Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Asymmetric Organocatalytic Sequential Reaction of Structurally Complex Cyclic Hemiacetals and Functionalized Nitro-olefins To Synthesize Diverse Heterocycles

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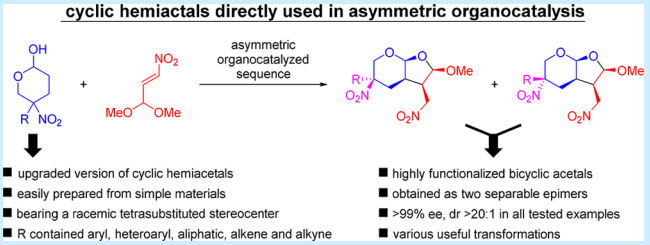
Supporting Information

ABSTRACT: Structurally complex cyclic hemiacetals bearing a racemic tetrasubstituted stereocenter have been prepared in a concise manner and were successfully used in an organocatalytic enantioselective sequence to react with functionalized nitro-olefins, providing bicyclic acetal-containing compounds as two separable epimers with excellent stereoselectivity. The reaction showed broad substrate scope, with respect to the starting hemiacetals. Moreover, this protocol allows the synthetic transformation of the products to various interesting heterocyclic compounds with substantial structural diversity and broad functionality.

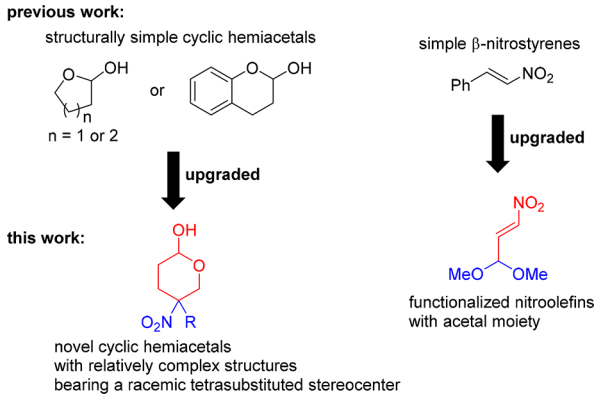


The chiral cyclic acetal moiety is found as a key structural subunit in many bioactive natural products and pharmaceutically active compounds.[1] This structural subunit can also be found in many versatile synthetic building blocks of value for constructing complex oxygen-containing heterocycles.[2] Thus, the development of concise and efficient enantioselective routes to molecules bearing chiral cyclic acetal moieties is of great interest.

One of the most straightforward strategies is the direct modification of cyclic acetal- or hemiacetal-containing compounds, which provides rapid access to highly functionalized cyclic acetal- or hemiacetal-containing products for further useful transformations. Recently, we[3] and other researchers[4] have demonstrated that cyclic hemiacetals can be directly used as attractive precursors under enamine catalysis to access functionalized hemiacetal-containing products, which are useful intermediates for the synthesis of structurally and stereochemically diverse molecules. However, despite these impressive achievements, there are still certain shortcomings of these useful synthetic strategies (Scheme 1, top), which include (1) the application of starting cyclic hemiacetals with relatively simple structures; and (2) the employment of β-nitrostyrenes as reaction partners, with examples of such asymmetric reactions with functionalized nitro-olefins being much less developed,[4c] despite their potential to transform to structurally diverse products.

It is well-known that flash chromatography provides a rapid and inexpensive general method for the preparative separation of organic compounds.[5] Indeed, we found that this widely used purification protocol could be applied to separate the mixture of two epimeric products, which contain an acetal or hemiacetal structural moiety.[6] These characteristic features led us to speculate that, by the introduction of a racemic tetrasubstituted carbon center to enhance the structural complexity of the starting hemiacetals, two separated epimers might be finally obtained from stereoselective reactions after SiO_2 flash chromatography purification. Note that this designed strategy potentially provides an alternative approach for rapid assembly of molecules bearing a tetrasubstituted carbon stereogenic center, since the construction of tetrasubstituted carbon stereogenic center represents a very challenging, but demanding, area in organic synthesis.[7]

Scheme 1. Upgraded Version of Both Cyclic Hemiacetals and Nitro-olefins

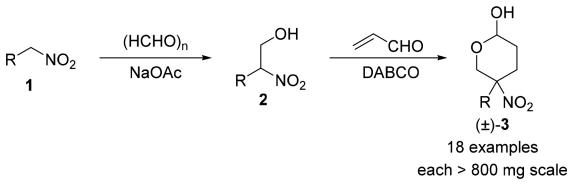


Received: May 1, 2018

DOI: 10.1021/acs.orglett.8b01386
Org. Lett. XXXX, XXX, XXX−XXX

With these considerations in mind, and as a continuation of our ongoing investigations on the development of new asymmetric organocatalytic approaches to construct chiral heterocyclic molecules applying cyclic hemiacetals as the starting materials, we herein document a highly efficient organocatalytic process that operates under mild reaction conditions to give structurally and stereochemically diverse molecules containing the chiral cyclic acetal moiety. In this designed target-oriented sequential process, the key hemiacetal intermediates could be easily generated by the reaction of the relatively complex starting hemiacetals with functionalized nitroolefins, and subsequent acid-induced oxocarbenium ion formation led to bicyclic acetal products. Note that all the required starting hemiacetals **3** bearing a racemic tetrasubstituted carbon center could be easily obtained on a >800 mg scale in a two-step conversion (Scheme 2; see the Supporting Information (SI) for more details. DABCO = 1,4-diazabicyclo[2.2.2]octane), including (1) the Henry reaction between the corresponding nitroalkanes **1** and paraformaldehyde,[8] and (2) the subsequent Michael addition of **2** with acrolein.[9]

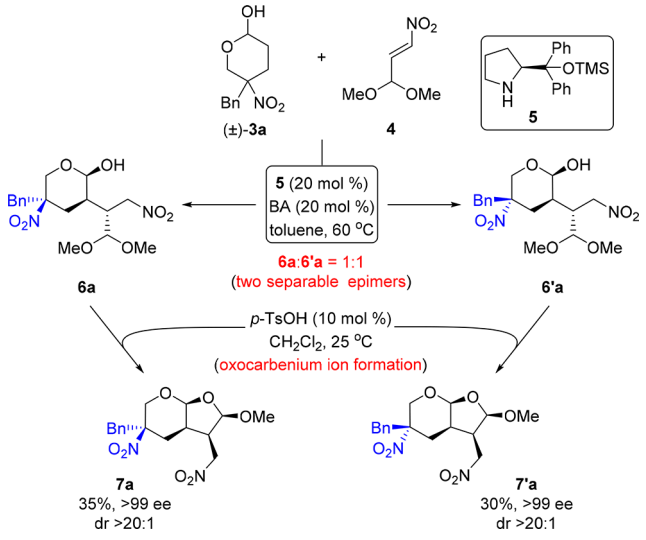
Scheme 2. Synthesis of the Required Starting Hemiacetals



Following our previously developed reaction conditions, we initially investigated the reaction of the easily synthesized hemiacetal (±)-**3a** and *β*-nitroacroleine dimethyl acetal **4**[10] in the presence of commercially available catalyst diphenylprolinol silyl ether **5**[11] at 60 °C, using benzoic acid (BA) as the acidic additive (Scheme 3, Bn = benzyl; TMS = trimethylsilyl).

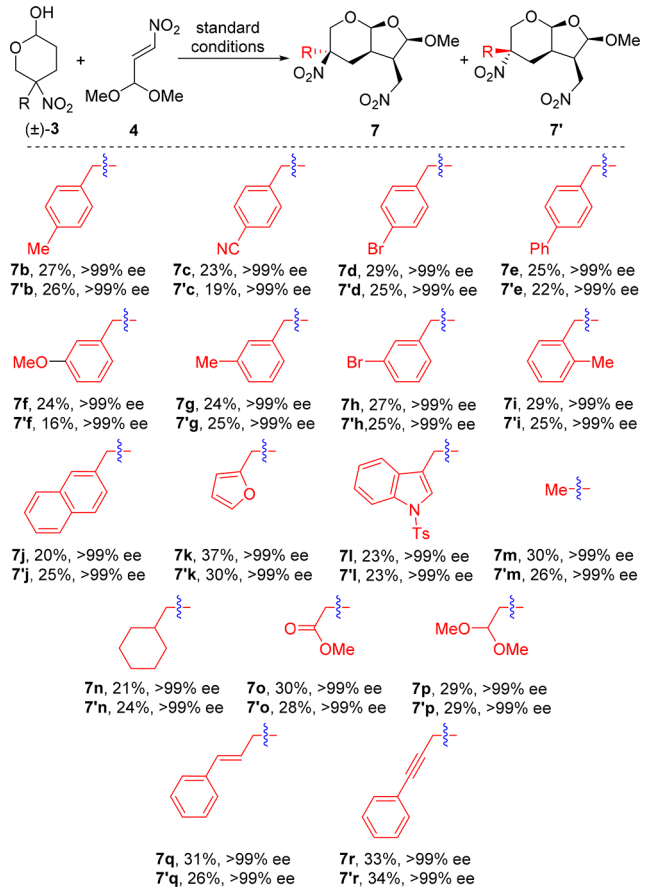
As expected, despite the starting cyclic hemiacetal (±)-**3a** possessing a racemic tetrasubstituted carbon center, **6a** and **6′a** were readily formed as two separable epimers after SiO_2 flash chromatography. Subsequent treatment of the functionalized hemiacetals **6a** and **6′a**, respectively, with catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH, 10 mol %) in CH_2Cl_2 at 25 °C gave the desired products **7a** and **7′a** in good yields (over two steps) with excellent enantioselectivity as a single diastereomer. With regard to the acid-induced oxocarbenium ion formation process, the other acid examined (trifluoroacetic acid, $BF_3{\cdot}Et_2O$, diphenylphosphate) gave slightly lower yields, but still with excellent stereoselectivities. (See the SI for full optimization studies.)

Scheme 3. Designed Sequence to Synthesize Epimeric 7a and 7′a



Inspired by these preliminary results, we further explored the scope of this sequential process with respect to the starting cyclic hemiacetals. As can be seen from Scheme 4, the reactions proceeded smoothly to provide the desired products in good yields with excellent stereoselectivities, regardless of the electronic nature and the position of the aromatic substituents (**7b**–**7j** and **7′b**–**7′j**). Heterocyclic substituents were also tolerated (**7k** and **7l**, a swell as **7′k** and **7′l**). Except for the methyl group, aliphatic substrates containing various functional groups, such as cyclohexyl, ester, and even dimethyl acetal, proved to be highly efficient in this transformation (**7m**–**7p** and **7′m**–**7′p**). Notably, the two-step sequential reactions of both alkene- and alkyne-bearing substrates proceeded smoothly to afford the desired products (**7q** and **7r**, as well as **7′q** and **7′r**), which could be potentially converted into highly functionalized chiral molecules.

Scheme 4. Scope of the Designed Sequence



It is particularly noteworthy that, in all cases examined, the products **7** and **7′** were formed as two separable epimers with complete stereocontrol (>99% enantiomeric excess (ee), diastereomeric ratio (dr) >20:1). Additionally, a key feature of this process is that a wide variety of cyclic hemiacetals, containing

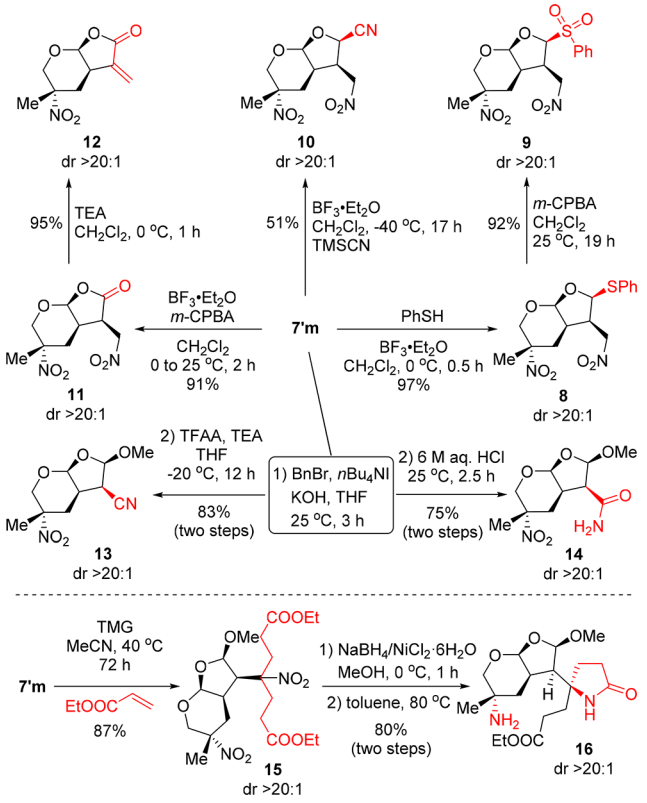
DOI: 10.1021/acs.orglett.8b01386
Org. Lett. XXXX, XXX, XXX−XXX

two racemic stereogenic centers and one tetrasubstituted center, can be employed to construct versatile and useful building blocks as a single diastereoisomer with high levels of structural complexity.

To show the preparative usefulness of this asymmetric sequential transformation, a large-scale reaction (8 mmol, 1290 mg) was successfully performed under conditions of lower catalyst loading (10 mol %). The products **7m** and **7′m** were obtained in good yield (over two steps; **7m**: 640 mg, 29%; **7′m**: 574 mg, 26%) with excellent enantioselectivities a single diastereoisomer (both of **7m** and **7′m**, >99% ee, dr >20:1).[12]

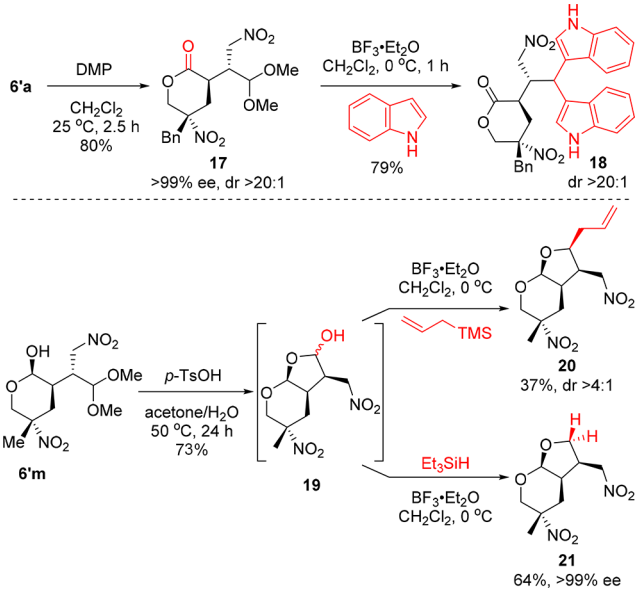
As mentioned previously, chiral cyclic acetal moieties are versatile building blocks for the synthesis of complex heterocycles. Accordingly, several selective transformations of the representative acetal **7′m** were carried out to further explore the utility of this synthetic strategy (see Scheme 5; TFAA = trifluoroacetic anhydride, TEA = triethylamine, THF = tetrahydrofuran). In the presence of $BF_3{\cdot}Et_2O$, **7′m** reacted with thiophenol and TMSCN, respectively, to give bicyclic acetal **8** and **10**. The S atom in **8** could be oxidized, leading to the sulfone **9** in 92% yield with 3-chloroperbenzoic acid (*m*-CPBA) as an oxidant. Treatment of **7′m** with $BF_3{\cdot}Et_2O$ and *m*-CPBA afforded lactone **11**, and the subsequent denitration process with triethylamine as the base provided the bicyclic lactone **12** bearing an *exo*-methylene group.[13] The conversion of nitroalkane into nitrile **13**[14] and amide **14**, respectively, could also be realized via a two-step sequence under mild conditions with the enantioselectivity maintained. Double addition product **15** could be readily accessed from the reaction of **7′m** and ethyl acrylate, catalyzed by tetramethylguanidine (TMG). The conversion of **15** to lactam **16** could be achieved through a two-step process involving reduction of the nitro group and enantioselective desymmetrization via intramolecular aminolysis of ester heating in toluene at 80 °C.

Scheme 5. Useful Transformations of Acetal 7′m



Furthermore, the Michael addition products **6** and **6′** are also useful intermediates for further transformations. For example, oxidation of hemiacetal **6′a** with Dess–Martin periodinane (DMP) afforded the corresponding monocyclic lactone **17** in 80% yield, and two indole groups were next installed by treating **17** with $BF_3{\cdot}Et_2O$ to give **18** in 79% yield. The hydrolysis of **6′m** catalyzed by *p*-TsOH in aqueous acetone afforded bicyclic hemiacetal **19**, which underwent $BF_3{\cdot}Et_2O$-catalyzed Hosomi–Sakurai allylation with allyltrimethylsilane[15] led to acetal **20** in high yield with excellent stereoselectivity. $BF_3{\cdot}Et_2O$-catalyzed reduction with Et_3SiH gave the bicyclic acetal **21**. (See Scheme 6.)

Scheme 6. Useful Transformations of Hemiacetal 6′a and 6′m



The absolute configuration of product **7′m** and **10** were unequivocally determined by X-ray crystallographic analysis (see Figure 1; the H atoms are omitted for clarity), and all other products were assigned by analogy.

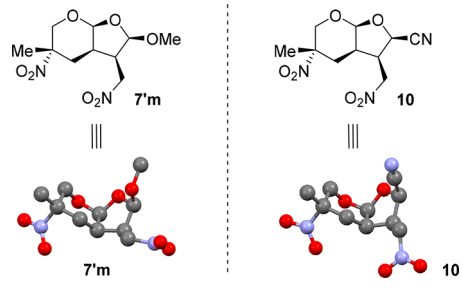


Figure 1. X-ray structures of products **7′m** and **10**.

A plausible mechanism is suggested in Scheme 7 to rationalize the formation of two epimeric products **7m** and **7′m**. Initially, the enamine intermediate **A**, which is generated from the reaction of **5** and (±)-**3m**, attacked the nitro-olefin **4** from the Re face followed by intramolecular acetalization, leading to two isolable epimeric hemiacetals **6m** and **6′m**. The nucleophilic attack of the hydroxy group to the Si face of the oxocarbenium ion moiety,

DOI: 10.1021/acs.orglett.8b01386
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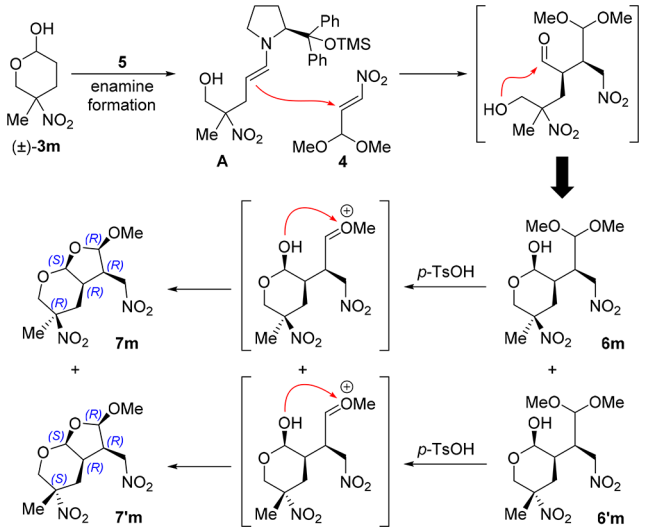
Scheme 7. Plausible Reaction Mechanism



induced by *p*-TsOH, offers the final O,O-acetals **7m** and **7′m**, respectively, in a diastereopure and enantiopure form.

In summary, a series of cyclic hemiacetals with relatively complex structures bearing a racemic tetrasubstituted stereogenic centers have been prepared using a concise method. We have also successfully developed efficient sequential reactions of the synthesized racemic hemiacetals, and functionalized nitroolefins provide multisubstituted bicyclic acetals as two separable epimers with complete stereocontrol. This process is operationally simple and tolerates various substituted cyclic hemiacetals. Moreover, the reaction can be readily scaled up to 8 mmol without an observable loss in yield or stereoselectivity. The obtained bicyclic acetal products could be transformed to various interested heterocyclic compounds with substantial structural diversity and broad functionalities. Further studies would find more valuable applications, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01386.

Detailed optimization, experimental procedures, spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1837950 and 1837951 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC-Shandong Joint Fund for Marine Science Research Centers (No. U1606403), the Scientific and Technological Innovation Project Financially Supported by Qingdao National Laboratory for Marine Science and Technology (No. 2015ASKJ02-06), and the Fundamental Research Funds for the Central Universities (Nos. 201562031 and 201762011).

■ REFERENCES

(1) (a) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(2) (a) Felix, W.; Rimbach, G.; Wengenroth, H. *Arzneim.-Forsch.* **1969**, *19*, 1860. (b) Rehnberg, N.; Sundin, A.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5477. (c) Schmalz, H.-G.; Heβler, E.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1994**, *35*, 4543. (d) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (e) Mavragani, C. P.; Moutsopoulos, H. M. *Clin. Rev. Allergy Immunol.* **2007**, *32*, 284.

(3) (a) Liu, Y.-K.; Li, Z.-L.; Li, J.-Y.; Feng, H.-X.; Tong, Z.-P. *Org. Lett.* **2015**, *17*, 2022. (b) Li, J.-Y.; Li, Z.-L.; Zhao, W.-W.; Liu, Y.-K.; Tong, Z.-P.; Tan, R. *Org. Biomol. Chem.* **2016**, *14*, 2444. (c) Liu, C.; Liu, Y.-K. *J. Org. Chem.* **2017**, *82*, 10450. (d) Zhao, W.-W.; Liu, Y.-K. *Org. Chem. Front.* **2017**, *4*, 2358. (e) Chen, Y.-H.; Sun, X.-L.; Guan, H.-S.; Liu, Y.-K. *J. Org. Chem.* **2017**, *82*, 4774.

(4) (a) Wang, J.; Qian, P.; Hu, Y.; Yang, J.; Jiang, J.; Chen, S.; Zhang, Y.; Zhang, S. *Tetrahedron Lett.* **2015**, *56*, 2875. (b) Zhu, Y.; Qian, P.; Yang, J.; Chen, S.; Hu, Y.; Wu, P.; Wang, W.; Zhang, W.; Zhang, S. *Org. Biomol. Chem.* **2015**, *13*, 4769. (c) Yang, J.; Qiu, G.; Jiang, J.; Hu, Y.; Chen, S.; Zhang, S.; Zhang, Y. *Adv. Synth. Catal.* **2017**, *359*, 2184.

(5) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923 and references therein.

(6) (a) Cai, P.-W.; You, Z.-H.; Xie, L.-H.; Tan, R.; Tong, Z.-P.; Liu, Y.-K. *Synthesis* **2016**, *48*, 2581. (b) You, Z.-H.; Chen, Y.-H.; Liu, Y.-K. *Org. Biomol. Chem.* **2016**, *14*, 6316. (c) Li, J.-Y.; Yu, K.-W.; Xie, C.-C.; Liu, Y.-K. *Org. Biomol. Chem.* **2017**, *15*, 1407. (d) You, Z.-H.; Chen, Y.-H.; Wu, X.-N.; Liu, Y.-K. *Adv. Synth. Catal.* **2017**, *359*, 4260.

(7) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (d) Sachleben, R. A.; Bryan, J. C.; Engle, N. L.; Haverlock, T. J.; Hay, B. P.; Urvoas, A.; Moyer, B. A. *Eur. J. Org. Chem.* **2003**, *2003*, 4862. (e) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (f) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (g) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (h) Marek, I. *Chem.—Eur. J.* **2008**, *14*, 7460.

(8) Zhang, F.; Wei, M.; Dong, J.; Zhou, Y.; Lu, D.; Gong, Y.; Yang, X. *Adv. Synth. Catal.* **2010**, *352*, 2875.

(9) Xiong, G.; Wei, M.; Zhou, Y.; Li, Y.; Zhang, F.; Gong, Y. *Synthesis* **2011**, *2011*, 3439.

(10) (a) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (b) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135. (c) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem.—Eur. J.* **2008**, *14*, 9357. (d) Wiesner, M.; Neuburger, M.; Wennemers, H. *Chem.—Eur. J.* **2009**, *15*, 10103. (e) White, N. A.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 8504. (f) Candy, M.; Durand, T.; Galano, J.-M.; Oger, C. *Eur. J. Org. Chem.* **2016**, *2016*, 5813. (g) Schnitzer, T.; Wennemers, H. *J. Am. Chem. Soc.* **2017**, *139*, 15356.

(11) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(12) See the Supporting Information for more details.

(13) (a) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *19*, 419. (b) Li, Y.; Ibsen, L.; Jørgensen, K. A. *Org. Lett.* **2017**, *19*, 1200.

(14) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612.

(15) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, *5*, 941.

DOI: 10.1021/acs.orglett.8b01386
Org. Lett. XXXX, XXX, XXX−XXX