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Transition-Metal-Catalyzed Synthesis of Aspergillide B: An Alkyne Addition Strategy

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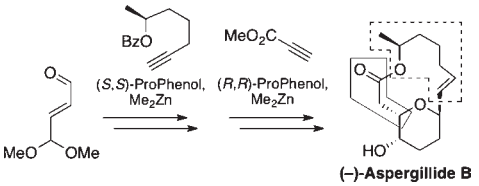
ABSTRACT



A catalytic enantioselective formal total synthesis of aspergillide B is reported. This linchpin synthesis was enabled by the development of new conditions for Zn-ProPhenol catalyzed asymmetric alkyne addition. This reaction was used in conjunction with ruthenium-catalyzed *trans*-hydrosilylation to affect the rapid construction of a late-stage synthetic intermediate of aspergillide B to complete a formal synthesis of aspergillide B in a highly efficient manner.

The aspergillides are a family of bioactive natural products originally derived from the marine fungus *aspergillus ostianus*.[1] Aspergillide A, B, and C, shown in Figure 1, share common macrolactone and pyran motifs but differ with respect to the stereochemistry at C3 and the unsaturation present in the pyran ring.[2]

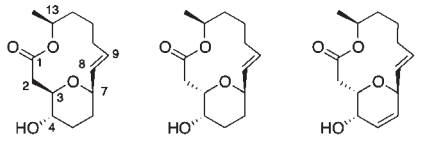


Figure 1. Aspergillide family of natural products.

These compounds exhibit cytotoxicity toward a number of different cancer cell lines including, HL-60 (human promyelocytic leukemia), MDA-MB-231 (human breast carcinoma), and HT1080 (human fibrosarcoma) cell lines.[3] These properties, along with the challenging structural features present, have motivated a number of groups to pursue the synthesis of aspergillides A–C.[4,5] Our interest in the aspergillides stems from the potential application of our zinc-catalyzed asymmetric alkynylation and ruthenium-catalyzed *trans*-hydrosilylation-desilylation methodologies

(1) Kito, K.; Ookura, S. Y.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett*. **2008**, *10*, 225.

(2) The structures of aspergillide A and B were revised in 2009 as a result of synthetic work by Hande and Uenishi. (a) Hande, S. M.; Uenishi, J. *Tetrahedron Lett*. **2009**, *50*, 189. The revised structures were later confirmed when X-ray crystal structures of the corresponding *m*-bromobenzoates were reported. (b) Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett*. **2009**, *38*, 384.

(3) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Chem.—Eur. J*. **2011**, *17*, 675.

(4) For previous syntheses of aspergillide B, see: (a) Nagasawa, T.; Kuwahara, S. *Biosci. Biotechnol. Biochem*. **2009**, *73*, 1893. (b) Díaz-Oltra, S.; Angulo-Pachón, C. A.; Kneeteman, M. N.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett*. **2009**, *50*, 3783. (c) Liu, J.; Xu, K.; He, J.; Zhang, L.; Pan, X.; She, X. *J. Org. Chem*. **2009**, *74*, 5063. (d) Fuwa, H.; Yamaguchi, H.; Sasaki, M. *Org. Lett*. **2010**, *12*, 1848. (e) Mueller Hendrix, A. J.; Jennings, M. P. *Tetrahedron Lett*. **2010**, *51*, 4260. (f) Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem., Int. Ed*. **2011**, *50*, 2618. (g) Kanematsu, M.; Yoshido, M.; Shishido, K. *Tetrahedron Lett*. **2011**, *52*, 1372 and also ref 2a.

(5) For previous syntheses of aspergillides A and C, see: Nagasawa, T.; Kuwahara, S. *Org. Lett*. **2009**, *11*, 761. Panarese, J. D.; Waters, S. P. *Org. Lett*. **2009**, *11*, 5086. Sabitha, G.; Reddy, D. V.; Rao, A. S.; Yadav, J. S. *Tetrahedron Lett*. **2010**, *51*, 4195. Kobayashi, H.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Chem. Commun*. **2011**, *47*, 7440. Kanematsu, M.; Yoshida, M.; Shishido, K. *Tetrahedron Lett*. **2011**, *52*, 1372. Izuchi, Y.; Kanomata, N.; Koshino, H.; Hongo, Y.; Nakata, T.; Takahashi, S. *Tetrahedron: Asymmetry* **2011**, *22*, 246. Nagasawa, T.; Nukada, T.; Kuwahara, S. *Tetrahedron* **2011**, *67*, 2882. Zúñiga, A.; Pérez, M.; Gonález, M.; Gómez, G.; Fall, Y. *Synthesis* **2011**, *20*, 3301. Srihari, P.; Sridhar, Y. *Eur. J. Org. Chem*. **2011**, 6690.

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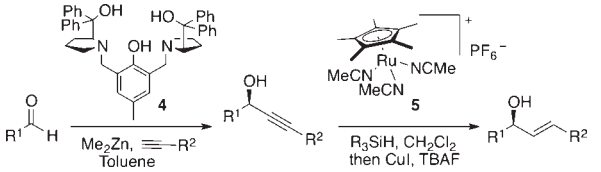
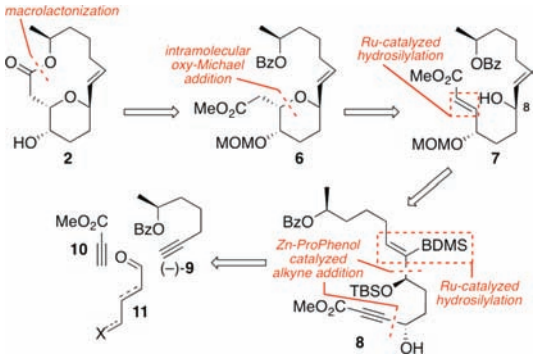
(Scheme 1) to provide access to two chiral allylic alcohol moieties that would ultimately lead to an efficient synthesis of aspergillide B.

Scheme 1. Sequential Application of Asymmetric Alkynylation and Ru-Catalyzed Hydrosilylation



This alkyne-based strategy envisioned to synthesize aspergillide B is outlined in Scheme 2. Retrosynthetic

Scheme 2. Retrosynthetic Analysis of Aspergillide B



disconnection of the macrolactone leads back to diester **6**, a late-stage intermediate used in a previous synthesis.[4d] Diastereoselective formation of the pyran ring was expected to arise from intramolecular oxy-Michael addition of the C8 hydroxyl group and the pendant α,β-unsaturated ester in **7**. It was anticipated that the two chiral allylic alcohol moieties could be prepared using Ru-catalyzed hydrosilylation of the corresponding propargylic alcohols. Lastly, asymmetric alkyne addition would be used to access the aforementioned propargylic alcohols via separate addition of (*S*)-hept-6-yn-2-yl benzoate ((−)-**9**) and methyl propiolate (**10**) to each end of a butane dialdehyde equivalent **11** which is serving as a linchpin.

The invention of the ProPhenol ligand **4** has led to the development of a number of catalytic enantioselective transformations, including a direct aldol reaction.[6] The ProPhenol ligand also facilitates the addition of a variety of alkynes to aryl and α,β-unsaturated aldehydes in excellent yield and enantioselectivity.[7] Typically, these reactions require the use of 2.8 equiv of alkyne and 2.95 equiv of Me_2Zn to obtain high levels of enantioselectivity.[8] At the outset, we recognized that the use of a superstoichiometric amount of alkyne (−)-**9** was particularly inefficient, given that this chiral intermediate is prepared using a multistep synthesis. Consequently, the use of a stoichiometric quantity of alkyne in ProPhenol-catalyzed alkynylations was investigated.

Using 1.2 equiv of alkyne (±)-**9**,[9] alkynylation of aliphatic aldehyde **11a** resulted in only a 22% yield of the desired product in 54% ee (entry 1, Table 1).[10] The traditional superstoichiometric conditions provided only modest improvements in yield and enantioselectivity (entreis 2, 3). Low yields of the desired product **12a** were primarily a consequence of competing aldol reactions.[11] The predominance of this side reaction led to the hypothesis that incomplete formation of the alkynylzinc nucleophile may be leaving significant amounts of basic dimethylzinc in the reaction mixture. Consequently, we examined a number of additives and methods that have been shown to facilitate the formation of alkynylzinc nucleophiles.[12] The use of *N*-methylimidazole (NMI), DMSO, and DMF resulted in lower yields of the desired product, **12a** (entries 4−6). Increasing the alkyne/Me_2Zn/(*S*,*S*)-**4** premix time and catalyst loading provided improved yields of propargylic alcohol **12b** (entries 7, 8). While the excess alkyne could be recovered quantitatively, this inefficiency along with the moderate yield and enantioselectivity prompted the investigation of the analogous unsaturated aldehyde, **11c**. The ProPhenol-catalyzed addition of (±)-**9** to **11c** provided a much improved 84% yield and 95% ee (entry 9). Reducing the stoichiometry of the alkyne to either 1.2 or 1.0 equiv provided a lower yield, although excellent ee was maintained in both cases (entries 10, 11). The moderate yield was presumably a consequence of poor reactivity, and a solution to this problem was

(6) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2009**, *122*, 12003. For subsequent applications of this ligand, see: Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572 and references cited therein.

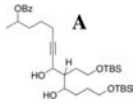
(7) (a) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8. (b) Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186.

(8) For a recent review on the enantioselective addition of alkynes to aldehydes, see: Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(9) (±)-**9** was prepared in 4 steps from 3-methyl cyclohexenone. See Supporting Information for experimental details. Le Drain, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473.

(10) The major method which can avoid such excesses is that of Carreira, but sometimes that too will require them. See: Frantz, D.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. Frantz, D.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. Anand, N.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. Reber, S.; Knoepfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, 6813. Also see Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524. Yue, Y.; Turlington, M.; Yu, X.-Q.; Pu, L. *J. Org. Chem.* **2009**, *74*, 8681 and ref 12c.

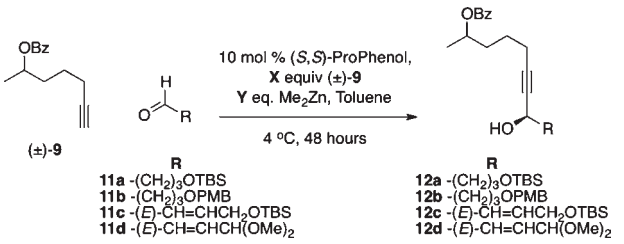
(11) The cross aldol side reaction produces a complex mixture of oligomers. The aldol side product **A** was isolated in 19% yield as a mixture of diastereomers from entry 1 (Table 1). HRMS-ESI (*m*/*z*): $[M+H]^+$ calculated for $C_{34}H_{61}O_6Si_2$, 621.4001; found, 621.3996.



(12) For selected discussions on the use of additives to facilitate alkynylzinc formation, see: (a) Gao, G.; Xie, R.-G.; Pu, L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5417. (b) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457. (c) Du, Y.; Turlington, M.; Zhou, X.; Pu, L. *Tetrahedron Lett.* **2010**, *51*, 5024.

found in the use of fumaraldehyde dimethyl acetal (**11d**). The inductive effects of the dimethyl acetal create a more

Table 1. Optimization of Alkyne Addition



entry	aldehyde	X/Y	conditions[a]	yield[b]	ee[c]
1	**11a**	1.2/1.5	20 mol% TPPO	22%	54%
2	**11a**	2.8/2.95	20 mol% TPPO	39%	62% (57%)[d]
3	**11a**	2.8/2.95	-	35%	45%
4	**11a**	1.2/1.3	30 mol% NMI	11%	72%
5	**11a**	1.2/1.4	4 eq. DMSO	4%	14%
6	**11a**	1.2/1.4	4 eq. DMF	10%	17%
7	**11b**	2.8/2.95	20 mol% TPPO, 24 h alkyne premix	58%	50%[d]
8	**11b**	2.8/2.95	40 mol% TPPO, 20 mol% ProPhenol, 24 h alkyne premix	69%	67%[d]
9	**11c**	2.8/2.95	c = 0.35 M	84%	95%
10	**11c**	1.2/1.5	20 mol% TPPO	56%	95%
11	**11c**	1.0/1.3	20 mol% TPPO	54%	95%
12	**11d**	1.0/1.3	20 mol% TPPO[e]	82%	90%

[a] All reactions were run on 0.1625 mmol scale using the standard ProPhenol alkynylation procedure and at a concentration of 0.5 M with respect to alkyne unless otherwise noted. [b] Isolated yield. [c] Enantiomeric excess determined by chiral HPLC analysis. [d] Enantiomeric excess determined by ^{1}H NMR analysis of the corresponding (*S*)-methyl mandelate. [e] Reaction performed with (−)-**9** on a 0.45 mmol scale. TPPO = triphenylphosphine oxide, NMI = *N*-methylimidazole.

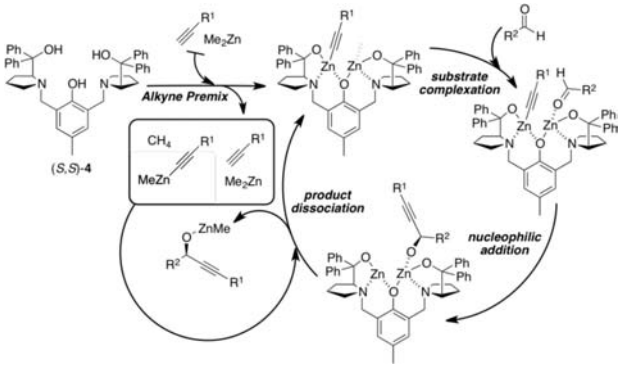
electrophilic aldehyde, and as a result, the desired propargylic alcohol **12d** was obtained in 82% yield (entry 12).

The results in Table 1 provide a number of new insights into the proposed reaction mechanism for ProPhenol-catalyzed alkyne addition (Scheme 3). Incomplete formation of the alkynylzinc nucleophile was confirmed by ^{1}H NMR analysis of a standard premix with 1-octyne, Me_2Zn and (*S*,*S*)-**4** in toluene-d_8.[13] Despite the entropically favored release of methane gas, deprotonation of the terminal alkyne was not observed in the absence of the ProPhenol ligand. The presence of significant amounts of dimethylzinc in the reaction mixture appears to have little effect on the outcome of alkyne additions to α,β-unsaturated aldehydes.[14] However, enolizable aldehydes suffer

(13) Approximately 28% conversion to the alkynylzinc species was observed based on integration of the peaks at 0.29 (s, 3H, $\mathbf{CH_3}$ZnC≡C) and −0.58 ppm (s, 6H, $\mathbf{(CH_3)_2}$Zn).

(14) Minor amounts of methyl addition side products have been isolated in only a small number of cases; see ref 7a for details.

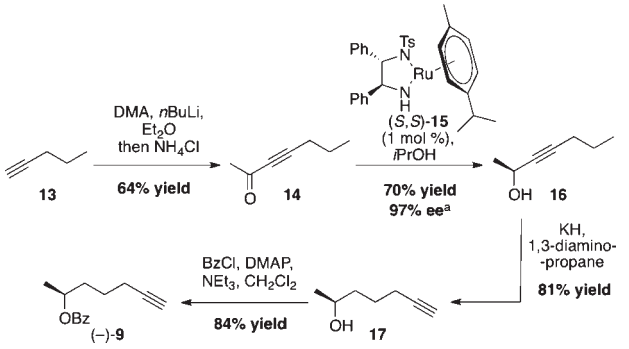
Scheme 3. Proposed Mechanism for ProPhenol-Catalyzed Alkyne Addition



from undesired aldol side reactions and typically only produce moderate yields of the desired propargylic alcohol. Methyl propiolate, a more acidic alkyne, has been shown to give significantly higher yields in addition to enolizable aldehydes under the standard conditions.[15]

The synthesis of aspergillide B commenced with the preparation of chiral alkyne (−)-**9** (Scheme 4),[16] taking

Scheme 4. Preparation of Alkyne (−)-**9**



[a] ee determined by chiral HPLC analysis of (−)-**9**.

advantage of the Noyori asymmetric hydrogenation[17] of ynone **14** and the alkyne zipper reaction of **16** to **17**.

Alkynylation of fumaraldehyde dimethyl acetal (**11d**)[18] using just 1 equiv of alkyne (−)-**9** and 10 mol % of the (*S*,*S*)-ProPhenol ligand provided **12d** in 82% yield and 90% de (Scheme 5).[19] Alkyne *trans*-hydrosilylation using benzyldimethylsilane (BDMS-H) and 2 mol %

(15) Trost, B. M.; Burns, A. C.; Bartlett, M. J.; Tautz, T.; Weiss, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1474.

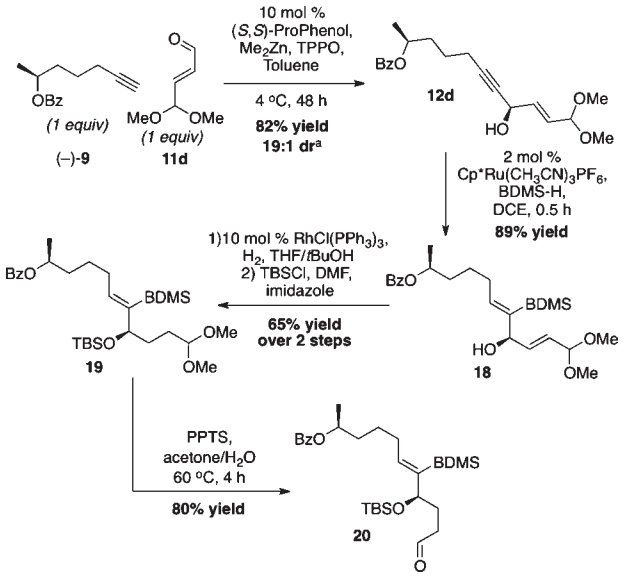
(16) Parenty, A.; Campagne, J.-M.; Aroulanda, C.; Lesot, P. *Org. Lett.* **2002**, *4*, 1663.

(17) Matsumara, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(18) Fumaraldehyde dimethyl acetal (**11d**) was prepared in one step from commercially available fumaraldehyde bis(dimethyl acetal). Coppola, G. M. *Synthesis* **1984**, 1021.

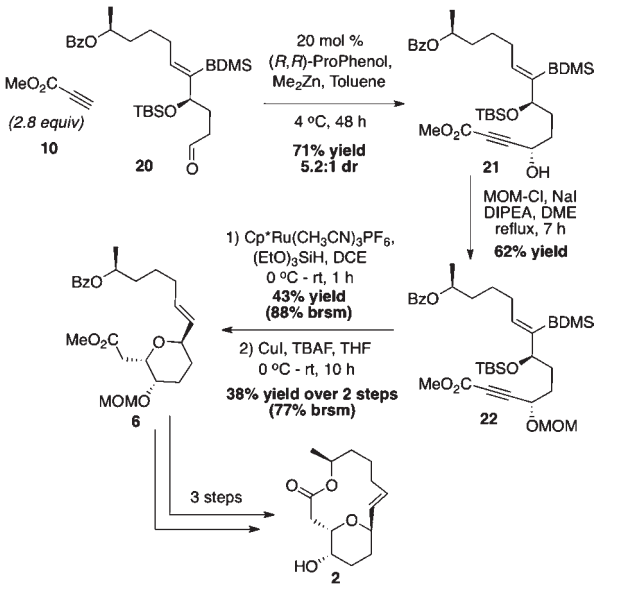
(19) For examples of the few methodologies capable of efficient Zn-catalyzed asymmetric alkynylation with < 1.2 equiv of alkyne, see: Kojima, N.; Nishijima, S.; Tsuge, K.; Tanaka, T. *Org. Biomol. Chem.* **2011**, *9*, 4425. Anand, N.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

Scheme 5. First Alkyne Addition in the Synthesis of Aspergillide B



[a] dr determined by chiral HPLC analysis.

Scheme 6. Formal Synthesis of Aspergillide B



of $Cp^*Ru(CH_3CN)_3PF_6$ provided vinyl silane **18**, regioselectively.[20] Hydrosilylation of propargylic alcohols under these conditions typically results in silylation at the β-position. The dramatic reversal in regioselectivity is thought to be a consequence of a coordinative interaction between ruthenium and the electron-poor alkene. The presence of the silicon on one of the double bonds provides a key for their differentiation toward hydrogenation. The disubstituted olefin of allylic alcohol **18** was then chemoselectively hydrogenated using Wilkinson's catalyst and silyl protected to give **19**.[21] Hydrolysis of the dimethyl acetal was performed under mild acid-catalyzed conditions, providing the desired aldehyde **20** for the second alkyne addition.

ProPhenol-catalyzed addition of methyl propiolate (**10**) to aldehyde **20** provided the desired propargylic alcohol **21** in 71% yield as a 5.2:1 mixture of diastereomers (Scheme 6).[22] Protection of the propargylic alcohol was followed by a chemoselective alkyne reduction using our hydrosilylation/protodesilylation protocol for formation of *E*-double bonds.[23] The basic reaction conditions used for this transformation resulted in spontaneous intramolecular oxy-Michael addition. Consequently, the desired 2,6-*anti* tetrahydropyran **6** was isolated in 38% yield (77% brsm) over 2 steps.[24] Compound **6** can be transformed into aspergillide B in 3 additional steps.[4d]

In summary, an enantioselective formal total synthesis of aspergillide B has been accomplished using sequential Zn-catalyzed alkyne addition and Ru-catalyzed *trans*-hydrosilylation–desilylation to access *E*-alkenes. The hydrosilylation–desilylation protocol not only provides the *E*-geometry but also allows chemoselective differentiation of the two double bonds in a susequent hydrogenation step. The development of new conditions for the Zn-ProPhenol catalyzed alkynylation has resulted in excellent yield and enantioselectivity using just 1 equiv of alkyne. Further research into the use of enolizable aldehydes in this methodology is currently underway.

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Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Trost, B. M.; Ball, Z. T.; Jöge, T. *Angew. Chem., Int. Ed.* **2003**, *115*, 3537. Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.

(21) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Chem. Commun.* **1965**, 131. O'Connor, C.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 2665.

(22) Diastereomeric ratio was determined by ^{1}H NMR of the cyclized compound **6**.

(23) Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922.

(24) The 2,6-*syn* diastereomer could not be observed by ^{1}H NMR of the crude reaction mixture. Given that 88% yield of **6** was obtained, the diastereomeric ratio is >7.3:1, *anti*/*syn*.

The authors declare no competing financial interest.