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Enantioselective Construction of Spirocyclic Oxindole Derivatives with Multiple Stereocenters via an Organocatalytic Michael/Aldol/Hemiacetalization Cascade Reaction

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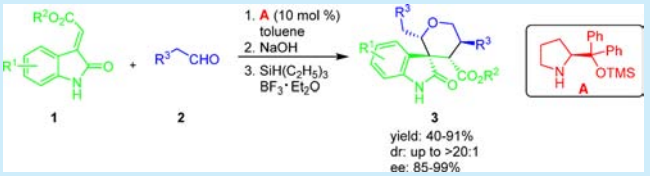
Supporting Information

ABSTRACT: An efficient organocatalytic Michael/aldol/hemiacetalization cascade reaction for construction of enantioenriched spirocyclic oxindoles fused with tetrahydropyrane has been developed. The desired highly functionalized 5′,6′-dihydro-2′*H*,4′*H*-spiro[indoline-3,3′-pyran]-2-one derivatives containing multiple stereogenic centers were obtained in moderate to high chemical yields and with high stereoselectivities.



The spirocyclic oxindole framework, which represents a privileged heterocyclic motif, widely exists in natural alkaloids and pharmacologically interesting compounds.[1] Particularly, the oxindole fused sophisticated structures with a tetrahydropyrane or chroman moiety (by means of oxa-spirooxindole) at the C3 position were documented as possessing remarkable biological activities (Figure 1).[2] Due to

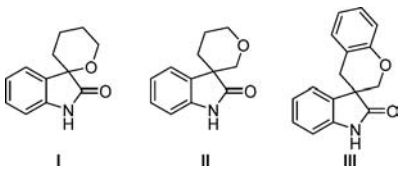


Figure 1. Tetrahydropyrane and chromane fused spirocyclic oxindole skeletons.

their significant medicinal value and structural complexities, these intriguing frameworks have emerged as attractive synthetic targets.[3] As such, a number of synthetic methods have been developed in pursuit of these kind of diversely functionalized spirocyclic oxindoles, including intermolecular alkylation,[4] transition metal mediated reactions,[5] cycloadditions,[6] sigmatropic rearrangements,[7] and organocatalytic tandem reactions.[8,9] However, methods toward the synthesis of oxa-spirooxindole derivatives in a catalytic asymmetric manner are still limited. There are some reports on stereoselective access to 3′,4′,5′,6′-tetrahydrospiro[indoline-3,2′-pyran]-2-type **I** and spiro[chromane-3,3′-indolin]-2′-type **III**, such as the oxa-Diels–Alder reaction,[10] Prins cyclization,[11] vinylogous aldol reaction,[12] and multicomponent cascade reaction.[13] However, to date, successful examples for the assembly of optically active 5′,6′-dihydro-2′*H*,4′*H*-spiro-[indoline-3,3′-pyran]-2-one **II** derivatives still remain unexplored. Due to our continued interest in organocatalytic cascade reactions, we became interested in developing a novel and efficient strategy for the enantioselective construction of the highly functionalized 5′,6′-dihydro-2′*H*,4′*H*-spiro[indoline-3,3′-pyran]-2-one **II** skeleton of biological significance.

To address this challenge, we sought to design an enantioselective domino reaction that would ideally involve the reaction of two simple and easily accessible starting materials. In 2010, Chen and co-workers reported an organocatalytic asymmetric [2 + 2 + 2] annulation reaction of cinnamaldehyde, aliphatic aldehydes and electron-deficient C═C and C═N double bond oxindole derivatives, affording the desired spirocyclic oxindoles in excellent results[14] (Scheme 1a). In this strategy, a Michael addition of aliphatic aldehyde to an electron-deficient oxindole olefin motif catalyzed by a chiral amine catalyst occurred with the generation of intermediate **IV** for the first step, followed by the reaction between **IV** and the other electrophile at the C3 position of the oxindole skeleton. After further intramolecular cyclization, the spirocyclic oxindole derivative was finally afforded. Given the fact that carbonyl compounds could be excellent electrophiles in many organic reactions, we envision if another molecule of aldehyde is used as the electrophile after the formation of **IV**, an aldol reaction of **IV** with the aldehyde would happen to afford intermediate **V**, and further hemiaminalization will provide a new tetrahydropyrane fused spirocyclic oxindole derivative. As part of our ongoing research on spirocyclic oxindoles,[15] we described herein an organocatalytic tandem reaction for the synthesis of chiral spirocyclic oxindoles with functional diversity through a rationally designed organocatalytic Michael/aldol/hemiacetalization cascade reaction strategy (Scheme 1b).

Our investigation started from the reaction of the organocatalytic Michael addition of aliphatic aldehydes and electron deficient olefin oxindoles. Indeed, the Michael addition reaction of ethyl (*E*)-2-(2-oxoindolin-3-ylidene)acetate **1a** (1.0 equiv)

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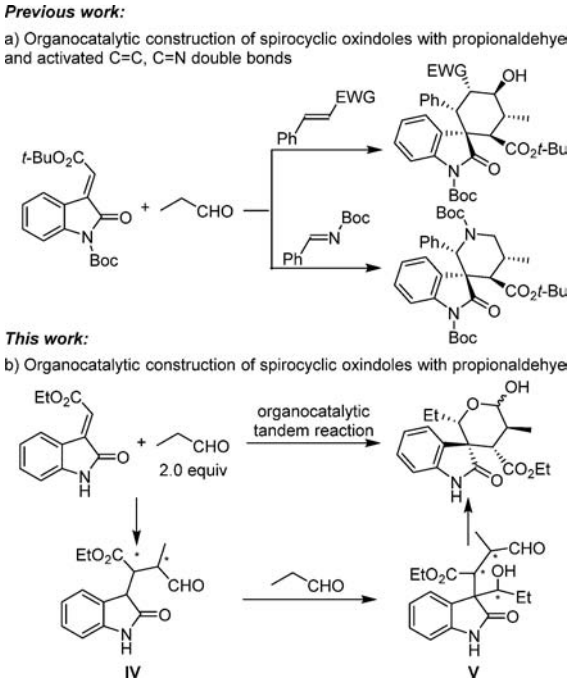
Scheme 1. Reaction of 3-Ylideneoxindoles, Propionaldehyde, and Different Electrophiles



and propionaldehyde **2a** (5.0 equiv) in the presence of chiral amine **A** (10 mol %) proceeded well at room temperature, and the Michael adduct could be afforded in high yield within 2 h. Unlike the cascade enamine−iminium−enamine sequence reported by Enders and co-workers, the 1,2-addition for the second step will not happen automatically, since a base is needed. When 1.0 equiv of $K_3PO_4·3H_2O$ was added to the reaction of the above-mentioned Michael adduct and propionaldehyde, the aldol/hemiaminalization reactions proceeded smoothly and afforded the desired spirocyclic oxindole hemiaminals in good yield but with low diastereoselectivity. To avoid this problem, the hemiaminals were directly reduced by Et_3SiH to give the tetrahydropyrane fused spirooxindole **3a** quantitatively. Then, a one-pot three-step reaction of the (*E*)-2-(2-oxoindolin-3-ylidene)acetate **1a** (1.0 equiv) and propionaldehyde **2a** (5.0 equiv) was carried out. Interestingly, **3a** was obtained in high yield (90%) and with good stereoselectivity (dr, 8:1; ee, 78%) (Scheme 2).

Further optimization of the reaction conditions was carried out in the presence of **A** by using different solvents, bases, and reaction temperatures (Table 1). From Table 1, we can see that

Scheme 2. Organocatalytic Michael/Aldol/ Hemiacetalization Cascade Reaction Strategy

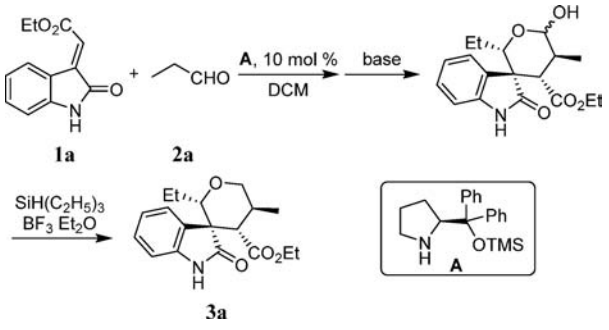
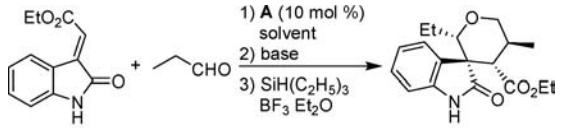


Table 1. Reaction Condition Optimization[a]



entry	base	solvent	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	$K_3PO_4·3H_2O$	DCM	90	8:1	78
2	$K_3PO_4·3H_2O$	H_2O	53	5:1	92
3	$K_3PO_4·3H_2O$	toluene	78	>20:1	89
4	$K_3PO_4·3H_2O$	Et_2O	52	3:1	89
5	$K_3PO_4·3H_2O$	DCE	90	>20:1	83
6	$K_3PO_4·3H_2O$	*n*-hexane	32	9:1	91
7	KOH	toluene	40	>20:1	93
8	CH_3CH_2ONa	toluene	60	>20:1	96
9	**NaOH**	**toluene**	**75**	**>20:1**	**98**
10	DIPEA	toluene	trace	—	—
11	DMAP	toluene	trace	—	—
12[e]	NaOH	toluene	66	>20:1	94
13[f]	NaOH	toluene	60	>20:1	93

[a]General conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), base (0.1 mmol), **A** (0.01 mmol), triethylsilane (0.3 mmol), and boron trifluoride etherate (0.3 mmol), solvent (1 mL) at rt. [b]Isolated yields after column chromatography. [c]Determined by ^{1}HNMR analysis. [d]Enantiomeric excess of **3a**, determined by HPLC on a chiral stationary phase (see the Supporting Information). [e]The reaction was carried out at 0 °C. [f]The reaction was carried out at −10 °C.

the yield and diastereoselectivity were significantly influenced when the reaction was carried out in different solvents. However, no significant variation in enantioselectivity was observed except DCM (78%) and DCE (83%) (Table 1, entries 1−6), and toluene proved to be the best. The desired product **3a** was obtained in 78% yield, 89% ee, and >20:1 dr. Next, a series of bases were tested. When inorganic bases such as NaOH, KOH, and EtONa were used, the enantioselectivity of **3a** was increased to > 90% and the diastereoselectivity was maintainable. The highest yield (75%) could be obtained with NaOH as the base in the reaction (Table 1, entries 7−9). However, the organic bases were found to be inferior for the reaction; only a trace amount of the desired product was detected (Table 1, entries 10−11). A further decrease of the reaction temperature to 0 °C and − 10 °C resulted in a slight decrease of the yield and enantioselectivity (Table 1, entries 12−13).

With the optimized reaction conditions in hand, we next explored the substrate scope of this cascade reaction (Table 2). It was found that the reaction could accommodate a broad range of substituted 3-ylideneoxindoles and provided the desired products in moderate to good yields with good to excellent diastereo- and enantioselectivities. 3-Ylideneoxindoles **3b−f** with different substitution groups at the C5−7 position had no significant impact on the yields and stereoselectivities. All desired spirooxindoles were afforded in 75−91% yields, >20:1 dr, and >97% ee (entries 2−8). The 3-ylideneoxindoles with methyl and benzyl esters were also good substrates for the reaction and provided the desired products in moderate to good yields and diastereoselectivities with excellent enantioselectivities (entries 9−13). Notably, the molecular diversity of the spirooxindole derivatives could be easily improved by changing the propionaldehyde to other aliphatic aldehydes. For most cases examined, slightly lower yields were observed, but

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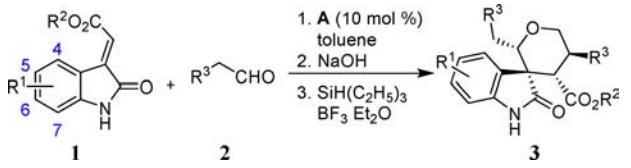
Table 2. Exploration of Substrate Scope[a]

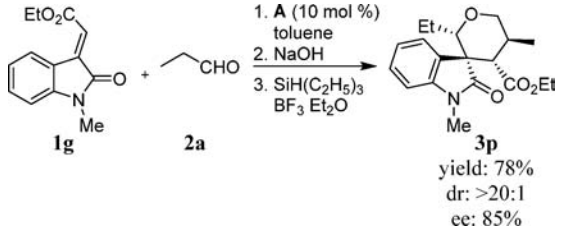


entry	R^1	R^2	R^3	3	yield (%)[b]	dr[c]	ee (%)[d]
1	H	Et	Me	**a**	75	>20:1	98
2	5-F	Et	Me	**b**	87	>20:1	98
3	5-Cl	Et	Me	**c**	89	>20:1	98
4	5-Br	Et	Me	**d**	83	>20:1	98
5	5-Me	Et	Me	**e**	75	>20:1	97
6	5-OMe	Et	Me	**f**	91	>20:1	98
7	6-Br	Et	Me	**g**	87	>20:1	99
8	5,7-$(Me)_2$	Et	Me	**h**	85	>20:1	96
9	H	Me	Me	**i**	83	>20:1	99
10	5-Me	Me	Me	**j**	47	20:1	91
11	H	Me	*n*-Pr	**k**	65	5:1	99
12	H	Me	*n*-Bu	**l**	67	12:1	99
13	H	Bn	Me	**m**	40	20:1	99
14	5-Cl	Et	Et	**n**	45	20:1	93
15	5-F	Et	*i*-Pr	**o**	46	20:1	85

[a]General conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), **A** (0.01 mmol), triethylsilane (0.3 mmol), and boron trifluoride etherate (0.3 mmol), toluene (1 mL) under rt. [b]Isolated yields after column chromatography. [c]Determined by ^{1}HNMR analysis. [d]Determined by HPLC on a chiral stationary phase.

the stereoselectivities were manitained at good to excellent levels (entries 11−12, 14−15). Furthermore, *N*-methyl protected oxindole olefin **1g** could also give desired product **3p** in good yield and with excellent diastereoselectivity, although the ee was lowered to 85% (Scheme 3).

Scheme 3. Reaction of *N*-Methyl Protected (*E*)-2-(2-Oxoindolin-3-ylidene)acetate and Propionaldehyde



To determine the stereochemistry of the tetrahydropyrane fused spirooxindoles, the absolute configuration of **3b** was confirmed by X-ray crystallographic analysis (Figure 2, CCDC 1439587). Catalyst **A** derived from L-proline exclusively provided ethyl (2′*S*,3*R*,4′*S*,5′*S*)-2′-ethyl-5-fluoro-5′-methyl-2-oxo-5′,6′-dihydro-2′*H*,4′*H*-spiro[indoline-3,3′-pyran]-4′-carboxylate (**3b**).

In conclusion, we have demonstrated herein an efficient organocatalytic Michael/aldol/hemiacetalization cascade reaction for the construction of enantio-enriched spirocyclic oxindoles fused with tetrahydropyrane. The desired tetrahydropyrane fused spirooxindole derivatives bearing four consecutive stereogenic centers were obtained in moderate to good yields and with high stereoselectivities in a one-pot manner. Further investigations of organocatalytic synthesis of other heterocyclic compounds with multiple chiral centers by using a similar strategy are underway in our laboratory.

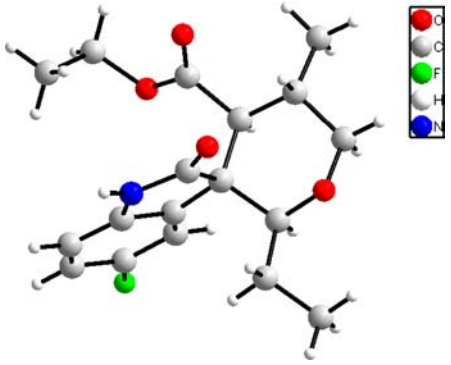


Figure 2. X-ray crystal structure of **3b**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00873.

Experimental procedures, spectral data, and X-ray data for all new compounds (PDF)

Crystallographic data for **3b** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews of spirooxindoles, see: (a) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (c) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (d) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (e) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (f) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36.

(2) (a) Padiya, K. J.; Nair, P. S.; Pal, R. R.; Chaure, G. S.; Gudade, G. B.; Parkale, S. S.; Manojkumar, V. L.; Swapnil, R. B.; Smita, A. B.; Sachin, D. S.; Palle, V. P.; Kamboj, R. K. Int. Patent WO2012/049555A1, 2012. (b) Kouznetsov, V. V.; Arenas, D. R. M.; Arvelo, F.; Forero, J. S. B.; Sojo, F.; Munoz, A. *Lett. Drug Des. Discovery* **2010**, *7*, 632. (c) Patel, D. V.; Gless, R. D. J.; Webb, H.; Heather, K.; Anandan, S. K.; Aavula, B. R. Int. Patent WO2008/073623A2, 2008.

(3) Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054.

DOI: 10.1021/acs.orglett.6b00873
Org. Lett. 2016, 18, 2387−2390

(4) (a) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043. (b) Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249.
(5) For a review, see: Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *2011*, 6821.
(6) (a) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem. - Eur. J.* **2010**, *16*, 12541. (b) Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120. (c) Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **2003**, *59*, 4615.
(7) (a) Cao, T.; Linton, E. C.; Deitch, J.; Berritt, S.; Kozlowski, M. C. *J. Org. Chem.* **2012**, *77*, 11034. (b) Ignatenko, V. A.; Zhang, P.; Viswanathan, R. *Tetrahedron Lett.* **2011**, *52*, 1269. (c) Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 3858. (d) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162. (e) Kawasaki, T.; Ogawa, A.; Terashima, R.; Saheki, T.; Ban, N.; Sekiguchi, H.; Sakaguchi, K.; Sakamoto, M. *J. Org. Chem.* **2005**, *70*, 2957. (f) Mao, Z.; Baldwin, S. W. *Org. Lett.* **2004**, *6*, 2425. (g) Booker-Milburn, K. I.; Fedouloff, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 4657. (h) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327.
(8) For a review, see: Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023.
(9) For selected examples, see: (a) Wu, M.-Y.; He, W.-W.; Liu, X.-Y.; Tan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 9409. (b) Chen, L.; Wu, Z.-J.; Zhang, M.-L.; Yue, D.-F.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 12668. (c) Cheng, J.-T.; Chen, X.-Y.; Gao, Z.-H.; Ye, S. *Eur. J. Org. Chem.* **2015**, *2015*, 1047. (d) Duan, S.-W.; Li, Y.; Liu, Y.-Y.; Zou, Y.-Q.; Shi, D.-Q.; Xiao, W.-J. *Chem. Commun.* **2012**, *48*, 5160. (e) Tan, B.; Candeias, N. R.; Barbas, C. F., III *Nat. Chem.* **2011**, *3*, 473. (f) Tan, B.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2011**, *133*, 4672. (g) Jiang, K.; Jia, Z.-J.; Chen, S.; Wu, L.; Chen, Y.-C. *Chem. - Eur. J.* **2010**, *16*, 2852.
(10) (a) Liu, L.; Daka, P.; Sarkisian, R.; Deng, Y.-M.; Wheeler, K.; Wang, H. *Synthesis* **2014**, *46*, 1339. (b) Zheng, J.-F.; Lin, L.-L.; Fu, K.; Zhang, Y.-L.; Liu, X.-H.; Feng, X.-M. *Chem. - Eur. J.* **2014**, *20*, 14493. (c) Cui, H.-L.; Tanaka, F. *Chem. - Eur. J.* **2013**, *19*, 6213. (d) Wang, J.-Q.; Crane, E. A.; Scheidt, K. A. *Org. Lett.* **2011**, *13*, 3086. (e) Ueno, S.; Ohtsubo, M.; Kuwano, R. *Org. Lett.* **2010**, *12*, 4332. (f) Shintani, R.; Hayashi, S.-Y.; Murakami, M.; Takeda, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3754. (g) Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5820.
(11) (a) Damera, K.; Yu, B.-C.; Wang, B.-H. *J. Org. Chem.* **2015**, *80*, 5457. (b) Subba Reddy, B. V.; Ghanty, S. *Synth. Commun.* **2014**, *44*, 2545. (c) Castaldi, M. P.; Troast, D. M.; Porco, J. A. *Org. Lett.* **2009**, *11*, 3362.
(12) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.-Q.; Yang, W.-G.; Tan, D.; Huang, K.-W.; Jiang, Z.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 6666.
(13) (a) Huang, Y.-M.; Zheng, C.-W.; Chai, Z.; Zhao, G. *Adv. Synth. Catal.* **2014**, *356*, 579. (b) Xie, X.; Peng, C.; He, G.; Leng, H.-J.; Wang, B.; Huang, W.; Han, B. *Chem. Commun.* **2012**, *48*, 10487.
(14) Jiang, K.; Jia, Z.-J.; Chen, S.; Wu, L.; Chen, Y.-C. *Chem. - Eur. J.* **2010**, *16*, 2852.
(15) (a) Xie, D.-B.; Yang, L.-M.; Lin, Y.-Q.; Zhang, Z.-M.; Chen, D.-D.; Zeng, X.-F.; Zhong, G.-F. *Org. Lett.* **2015**, *17*, 2318. (b) Lin, Y.-Q.; Yang, L.-M.; Deng, Y.; Zhong, G.-F. *Chem. Commun.* **2015**, *51*, 8330. (c) Tan, B.; Zhang, X.; Zhong, G.-F. *ARKIVOC* **2014**, *3*, 124. (d) Yang, L.-M.; Wang, F.; Chua, P. J.; Lv, Y.-B.; Zhong, L.-J.; Zhong, G.-F. *Org. Lett.* **2012**, *14*, 2894. (e) Tan, B.; Zeng, X.-F.; Leong, W. W. Y.; Shi, Z.-G.; Barbas, C. F., III; Zhong, G.-F. *Chem. - Eur. J.* **2012**, *18*, 6414.

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