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Intramolecular Mannich and Michael Annulation Reactions of Lactam Derivatives Bearing Enals To Afford Bicyclic N-Heterocycles

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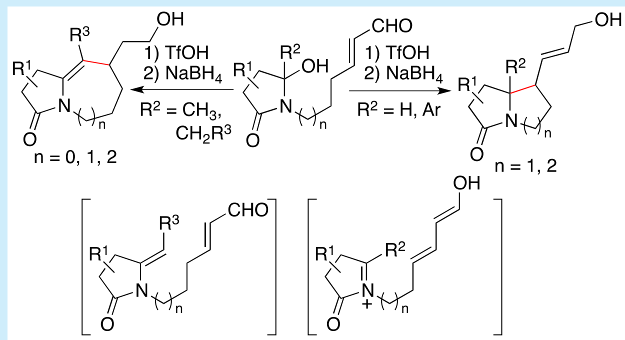
Supporting Information

ABSTRACT: Acid-catalyzed intramolecular vinylogous Mannich reactions and intramolecular Michael reactions affording pyrrolizinone-fused N-heterocycles from hydroxylactam derivatives bearing enals have been developed. Depending on the substituent on the hydroxylactam, the enal moiety acted either as a nucleophile (i.e., as an enol/enolate) or as an electrophile to react with the *N*-acyliminium ion or enamide generated from the hydroxylactam moiety, respectively. The reactions were demonstrated in the construction of fused N-heterocycles with 5- to 8-membered rings.



Bicyclic N-heterocycles bearing pyrrolidine rings or pyrrolidin-2-one moieties, such as pyrrolizines,[1] indolizines,[2] indolizinones,[2] pyrroloazepines,[3] and pyrroloazocine,[3] are present in bioactive natural products[1−3] (Figure 1).

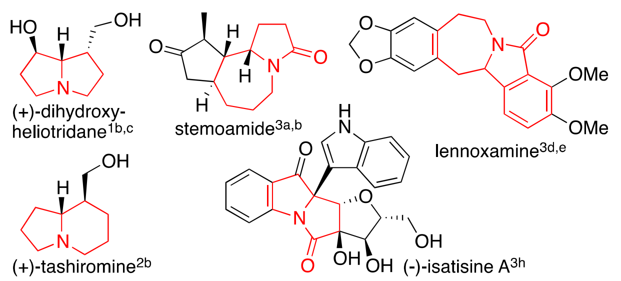
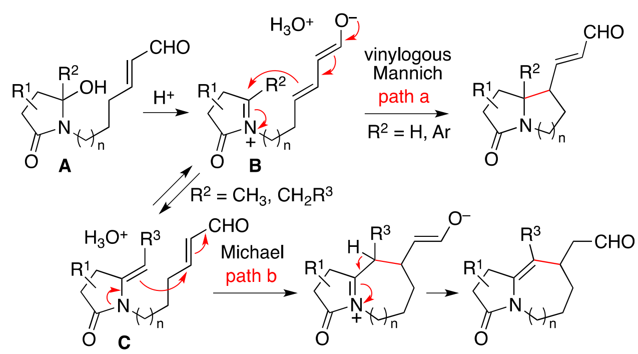


Figure 1. Bioactive natural products with pyrrolizine and related bicyclic N-heterocycle cores.

Methods for the synthesis of these N-heterocycles are of interest in drug discovery and related research.[1−3] Whereas various methods for the synthesis of the N-heterocycles have been reported, each can be used only for the synthesis of certain types of N-heterocycles.[1−4] Here we report a strategy that allows the synthesis of various pyrrolidinone-fused bicyclic N-heterocycles with different ring sizes (Scheme 1).

In our strategy, hydroxylactam enals **A** are used as starting materials. We hypothesized that, depending on the substituents on the lactam ring of **A**, the cyclization would occur either through the intramolecular vinylogous Mannich reaction of the enal enolate or the enol with the N-acyliminium ion **B** generated in situ (Scheme 1, path a) or through the intramolecular Michael addition reaction of enamide **C**,

Scheme 1. Reaction Paths Leading to Pyrrolidinone-Fused Bicyclic N-Heterocycles



which is generated from *N*-acyliminium ion **B**, with the enal moiety (Scheme 1, path b).

Hydroxylactam derivatives[5,6] have been used as starting materials for the synthesis of fused N-heterocyclic systems; in these reactions, *N*-acyliminium ions[7] are generated in situ and are used as electrophiles to react with nucleophiles to lead to the formation of a new ring.[5,6] Nucleophiles and nucleophile precursors previously used in these reactions include allylsilanes,[5a,d] alkenes,[5b,e,f,j] alkynes,[5h,k] heteroaryls,[5c,i] enamides,[5g] acetals,[5l−n] dithioacetals,[6a] and enals[5o,6c−e] (in previously reported examples, the hydroxylactam enals were used for Morita−Baylis−Hillman reactions[5o,6c−e]). In these reported reactions, for each method, the substituents on the hydroxylactam ring and the ring size that can be synthesized

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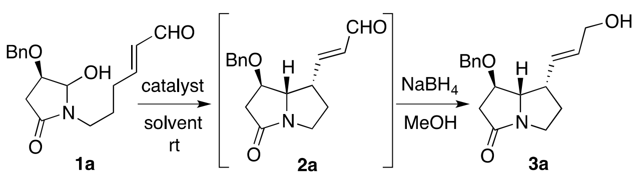
are limited. Only a few examples of construction of rings larger than six-membered rings in these reactions have been reported.[5f,g,i,l−n,6e]

We hypothesized that the use of hydroxylactam derivatives with enolizable substituents at the carbon bearing the hydroxy group would alter the reaction mode (Scheme 1, path b) and expand the range of the fused N-heterocycles that can be synthesized. When enamides would be generated from the *N*-acyliminium ions, the enamides[5g,8,9] should act as nucleophiles, and the bond formation positions will differ from those of the reactions that the *N*-acyliminium ions act as electrophiles (path a). With the reactions of the enamides, the construction of seven- and eight-membered rings should be readily achieved. We designed an *α*,*β*-unsaturated aldehyde (or enal) to serve as the reacting group with the *N*-acyliminium ions (path a) and with enamides (path b), because the *α*,*β*-unsaturated aldehyde moiety can act as a nucleophile[10] (as an enol or an enolate) and as an electrophile[11] (as a Michael reaction acceptor).

First, the Mannich reaction of the enal donor with the *N*-acyliminium ion generated in situ (Scheme 1, path a) was examined using hydroxylactam enal **1a** to afford hexahydropyrrolizinone derivative **2a**, which was directly reduced by $NaBH_4$ to give **3a** (Table 1). Enantiomerically pure hydroxylactam **1a** was synthesized from (*R*)-(+)-malic acid (Supporting Information). When TfOH was used as an acid catalyst in CH_3CN, **3a** was obtained in high yields with high diastereoselectivity (entries 3−5). Although conditions with a high loading of TfOH gave the product in a short time, the use of 0.3 equiv of TfOH relative to **1a** at room temperature (25 °C) led to the formation of the product in a high yield as almost a single diastereomer within a reasonable reaction time (75%, dr >20:1, after 20 h, entry 5).

Table 1. Screening of Catalysts and Conditions for the Formation of 2a from 1a[a]



entry	catalyst (equiv)	solvent	time (h)	yield (%)[b]	dr[c]
1	$BnNH_2$ (0.3)−PhCOOH (0.4)	CH_3CN	24	−[d]	−[d]
2	Pyrrolidine (0.3)−PhCOOH (0.4)	CH_3CN	24	−[d]	−[d]
3	TfOH (1.0)	CH_3CN	8	80	>20:1
4	TfOH (0.5)	CH_3CN	12	78	>20:1
5	TfOH (0.3)	CH_3CN	20	75	>20:1
6	TfOH (0.2)	CH_3CN	30	68	>20:1
7	TfOH (0.1)	CH_3CN	40	63	>20:1
8	TfOH (0.3)	toluene	48	<10	-
9	TfOH (0.3)	acetone	48	50	>20:1
10	TfOH (0.3)	THF	48	50	>20:1
11	TsOH (0.3)	CH_3CN	24	50	6:1
12	MeOTf (0.3)	CH_3CN	24	63	10:1
13	MsOH (0.3)	CH_3CN	36	50	10:1
14	$BF_3.OEt_3$ (0.3)	CH_3CN	24	45	10:1
15	TMSOTf (0.3)	CH_3CN	24	73	18:1
16	TfOH (0.3)	CH_3CN	72	70	>20:1
17[e]	TfOH (0.3)	CH_3CN	72	40	>20:1

[a]Reaction conditions (first step): **1a** (0.11 mmol), catalyst (equiv), solvent (1.0 mL) at room temperature (25 °C) for indicated time; see Supporting Information for details. [b]Isolated yield of **3a** from **1a**. [c]Data of **2a** before purification, determined by ^1H NMR analysis. [d]**2a** was not formed (**1a** remained). [e]Reaction at 0 °C.

In previous reports, vinylogous reactions of enals were often performed in the presence of amine-based catalysts to form enamines[10a−f] as intermediates or in the presence of metal catalysts to form enolates[10g] as intermediates. In the reaction of **1a**, the acid catalysis worked for the formation of the enol/enolate from the enal group as well as the formation of the iminium ion from the hydroxylactam to afford **2a**; the use of silyl enol ether derivatives[12] of the enal was not required to give the product.

Next, the scope of the intramolecular vinylogous Mannich reaction was evaluated using various hydroxylactam enals **1**, in which R^2 is H or Ph, to afford bicyclic N-heterocycles **3** under the conditions identified for the formation of **3a**, i.e., in the presence of TfOH (0.3 equiv) in CH_3CN (Scheme 2). For the formation of **3a−e**, single enantiomers **1a−e** were used as starting materials. Depending on the methylene chain length of **1**, five- and six-membered rings were constructed. Desired products were obtained from the reactions of hydroxylactam derivatives bearing benzyloxy, methoxy, or *p*-methoxybenzyloxy groups, dibenxyloxy groups, or fused benzene or substituted benzene rings. For the reactions constructing five-membered rings, the products were obtained as single diastereomers in most cases (dr >20:1 for **3a−c**, **3f−i**, and **3k**; dr 10:1 for **3d**). For the reactions generating six-membered rings, two diastereomers were formed, and each diastereomer of **3e** and of **3j** was isolated as the single diastereomer by usual purification. The hydroxylactam enal bearing a substituent at the enal *α*-position was also converted to the desired product (formation of **3h**). The pyrrolizinone derivative bearing a tetrasubstituted carbon center was also constructed (formation of **3i**). The hydroxylactam bearing an enone moiety instead of an enal moiety also afforded the corresponding desired product (formation of **3k**). Whereas five- and six-membered rings were readily constructed through the intramolecular vinylogous Mannich reactions, formation of seven-membered rings was not observed under the same conditions.

The stereochemistries of **3a** and (±)-**2f** were determined to be as shown in Scheme 2 by X-ray crystal structural analysis of their derivatives (see below and the Supporting Information).

Next, the intramolecular Michael reactions via the formation of the enamides (Scheme 1, path b) were examined (Scheme 3). When the reaction to form **3l** was tested in the presence of TfOH (0.3 equiv to **1**) in CH_3CN, which was the same conditions used for the intramolecular Mannich reactions to form **3a−k**, the reaction was faster than the reactions shown in Scheme 2. Reducing the loading of TfOH to 0.1 equiv to **1** also afforded **3l** in the same yield. Thus, the intramolecular Michael reactions of various substrates **1l−u** were performed in the presence of TfOH (0.1 equiv). In all the cases, the intramolecular Michael reaction step was completed within 1 h. Depending on the chain length between the amide group nitrogen and the enal group, products with six-, seven-, and eight-membered rings **3l−u** were obtained. Although the reactions were performed in the presence of TfOH, product **3r**, which has an acetal group, was obtained from **1r**. Product **3u**, which has an oxygen-containing eight-membered ring, was also obtained.

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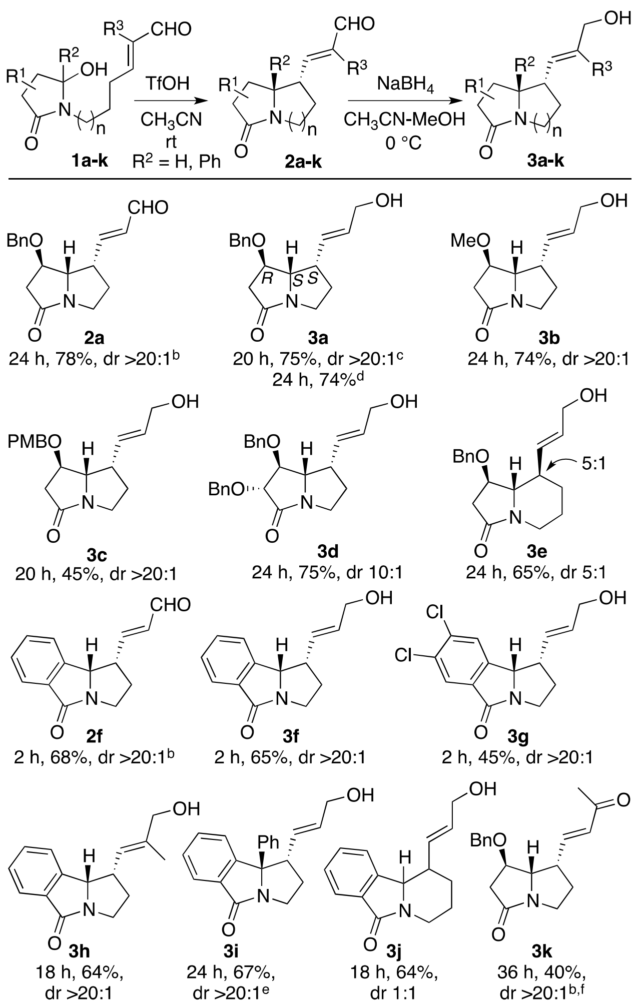
Scheme 2. Scope of the Intramolecular Vinylogous Mannich Reactions[a]



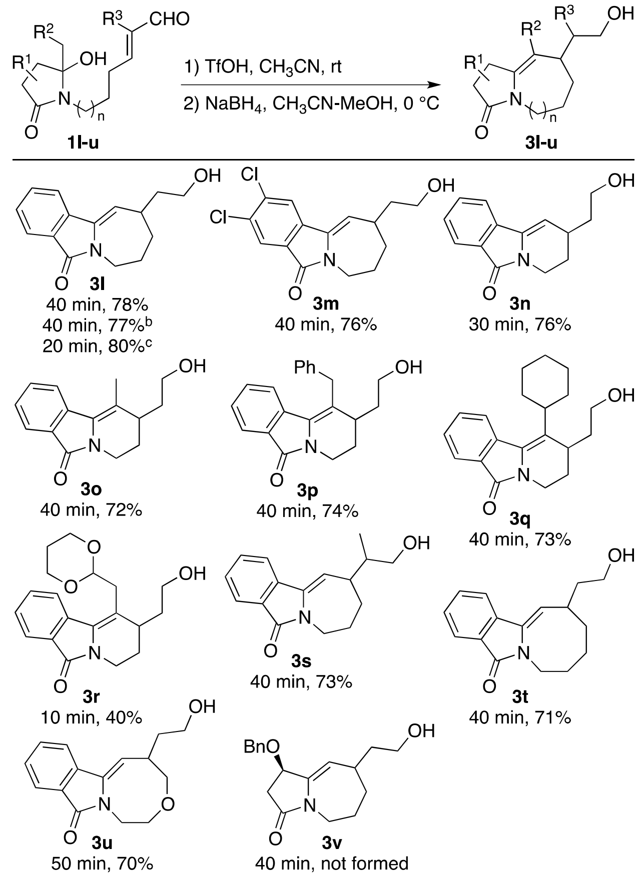
[a]Conditions: **1** (0.1 mmol, 1.0 equiv) and TfOH (0.3 equiv) in CH_3CN (1.0 mL) at rt (25 °C) for the indicated time, then reduction using $NaBH_4$, except where noted. Isolated yield of **3** from **1** is listed. The dr values of **2** determined by ^1H NMR analysis before purification are shown. [b]No reduction step was used. [c]Data taken from Table 1, entry 5. [d]A 1 g-scale reaction; **1a** (3.6 mmol). [e]Formation of **2** was performed in THF. [f]Corresponding ketone (not aldehyde) was used as the starting material.

Whereas aryl-group-fused hydroxylactam enals afforded the intramolecular Michael reaction products, product **3v** was not formed from the corresponding starting material under the same conditions as those used for the formation of **3l–u**.

When the reaction of the formation of **1l** was stopped at an early stage of the reaction, enamide **4** and **2l** were obtained (Scheme 4). When enamide **4** was treated under the same conditions with TfOH, product **2l** was formed. These results indicate that the enamide is the intermediate of the reaction for the formation of **2l** from **1l**. Similarly, (*E*)- and (*Z*)-isomers of enamide **5** were isolated, and these were also transformed to product **2p** (Scheme 4).

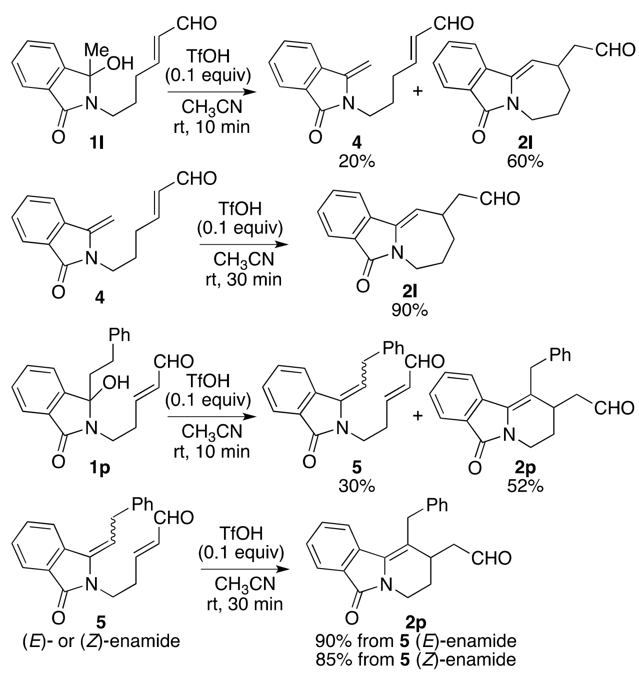
In previously reported reactions, when five-membered hydroxylactam derivatives with enolizable substituents at the carbon bearing the hydroxy group were used for the formation of fused N-heterocycles, products obtained were only through the *N*-acyliminium ions.[5c,d,l] Thus, the formation of the

Scheme 3. Scope of the Intramolecular Michael Reactions



[a]Conditions: **1** (0.1 mmol, 1.0 equiv) and TfOH (0.1 equiv) in CH_3CN (1.0 mL) at rt (25 °C) for the indicated time, then reduction using $NaBH_4$. [b]A 1-g scale reaction. [c]TfOH (0.3 equiv).

Scheme 4. Isolation of Enamide Intermediates and the Reactions of the Enamides



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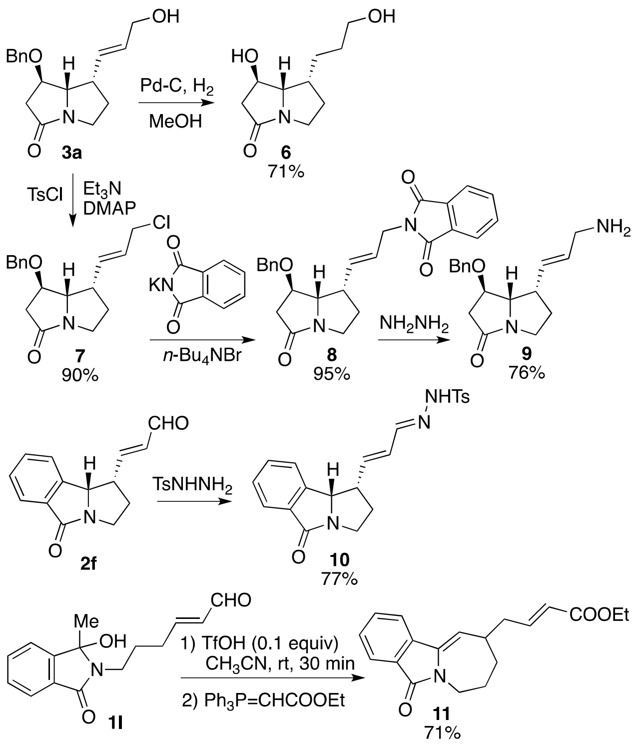
enamide intermediates to lead to products **3l−u** shown in Scheme 3 is notable.

To demonstrate the utility of the reactions, products **2** and **3** were transformed to various derivatives **6−11** (Scheme 5; see

Scheme 5. Transformations of the Products



also Supporting Information for additional transformations). X-ray crystal structural analyses of **8** and **10** (CCDC 1950699 and CCDC 1950700, respectively) were used to deduce the stereochemistry of **3a** and **3f**, respectively. Further, direct transformation after the intramolecular Michael reaction was also tested; the intramolecular Michael addition reaction of **1l** followed by Wittig reaction afforded **12** in one pot.

In summary, we have developed intramolecular vinylogous Mannich reactions and intramolecular Michael reactions of hydroxylactam derivatives bearing enal groups to afford pyrrolidinone-fused N-heterocycles. With these reactions, oxy-functionalized products retaining the starting material chirality and benzene-fused products were synthesized. Depending on the substituent on the hydroxylactam derivatives, the C−C bond formation proceeded through either the enal enolate (or enol) addition to the N-acyliminium ion or the enamide addition to the enal. With a nonenolizable substituent, a pyrrolizinone derivative bearing a tetrasubstituted carbon center was obtained. With enolizable substituents, construction of rings larger than a six-membered ring was achieved. Our strategy allowed the construction of five- to eight-membered rings to lead to various pyrrolidinone-fused N-heterocycles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03210.

Experimental procedures, characterization data of compounds (PDF)

NMR spectra (PDF, PDF, PDF)

Accession Codes

CCDC 1950699−1950700 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.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2017**, *34*, 62. (b) Mulzer, J.; Scharp, M. *Synthesis* **1993**, *1993*, 615. (c) Hashimura, K.; Tomita, S.; Hiroya, K.; Ogasawara, K. A. *J. Chem. Soc., Chem. Commun.* **1995**, 2291.

(2) (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (b) Suga, H.; Hashimoto, Y.; Yasumura, S.; Takezawa, R.; Itoh, K.; Kakehi, A. *J. Org. Chem.* **2013**, *78*, 10840. (c) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988.

(3) (a) Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokoyama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. *J. Am. Chem. Soc.* **2017**, *139*, 18386. (b) Hou, Y.; Shi, T.; Yang, Y.; Fan, X.; Chen, J.; Cao, F.; Wang, Z. *Org. Lett.* **2019**, *21*, 2952. (c) Miloserdov, F. M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393. (d) Taniguchi, T.; Iwasaki, K.; Uchiyama, M.; Tamura, O.; Ishibashi, H. *Org. Lett.* **2005**, *7*, 4389. (e) Yao, T.; Guo, Z.; Liang, X.; Qi, L. *J. Org. Chem.* **2018**, *83*, 13370. (f) Zhu, W.; Tong, S.; Zhu, J.; Wang, M.-X. *J. Org. Chem.* **2019**, *84*, 2870. (g) Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. *Org. Lett.* **2015**, *17*, 4838. (h) Zhang, X.; Mu, T.; Zhan, F.; Ma, L.; Liang, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 6164. (i) Volvoikar, P. S.; Tilve, S. G. *Tetrahedron Lett.* **2018**, *59*, 2567.

(4) (a) Honma, T.; Hashimoto, N.; Hayashi, K.; Kawanishi, N.; Fukasawa, K.; Takaki, T.; Ikeura, C.; Ikuta, M.; Suzuki-Takahashi, I.; Hayama, T.; Nishimura, S.; Morishima, H. *J. Med. Chem.* **2001**, *44*, 4628. (b) Boulahjar, R.; Ouach, A.; Matteo, C.; Bourg, S.; Ravache, M.; Guevel, R. L.; Marionneau, S.; Oullier, T.; Lozach, O.; Meijer, L.; Guguen-Guillouzo, C.; Lazar, S.; Akssira, M.; Troin, Y.; Guillaumet, G.; Routier, S. *J. Med. Chem.* **2012**, *55*, 9589. (c) Chiurato, M.; Routier, S.; Troin, Y.; Guillaumet, G. *Eur. J. Org. Chem.* **2009**, *2009*, 3011. (d) Oukoloff, K.; Buron, F.; Routier, S.; Jean, L.; Renard, P.-Y. *Eur. J. Org. Chem.* **2015**, *2015*, 2450. (e) Saikia, A. K.; Das, M. *J. Org.*

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Org. Lett. XXXX, XXX, XXX−XXX

Chem. **2018**, *83*, 6178. (f) Zeidan, N.; Beisel, T.; Ross, R.; Lautens, M. *Org. Lett.* **2018**, *20*, 7332.
(5) (a) Park, Y.; Schindler, C. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 14848. (b) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (c) Raheem, I.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (d) Liu, H.; Yu, J.; Li, X.; Yan, R.; Xiao, J.-C.; Hong, R. *Org. Lett.* **2015**, *17*, 4444. (e) Li, X.; Li, C.; Zhang, W.; Lu, X.; Han, S.; Hong, R. *Org. Lett.* **2010**, *12*, 1696. (f) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036. (g) Andna, L.; Miesch, L. *Org. Lett.* **2018**, *20*, 3430. (h) Gharpure, S.; Shelke, Y. G.; Kumar, D. P. *Org. Lett.* **2015**, *17*, 1926. (i) Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMills, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914. (j) Indukuri, K.; Unnava, R.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 10629. (k) Das, M.; Saikia, A. K. *J. Org. Chem.* **2018**, *83*, 6178. (l) Srinivas, K.; Singh, N.; Das, D.; Koley, D. *Org. Lett.* **2017**, *19*, 274. (m) Koley, D.; Srinivas, K.; Krishna, Y.; Gupta, A. *RSC Adv.* **2014**, *4*, 3934. (n) Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13196. (o) Alonso-Fernandez, J.; Benaiges, C.; Casas, E.; Alibes, R.; Bayon, P.; Busque, F.; Alvarez-Larena, A.; Figueredo, M. *Tetrahedron* **2016**, *72*, 3500.
(6) Alkoxylactam and acyloxylactam derivatives have also been used for the synthesis of fused N-heteocycles: (a) Chamberlin, A. R.; Chung, J. Y. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (b) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833. (c) Myers, E. L.; de Vries, J. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1893. (d) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Chem. - Eur. J.* **2009**, *15*, 12754. (e) Kurasaki, H.; Okamoto, I.; Morita, N.; Tamura, O. *Org. Lett.* **2009**, *11*, 1179. (f) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070.
(7) Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811.
(8) (a) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. (b) Wang, M.-X. *Chem. Commun.* **2015**, *51*, 6039.
(9) (a) Yang, L.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Am. Chem. Soc.* **2009**, *131*, 10390. (b) Yang, L.; Lei, C.-H.; Huang, Z.-T.; Wang, M.-X. *Org. Lett.* **2010**, *12*, 3918. (c) Tong, S.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2012**, *51*, 4417. (d) He, L.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2014**, *16*, 5972. (e) Xu, X.-M.; Lei, C.-H.; Tong, S.; Zhu, J.; Wang, M.-X. *Org. Chem. Front.* **2018**, *5*, 3138. (f) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708. (g) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833. (h) Ryder, G. M.; Wille, U.; Willis, A. C.; Pyne, S. G. *Org. Biomol. Chem.* **2019**, *17*, 7025.
(10) Examples of vinylogous reactions of enals (enals act as nucleophiles): (a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (c) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540. (d) Basu, S.; Gupta, V.; Nickel, J.; Schneider, C. *Org. Lett.* **2014**, *16*, 274. (e) Feng, J.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2017**, *82*, 1412. (f) Kutwal, M. S.; Dev, S.; Appayee, C. *Org. Lett.* **2019**, *21*, 2509. (g) Zhong, F.; Yue, W.-J.; Zhang, H.-J.; Zhang, C.-Y.; Yin, L. *J. Am. Chem. Soc.* **2018**, *140*, 15170.
(11) Examples of Michael addition reactions to enals: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Austin, J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (d) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (e) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540. (f) Dell'Amico, L.; Albrecht, L.; Naicker, T.; Poulsen, P. H.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 8063. (g) Guo, Q.; Fraboni, A. J.; Brenner-Moyer, S. E. *Org. Lett.* **2016**, *18*, 2628. (h) Hayashi, Y.; Umekubo, N. *Angew. Chem., Int. Ed.* **2018**, *57*, 1958. (i) Hayashi, Y.; Yamada, T.; Sato, M.; Watanabe, S.; Kwon, E.; Iwasaki, K.; Umemiya, S. *Org. Lett.* **2019**, *21*, 5183. (j) Marshall, J. A.; Herold, M.; Eidam, H. S.; Eidam, P. *Org. Lett.* **2006**, *8*, 5505. (k) Palais, L.; Babel, L.; Quintard, A.; Belot, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 1988.
(12) (a) Gieseler, M. T.; Kalesse, M. *Org. Lett.* **2011**, *13*, 2430. (b) Gonzales, A. S.; Arrayas, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335.

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