Organic LETTERS

Letter

pubs.acs.org/OrgLett

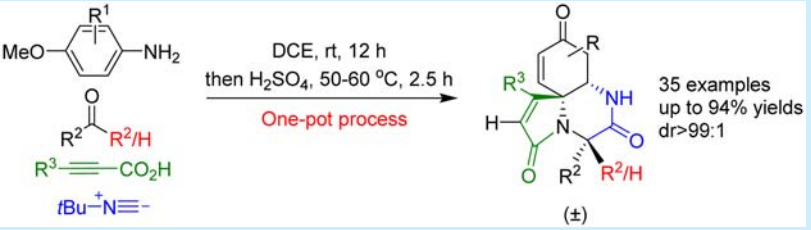
Synthesis of Alkaloid-Mimicking Tricyclic Skeletons by Diastereo- and Regioselective Ugi/*ipso*-Cyclization/Aza-Michael Cascade Reaction in One-Pot

D. Yugandhar,[†,‡] Sunu Kuriakose,[†] Jagadeesh Babu Nanubolu,[§] and Ajay Kumar Srivastava*[,†,‡]

[†]Medicinal Chemistry and Pharmacology Division, [§]Center for X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500 007, India

[‡]Academy of Scientific and Innovative Research, New Delhi, 110 025, India

Supporting Information



ABSTRACT: A one-pot process has been developed for preparing alkaloid-like tricyclic skeletons by employing an Ugi reaction, an acid mediated *ipso*-cyclization and an aza-Michael addition. The transformation is operationally simple and provides products in a diastereo- and regioselective manner with good-to-excellent yields.

Isocyanide-based multicomponent reactions (IMCRs) have played a vital role in exploring the uncharted chemical space for the identification of novel scaffolds.[1] The newly discovered structural frameworks facilitate the development of novel leads in drug discovery research.[2] Owing to their wide scope, atom economy, and operationally simple experimental procedures, IMCRs have been used significantly in the total synthesis of complex natural products.[3] Among various IMCRs, the Ugi reaction has become extremely popular as it provides building blocks with a cluster of functionalities that can be magnificently exploited for newer transformations, often termed as post-Ugi modifications.[4] Though a number of metal mediated post-Ugi modifications have been reported,[5] metal-free post-Ugi transformations for complex scaffolds are comparatively less explored. Recently two elegant syntheses of nitrogen containing polycyclic cores by novel post-Ugi modifications have been reported from the research groups of Andreana[6] and Van der Eycken.[7] As a part of our ongoing research program toward the development of novel scaffolds with anticancer properties, we were interested in exploring the uniquely functionalized oxa/azaspiro[4,5]-trienones. The initial studies showcasing the anticancer potential of azaspiro[4,5]trienones,[8] prompted us to further explore the azaspirocyclic structures toward identifying a better pharmacophore.

A literature survey shows that azaspirofused tricyclic cores are found profusely in several naturally occurring alkaloids that exhibit good anticancer potential by damaging cancer cell DNA; for example, cylindricines C (**I**),[9] lepadiformine (**II**),[10] and fasicularin (**III**)[11] exhibit good in vitro cytotoxicity against Vero and KB cells (IC_{50} = 14−16.8 μg/mL) (Figure 1). Herein, we

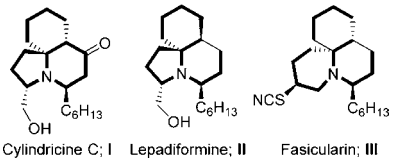


Figure 1. Representative alkaloids with azaspirofused tricyclic skeletons.

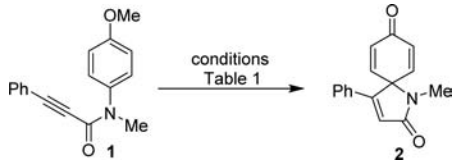
report a one-pot process for the synthesis of azaspirofused tricyclic skeletons via Ugi four-component condensation (U4CC), acid mediated *ipso*-cyclization and aza-Michael addition executed in a cascade manner.

We hypothesized that under acidic conditions, Ugi adduct **7** could undergo *ipso*-cylization followed by intramolecular aza-Michael addition to afford the tricyclic core **9**.[12] In our initial attempts to obtain the spirocyclic core, model substrate **1**, synthesized by coupling of *N*-methyl-*p*-anisidine and 3-phenyl-propiolic acid, was subjected to *ipso*-cyclization (5-*endo*-*dig*) by treatment with various acids (Table 1). To our delight, formation of spirocyclic product **2** was observed in each case. However, triflic acid and sulfuric acid were found to be the most suitable for *ipso*-cyclization, providing the desired product **2** in 89% and 94% yields, respectively (entries 1 and 3, Table 1). Spirocyclic product **2** was characterized by NMR and mass spectroscopy. In the 500 MHz ^{1}H NMR spectrum of **2** in $CDCl_3$, disappearance of the methoxy protons (OCH_3) at δ 3.77 ppm was observed alongside

Received: January 18, 2016
Published: February 23, 2016

DOI: 10.1021/acs.orglett.6b00164
Org. Lett. 2016, 18, 1040−1043

Table 1. Screening of the Acids for *ipso*-Cyclization[a]



entry	acid	solvent	temp (°C)/*t* (h)	% conversion (% yield)[b]
1	triflic acid	DCE	0–60/2.5	100(89)
2	TFA	DCE	0–60/10	10
3	H_2SO_4	DCE	0–60/2.5	100(94)
4	$AlCl_3$	DCE	0–60/10	60
5	*p*-TSA	DCE	0–60/10	50
6	$BF_3{\cdot}OEt_2$	DCE	0–60/10	10

[a]All the reactions were performed with (3 equiv) of acid in a 5 mL screw cap culture vial. [b]Isolated yield.

appearance of a singlet at δ 6.67 ppm for the hydrogen α- to the amide carbonyl (see Supporting Information).

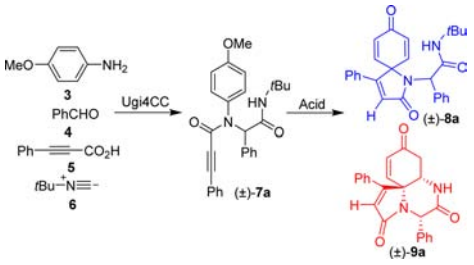
Having optimized the conditions for *ipso*-cyclization, Ugi adduct **7a** was tested for *ipso*-cyclization and further transformations under similar reaction conditions (entries 1 and 2, Table 2). Compound **7a** was readily obtained by Ugi four-component condensation of *p*-anisidine **3**, benzaldehyde **4**, 3-phenylpropiolic acid **5**, and *tert*-butyl isocyanide **6** in methanol.

At room temperature, **7a** afforded only spirocyclic product **8a** with minor tricyclic product **9a** (data not shown). However, at 60 °C, product **8a** was completely converted to **9a** (entries 1 and 2, Table 2). Structures of **8a** and **9a** were confirmed by their spectral properties. In the 500 MHz ^{1}H NMR spectrum of **8a** in $CDCl_3$, the *tert*-butyl protons appeared at δ 1.32 ppm as singlet and α- and β-protons of the enone moiety appeared as four distinct double doublets at δ 6.82, 6.55, 6.42, and 6.29 ppm. Formation of tricyclic skeleton **9a** was evident from the ^{1}H NMR spectrum of compound **9a** in $CDCl_3$, where the newly generated protons after aza-Michael addition appeared at δ 4.13 ppm along with two double doublets at δ 2.08 and 2.33 ppm, and *N*-*tert*-butyl peak was not found. It is noteworthy that no diastereomeric peaks were obtained in the ^{1}H NMR spectrum of the crude reaction mixture of **9a**.

In a desire to combine the Ugi reaction, *ipso*-cyclization and aza-Michael addition in one-pot, Ugi adduct **7a** was treated *in situ* with triflic acid and concentrated sulfuric acid (entries 3 and 4, Table 2) but no formation of tricyclic product **9a** was observed and most of the **7a** remained unreacted. Changing the solvent from methanol to acetonitrile did not improve the formation of **9a**. However, dichloromethane and 1,2-dichloroethane gave **9a** in good yields with DCE found to be better for the Ugi reaction, with complete conversion in the overall transformation (entries 5–10, Table 2). Considering the observations in Table 2, DCE was chosen as the solvent for carrying out the overall transformation, whereas H_2SO_4 was the most suited acid.

To access the generality of this one-pot transformation, a number of aromatic and aliphatic aldehydes, substituted anisidines, and propiolic acids were subjected to the optimized reaction conditions (Figure 2). In most cases, clean formation of the tricyclic products was observed (**9a–t**, Figure 2). However, the Ugi adduct derived from 2-nitrobenzaldehyde afforded a low yield of the tricyclic product in poor diastereoselectivity (**9u**, Figure 2). Additionally, the 2-bromo-4,5-methylenedioxybenzaldehyde-derived Ugi adduct did not produce any tricyclic product (**9v**, Figure 2). In comparison to the 3-phenylpropiolic acid,

Table 2. Optimization of the Reaction Conditions[a]



entry	acid	solvent	conditions[a]	% conversion[b] (% yield)[c] (±)–**8a**	(±)–**9a**
1	triflic acid	DCE	60 °C, 3 h	0	100 (78)
2	concn H_2SO_4	DCE	60 °C, 2.5 h	0	100 (85)
3[e]	concn H_2SO_4	MeOH	rt, 12 h/60 °C, 18 h	7	0
4[e]	triflic acid	MeOH	rt, 12 h/60 °C, 18 h	10	0
5[e]	concn H_2SO_4	ACN	rt, 12 h/60 °C, 18 h	80	*d*
6[e]	Triflic acid	ACN	rt, 12 h/60 °C, 18 h	45	55
7[e]	concn H_2SO_4	DCM	rt, 12 h/reflux, 2–3 h	0	100 (80)
8[e]	triflic acid	DCM	rt, 12 h/reflux, 2–3 h	*d*	90 (73)
9[e]	concn H_2SO_4	DCE	rt, 12 h/60 °C, 2–3 h	0	100 (85)
10[e]	triflic acid	DCE	rt, 12 h/60 °C, 2–3 h	*d*	95 (77)

[a]All the reactions were performed with (5 equiv) of acid, in a 5 mL screw cap culture vial. [b]Percentage of conversion based on ^{1}H NMR spectrum analysis. [c]Isolated yield. [d]Noncharacterizable products. [e]Ugi reaction and acid mediated cyclizations performed in one-pot.

butynoic acid derived Ugi adducts displayed poor reactivity in the acid mediated transformations resulting in the formation of products **10a,b** in relatively low yields. Interestingly, the unsymmetrically substituted *p*-anisidines afforded single regioisomers **11a–d** in good yields, where aza-Michael addition occurred at the less hindered enone. However, *o*-nitro-*p*-anisidine did not yield any tricyclic product **11e** and decomposition of Ugi adduct was observed in extended reaction time with increased amount of sulfuric acid.

The reactions with symmetrically substituted *p*-anisidines also worked well and tricyclic products **12a–c** were isolated in good yield. Surprisingly, 2,6-difluoro-*p*-anisidine showed formation of an Ugi adduct, but no trace of tricyclic product **12d** was observed after the addition of sulfuric acid, probably due to steric crowding at the β- position of the enone moiety. Aliphatic carbonyls such as acetone and cyclohexanecarboxaldehyde were found to be suitable for the transformation with tricyclic products **13a,b** being isolated in good yields. In most of the cases, tricyclic products were isolated by a simple workup procedure and no column purification was needed. However, in a few cases, chromatographic purification was necessary (see Supporting Information). To check the suitability of this process for bulk synthesis, compound **9a** was synthesized at a 2 g scale (yield = 68%).

DOI: 10.1021/acs.orglett.6b00164
Org. Lett. 2016, 18, 1040–1043

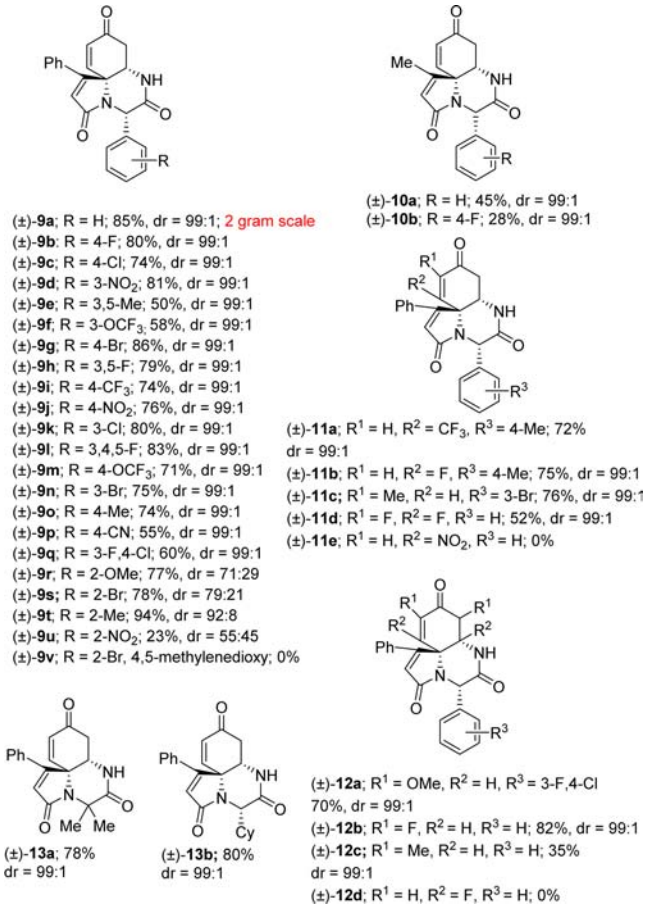
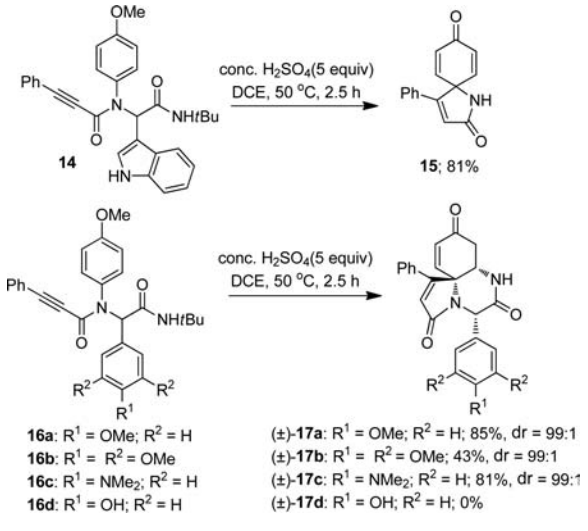


Figure 2. Scope of the reaction. Reaction conditions: DCE, rt, 12 h then concn H_2SO_4 (5 equiv), 2−3 h at 60 °C.

In another effort, we became interested in exploring the selectivity of the *ipso*-cyclization reaction of substrates **14**, **16a**−**d**, in which the additional possibility of *ipso*-cyclization arose via a 6-*endo*-*dig* pathway.

Treatment of Ugi adduct **14** with sulfuric acid in DCE yielded azaspiro[4,5]trienone **15** by elimination of the indolyl part (see Supporting Information), whereas **16a**−**c** reacted predominantly

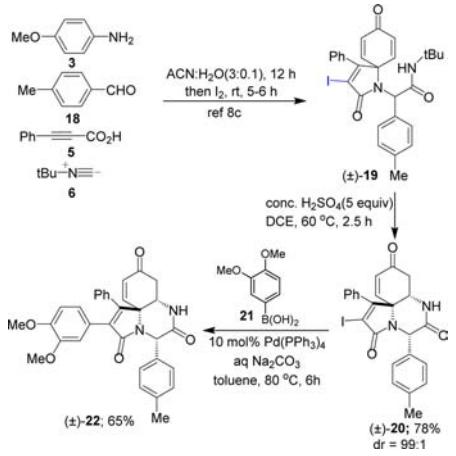
Scheme 1. Reaction of Substrates with More Possibilities of *ipso*-Cyclizations



through a 5-*endo*-*dig* pathway to afford the tricyclic products **17a**−**c**. Ugi adduct **16d**, derived from *p*-hydroxybenzaldehyde decomposed on acid treatment and no characterizable product was obtained.

To extend our method for the construction of fully functionalized azaspirofused tricyclic scaffolds, iodo-substituted spirocyclic substrate **19** which was obtained by performing a Ugi reaction and iodine catalyzed *ipso*-cyclization in one pot,[8c] was treated with sulfuric acid to afford the tricyclic product **20**. Compound **20** nicely reacted with boronic acid **21** under Suzuki conditions to provide **22** in 50% overall yield from **19** (Scheme 2).

Scheme 2. Synthesis of Fully Functionalized Azaspirofused Tricyclic Product



To help establish the structural features, X-ray crystallographic data of compound **9g** was examined, which unambiguously confirmed the tricyclic skeleton and geometrical orientations (Figure 3). Additionally, we also obtained the X-ray crystallo-

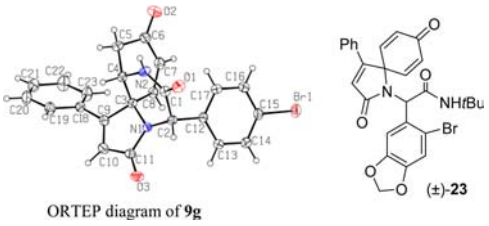


Figure 3.

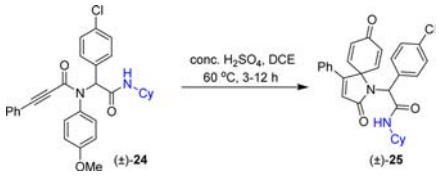
graphic data of bicyclic product **23** that was synthesized by quenching the cascade reaction among *p*-anisidine, 2-bromo-4,5-methylenedioxybenzaldehyde, 3-phenylpropiolic acid, and *tert*-butylisocyanide at the *ipso*-cyclization stage (Figure 3, See Supporting Information for details).

We observed that cleavage of the *tert*-butyl group was necessary before aza-Michael addition, as no tricyclic product was obtained with a *tert*-butyl appendage, probably due to this group hindering the aza-Michael addition. A similar outcome was observed with cyclohexylisocyanide, where only bicyclic azaspiro[4,5]trienone **25** was obtained after treatment of the Ugi adduct **24** with sulfuric acid, as deprotection of the *N*-cyclohexyl group could not take place (Scheme 3).

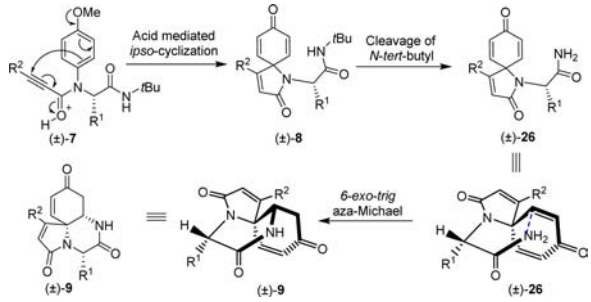
Accordingly, a plausible reaction mechanism for the overall transformation is depicted in Scheme 4. After completion of the

DOI: 10.1021/acs.orglett.6b00164
Org. Lett. 2016, 18, 1040−1043

Scheme 3



Scheme 4. Plausible Reaction Mechanism



Ugi condensation, adduct **7** undergoes acid catalyzed intramolecular *ipso*-cyclization in 5-*endo*-*dig* manner to afford the bicyclic azaspiro[4,5]trienone **8**. Deprotection of the *N*-*tert*-butyl by excess sulfuric acid affords acetamide **26** that produced the tricyclic product **9** through an intramolecular aza-Michael addition proceeding via a 6-*exo*-*trig* pathway.

In conclusion, a convenient method for the synthesis of alkaloid-mimicking azaspirofused tricyclic skeletons has been developed that employs an Ugi reaction and acid mediated *ipso*-cyclization/aza-Michael addition in one pot. Notably, this process generates one quaternary center, and three stereogenic centers in a highly diastereo- and regioselective manner. Use of inexpensive sulfuric acid and the easy purification procedure, makes this process highly adoptable for library generation of small molecules for drug discovery research. The suitability of this method for bulk synthesis was also demonstrated by synthesizing 2 g of tricyclic product **9a**. The method is highly general and can be utilized for the synthesis of a vast variety of fully functionalized azaspirofused tricyclic scaffolds. Overall, the present synthetic methodology provides a robust and metal free route to produce a diverse collection of biologically relevant small molecule libraries and can also be utilized for the total synthesis of complex alkaloids. Investigation of the pharmaceutical potential of these newly synthesized compounds and application of the current method in total synthesis of azaspirosfused tricyclic core containing alkaloids are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00164.

Detailed experimental procedures, ^1H and ^{13}C NMR, mass, HRMS and IR data of all the newly synthesized compounds, and X-ray crystallographic data of compounds **9g** (CCDC1431687) and **23** (CCDC1431686) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aksrivastava@iict.res.in. Tel.: (+91)-40-2719-1646.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from CSIR, New Delhi under 12th Five Year Plan project "THUNDER (BSC0102)" and "Affordable Cancer Therapeutics-ACT (CSC0301)" is highly acknowledged. D.Y. thanks UGC, New Delhi, for providing a Senior Research Fellowship (UGC-SRF).

■ REFERENCES

(1) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323. (c) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234. (d) Gore, R. P.; Rajput, A. P. *Drug Invent. Today* **2013**, *5*, 148. (e) Neochoritis, C. G.; Stotani, S.; Mishra, B.; Dömling, A. *Org. Lett.* **2015**, *17*, 2002. (f) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709. (g) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *Org. Lett.* **2006**, *8*, 4019. (h) Raman, D. J.; Miguel Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (i) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem.* **2014**, *10*, 544.

(2) (a) Zhang, W. *Comb. Chem. High Throughput Screening* **2007**, *10*, 219. (b) Beck, B.; Larbig, G.; Mejat, B.; Magnin-Lachaux, M.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 1047. (c) Moliner, F. D.; Banfi, L.; Riva, R.; Basso, A. *Comb. Chem. High Throughput Screening* **2011**, *14*, 782. (d) Krasavin, M.; Bushkova, E.; Parchinsky, V.; Shumsky, A. *Synthesis* **2010**, *6*, 933.

(3) (a) Ulaczyk-Lesank, A.; Hall, D. G. *Curr. Opin. Chem. Biol.* **2005**, *9*, 266. (b) Touré, B. B.; Hall, D. G. Multicomponent Reactions in the Total Synthesis of Natural Products. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; p 342. (c) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screening* **1970**, *4*, 1–34.

(4) (a) Marcaccini, S.; Torroba, T. Post-condensation Modifications of the Passerini and Ugi Reactions. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 33. (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Xu, Z.; Moliner, F. D.; Cappelli, A. P.; Hulme, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8037.

(5) Sharma, U. K.; Sharma, N.; Vachhani, D. D.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2015**, *44*, 1836 and references cited therein.

(6) Santra, S.; Andreana, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418.

(7) (a) Modha, S. G.; Kumar, A.; Vachhani, D. D.; Jacobs, J.; Sharma, S. K.; Parmar, V. S.; Meervelt, L. V.; Van der Eycken, E. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 9572. (b) Schröder, F.; Ojeda, M.; Erdmann, N.; Jacobs, J.; Luque, R.; Noël, T.; Meervelt, L. V.; Van der Eycken, J.; Van der Eycken, E. V. *Green Chem.* **2015**, *17*, 3314.

(8) (a) Archana, S.; Geesala, R.; Rao, N. B.; Satpati, S.; Puroshottam, G.; Panasa, A.; Dixit, A.; Das, A.; Srivastava, A. K. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 680. (b) Yugandhar, D.; Nayak, V. L.; Archana, S.; Shekar, K. C.; Srivastava, A. K. *Eur. J. Med. Chem.* **2015**, *101*, 348. (c) Yugandhar, D.; Srivastava, A. K. *ACS Comb. Sci.* **2015**, *17*, 474.

(9) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531.

(10) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691.

(11) (a) Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004. (b) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K. *Tetrahedron Lett.* **1997**, *38*, 363. (c) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.

(12) Rodriguez-Solla, H.; Concellon, C.; Tuya, P.; Santiago Garcia-Granda, S.; Diaz, M. R. *Adv. Synth. Catal.* **2012**, *354*, 295.

DOI: 10.1021/acs.orglett.6b00164
Org. Lett. 2016, 18, 1040–1043