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Allyl Sulfones as Precursors to Allylzincs in the Palladium-Catalyzed Zinc-ene Cyclization: Highly Efficient Synthesis of Enantiopure (–)-Erythrodiene†

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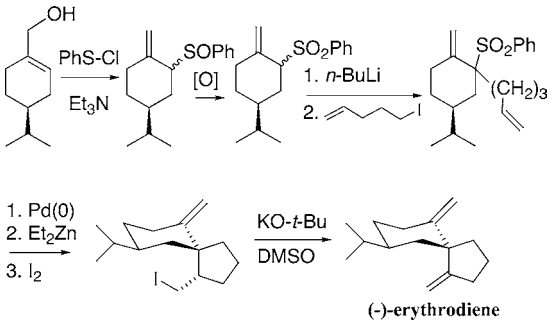
ABSTRACT

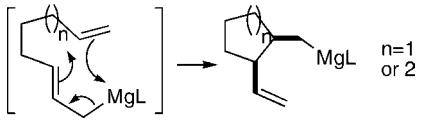


Easily prepared allyl phenyl sulfones, capable of introduction of the alkene by electrophilic α-substitution, are superior to allyl acetates as substrates for Pd-catalyzed Zn-ene cyclizations, providing C5 or C_4N rings with *cis*-1,2-vinyl and -CH_2Zn substituents. Several examples, with different methods of substrate preparation, are presented.

Magnesium-ene cyclizations (Scheme 1) have been used in a number of elegant syntheses, especially by Oppolzer.[1] They are highly stereoselective with vinyl and CH_2Mg substituents oriented in a cis fashion on the new rings. Li-ene cyclizations occur at lower temperatures but are thermodynamically unfavorable.[2,3]

There are several clues that carbometalations via the Zn-ene process are far more facile than those proceeding by the Mg-ene process.[4] Furthermore, many functional groups that are unstable in the presence of Grignard reagents can survive in the presence of organozinc compounds.[5]

Scheme 1. Mg-Ene Cyclization



Zn-ene cyclizations had not been well studied until the appearance of Oppolzer's work on Pd-catalyzed Zn-ene cyclizations using allyl acetate precursors.[6] The mechanism is thought to involve Pd(0) insertion into the allyl acetate to generate a π-allyl palladium intermediate that undergoes transmetalation with diethylzinc to give the corresponding

† Taken in part from the Ph.D. Thesis of Kai Deng, University of Pittsburgh, Pittsburgh, PA, 2004.

(1) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38−52. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941−1948. (c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5, pp 29−61.

(2) Cheng, D.; Zhu, S.; Liu, X.; Norton, S. H.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241−10242.

(3) Cheng, D.; Knox, K. R.; Cohen, T. *J. Am. Chem. Soc.* **2000**, *122*, 412−13.

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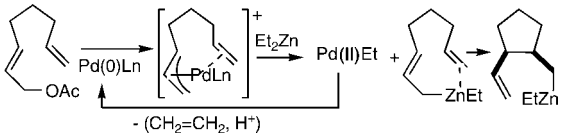
allylzinc intermediate together with an ethyl palladium species (Scheme 2). The allylzinc undergoes the Zn-ene

Scheme 2. Oppolzer's Mechanism for the Palladium-Catalyzed Zinc-ene Cyclization



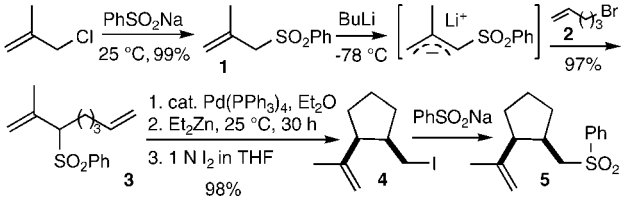
cyclization to produce a species capable of being trapped by electrophiles to give functionalized products. The Pd atom attached to the ethyl group undergoes PdH elimination to release ethylene and regenerate the Pd(0) catalyst. The stereochemistry of the products was thought[6a] to be cis on the basis of the fact that the ^{13}C chemical shifts of the ring carbon atoms bearing the substituents in the electrophile-trapped products were within the range found for the 3- and 4-carbon atoms in 3,4-dimethyl and 3,4-diethyl-*N*-methylpyrrolidines and in a different range than those of the corresponding trans-disubstituted pyrrolidines.[7,8]

On the basis of this elegant work and the extensions of it described below, we envisioned a great increase in the versatility of Pd-catalyzed Zn-ene cyclizations by replacing the allyl acetates with allyl phenyl sulfones as precursors. Trost[9] had demonstrated that allyl phenyl sulfones could serve as substrates for allyl palladium formation, while Julia[10] had shown that allyl palladiums generated in this way could be reduced by diethylzinc to generate allylzincs capable of undergoing intermolecular addition to aldehydes. Due to the wide variety of methods available for producing allyl phenyl sulfones (see below) along with their valuable feature of readily losing an α-proton to form an allylic anion that reacts with alkylating agents virtually exclusively at the α-position,[11] we expected that many substrates for Pd-catalyzed allylzincation could be constructed in a highly efficient, connective manner. The use of allyl phenyl sulfones as precursors for Pd-catalyzed allylzincation of unactivated alkenes has not been reported.

We now present four syntheses involving four different concepts for preparing in a highly efficient manner the allyl sulfones required for α-alkylation and intramolecular carbozincation. Furthermore, we provide the first definitive evidence that the Pd-catalyzed Zn-ene cyclization provides cis-disubstituted five-membered rings as in the Mg case; this fact has some bearing on the question of whether this is a Zn-ene rather than a Pd-ene cyclization.

One example of the production of a simple allyl phenyl sulfone is illustrated by the production of methallyl phenyl sulfone **1**[12] by treatment of methallyl chloride with commercial $C_6H_5SO_2Na$ (Scheme 3**)**. The allyl phenyl sulfone

Scheme 3. Zn-Ene Cyclization Utilizing an Allyl Sulfone Prepared from an Allyl Chloride



anion, generated by treatment of **1** with *n*-butyllithium, is alkylated exclusively at the α-position by 1-bromo-4-pentene **2** to provide a high yield of cyclization substrate **3**. Subjecting **3** to 10 mol % $Pd(PPh_3)_4$ and 6 equiv of Et_2Zn affords the cyclopentane derivative **4**, after iodination, in excellent yield as the only detectable product. The cis stereochemistry of **4** was established by converting a sample to the corresponding sulfone **5**; both the ^{13}C and ^{1}H NMR spectra of the latter were identical with those reported for the same compound, the X-ray crystal structure of which had been determined.[13] This definitive evidence for the stereochemistry of the cyclization product lends strong credence to the suggestions of Oppolzer and Schröder that the main products of the Pd-catalyzed Zn-ene cyclizations are indeed rings bearing adjacent cis substituents. It also provides some support, albeit weak, for their contention that this is a Zn-ene cyclization rather than a Pd-ene cyclization, followed by Zn−Pd exchange; the Pd-ene cyclization in an analogous system, although under somewhat different conditions, yields a trans product.[6a,14]

Since allyl phenyl sulfides are readily available by a wide variety of procedures[15,16] and since they are easily oxidized to sulfones by a variety of selective reagents,[17] such oxidation

(4) Intermolecular comparisons: Lehmkuhl, H.; Reinehr, D.; Hennenberg, D.; Schomburg, G.; Schroth, G. *Ann. Chem.* **1975**, 119−144. Lehmkuhl, H.; Nehl, H. *J. Organomet. Chem.* **1973**, *60*, 1−10. Lehmkuhl, H.; Doring, I.; Nehl, H. *J. Organomet. Chem.* **1981**, *221*, 123−130. Intramolecular comparisons: Courtemanche, G.; Normant, J.-F. *Tetrahedron Lett.* **1991**, *32*, 5317−5320. Meyer, C.; Marek, I.; Normant, J.-F.; Platzer, N. *Tetrahedron Lett.* **1994**, *35*, 5645−5648. Lorthiois, E.; Marek, I.; Meyer, C.; Normant, J.-F. *Tetrahedron Lett.* **1995**, *36*, 1263−1266. Lorthiois, E.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1997**, *38*, 89−92.

(5) Review: Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8319.

(6) (a) Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* **1994**, *35*, 7939−7942. (b) In the previous year, it had been shown that allylzinc species, capable of adding to an aldehyde, could be generated from allyl esters in the presence of 1 equiv of diethylzinc and a catalytic quantity of $Pd(PPh_3)_4$; Yasui, K.; Goto, Y.; Yajima, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, T. *Tetrahedron Lett.* **1993**, *34*, 7619−7622.

(7) Hawthorne, D. G.; Johns, S. R.; Willing, R. I. *Aust. J. Chem.* **1976**, *29*, 315−326.

(8) Since the ring substituents in the cyclizations described in ref 6a are very different from simple alkyl groups of ref 7 and in most cases the rings are quite different than in the model systems,[7] we consider that there is considerable uncertainty about the stereochemistry and even the mechanism of the Pd-catalyzed Zn-ene cyclization; see below.

(9) Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5979−5981.

(10) Clayden, J.; Julia, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1905−1906.

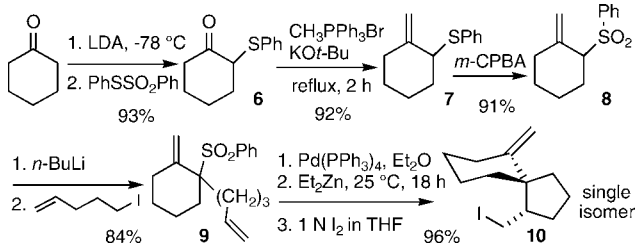
(11) (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: New York, 1993; pp 106, 116. (b) Kocienski, P. J. *Tetrahedron Lett.* **1979**, *20*, 441−442. (c) Phillips, E. D.; Warren, E. S.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 307−320. (d) Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 123−125.

(12) Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396−405.

(13) Liu, C. Q.; Kudo, K.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1996**, *61*, 494−502.

is a very versatile procedure for preparing allyl phenyl sulfones. One example, used in the preparation of the spirocyclic alkyl iodide **10**, is shown in Scheme 4. Oxidation

Scheme 4. Use of an Allyl Sulfone Prepared by Oxidation of an Allyl Phenyl Sulfide



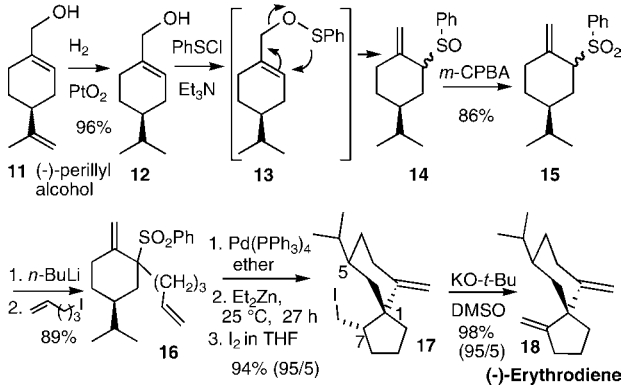
of the readily prepared allyl phenyl sulfide **7**[16] with *m*-CPBA gave the corresponding allyl phenyl sulfone **8** in 91% yield.

Alkylation[18] of the sulfone-stabilized allyl anion with 1-iodo-4-pentene[19] occurred in 84% yield. Treating the alkylation product **9** with 5 mol % $Pd(PPh_3)_4$, followed by the addition of 6 equiv of Et_2Zn, led to the generation of the allylzinc, which readily attacked the tethered olefin. After 18 h at 25 °C, I_2 was added to quench the reaction. A single diastereomer[20] of **10** was obtained in 96% yield.

Encouraged by the easy assembly of spirobicyclic molecule **10**, we turned our attention to the synthesis of (−)-erythrodiene **18**, a sesquiterpene isolated from the Caribbean gorgonian coral *Erythropodium caribaeorum*.[21] The rare spirobicylo[4.5]decane skeleton of **18** has attracted considerable synthetic effort over the past decade, and two syntheses of this molecule have been reported to date. The first synthesis[22] used an intramolecular alkyne carbomercuration reaction to construct the spirocarbon center with moderate diastereoselectivity. In total, 10 steps were performed with an overall yield of 35%. The second synthesis[23] used an allyl acetate as the substrate for the Pd-catalyzed Zn-ene cyclization to construct the spiro carbon center with excellent diastereoselectivity. A total of 11 steps were performed with an overall yield of 24%.

A main purpose of our attempt to synthesize **18** was to determine any advantages of using an allyl phenyl sulfone instead of an allyl acetate to synthesize the same target from the same starting material, natural (−)-perillyl alcohol **11**, utilizing the same Pd-catalyzed Zn-ene cyclization strategy as that used by the Oppolzer group[23] but with an allyl phenyl sulfone rather than an allyl acetate as a cyclization substrate. The allylic alcohol **12** was prepared by hydrogenation of **11** (Scheme 5).[22,23] Treating **12** with PhSCl[24] and Et_3N produced

Scheme 5. Synthesis of (−)-Erythrodiene Utilizing an Allyl Sulfone Prepared by Oxidation of an Allyl Phenyl Sulfoxide Derived from a [2,3]-Sigmatropic Rearrangement



intermediate **13**, which underwent a facile [2,3]-sigmatropic rearrangement to afford allyl phenyl sulfoxide **14** in 89% yield.[24,25] Oxidation of **14** afforded the corresponding allyl phenyl sulfone **15** in 86% yield. Alkylation of **15** as in Scheme 4 afforded the allyl phenyl sulfone cyclization substrate **16** in 89% yield as two diastereomers in a ratio of 4:1 (NMR). Treating **16** with $Pd(PPh_3)_4/Et_2Zn$ generated the allylzinc intermediate that smoothly executed carbozincation of the terminal alkene to afford, after an iodine quench, a 94% yield of a mixture of two diastereomers in a ratio of 95:5, a selectivity similar to that observed in the Oppolzer synthesis using an allyl acetate as the precursor of the allylzinc species.[23] However, the use of the most common Pd(0) source, $Pd(PPh_3)_4$, in his reaction gave a poor yield; a special combination of $Pd(OAc)_2/PBu_3$ was required, and the

(14) Limitations of this cyclization procedure became evident when attempts to cyclize the analogues of **3** bearing methyl groups on either terminus of the nonallylic alkene were unsuccessful. It is conceivable that special reaction conditions such as those required in a literature synthesis of (−)-erythrodiene (see below) would be successful. Other conditions were not tried.

(15) For examples, see: (a) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208−1213. (b) Giese, B.; Mazundar, P. *Chem. Ber.* **1981**, *114*, 2859−2865. (c) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655−1659. (d) Binns, M. R.; Haynes, R. K.; Lambert, D. E.; Schober, P. A. *Tetrahedron Lett.* **1985**, *26*, 3385−3388. (e) Guo, B.-S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710−4711. (f) Hannaby, M.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 303−311. (g) Sato, T.; Hiramura, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1989**, *30*, 2821−2824. (h) Behrens, K.; Kneisel, B. O.; Noltemeyer, M.; Bruckner, R. *Liebigs Ann. Chem.* **1995**, 385−400. (i) Wang, X. Z.; Wu, Y. L.; Jiang, S. D.; Singh, G. *Tetrahedron Lett.* **1999**, *40*, 8911−8914.

(16) Cohen, T.; Guo, B. S. *Tetrahedron* **1986**, *42*, 2803−2808.

(17) (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287−1290. (b) Bortolini, O.; Di Furia, F.; Modena, G.; Seraglia, R. *J. Org. Chem.* **1985**, *50*, 2688−2690. (c) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924−4925. (d) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X. Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469−2476. (e) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772−10773. (f) Choudary, B. M.; Reddy, C. R. V.; Prakash, B. V.; Kantam, M. L.; Sreedhar, B. *J. Chem. Soc., Chem. Commun.* **2003**, 754−755.

(18) Gais, H. J.; Gumpel, M. V.; Raabe, G.; Mueller, J.; Braun, S.; Lindner, H. J.; Rohs, S.; Runsink, J. *Eur. J. Org. Chem.* **1999**, *7*, 1627−1652.

(19) Padwa, A.; Kamigata, N. *J. Am. Chem. Soc.* **1977**, *99*, 1871−1880. The use of 1-bromo-4-pentene as an alternative electrophile provided no desired product under the same reaction conditions.

(20) Stereochemistry is assumed on the basis of the results in Scheme 3 and the reported structures of all other kinetic products of metallo-ene cyclizations using main group organometallics.

(21) Pathirana, C.; Fenical, W.; Corcoran, E.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 3371−3372.

(22) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773−2779.

(23) Oppolzer, W.; Flachsmann, F. *Helv. Chim. Acta* **2001**, *84*, 416−430.

(24) Hua, D. H.; Venkaraman, S.; Ostrander, R. A.; Sinai, G. Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507−515.

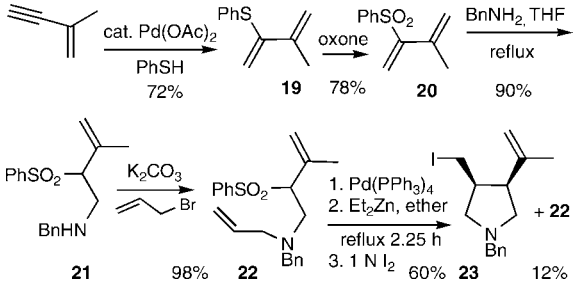
(25) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147−155.

use of 20 equiv of Et_2Zn was crucial in obtaining a high yield of the cyclization product. Of considerable significance for the comparison of allyl sulfones with allyl acetates as substrates in these cyclizations is the finding that in our (−)-erythrodiene synthesis (Scheme 5), using **16** as the substrate for the Zn-ene cyclization and $Pd(PPh_3)_4$ together with 6 equiv of Et_2Zn was highly successful. No effort was made to optimize the amount of Et_2Zn used.

Dehydroiodination of the mixture of iodides produced a 95:5 mixture of (−)-erythrodiene **18** and its diastereomer in almost quantitative yield. A pure sample of **18**, obtained from the mixture of diastereomers by chromatography on silica impregnated with $AgNO_3$, had identical NMR spectroscopic properties and rotation ($[\alpha]_D$ −112°) to those reported.[22,23] The same diastereoselectivity between iodide **17** and (−)-erythrodiene **18** derived from it shows that the chiral center at C7 must have been generated in a completely diastereoselective manner during cyclization and that the stereochemical divergence comes from the relationship between the spiro carbon center at C1 and the carbon atom C5 bearing the isopropyl group. In total, six linear steps were used to obtain (−)-erythrodiene starting from commercially available (−)-perillyl alcohol with an overall yield of 60%. The synthesis utilizing the allyl acetate[23] required 11 steps starting with the same alcohol, and the overall yield was 24%. Such a dramatic improvement in yield and efficiency is a testament to the power of the allyl phenyl sulfone approach to (−)-erythrodiene and more generally demonstrates the connective power and synthetic utility of allyl phenyl sulfones in these reactions.

We envisioned that the addition of a primary amine to 2-phenylsulfonyl-3-methyl-1,3-butadiene **20** would be especially useful because the resulting product is an allyl phenyl sulfone,[26] which can be further elaborated to synthesize a precursor for the Zn-ene cyclization. As illustrated in Scheme 6, **20**[27] added benzylamine smoothly to afford the desired allyl phenyl sulfone **21** in 90% yield. N-Allylation[28] provided the cyclization substrate **22** in 98% yield. When **22** was treated with $Pd(PPh_3)_4/Et_2Zn$, the Zn-ene cyclization proceeded to afford cyclization product **23** in a moderate unoptimized yield of 60% (68% based on consumed reactant)

Scheme 6. Synthesis of a Cis-3,4-disubstituted Pyrrolidine from an Allyl Sulfone Derived by 1,2-Addition of an Amine to a 2-Phenylsulfonyl-1,3-butadiene



with high stereoselectivity (>40:1) as determined by GC.[29] The ease of assembly of **22** and the exquisite stereoselectivity bode well for a synthesis of the highly biologically active (−)-kainic acid[30] that is under way in this laboratory.

Because of the ease of preparation of allyl phenyl sulfones, they are considerably superior to allyl acetates as substrates in Pd-catalyzed Zn-ene cyclizations. In the synthesis of (−)-erythrodiene, the sulfone method required about half of the number of steps and led to a doubling of the yield as compared to use of the allyl acetate substrate; in addition, special cyclization conditions were not required as was the case with the acetate. Several other five-membered rings, including a pyrrolidine, were prepared from other allyl phenyl sulfone substrates that were generated by diverse methods.

Acknowledgment. We thank the US−Israel Binational Science Foundation (Grant 2000155), the US National Science Foundation (Grant 0102289), and The Dreyfus Foundation (Senior Scientist Mentor Initiative SI-03-007) for support of this work. We also thank Professor Ilan Marek for useful suggestions.

Supporting Information Available: Experimental procedures and compound characterizations, including NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The largely 1,2-addition of a secondary amine to 2-phenylsulfonyl-1,3-butadiene has been reported: Bäckvall, J.-E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396−6403.

(27) Bäckvall, J. E.; Ericsson, A. *J. Org. Chem.* **1994**, *59*, 5850−5851.

(28) Kemp, M. I.; Whitby, R. J.; Coote, S. J. *Synthesis* **1998**, 557−568.

(29) Lowered yield in this case is probably the result of elimination of zinc allyl amide in the allylzinc intermediate. The latter presumably undergoes competitive cyclization and elimination as noted in an analogous case in which an allyl acetate substrate was used.[6a] Corresponding allylmagnesium intermediates give only elimination: Oppolzer, W.; Gaudin, J.-M.; Bedoya-Zurita, M.; Hueso-Rodriguez, J.; Robyr, C. *Tetrahedron Lett.* **1988**, *29*, 4709−4712.

(30) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467−1470 and reference therein.