Organic LETTERS

Letter

pubs.acs.org/OrgLett

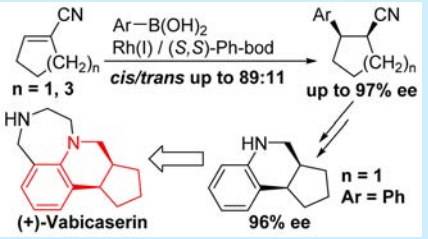
Cycloalkene Carbonitriles in Rhodium-Catalyzed 1,4-Addition and Formal Synthesis of Vabicaserin

Wojciech J. Dziechciejewski, Regina Weber, Oliver Sowada, and Mike M. K. Boysen*

Leibniz University of Hannover, Institute of Organic Chemistry, Schneiderberg 1B, D-30167 Hannover, Germany

Supporting Information

ABSTRACT: Cycloalkenes with exocyclic acceptor substituents still remain challenging substrates for enantioselective rhodium-catalyzed 1,4-addition. Cycloalkene carbonitriles and carboxylates have been investigated, and a highly diastereo- and enantioselective protocol for 1,4-addition to cyclopentene and cycloheptene carbonitrile has been developed. This new asymmetric transformation was subsequently applied in the asymmetric formal synthesis of the drug candidate Vabicaserin.

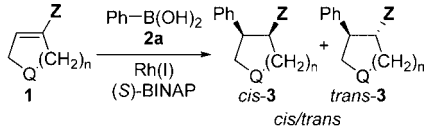


Since the first report by Hayashi and Miyaura in 1998,[1] asymmetric rhodium(I)-catalyzed 1,4-addition has evolved into an attractive method for C−C bond formation under concomitant setup of one new stereocenter. The reaction scope comprises cyclic or acyclic enones and enoates as electrophiles and aryl- or alkenylboronic acids as nucleophiles, yielding products in excellent enantioselectivity.[2] Apart from these, there still remain interesting nucleo- and electrophiles, which have received little attention or are known as taxing.

In the course of our work on challenging substrates for 1,4-additions, we have recently performed an extensive study on heteroaryl boronates as nucleophiles.[3] In this letter we are presenting the highly stereoselective 1,4-addition to cycloalkene carbonitriles as electrophiles and its application in an efficient asymmetric formal synthesis of the antipsychotic drug candidate Vabicaserin.

Cycloalkenes with exocyclic acceptor substituents are attractive substrates for 1,4-additions, as they yield products with two new contiguous stereocenters. Nevertheless, these electrophiles have rarely been explored, probably due to the reduced reactivity of their trisubstituted double bond[4] and diastereoselectivity issues. While the stereocenter at the β-position is set up by the addition of the chiral arylrhodium species, the stereocenter at the α-position generated by diastereoselective protonation of the transient rhodium enolate.[5] Most reports on this substrate class concern nitrocycloalkenes: In the first study by Hayashi, nitrocyclohexene **1a** mainly yielded *cis*-**3aa**, while nitrocycloheptene **1c** gave predominantly *trans*-**3ca**; both products were isolated in high enantiomeric excess.[6] Nitrocyclopentene **1b**, on the other hand, gave only 73% ee and very low diastereoselectivity in favor of *trans*-**3ba**.[6] (Scheme 1). Later, 1,4-additions to a nitrocyclohexene with an allylic acetate residue[7] and to dihydronitronaphthalenes[8] were reported. The only enantioselective example not involving a nitro group as an acceptor substituent was published with pyrroline carboxylate **1d**, yielding exclusively *trans*-**3da** in high ee.[9]

Scheme 1. Examples for Enantioselective 1,4-Additions to Cycloalkenes with Exocyclic Acceptor Substituents



Z = NO_2, Q = CH_2	**a**	n = 2	89%	87:13	98% ee
	b	n = 1	93%	40:60	73% ee
	c	n = 3	73%	17:83	91% ee
Z = CO_2tBu, Q = N-Bn	**d**	n = 1	89%	> 1:99	96% ee

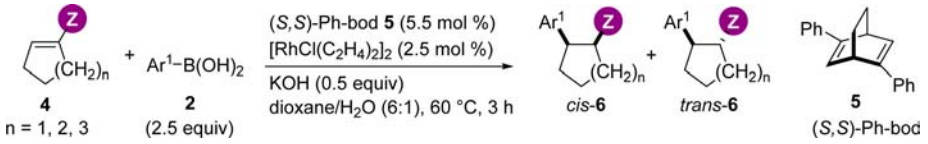
For our investigation, we selected cycloalkene carbonitriles and carboxylates **4**. To the best of our knowledge, electrophiles **4** are unprecedented in enantioselective 1,4-addition; only the substrate-controlled reaction of a chiral cyclopentene carbonitrile has been reported.[10] Even examples employing acyclic α,β-unsaturated nitriles are few and restricted to highly activated substrates carrying two nitriles or one nitrile and one ester group at the α-position.[11,12]

Nowadays, chiral dienes are the ligands of choice for rhodium-catalyzed 1,4-additions.[13] For our study, we selected (*S,S*)-Ph-bod (**5**) developed by Hayashi's group,[14] a ligand giving excellent results for a wide range of substrates. First, cyclohexene carbonitrile **4a** and cyclohexene carboxylate **4b** were reacted with phenylboronic acid **2a** (Table 1). Very surprisingly, both electrophiles failed to yield any of the expected products (entries 1 and 2). In contrast, cyclopentene carbonitrile **4c** smoothly underwent 1,4-addition with **2a** with good diastereoselectivity in favor of *cis*-**6ca**, which was isolated in 90% ee (entry 3). Interestingly, the minor diastereomer *trans*-**6ca** was formed in significantly lower enantioselectivity (72% ee). These results are in striking contrast to the ones reported for nitrocycloalkenes (cf. Scheme 1), where excellent

Received: June 26, 2015
Published: August 14, 2015

DOI: 10.1021/acs.orglett.5b01849
Org. Lett. 2015, 17, 4132−4135

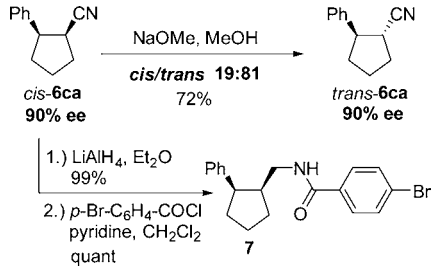
Table 1. Asymmetric 1,4-Addition of Arylboronic Acids to Cycloalkene Carbonitriles and Carboxylates



	electrophile 4			boronic acid 2		1,4-adduct 6				
entry		*n*	Z		Ar^1		yield [%][a]	*cis*/*trans*[b]	ee *cis* [%][c]	ee *trans* [%][d]
1	**4a**	2	CN	**2a**	Ph	**6aa**	no reaction	–	–	–
2	**4b**	2	CO_2Me	**2a**	Ph	**6ba**	no reaction	–	–	–
3[e]	**4c**	1	CN	**2a**	Ph	**6ca**	**75**	**75:25**	**90**	72
4[f]	**4c**	1	CN	**2a**	Ph	**6ca**	**86**	**86:14**	**95**	32
5	**4c**	1	CN	**2b**	*o*-MeO-C_6H_4	**6cb**	**76**	**74:26**	**95**	59
6	**4c**	1	CN	**2c**	*p*-MeO-C_6H_4	**6cc**	**70**	**82:18**	**96**	66
7	**4c**	1	CN	**2d**	*p*-F_3C-C_6H_4	**6cd**	**94**	**89:11**	**97**	29
8	**4d**	1	CO_2Me	**2a**	Ph	**6da**	88	32:68	91	54
9	**4d**	1	CO_2Me	**2b**	*o*-MeO-C_6H_4	**6db**	**67**	**48:52**	**98**	**94**
10[e]	**4e**	3	CN	**2a**	Ph	**6ea**	73	64:36	82	73
11[e]	**4e**	3	CN	**2b**	*o*-MeO-C_6H_4	**6eb**	**75**	**71:29**	**94**	**92**
12[e]	**4e**	3	CN	**2c**	*p*-MeO-C_6H_4	**6ec**	71	65:35	88	49
13[e]	**4e**	3	CN	**2d**	*p*-F_3C-C_6H_4	**6ed**	71	57:43	88	80

[a]Isolated yield after chromatography. [b]Determined by ^1H NMR. [c]Determined by chiral GC. [d]Determined by chiral HPLC. [e]With 1.0 equiv of KOH. [f]With 0.5 equiv of PMP.

Scheme 2. Basic Epimerization of *cis*-6ca and Preparation of *para*-Bromobenzamide 7



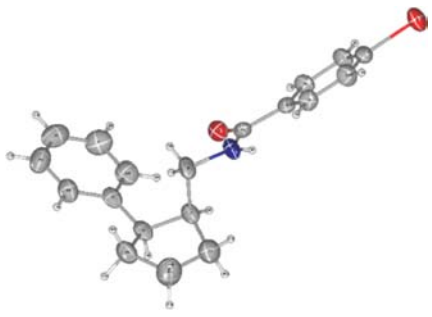
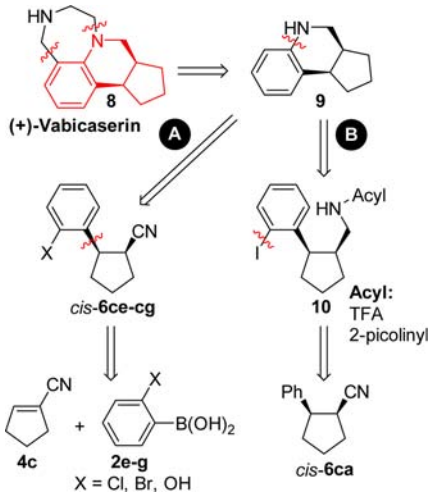


Figure 1. X-ray crystal structure of *para*-bromobenzamide **7**.

Scheme 3. Retrosynthetic Approach to Vabicaserin

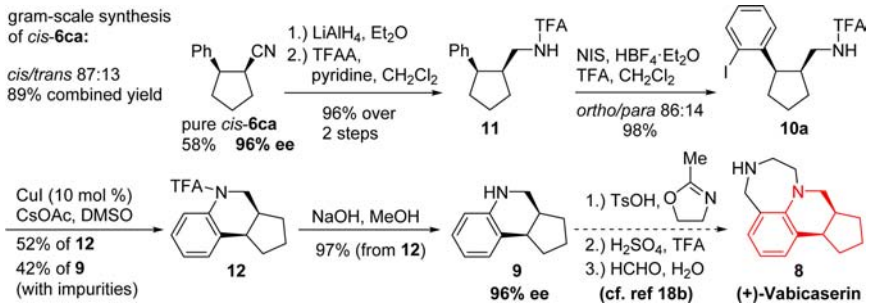


ee and a high dr of 87:13 in favor of the *cis*-product was observed for cyclohexene-derived electrophile **1a**, while the cyclopentene congener **1b** gave poor dr and ee.[6] Both, the diastereo- and enantioselectivity of the 1,4-addition with carbonitrile **4c** could be further improved (*cis*/*trans* 86:14; 95% ee for *cis*-**6ca**) by switching the base from KOH to 1,2,2,6,6-pentamethylpiperidine (PMP)[15] (entry 4). Subsequently, we explored nitrile **4c** in 1,4-additions with arylboronic acids **2b**–**2d** carrying electron-donating methoxy groups or an electron-withdrawing trifluoromethyl residue. As in the case with **2a**, the reactions proceeded with high *cis*-selectivity and while the ee for the minor *trans*-diastereomers was again only modest, the major products **6cb**-**6cd** were formed in 95–97% ee (entries 5–7).

Next, we studied the reaction of cyclopentene carboxylate **4d** with boronic acid **2a**. This also yielded the expected products, but this time with moderate diastereoselectivity in favor of *trans*-**6da**. Unfortunately, the *trans*-compound was formed in only low ee, while 91% ee was observed for the minor product *cis*-**6da** (entry 8). With *ortho*-methoxyphenylboronic acid **2b**, a near 1:1 mixture of *cis*- and *trans*-**6db** was isolated, but this time, the ee was high for both diastereomers, with 98 and 92% ee respectively (entry 9). As diastereoselectivities with ester **4d** were generally lower than with nitrile analogue **4c**, we did not perform any further experiments with **4d**. While the reaction with cyclohexene carbonitrile **4a** had been unsuccessful (entry 1), the higher homologue cycloheptene carbonitrile **4e** proved to be a suitable substrate (entries 10–13). In most cases, however, the diastereoselectivity was only low but again in favor of the *cis*-configured products, which were obtained in higher

DOI: 10.1021/acs.orglett.5b01849
Org. Lett. 2015, 17, 4132–4135

Scheme 4. Formal Synthesis of (+)-Vabicaserin (8) from 1,4-Addition Product *cis*-6ca



enantioselectivity than the *trans*-diastereomers (entries 10, 12 and 13). The best result for electrophile **4e** was obtained with boronic acid **2b**, yielding the diastereomeric addition products **6eb** both in >90% ee and a *cis*/*trans* ratio of 71:29 (entry 11). These findings are also in contrast to the results reported by Hayashi, who observed a distinctly *trans*-selective reaction for nitrocycloheptene[6] (cf. Scheme 1).

At this stage, it is difficult to give a satisfactory explanation for the rather large variation of the *cis*/*trans* diastereoselectivities observed for electrophiles **4c**–**e** and the failure of the reaction for **4a,b** (cf. Table 1). In the literature, 2-phenyl cyclohexane nitronate[16] and the enol derived from 1-phenyl-2-benzoylcyclohexane[17] have been reported to predominantly yield *cis*-configured products upon protonation under kinetic conditions. Preferential formation of *cis*-configured products from **4c** may therefore be rationalized by a kinetically controlled protonation of a transient nitrile enolate. In order to exclude the possibility of an epimerization of *cis*-**6ca** during the reaction, we subjected a pure sample to the reaction conditions (0.5 equiv of KOH, dioxane/H_2O 6:1, 60 °C) in the absence and presence of the rhodium catalyst, and in both cases, *cis*-**6ca** was recovered unchanged. We are currently conducting further studies to elucidate possible reasons for the varying *cis*/*trans* diastereoselectivities observed for **4c**–**e**.

With the 1,4-addition of boronic acids to cyclopentene carbonitrile described in Table 1, we have successfully established a new, highly diastereoselective and enantioselective approach to chiral 1,2-*cis*-disubstituted cyclopentanes. Even though the *trans*-products are isolated as minor diastereomers in only modest ee, it should be noted that they can be obtained in high ee from the major *cis*-products. Epimerization of enantioenriched *cis*-**6ca** with sodium methoxide in methanol led to the thermodynamically more stable diastereomer *trans*-**6ca** in good yield and high dr without erosion of the enantiomeric excess (Scheme 2).

In order to elucidate the absolute configuration of the addition products from Table 1, *cis*-**6ca** was converted into *para*-bromobenzamide **7**, via hydride reduction[18] and amidation[19] (Scheme 2). X-ray crystal structure analysis of **7** unequivocally established the absolute configuration of *cis*-**6ca** as (1*S*,2*R*)[20] (Figure 1).

To demonstrate the synthetic value of the new 1,4-addition to cyclopentene carbonitrile, we decided to employ this method in the formal synthesis of the drug candidate Vabicaserin. Developed by Wyeth as a selective agonist of the 5-hydroxytryptamine 2 C receptor, (−)-Vabicaserin (SCA-136) is under evaluation for its antipsychotic properties.[21] Syntheses of enantioenriched Vabicaserin have been reported previously, using chiral resolution[22] or asymmetric hydrogenation reactions of 1,2-disubstituted cyclopentenes[23] and quinolinium salts,[24] respectively.

For a stereoselective synthesis of Vabicaserin (**8**), we envisioned the retrosynthetic approach in Scheme 3. Tetracyclic **8** can be prepared from **9** by known methods. The tricyclic core structure **9** can be accessed via pathway **A** using cyclopentane carbonitriles *cis*-**6ce**–**cg** as key intermediates, which may be prepared by 1,4-addition of phenylboronic acids **2e**–**g** carrying an *ortho*-halogen or hydroxy group to carbonitrile **4c**. But even though *ortho*-modified substrate **2b** had produced the desired adduct, the reaction with **2e**–**g** only led to complex mixtures or decomposition of the boronic acids, rendering this approach unsuccessful.

Since introduction of an *ortho*-functionalized phenyl residue by 1,4-addition had failed, we set up alternative retrosynthetic pathway **B** (Scheme 3). In this approach, **9** is prepared from *ortho*-iodo amide **10**, which may be accessed by a late-stage halogenation: Barluenga[25] and Chen[26] reported the direct *ortho*-iodination of β- and γ-aryl alkylamides with TFA or 2-picolinyl residues. This reaction gives fair to high *ortho*/*para* ratios, but the scope is so far restricted to acyclic substrates. The precursor for iodide **10** should be available from *cis*-**6ca**, the major 1,4-addition product of **4c** with phenylboronic acid **2a**, via reduction and amidation.

The new synthetic approach is summarized in Scheme 4. First, we repeated the 1,4-addition of phenylboronic acid **2a** to nitrile **4c** with 1.00 g (10.74 mmol) of the electrophile.[27] This produced an excellent combined yield of *cis*- and *trans*-**6ca** (1.63 g, 9.51 mmol) which were isolated in a ratio of 87:13. From this mixture, 1.06 g (6.20 mmol) of *cis*-**6ca** (58% yield) was isolated in 96% ee and subsequently transformed into TFA amide **11** by reduction[18] and amidation.[25] Iodination of **11** was performed using Chen's protocol with NIS[26] rather than IPy_2BF_4 as reported by Barluenga.[25] In our first attempt at 0 °C, we observed an *ortho*,*para*-diiodinated compound as the major product, but decreasing the temperature to −20 °C led to the desired iodide **10a**, which was isolated in excellent yield and an *ortho*/*para* ratio of 86:14. With **10a** in hand, the stage was set for the cyclization to **9**. Ullmann C–N coupling under conditions previously described by Chen[26] yielded the *N*-TFA substituted product **12** along with an impure fraction of amine **9**. Removal of the TFA group from **12** yielded pure tricyclic amine **9** in 96% ee. This compound can be transformed into the (+)-enantiomer of Vabicaserin via a known route in three steps.[22b]

In summary, we have described new enantioselective 1,4-addition reactions with cycloalkenes carrying exocyclic acceptor substituents. Cyclopentene carbonitrile yielded *cis*-configured products in high dr and excellent ee. This new transformation was successfully applied as a key step in the formal synthesis of

DOI: 10.1021/acs.orglett.5b01849
Org. Lett. 2015, 17, 4132–4135

Vabicaserin. Further studies on the factors governing *cis/trans* ratios of the new 1,4-addition reaction and its failure for cyclohexene-derived electrophiles are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01849.

Full experimental details, characterization data, copies of spectra and chromatograms (PDF)
CIF file for compound **7** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mike.boysen@oci.uni-hannover.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to Prof. Dr. Ekkehard Winterfeldt, deceased October 11th 2014. Financial support by the DFG (BO 1938/5-1) and a Heisenberg Fellowship for M.M.K.B. (BO 1938/4-1) is gratefully acknowledged. We thank Dr. Gerald Dräger, Institute of Organic Chemistry, Leibniz University of Hannover, for the X-ray crystallographic analysis of *para*-bromobenzamide **7**.

■ REFERENCES

(1) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. J. *J. Am. Chem. Soc.* **1998**, *120*, 5579.
(2) Reviews: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95.
(3) Albrecht, F.; Sowada, O.; Fistikci, M.; Boysen, M. M. K. *Org. Lett.* **2014**, *16*, 5212.
(4) The reduced reactivity of electrophiles with trisubstituted double bonds is well-known for acyclic substrates and has been ascribed to steric hindrance: (a) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (b) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.
(5) Diastereoselective protonation of rhodium enolates originating from acyclic dehydro amino acids with 1,1-disubstituted double bonds: (a) Navarre, L.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719. (b) Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.
(6) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.
(7) Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2005**, *7*, 4285.
(8) Hajra, S.; Ghosh, R.; Chakrabarti, S.; Ghosh, A.; Dutta, S.; Dey, T. K.; Malhotra, R.; Asijaa, S.; Roy, S.; Dutta, S.; Basu, S. *Adv. Synth. Catal.* **2012**, *354*, 2433.
(9) Belyk, K. M.; Beguin, C. D.; Palucki, M.; Grinberg, N.; DaSilva, J.; Askin, D.; Yasuda, N. *Tetrahedron Lett.* **2004**, *45*, 3265.
(10) Campos, K. R.; Klapars, A.; Kohmura, Y.; Pollard, D.; Ishibashi, H.; Kato, S.; Takezawa, A.; Waldman, J. H.; Wallace, D. J.; Chen, C.; Yasuda, N. *Org. Lett.* **2011**, *13*, 1004.
(11) For an example see: Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589.
(12) α,β-Unsaturated nitriles are known as recalcitrant acceptors in 1,4-additions: Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.
(13) Reviews: (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (b) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31.
(14) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.
(15) PMP in Pd-catalyzed carboiodination: Petrone, D. A.; Yoon, H.; Weinstabl, H.; Lautens, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7908.
(16) Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5939.
(17) (a) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549. (b) Zimmerman, H. E.; Wang, P. *J. Org. Chem.* **2003**, *68*, 9226.
(18) Lorenzo, J.; Delgado, A.; Montaña, Á. M.; Mesas, J. M.; Alegre, M.-T.; del Carmen Rodríguez, M.; Avilés, F.-X. *Eur. J. Med. Chem.* **2014**, *83*, 374.
(19) Rovis, T.; Dirocco, D.; Guiles, J. WO 2012/9372 A2, 2012.
(20) CCDC 1408648. The absolute configurations of the other 1,4-addition products was assigned by analogy to that of *para*-bromobenzamide **7**.
(21) Dunlop, J.; Watts, S. W.; Barrett, J. E.; Coupet, J.; Harrison, B.; Mazandarani, H.; Nawoschik, S.; Pangalos, M. N.; Ramamoorthy, S.; Schechter, L.; Smith, D.; Stack, G.; Zhang, J.; Zhang, G.; Rosenzweig-Lipson, S. *J. Pharmacol. Exp. Ther.* **2011**, *337*, 673.
(22) (a) Megati, S.; Bhansali, S.; Dehnhardt, C.; Deshmukh, S.; Fung, P.; MacEwan, M.; Tinder, R. J. WO 2009/039362A2, 2009. (b) Neelamegam, R.; Hellenbrand, T.; Schroeder, F. A.; Wang, C.; Hooker, J. M. *J. Med. Chem.* **2014**, *57*, 1488.
(23) Feigelson, G. B. US 2007/0088022 A1, 2007.
(24) Dragan, V.; McWilliams, J. C.; Miller, R.; Sutherland, K.; Dillon, J. L.; O'Brien, M. K. *Org. Lett.* **2013**, *15*, 2942.
(25) Barluenga, J.; Álvarez-Guitiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1281.
(26) Nack, W. A.; He, G.; Zhang, S.-Y.; Lu, C.; Chen, G. *Org. Lett.* **2013**, *15*, 3440.
(27) For experimental details see Supporting Information.

DOI: 10.1021/acs.orglett.5b01849
Org. Lett. 2015, 17, 4132−4135