Organic LETTERS

Letter

pubs.acs.org/OrgLett

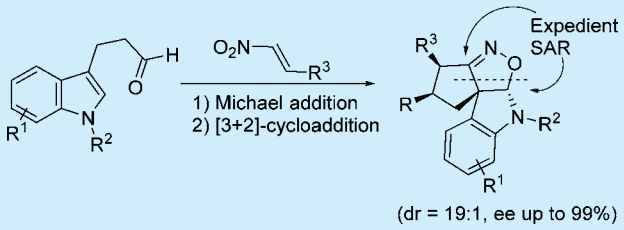
An Organocatalysis Based Carbocyclic Spiroindoline Synthesis Enables Facile Structure–Activity Relationship (SAR) Study at C2 Position

Yongsheng Zheng, Jacob Cleaveland, David Richardson, and Yu Yuan*

Department of Chemistry, University of Central Florida, Orlando, Florida 32816, United States

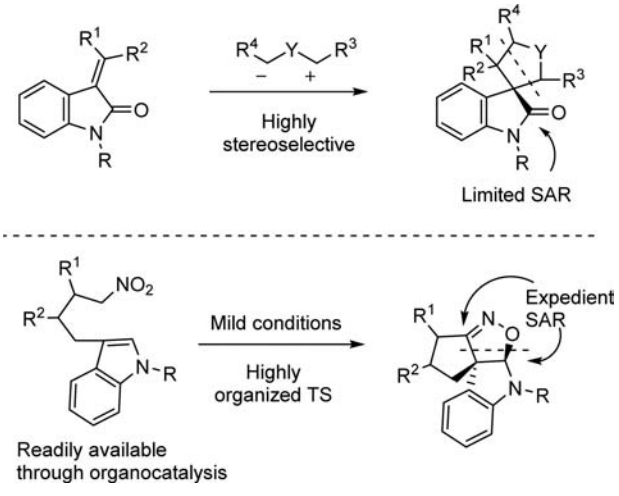
Supporting Information

ABSTRACT: An asymmetric synthesis of carbocyclic spiroindoline by sequential Michael reaction and [3 + 2]-cycloaddition is described. This protocol demonstrates excellent enantio- and diastereoselectivity with broad functional group tolerance. A diverse range of spiroindolines were prepared by this approach, and the products served as ideal substrates for C2 derivatization.



Spiroindoline scaffolds are widely present in bioactive natural products and medicinally relevant synthetic compounds.[1] Their broad pharmacological indications in conjunction with their structural complexity allow this family of alkaloids to be under intense investigation.[2] Among the established catalytic enantioselective methods, reactions employing 3-alkylidene oxindoles are probably the most thoroughly studied. Taking advantage of the polarized α,β-unsaturated system, two major variants of spiroindoline syntheses, namely cycloaddition and annulation, have been achieved in a stereoselective manner and enantiomerically pure spirooxindoles were accessible by proper catalysis.[3] The carbonyl group of 3-alkylidene oxindole activates the C–C double bond as an excellent Michael acceptor, but it limits the further functionalization at this position (Scheme 1). From a medicinal chemistry perspective, spiroinolines with a tunable C2 position will provide valuable structure–activity relationship (SAR) information to guide the design of related new chemical entities; thus, a general strategy to access C2 prefunctionalized spiroindoline is crucial for drug development.[4]

Scheme 1. Spiroindoline Synthesis from Oxindole and Indole



Compared to methods based on oxindole substrates, stereoselective synthesis of carbocyclic spiroindoline directly from indole has not been fully developed. Nucleophilic attack to a pendant electrophile followed by dearomatization is a major strategy to prepare such compounds. The nucleophilic indole moiety is able to attack an η^3 allylic metal electrophile[5] or a Lewis acid activated π system to give the ring closure products.[6] As shown in Scheme 1, we envision that an intramolecular cycloaddition reaction between indole and a tethered nitrogen dipole will proceed via a highly organized transition state to furnish a carbo spirocyclic adduct with a quaternary chiral center. By this means, the problem of synthesizing polysubstituted spiral indoline is solved by a cycloaddition reaction with a densely functionalized substrate, possessing a pendant dipole-dipolarophile at the flanking ends of the molecule. The reasons for choosing a nitro group based dipole are threefold. First, nitrile oxide and silyl nitronate[7] have been used in a cycloaddition with different alkynes or alkenes, providing reliable methods for isoxazole and isoxazoline preparation. Second, due to the rapid development of organocatalysis since the early 2000s, it is convenient to incorporate a nitro group by an enantioselective Michael reaction.[8] Last, the aminal functional group at the C2 position of the indoline product can be easily modified by various nucleophiles, which makes SAR evaluations of the pharmacophore readily available. Herein we describe a general approach for the synthesis of enantiomerically pure 3-spiroindolines by

Received: July 16, 2015
Published: August 14, 2015

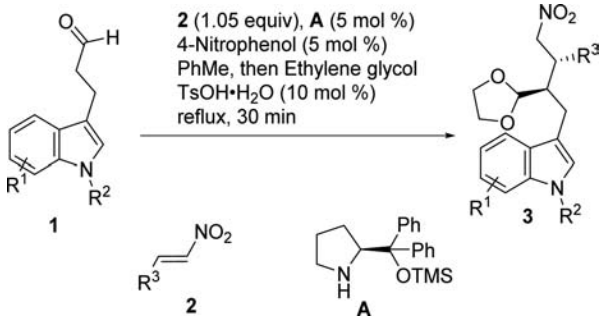
DOI: 10.1021/acs.orglett.5b02031
Org. Lett. 2015, 17, 4240–4243

sequential Michael reaction and [3 + 2]-cycloaddition, which serve as ideal substrates for C2 derivatization.

Our investigation commenced at the preparation of suitable precursors for the proposed cyclization. As illustrated in Scheme 1, the dipole and dipolarophile are separated by a three-carbon linker, which can be quickly assembled by a Michael reaction between indolyl propionaldehyde **1** and nitroolefin **2**. Small organic molecule catalyzed enantioselective Michael reactions have been extensively studied, and many highly effective catalysts have been identified to enable stereoselective aldehyde addition to nitroolefin.[9] Among these catalysts, diphenylprolinol silyl ether **A**[10] is a proven organocatalyst for Michael additions, and we anticipate that the indolyl group in **1** will not significantly alter the aldehyde reactivity; thus, we chose silyl ether **A** to catalyze the conjugate addition. Indeed, indolyl propionaldehyde **1** easily added to nitroolefin **2** under the effect of silyl ether **A** to afford highly optically pure Michael adducts with excellent diastereoselectivity. To mitigate complications in the following [3 + 2]-cycloaddition, we converted the aldehyde group to the corresponding acetal in order to avoid potential epimerization at the α center.[11] We compared the diastereomeric ratios (dr) of **3a** and the immediate Michael adduct and confirmed that the acidic acetalization conditions caused no diastereomeric erosion. Under these established conditions, cyclization precursors **3a**–**3s** were prepared in good yields and stereoselectivity (Table 1). Generally speaking, substitutions on the indole moiety or on the nitrostyrene are well tolerated. Michael adducts with excellent enantiomeric excess (ee) and dr were obtained in good yields (**3a**–**3o** and **3r**–**3s**). However, a high dr for aliphatic nitroalkenes was difficult to achieve in the conjugate addition (**3p** and **3q**).

With the cyclization precursors in hand, we turned our attention to the [3 + 2]-cycloaddition and the optimization is summarized in Table 2. Cyclization of **3a** in the presence of

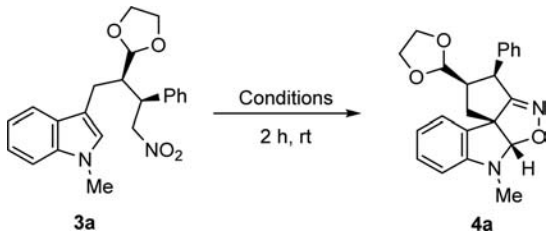
Table 1. Preparation of Cyclization Precursor



entry	3	R^1, R^2, R^3	yield[a]	ee (%) (dr)[b]
1	**3a**	H, Me, Ph	73%	98 (10:1)
2	**3b**	H, Bn, Ph	85%	92 (10:1)
3	**3c**	4-OBn, Bn, Ph	83%	99 (7:1)
4	**3d**	4-Me, Bn, Ph	73%	98 (10:1)
5	**3e**	5-Me, Bn, Ph	80%	91 (12:1)
6	**3f**	6-Me, Bn, Ph	81%	99 (9:1)
7	**3g**	6-F, Bn, Ph	85%	99 (7:1)
8	**3h**	5-Br, Bn, Ph	75%	96 (10:1)
9	**3i**	4-OMe, Me, Ph	92%	96 (19:1)
10	**3j**	5-Br, Me, Ph	83%	98 (9:1)
11	**3k**	H, Me, 4-F-C_6H_4	85%	99 (16:1)
12	**3l**	H, Me, 4-CF_3-C_6H_4	82%	99 (17:1)
13	**3m**	H, Me, 4-Br-C_6H_4	87%	99 (10:1)
14	**3n**	H, Me, 4-OMe-C_6H_4	88%	99 (13:1)
15	**3o**	H, Me, 4-NO_2-C_6H_4	77%	99 (14:1)
16	**3p**	H, Me, $BnOC_2H_4$	80%	99 (7:1)
17	**3q**	H, Me, $BnOC_4H_8$	79%	99 (5:1)
18	**3r**	2-Me, Me, Ph	91%	99 (8:1)
19	**3s**	2-Me, Me, 4-F-C_6H_4	78%	99 (8:1)

[a]Isolated yield. [b]Determined by crude NMR.

Table 2. Optimization of the Cycloaddition



entry	conditions[a]	solvent	dr[b]	yield[c]
1	Ac_2O/DMAP/iPr_2NEt	MeCN	10:1	41%
2	TMSCl/Et_3N[d]	PhMe	_	nr
3	PhNCO/Et_3N[d]	PhMe	16:1	74%
4	Boc_2O/DMAP[e]	PhMe	10:1	71%
5	Boc_2O/DMAP[f]	DCM	11:1	81%
6	Boc_2O/DMAP[g]	THF	16:1	82%
7	Boc_2O/DMAP	DMF	11:1	81%
8	**Boc_2O/DMAP[h]**	**MeCN**	**17:1**	**88%**

[a]See Supporting Information for details. [b]Determined by crude NMR; the dr of **3a** is 10:1. [c]Isolated yield. [d]70 h. [e]30 h. [f]24 h. [g]44 h. [h]50 °C.

Ac_2O, 4-dimethylaminopyridine (DMAP), and iPr_2NEt proceeded quickly at room temperature to afford **4a** in only low yield, whereas the TMSCl/Et_3N[12] combination was ineffective for the cyclization and the starting material was recovered. Other conditions such as PhNCO/Et_3N[13] and Boc_2O/DMAP[14] provided higher yields for the desired product, however at a slower rate. Because the Boc_2O/DMAP condition gave a cleaner reaction, we further optimized other parameters for this combination. Screening of solvents led to the identification of MeCN as the optimal media in terms of dr and yield, and a slightly elevated temperature (50 °C) made the reaction reach completion within 2 h in 88% yield.

To evaluate the generality of the cyclization, precursors **3b**–**3q** were subjected to the optimized conditions (2.4 equiv of Boc_2O, 0.2 equiv of DMAP in MeCN, 50 °C) and results are summarized in Figure 1. Reactions of indolyl propionaldehydes bearing an electron-donating group such as 4-OMe, 4-OBn, 4-Me, 5-Me, 6-Me (**4c**–**4f** and **4i**) or an electron-withdrawing group such as 5-Br, 6-F (**4g**–**4h** and **4j**) on the indole moiety all gave the desired indoline products in good yields and dr. The relative stereochemistry of the product was established by NOE experiment.[15] Other functional groups, originating from nitroalkene moieties, were also well tolerated (**4k**–**4q**), and the tricyclic indolines were obtained in similar good yields and dr. One exception was the substrate with an additional nitro group, even in the absence of an α-proton, which was extensively decomposed (**4o**) under current conditions. To our great pleasure, when the cyclization condition was applied to 2-methyl indolyl substrates, spiroindoline products were produced in excellent yields and selectivity (**4r** and **4s**).

To prove that our current methodology is offering a straightforward pathway to C2 analogues of spiroindolines,

DOI: 10.1021/acs.orglett.5b02031
Org. Lett. 2015, 17, 4240–4243

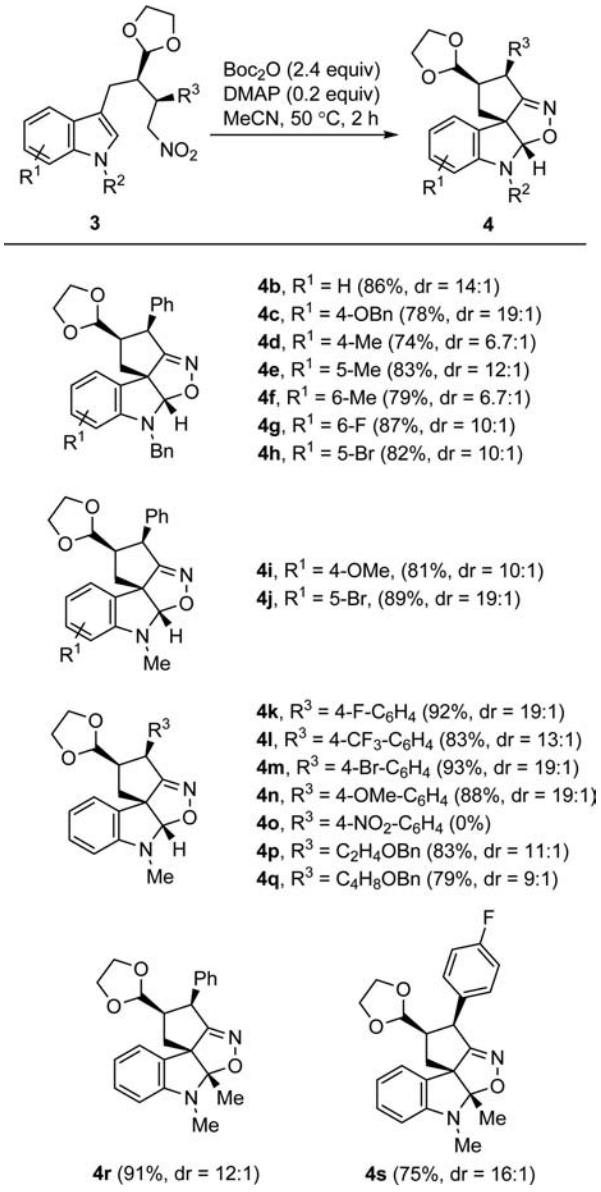
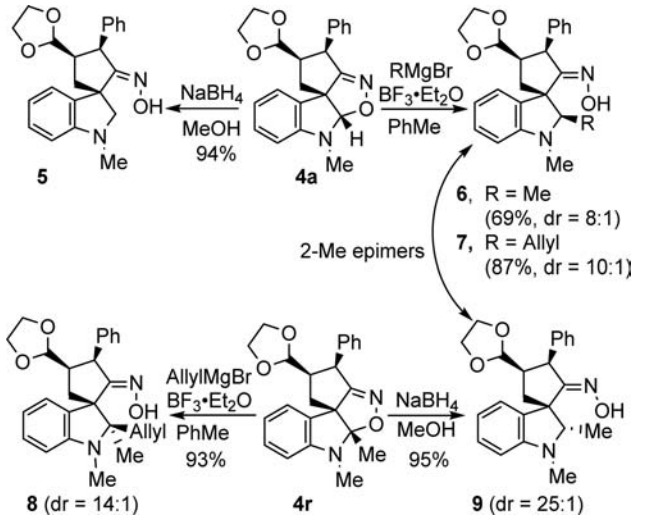


Figure 1. Substrate scope for the cyclization.

we chose cycloadducts **4a** and **4r** for selective modifications (Scheme 2). While direct $NaBH_4$ reduction of **4a** afforded C2 unsubstituted indoline **5** in 94% yield, Lewis acid assisted substitution reaction at C2 was also possible: methyl and allyl Grignard reagents were able to selectively add to the spiroindoline in the presence of $BF_3{\cdot}Et_2O$, and excellent yields along with good diastereoselectivity were obtained in both cases (**6** and **7**). We also extended the modification conditions to C2 substituted cycloadduct **4r**, and desired analogues were obtained in good yields and dr. Notably, compound **6** is an epimer of **9** with all other chiral centers in the same configuration except for C2, and this stereochemical outcome demonstrated the power and versatility of our methodology. Furthermore, allylation of **4r** gave indoline **8** bearing a tertiary aminoalkyl center next to a full carbon quaternary center, which was difficult to prepare by other methods.

In summary, we have developed a general approach to access carbocyclic spiroindolines through sequential Michael addition, dipolar cycloaddition reactions. This cascade demonstrates excellent functional group tolerability and affords complex

Scheme 2. Derivatization of the Cycloadducts



structures in high stereochemical purity. The cycloadducts are important intermediates for SAR studies, and complementary stereochemistry at the C2 position is conveniently achieved by nucleophilic addition. Evaluation of the antimalarial activity of the cycloadducts and their derivatives 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.5b02031.

Experimental details and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yu.yuan@ucf.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the University of Central Florida is gratefully acknowledged.

■ REFERENCES

(1) For selected bioactive spiroindolines, see: (a) Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135−136. (b) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430−9435. (c) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861−1873. (d) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Paez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175−1180.

DOI: 10.1021/acs.orglett.5b02031
Org. Lett. 2015, 17, 4240−4243

(2) For selected reviews on spiroindoline synthesis: (a) Bonjoch, J.; Sole, D. *Chem. Rev.* **2000**, *100*, 3455−3482. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (c) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *2009*, 3003−3025. (d) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447−457.
(3) For selected examples: (a) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (b) Tan, B.; Candeias, N. R.; Barbas, C. F., III *Nat. Chem.* **2011**, *3*, 473−477. (c) Albertshofer, K.; Tan, B.; Barbas, C. F., III *Org. Lett.* **2012**, *14*, 1834−1837. (d) Jiang, K.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2382−2385. (e) Li, J.; Wang, N.; Li, C.; Jia, X. *Chem. - Eur. J.* **2012**, *18*, 9645−9650. (f) Sun, W.; Zhu, G.; Wu, C.; Hong, L.; Wang, R. *Chem. - Eur. J.* **2012**, *18*, 6737−6741. (g) Noole, A.; Ilmarinen, K.; Jaerving, I.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2013**, *78*, 8117−8122. (h) Sun, J.; Xie, Y.-J.; Yan, C.-G. *J. Org. Chem.* **2013**, *78*, 8354−8365. (i) Trost, B. M.; Bringley, D. A.; Zhang, T.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 16720−16735. (j) Ball-Jones, N. R.; Badillo, J. J.; Tran, N. T.; Franz, A. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 9462−9465. (k) Stiller, J.; Kowalczyk, D.; Jiang, H.; Jørgensen, K. A.; Albrecht, L. *Chem. - Eur. J.* **2014**, *20*, 13108−13112. (l) Sun, W.; Hong, L.; Zhu, G.; Wang, Z.; Wei, X.; Ni, J.; Wang, R. *Org. Lett.* **2014**, *16*, 544−547. (m) Zhou, J.; Wang, Q.-L.; Peng, L.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2014**, *50*, 14601−14604.
(4) Podoll, J. D.; Liu, Y.; Chang, L.; Walls, S.; Wang, W.; Wang, X. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 15573−15578.
(5) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1680−1683.
(6) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350−1353.
(7) For selected book reviews, see: (a) Grundmann, C.; Grunanger, P. *The Nitrile Oxides*; Springer-Verlag: Berlin, 1971. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*; VCH: Weinheim, 1988. (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
(8) For selected reviews, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *2007*, 1701−1716. (b) Li, N.; Xi, G.; Wu, Q.; Liu, W.; Ma, J.; Wang, C. *Chin. J. Org. Chem.* **2009**, *29*, 1018−1038. (c) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627−2648.
(9) (a) Kotrusz, P.; Toma, S.; Schmalz, H. G.; Adler, A. *Eur. J. Org. Chem.* **2004**, *2004*, 1577−1583. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212−4215. (c) Quintard, A.; Bournaud, C.; Alexakis, A. *Chem. - Eur. J.* **2008**, *14*, 7504−7507. (d) Wang, W.-H.; Abe, T.; Wang, X.-B.; Kodama, K.; Hirose, T.; Zhang, G.-Y. *Tetrahedron: Asymmetry* **2010**, *21*, 2925−2933. (e) Xiao, J.; Xu, F.-X.; Lu, Y.-P.; Loh, T.-P. *Org. Lett.* **2010**, *12*, 1220−1223. (f) Arakawa, Y.; Wiesner, M.; Wennemers, H. *Adv. Synth. Catal.* **2011**, *353*, 1201−1206.
(10) (a) Mielgo, A.; Palomo, C. *Chem. - Asian J.* **2008**, *3*, 922−948. (b) Marques-Lopez, E.; Herrera, R. P. *Curr. Org. Chem.* **2011**, *15*, 2311−2327. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248−264.
(11) Bonne, D.; Salat, L.; Dulcere, J.-P.; Rodriguez, J. *Org. Lett.* **2008**, *10*, 5409−5412.
(12) Torssell, K.; Zeuthen, O. *Acta Chem. Scand. B* **1978**, *32*, 118−124.
(13) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339−5342.
(14) Basel, Y.; Hassner, A. *Synthesis* **1997**, *1997*, 309−312.
(15) See Supporting Information.

DOI: 10.1021/acs.orglett.5b02031
Org. Lett. 2015, 17, 4240−4243