–6] all-carbon tricyclic fused cores are present in various natural products and drug molecules;[11] in particular, they are found in the taiwaniaquinoid and diterpenoid families (Figure 1). Such unique [6–5–6]-*abeo*-abietane skeleton family members have shown aromatase inhibitor activity and are also used as drugs for the treatment of estrogen-dependent cancers.[12]

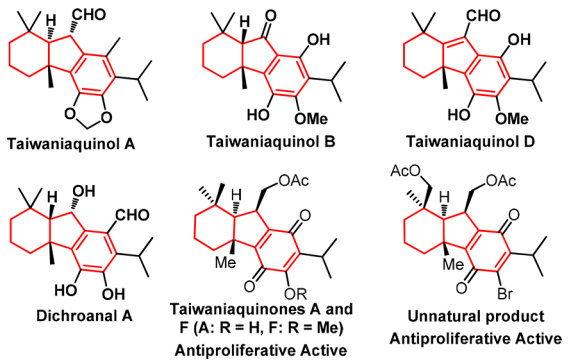


Figure 1. Natural products containing [6–5–6] all tricyclic carbon skeleton.

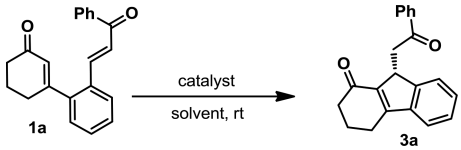
Fascinated by these [6–5–6] all-carbon tricyclic skeletons, we hypothesized that cyclohexenone tethered to another enone at the β-position would chemoselectively participate in chiral dienamine formation followed by a Michael addition to provide the RC-type adduct in high enantioselectivity (as shown in Scheme 1a).

To execute our hypothesis, we began our investigation by using β-aryl-substituted cyclohexenone tethered with aromatic enone as model substrate **1a**. The major obstacles were the inherent difficulties due to the multiple potential enolate sites generated from dienamine, which may reduce the regioselectivities.

Despite these complexities, we strictly focused on overcoming the challenges regarding enantio- and regioselectivity issues. Various chiral primary amines derived from cinchona alkaloid ($\mathbf{C_1}$–$\mathbf{C_3}$) were surveyed in toluene at room temperature (Table 1). To our delight, all of the chiral amines afforded the desired product with good regiospecificity but moderate enantioselectivities (entries 1–3). Then we envisioned engineering our catalyst design to improve the selectivity by introducing the push–pull strategy where primary amine activated the ketone (HOMO) and thiourea/squaramide activated the enone moiety.[13,14] As per the analysis, catalyst $\mathbf{C_5}$ showed a sharp increase in enantioselectivity with 94% ee and 56% yield (entry 5).

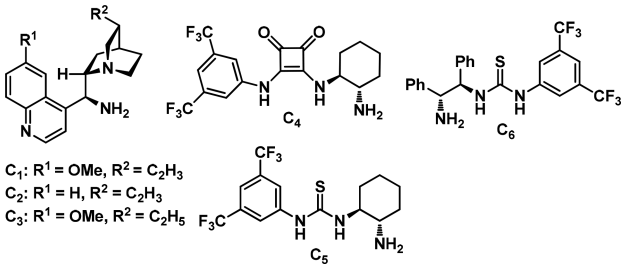
Next, arrays of bifunctional catalysts (see the Supporting Information) were screened, and catalyst $\mathbf{C_5}$ was found to be the best in terms of enantioselectivity. A quick study of all of the parameters such as solvent, catalyst loading, and temperature (see the Supporting Information) revealed that 10 mol % catalyst $\mathbf{C_5}$ in xylene at room temperature were the optimum conditions to furnish our desired product **3a** with 93% ee and 82% NMR yield (Table 1, entry 7).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	t (h)	yield[b] (%)	% ee[c]
1	C_1	toluene	72	38	20
2	C_2	toluene	72	35	51
3	C_3	toluene	72	33	16
4	C_4	toluene	72		ND
5	C_5	toluene	96	56	94
6	C_6	toluene	96		ND
7	$\mathbf{C_5}$	**xylene**	**96**	**82** (78)	**93**
8	C_5	mesitylene	96	84 (80)	90
9	C_5	HFIP	96		ND
10	C_5	THF	96	10	86
11	C_5	DCM	96	18	94
12	C_5	benzene	96	80	74

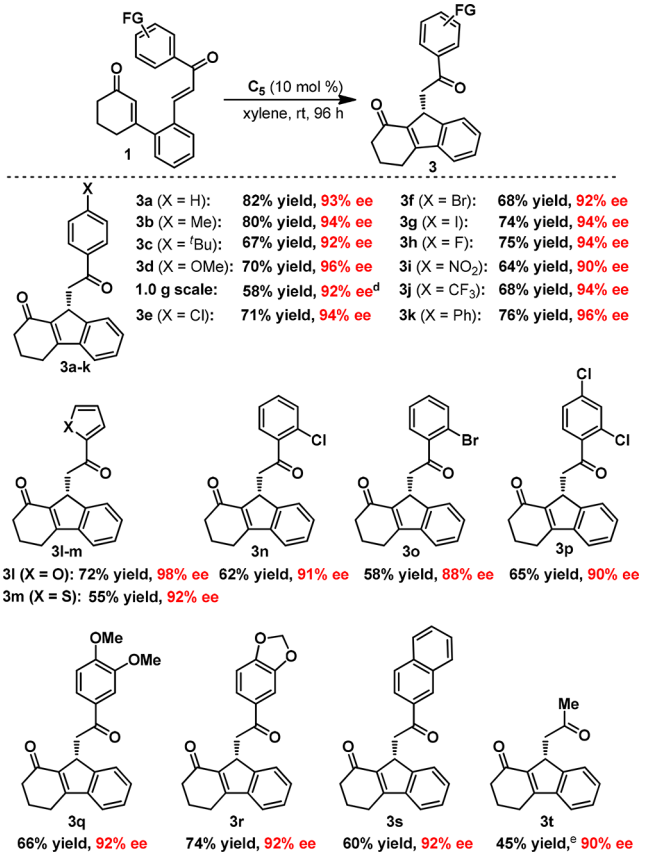
[a]Reaction conditions: **1** (0.05 mmol), **C** (0.005 mmol, 10 mol %) at rt. [b]Yields were determined from ^{1}H NMR by using diphenyl acetonitrile as an internal standard; isolated yields are shown in parentheses. [c]The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. ND = not determined.



Using these optimized reaction conditions, we interested in exploring the substrate scope on the tethered enone moiety, which is summarized in Scheme 2. The generality of the reaction was proved in terms of regio- and enantioselectivity. The reactions with substrates having electron-donating groups such as *p*-Me (**3b**), *p*-^{t}Bu (**3c**), *p*-OMe (**3d**), and *p*-Ph (**3k**) and an electron-withdrawing group such as *p*-Cl (**3e**), *p*-Br (**3f**), *p*-F (**3h**), *p*-NO_2 (**3i**), and *p*-CF_3 (**3j**) on the aryl moiety proceeded smoothly to provide the [6–5–6] tricyclic skeleton in high yields with excellent enantioselectivities. Moreover, irrespective of the position of substitution on the aryl ring, such as *o*-Cl (**3n**), *o*-Br (**3o**), 2,4-di-Cl (**3p**), or 3,4-di-OMe (**3q**), the reaction proceeded well to afford the RC adduct with high enantioselectivity. The heteroaryl moieties such as furyl (**3l**) and thiophene-yl (**3m**) were well tolerated under these reaction conditions. Even a difficult substrate such as aliphatic enone also took part in these reaction conditions and led to the desired product with high enantioselectivity. In some cases (e.g., **3c**, **3f**, **3g**, **3i**, and **3m–p**), the yields were good to moderate. In such cases, no other products were obtained; only the reactants were recovered. To show the synthetic utility of this methodology, a gram-scale reaction was performed with **1d**, and **3d** was achieved with a very little decrease in enantioselectivity (96% to 92% ee). However, after single

DOI: 10.1021/acs.orglett.7b03959
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Substrate Scope (Variation on Outer Aryl Ring)[a–d]



[a]Reaction conditions: **1** (0.1 mmol), C_5 (0.01 mmol, 10 mol %) in xylene (2 mL) at rt. [b]Yields shown are of isolated products. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d]Enantiomeric excess and yield on a 1.0 g scale reaction. [e]In the case of low-yielding reaction, the starting substrates were recovered.

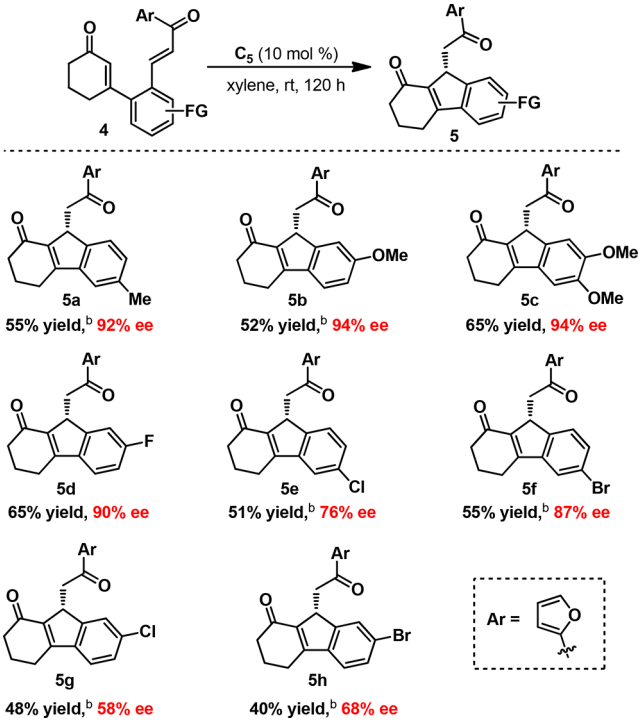
crystallization, the optically pure compound was obtained. The absolute configuration (*R*) of the [6–5–6] core was confirmed by X-ray analysis of **3g** (see the SI).

Furthermore, the substitutions on the internal aryl moiety were examined and the multisubstituted [6–5–6] tricyclic skeleton was observed with good to excellent enantioselectivities (Scheme 3). A small decrease in enantioselectivity was observed for the substrates with halogen substitution at the meta-position, e.g., *m*-Cl (**5g**) and *m*-Br (**5h**). A combined effect of electronic as well as steric conditions (less interaction between substrate and catalyst in the transition state) could be the reason for such moderate yields and selectivities. However, the use of cyclopentenone instead of cyclohexenone did not react to provide the desired product under these reaction conditions. When the α-position was blocked by a methyl group, interestingly, a γ-alkylation of the same was observed with 2:1 diastereoselectivity (see Scheme 4).

The experimental results and stereochemical outcome of the current reaction promoted us to propose a probable transition state which is shown in Scheme 5.

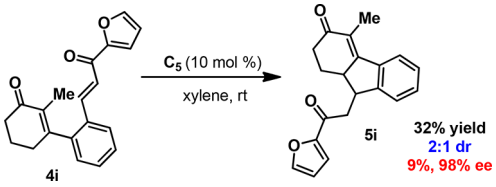
To execute the synthetic utility of the current methodology, an all-carbon quaternary center was installed (see Scheme 6) by the treatment of **3d** with methylmagnesium bromide in the presence of copper(I) bromide to furnish **6** without loss of any

Scheme 3. Substrate Scope (Variation on Internal Aryl Ring)

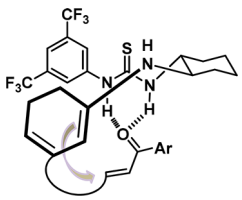


[a]Reaction conditions are the same as in Scheme 2. [b]In the case of low-yielding reactions, the starting substrates were recovered.

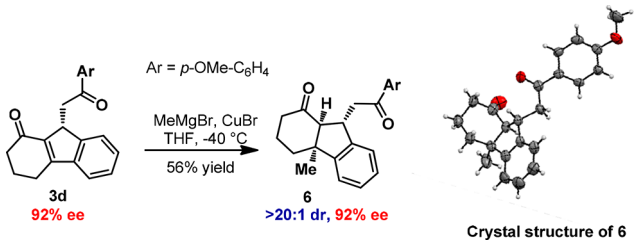
Scheme 4. Reaction of α-Methyl Enone



Scheme 5. Proposed Transition State



Scheme 6. Synthetic Elaboration



selectivity (>20:1 dr, 92% ee). The hydrogenation of the enone was also carried out. However, a mixture of products was obtained (see the SI).

DOI: 10.1021/acs.orglett.7b03959
Org. Lett. XXXX, XXX, XXX–XXX

In conclusion, we have developed a unique strategy for RC-type reaction of 3-aryl cyclohexenone tethered to an enone moiety at the *ortho*-position on the aryl moiety to provide an uncommon [6−5−6] all-carbon tricyclic skeleton with excellent enantioselectivity. This report may open a new era for primary amines in dienamine catalysis for RC- and MBH-type reactions in extremely sterically hindered substrates to obtain a critical C−C bond in enantiomerically enriched form.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03959.

Experimental procedures and characterization data (PDF)

NMR spectra for all products (PDF)

Accession Codes

CCDC 1568745 and 1585234 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*pghorai@iiserb.ac.in

ORCID

Prasanta Ghorai: 0000-0001-5120-2700

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been funded by IISER Bhopal and CSIR, India. S.M. and S.S. thank UGC and CSIR, New Delhi, India, respectively, for fellowships. We thank Mr. Darpan Agarwal (IISER Bhopal) for his help.

■ REFERENCES

(1) (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815. (b) Morita, K. Japan Patent 6803364, 1968. (c) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972. For reviews on MBH reactions, see: (d) Huang, W.-Y.; Anwar, S.; Chen, K. *Chem. Rec.* **2017**, *17*, 363. (e) Pellissier, H. *Tetrahedron* **2017**, *73*, 2831. (f) Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68. (g) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447. (h) Declerck, V.; Martínez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (i) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. (j) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. For selected reports on MBH reactions, see: (k) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231. (l) Lindner, C.; Liu, Y.; Karaghiosoff, K.; Maryasin, B.; Zipse, H. *Chem. - Eur. J.* **2013**, *19*, 6429. (m) Yoshida, Y.; Sako, M.; Kishi, K.; Sasai, H.; Hatakeyama, S.; Takizawa, S. *Org. Biomol. Chem.* **2015**, *13*, 9022.

(2) For the intramolecular RC reaction, see reviews: (a) Chandra Bharadwaj, K. *RSC Adv.* **2015**, *5*, 75923. (b) Xie, P.; Huang, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6213. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (d) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069. For selected reports, see: (e) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (f) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (g) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256. (h) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423. (i) Osuna, S.; Dermenci, A.; Miller, S. J.; Houk, K. N. *Chem. - Eur. J.* **2013**, *19*, 14245. (j) Su, X.; Zhou, W.; Li, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 6874. (k) Dong, X.; Liang, L.; Li, E.; Huang, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 1621. (l) Zhou, W.; Su, X.; Tao, M.; Zhu, C.; Zhao, Q.; Zhang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14853. (m) Yao, W.; Dou, X.; Wen, S.; Wu, J.; Vittal, J. J.; Lu, Y. *Nat. Commun.* **2016**, *7*, 13024. (n) Li, S.; Liu, Y.; Huang, B.; Zhou, T.; Tao, H.; Xiao, Y.; Liu, L.; Zhang, J. *ACS Catal.* **2017**, *7*, 2805. (o) Jin, H.; Zhang, Q.; Li, E.; Jia, P.; Li, N.; Huang, Y. *Org. Biomol. Chem.* **2017**, *15*, 7097.

(3) Representative applications of intramolecular Rauhut−Currier adducts in total synthesis: (a) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737. (b) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11955. (c) Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12064. (d) Dermenci, A.; Selig, P. S.; Domaoal, R. A.; Spasov, K. A.; Anderson, K. S.; Miller, S. J. *Chem. Sci.* **2011**, *2*, 1568. (e) Jeon, S.; Han, S. *J. Am. Chem. Soc.* **2017**, *139*, 6302.

(4) For asymmetric MBH reaction of *β*,*β*-disubstituted enone, see: (a) Satpathi, B.; Ramasastry, S. S. V. *Angew. Chem., Int. Ed.* **2016**, *55*, 1777. (b) Satpathi, B.; Ramasastry, S. S. V. *Synlett* **2016**, *27*, 2178. (c) Satpathi, B.; Wagulde, S. V.; Ramasastry, S. S. V. *Chem. Commun.* **2017**, *53*, 8042.

(5) For selected reviews on asymmetric amino catalysis, see: (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360. (c) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (d) Ramachary, D. B.; Ramakumar, K. *Eur. J. Org. Chem.* **2011**, *2011*, 2599. (e) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659.

(6) Recent articles on dienamine catalysis: (a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, *2012*, 865. (b) Christmann, M.; Bräse, S. *Asymmetric synthesis: More methods and applications*, Eds.; Wiley-VCH: Weinheim, 2012; pp 43−48. (c) Silvi, M.; Cassani, C.; Moran, A.; Melchiorre, P. *Helv. Chim. Acta* **2012**, *95*, 1985. (d) Appayee, C.; Fraboni, A. J.; Brenner-Moyer, S. E. *J. Org. Chem.* **2012**, *77*, 8828. (e) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474. (f) Li, J.-L.; Zhou, S.-L.; Han, B.; Wu, L.; Chen, Y.-C. *Chem. Commun.* **2010**, *46*, 2665. (g) Arimitsu, S.; Yonamine, T.; Higashi, M. *ACS Catal.* **2017**, *7*, 4736.

(7) *α*-Selective addition of enone via amine-based dienamine activation: (a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (b) Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 3821. (c) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660. (d) Han, B.; Xiao, Y.-C.; Yao, Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 10189. (e) Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70. (f) Feng, X.; Zhou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *J. Am. Chem. Soc.* **2012**, *134*, 19942. (g) Xia, A.-B.; Xu, D.-Q.; Wu, C.; Zhao, L.; Xu, Z.-Y. *Chem. - Eur. J.* **2012**, *18*, 1055. (h) Lee, J. H.; Deng, L. *J. Am. Chem. Soc.* **2012**, *134*, 18209. (i) Tian, X.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 5360. (j) Mose, R.; Jensen, M. E.; Preegel, G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 13630.

(8) *γ*-Selective addition of enone via amine-based dienamine activation: (a) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (b) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20642. (c) Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6418. (d) Di Iorio, N.; Righi, P.; Mazzanti, A.; Mancinelli, M.; Ciogli, A.; Bencivenni, G. *J. Am. Chem. Soc.* **2014**, *136*, 10250. (e) Yin, X.; Zheng, Y.; Feng, X.; Jiang, K.; Wei, X.-Z.; Gao, N.; Chen, Y.-C. *Angew. Chem.,*

DOI: 10.1021/acs.orglett.7b03959
Org. Lett. XXXX, XXX, XXX−XXX

Int. Ed. **2014**, *53*, 6245. (f) Zou, C.; Zeng, C.; Liu, Z.; Lu, M.; Sun, X.; Ye, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 14257.

(9) Recent articles on MBH reaction via dienamine activation: (a) Chen, S.-H.; Hong, B.-C.; Su, C. F.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 8899. (b) Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *46*, 1878. (c) Vesely, J.; Dziedzic, P.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6900.

(10) Intramolecular Rauhut−Currier cyclizations of α,β-unsaturated aldehydes based on dienamine activation: (a) Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M. *Org. Lett.* **2009**, *11*, 4116. (b) Marqués-López, E.; Herrera, R. P.; Marks, T.; Jacobs, W. C.; Christmann, M. *Synthesis* **2013**, *45*, 1016.

(11) (a) Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419. (b) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871. (c) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493.

(12) (a) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742. (b) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911.

(13) For an asymmetric push−pull strategy, see: (a) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46. (b) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711. (c) Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 11114.

(14) Our contribution to asymmetric push−pull strategy: (a) Ravindra, B.; Das, B. G.; Ghorai, P. *Org. Lett.* **2014**, *16*, 5580. (b) Maity, S.; Parhi, B.; Ghorai, P. *Angew. Chem., Int. Ed.* **2016**, *55*, 7723. (c) Reddy, R. R.; Gudup, S. S.; Ghorai, P. *Angew. Chem., Int. Ed.* **2016**, *55*, 15115. (d) Hazra, G.; Maity, S.; Bhowmick, S.; Ghorai, P. *Chem. Sci.* **2017**, *8*, 3026. (e) Midya, A.; Maity, S.; Ghorai, P. *Chem. - Eur. J.* **2017**, *23*, 11216. (f) Maity, S.; Saha, M.; Hazra, G.; Ghorai, P. *Org. Lett.* **2017**, *19*, 5872.

DOI: 10.1021/acs.orglett.7b03959
Org. Lett. XXXX, XXX, XXX−XXX