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Stereoselective Synthesis of Substituted Oxocene Cores by Lewis Acid Promoted Cyclization

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Supporting Information

ABSTRACT: Substituted oxocene derivatives have been synthesized by Lewis acid catalyzed reactions of ε-hydroxyalkene and substituted aromatic aldehydes. The $Cu(OTf)_2$-bis-phosphine catalyzed reaction typically provides substituted dihydropyran derivatives through an olefin migration followed by a Prins cyclization. The corresponding reaction catalyzed by TMSOTf or $BF_3{\cdot}OEt_2$ provided eight-membered cyclic ethers (oxocenes), selectively. This methodology provides convenient access to a variety of 2,4,8-trisubstituted oxocenes in good yields and excellent diastereoselectivities.

Substituted medium-sized cyclic ethers, particularly eight-membered oxocane and oxocene derivatives, are structural features in a variety of bioactive natural products.[1,2] This includes lauthisan (**1**, Figure 1), helianane (**2**), laurencin (**3**), and others.[3−6] As a result, stereoselective synthesis of these medium-sized oxocyclic rings has been the subject of much interest over the years.[7] Unlike six-membered ring compounds, construction of eight-membered rings from acyclic precursors is problematic due to factors related to entropy, as well as developing transannular and torsional strains.[8,9] A number of methods including cycloadditions,[10] ring expansions,[11,12] ring-closing metathesis,[13,14] and intramolecular acetal−alkene cyclizations[15,16] have been developed. A number of these methods were utilized in the synthesis of bioactive molecules.[7] A majority of these synthetic approaches, however, involve intramolecular reactions, especially in the case of the synthesis of oxocene core structures.

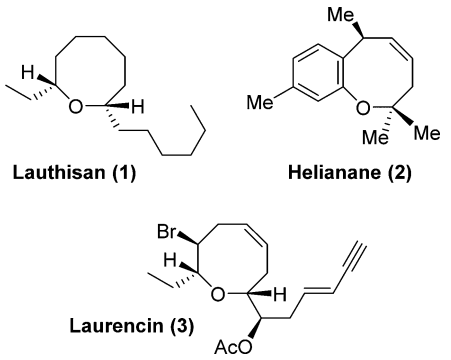
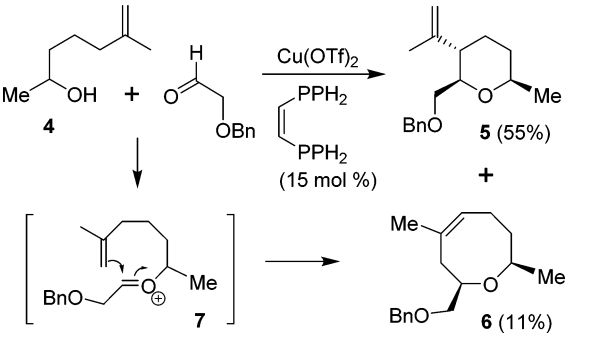


Figure 1. Structures of oxacyclic natural products.

An intermolecular reductive cyclization leading to oxocene cores was reported by Solladie and co-workers.[17] We recently reported that the reaction of substituted alkenol **4** with benzyloxyacetaldehyde in the presence of a catalytic amount of $Cu(OTf)_2$ and bis-phosphine complex provided the olefin migration and Prins cyclization product **5** (55% yield) along with a small amount of eight-membered cyclic ether **6** (11% yield, Scheme 1).[18,19] Presumably, the 2,8-substituents in **6** are in a *cis*-relationship, as depicted, and the oxocene product was formed by a nucleophilic attack of the olefin onto the oxocarbenium ion **7**, followed by elimination.

Scheme 1. Formation of THP and Oxocene Products



In an effort to access substituted oxocene derivatives, we investigated this reaction with a variety of Lewis acids and reaction conditions. Herein, we report the results of our investigations leading to the synthesis of 2,4,8-trisubstituted oxocenes in a highly diastereoselective manner. We initially investigated the Lewis acid catalyzed cyclization using 6-methylhept-6-en-2-ol (**4**) and *p*-nitrobenzaldehyde as the model substrates, as shown in Scheme 2. The use of 10 mol % of $Sc(OTf)_3$ as the Lewis acid in CH_2Cl_2, in the presence of *p*-TsOH and 4 Å molecular sieves at 23 °C, resulted in tetrahydropyran derivative **8** as the major product and oxocene

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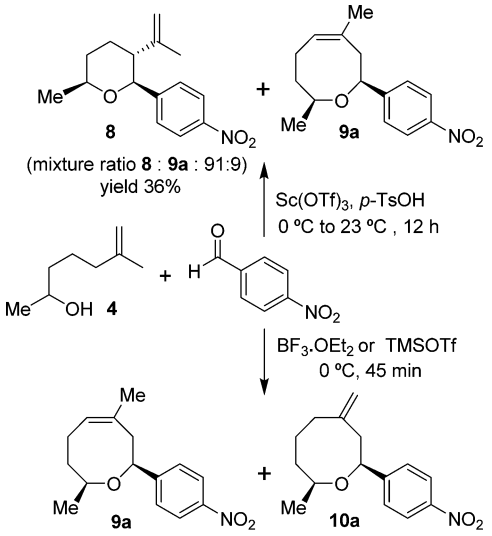
Scheme 2. Formation of Oxocene Products



derivative **9a** as the minor product in 36% combined yield. The ratios of products (**9a**:**8**) were 9:91 by ^{1}H NMR analysis.

With the aim of forming oxocene **9a** as the major product directly, we explored a number of oxophilic Lewis acids for this cyclization. Overman and co-workers reported efficient construction of medium-sized ring ethers by an intramolecular Prins-type reaction of mixed acetals using $BF_3{\cdot}OEt_2$ as the Lewis acid in *t*-BuOMe.[20] We first examined the reaction of alkenol **4** with *p*-nitrobenzaldehyde using a catalytic amount of $BF_3{\cdot}OEt_2$ in CH_2Cl_2. As it turns out, $BF_3{\cdot}OEt_2$-catalyzed cyclization provided mainly oxocene product **9a**. We have not been able to identify any 6-membered Prins product **8** by ^{1}H NMR analysis of the crude products. The trace amount of minor product appeared to be the *exo*-olefin product. As shown in Table 1, a catalytic amount (20 mol %) of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 provided a 38% yield of oxocene product **9a** as the major product (entry 2). The use of 40 mol % of $BF_3{\cdot}OEt_2$ resulted in a lower yield of oxocene cyclization product **9a** (entry 3). The use of $BF_3{\cdot}OEt_2$ (3 equiv) in *t*-BuOMe provided a 33% yield of oxocene product **9a** (entry 4). To further improve yields, we then explored TMSOTf in a number of solvent systems.[21] As it turns out, 1 equiv of TMSOTf in a variety of solvents afforded cyclization product oxocene **9a** as the major product. The choice of diethyl ether in the presence of molecular sieves at 0 °C for 15 min provided oxocene **9a** in 60% yield (entry 6). The presence of 4 Å molecular sieves did not improve the yield of oxocene product, but it did improve the *endo/exo* ratio (entries 5 and 6). The use of toluene resulted in a lower *endo/exo* ratio. The reaction in DME provided a comparable yield; however, cyclization products were obtained in an 81:19 ratio (entry 8). These ratios were determined on the basis of ^{1}H NMR analysis of the benzylic protons, as the products could not be separated by silica gel chromatography. This Prins-type cyclization provided the best result when THF was used as the solvent in the presence of 4 Å molecular sieves. As shown, oxocene product **9a** was obtained essentially as a single product (mixture ratio 98:2) in 73% isolated yield (entry 9). The reaction in a mixture of CH_2Cl_2 and THF also provided comparable yields and mixture ratios (entries 10 and 11). The use of TMSOTf in *t*-BuOMe provided a 46% yield (88:12) of oxocene product **9a** (entry 12).

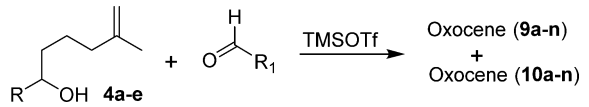
We then examined the substrate scope of this intermolecular process. As shown in Table 2, a variety of alkyl substituents on the alkyl group of the alkenol substrate were accommodated (entries 1−4). The structures of the major *endo*-products are shown in Figure 2. The electron-withdrawing nitro group on the *ortho*, *meta*, or *para* position of the benzene ring of the benzaldehyde provided a good yield of oxocene product and excellent *endo/exo* ratios (entries 5−7). Incorporation of *p*-F, *p*-CF_3, or *p*-Cl groups provided moderate yields of oxocene derivatives, and the *endo/exo* ratio decreased at the same time (entries 8−10). The reaction with dihydrocinnamaldehyde afforded 35% yield of oxocene derivative **9k**, and the *endo/exo* olefin ratio was 94:6 (entry 11). Also, reaction with benzyloxyacetaldehyde provided oxocene derivative **6** in 24% yield (entry 12). However, 3-(4-methoxybenzyloxy)propanal and 3-(*tert*-butyldimethylsilyloxy)propanal failed to provide any oxocene product. The reaction with *m*-methyl- or 2-naphthalde-

Table 1. $BF_3{\cdot}OEt_2$- and TMSOTf-Catalyzed Reactions[a]

entry	solvent	Lewis acid	equiv[b]	yield (%)	ratio **9a**:**10a**
1[c]	CH_2Cl_2	$BF_3{\cdot}OEt_2$	0.1	14	98:2
2[c]	CH_2Cl_2	$BF_3{\cdot}OEt_2$	0.2	38	98:2
3[c]	CH_2Cl_2	$BF_3{\cdot}OEt_2$	0.4	21	98:2
4[c]	*t*-BuOMe	$BF_3{\cdot}OEt_2$	3.0	33	76:24
5[c]	Et_2O	TMSOTf	1.0	60	95:5
6	Et_2O	TMSOTf	1.0	60	98:2
7	toluene	TMSOTf	1.0		68:32[d]
8	DME	TMSOTf	1.0	58	81:19
9	THF	TMSOTf	1.0	73	98:2
10	CH_2Cl_2−THF (1:1)	TMSOTf	1.0	68	98:2
11	CH_2Cl_2−THF (3:1)	TMSOTf	1.0	68	98:2
12	*t*-BuOMe	TMSOTf	1.0	46	88:12

[a]Conditions: 1 equiv of 6-methylhept-6-en-2-ol, 1.2 equiv of *p*-nitrobenzaldehyde, 0.1 M solution, 0 °C, 60 mg of molecular sieves, ratio is *endo/exo*. [b]equiv = equivalent of Lewis acid. [c]No molecular sieves were used. [d]No purification was conducted because the crude ratio was low.

Table 2. TMSOTf-Catalyzed Synthesis of Oxocenes[a]



entry	R	R_1	compd	ratio (**9**:**10**)[b]	yield[c] (%)
1	H	*p*-NO_2Ph	**9b**	90:10	70
2	Et	*p*-NO_2Ph	**9c**	90:10	87
3	*i*-Pr	*p*-NO_2Ph	**9d**	91:9	62
4	Ph	*p*-NO_2Ph	**9e**	91:9	39
5	Me	*p*-NO_2Ph	**9a**	98:2	73
6	Me	*m*-NO_2Ph	**9f**	91:9	65
7	Me	*o*-NO_2Ph	**9g**	97:3	58
8	Me	*p*-FPh	**9h**	90:10	20
9	Me	*p*-CF_3Ph	**9i**	92:8	37
10	Me	*p*-ClPh	**9j**	93:7	18
11	Me	Ph(CH_2)$_2$	**9k**	94:6	35
12	Me	CH_2OBn	**6**	98:2	24
13	Me	*m*-MePh	**9l**	92:8	8
14	Me	2-naphth	**9m**	94:6	16
15	Me	*p*-F-*m*-NO_2Ph	**9n**	91:9	41

[a]Reaction conditions are from entry 8, Table 1. [b]The *endo/exo* ratio was determined by ^{1}H NMR. [c]Isolated yield of combined products.

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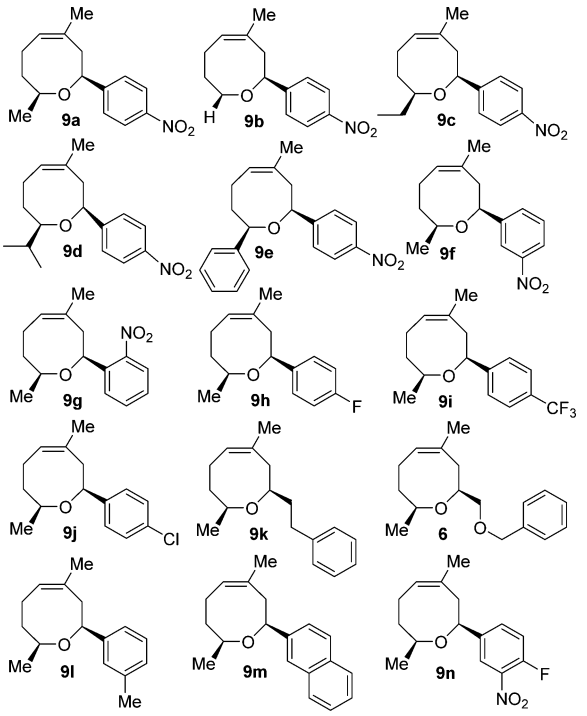


Figure 2. Structure of major isomer.

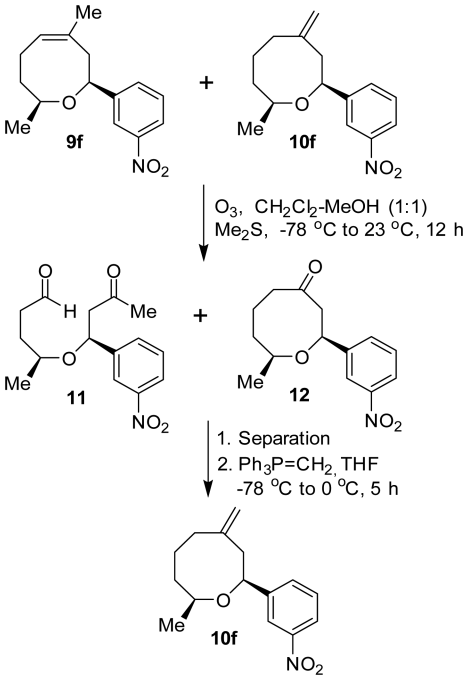
hyde provided only 8% and 16% yields of the corresponding oxocene derivatives, respectively (entries 13 and 14). The reaction with 4-fluoro-3-nitrobenzaldehyde resulted in reduction of yield over the 3-nitrobenzaldehyde (entry 15). This condition was also utilized in the preparation of nearly 0.5 g quantity of oxocene derivative **9f**.[22]

Separation of endo and exo isomers proved difficult by silica gel chromatography or via HPLC methods. In order to confirm the identity of the exo derivative, we exposed the mixture of products from entry 6 (Table 2) to ozonolytic cleavage at −78 °C in a mixture (1:1) of methanol and CH_2Cl_2 (Scheme 3). The resulting products were separated by silica gel chromatography. Ketone **12** was then subjected to Wittig olefination with methylene triphenylphosphorane to provide pure *exo*-olefin derivative **10f**. The ^{1}H NMR and ^{13}C NMR of **10f** obtained in this manner matched completely with the minor product in the spectra containing the mixtures.

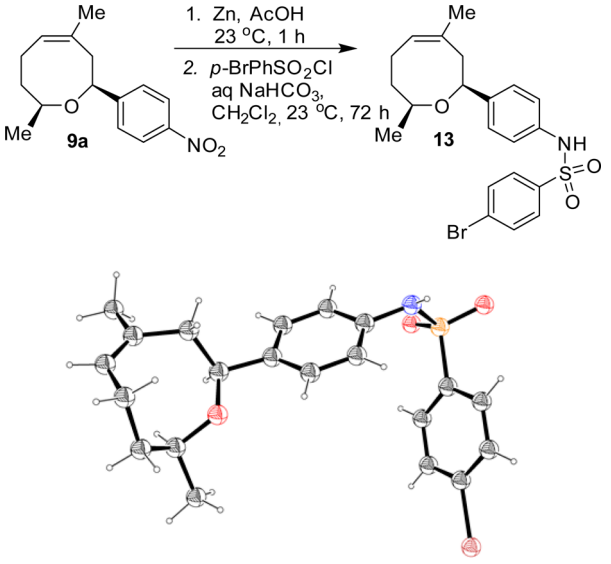
To determine the X-ray crystal structure, the main product **9a** (entry 6) was subjected to reduction with Zn dust in acetic acid as shown in Scheme 4.[23] The resulting aromatic amine was reacted with *p*-bromobenzenesulfonyl chloride in the presence of aqueous sodium bicarbonate solution to provide sulfonamide derivative **13**. This was recrystallized from ether/pentane at 23 °C for 48 h. The single-crystal X-ray analysis (Scheme 4) further supports the assignment of *cis*-stereochemistry.[24,25]

As shown in Table 2, the *endo*-olefin product was typically the major isomer observed by ^{1}H and ^{13}C NMR analysis. The stereochemical assignment of these compounds was carried out by ^{1}H NMR NOESY experiments of compound **9a** (Figure 3). The depicted conformation is chosen on the basis of the X-ray crystal structure. The observed strong NOESY correlation between H_E and H_D provided evidence of the assigned *cis*-relationship between the alkyl and aromatic ring in **9a**. Additional NOESY correlations between H_E–H_C, H_C–H_L, H_D–H_J, H_J–H_H, and H_F–H_G are due to a preferred conformation of the eight-membered oxocene ring.[26]

Scheme 3. Preparation of *exo*-Oxocene Isomer 10f



Scheme 4. Synthesis and X-ray Structure of 13[a]



[a]White = hydrogen, black = carbon, red = oxygen, blue = nitrogen, yellow = sulfur, brown = bromine.

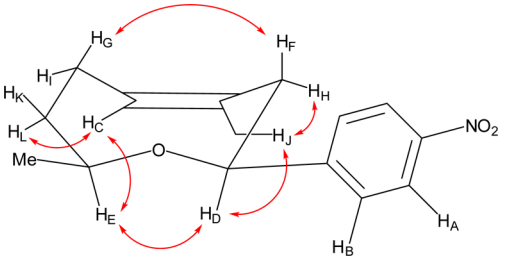


Figure 3. ^{1}H NMR NOESY of compound **9a**.

The stereochemical outcome of the current Prins-type cyclization, which provided *cis*-oxocene derivatives, can be

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rationalized on the basis of the transition-state models in Figure 4. The TMSOTf-catalyzed reactions of alkenol **4** and an aromatic aldehyde would lead to the formation of oxocarbenium ion intermediates **14a** and **14b**.

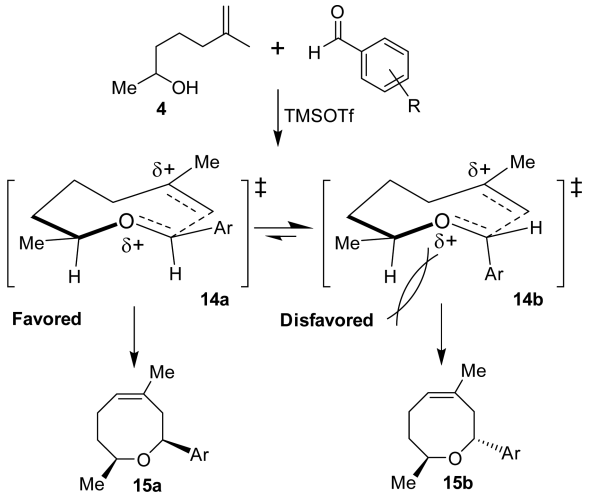

Figure 4. Stereochemical analysis for *cis*-oxocene products.

Subsequent cyclization followed by proton elimination is unlikely to proceed through transiton state **14b** as it shows unfavorable steric interactions. The cyclization is likely to proceed through transition state **14a** leading to *cis*-product **15a**. The formation of *trans*-product **15b** was not observed.

In summary, we have developed an unprecedented TMSOTf-catalyzed intermolecular Prins-type cyclization for the synthesis of a variety of oxocene derivatives. The use of various 1-alkyl-5-methylhex-5-en-l-ol and an appropriate aromatic aldehyde afforded a range of oxocene *endo*-olefin derivatives. A stereochemical model also provided explanation for the selective formation of 2,8-*cis*-oxocene derivatives in up to 87% yields and excellent diastereoselectivity for disubstituted derivatives. Mechanistic studies and application of these substituted oxocene derivatives are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03411.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Majumdar, K. C. *RSC Adv.* **2011**, *1*, 1152−1170.
(2) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48.
(3) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516−3517.
(4) Harrison, B.; Crews, P. *J. Org. Chem.* **1997**, *62*, 2646−2648.
(5) Kim, G.; Sohn, T.-I.; Kim, D.; Paton, R. *Angew. Chem., Int. Ed.* **2004**, *53*, 272−276.
(6) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193−4205.
(7) Kleinke, A. S.; Webb, D.; Jamison, T. F. *Tetrahedron* **2012**, *68*, 6999−7018.
(8) Kreiter, C. G.; Lehr, K.; Leyendecker, M.; Sheldrick, W. S.; Exner, R. *Chem. Ber.* **1991**, *124*, 3−12.
(9) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.
(10) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930.
(11) Guyot, B.; Pornet, J.; Miginiac, L. *J. Organomet. Chem.* **1989**, *373*, 279−288.
(12) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749−10784.
(13) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073−2077.
(14) Bamford, S. J.; Goubitz, K.; van Lingen, H. L.; Luker, T.; Schenk, H.; Hiemstra, H. *J. Chem. Soc. Perkin Trans. 1* **2000**, 345−351.
(15) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386−4399.
(16) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399−4403.
(17) Carreno, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladie, G. *Org. Lett.* **2005**, *7*, 2039−2042.
(18) Ghosh, A. K.; Nicponski, D. R. *Org. Lett.* **2011**, *13*, 4328−4331.
(19) Ghosh, A. K.; Kass, J.; Nicponski, D.; Keyes, C. *Synthesis* **2012**, *44*, 3579−3589.
(20) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966.
(21) Ullapu, P. R.; Kim, Y. S.; Lee, J. K.; Pae, A. N.; Kim, Y.; Min, S.-J.; Cho, Y. S. *Chem. - Asian J.* **2011**, *6*, 2092−2100.
(22) For experimental details, see the Supporting Information.
(23) Booth, G. Nitro Compounds, Aromatic. In *Ullmann's Encyclopedia of Industrial Chemistry*; John Wiley & Sons: New York, 2007.
(24) Single-crystal X-ray analysis was performed in our X-ray crystallography laboratory by Dr. Phil Fanwick, Department of Chemistry, Purdue University, West Lafayette, IN.
(25) CCDC 1437986 contains the supplementary crystallographic data for compound **13**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(26) Rhee, H. J.; Beom, H. Y.; Kim, H.-D. *Tetrahedron Lett.* **2004**, *45*, 8019−8022.

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Org. Lett. XXXX, XXX, XXX−XXX