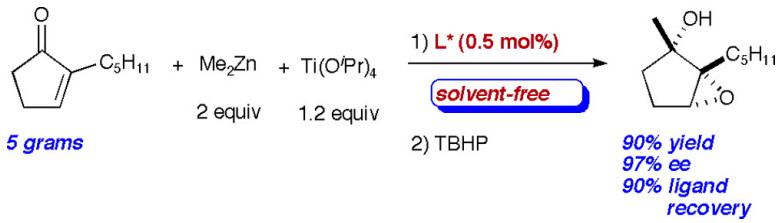
Article

A Green Chemistry Approach to a More Efficient Asymmetric Catalyst: Solvent-Free and Highly Concentrated Alkyl Additions to Ketones

Sang-Jin Jeon, Hongmei Li, and Patrick J. Walsh

J. Am. Chem. Soc., **2005**, 127 (47), 16416-16425• DOI: 10.1021/ja052200m • Publication Date (Web): 04 November 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 18 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 11/04/2005

A Green Chemistry Approach to a More Efficient Asymmetric Catalyst: Solvent-Free and Highly Concentrated Alkyl Additions to Ketones

Sang-Jin Jeon, Hongmei Li, and Patrick J. Walsh*

Contribution from the Department of Chemistry, P. Roy and Diana T. Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received April 6, 2005; E-mail: pwalsh@sas.upenn.edu

Abstract: There is a great demand for development of catalyst systems that are not only efficient and highly enantioselective but are also environmentally benign. Herein we report investigations into the catalytic asymmetric addition of alkyl and functionalized alkyl groups to ketones under highly concentrated and solvent-free conditions. In comparison with standard reaction conditions employing toluene and hexanes, the solvent-free and highly concentrated conditions permit reduction in catalyst loading by a factor of 2- to 40-fold. These new conditions are general and applicable to a variety of ketones and dialkylzinc reagents to provide diverse tertiary alcohols with high enantioselectivities. Using cyclic conjugated enones, we have performed a tandem asymmetric addition/diastereoselective epoxidation using the solvent-free addition conditions followed by introduction of a 5.5 M decane solution of *tert*-butyl hydroperoxide (TBHP) to generate epoxy alcohols. This one-pot procedure allows access to syn epoxy alcohols with three contiguous stereocenters with excellent enantio- and diastereoselectivities and high yields. Both the solvent-free asymmetric additions and asymmetric addition/diastereoselective epoxidation reactions have been conducted on larger scale (5 g substrate) with 0.5 mol % catalyst loadings. In these procedures, enantioselectivities equal to or better than 92% were obtained with isolated yields of 90%. The solvent-free and highly concentrated conditions are a significant improvement over previous solvent-based protocols. Further, this chemistry represents a rare example of a catalytic asymmetric reaction that is highly enantioselective under more environmentally friendly solvent-free conditions.

Introduction

In an era when synthetic chemists have demonstrated that even the most complex natural products can be prepared,[1−3] the focus of organic synthesis is shifting to the development of truly practical methods for their construction.[4−6] One of the challenges facing chemists this century, therefore, is to develop new transformations that are not only efficient, selective, and high yielding but that are also environmentally benign.[7,8] Historically, the most common measure for success of reactions has been the product yield. While reaction yields will always be important, alternative measures of success with respect to the "greenness" of a reaction, such as its *E* factor and the volume productivity, are now considered. The *E* factor[9] is defined as the ratio of weight waste to weight product, while the volume productivity[10] is defined as the grams product per liter of reaction medium. The *E* factor for many pharmaceuticals has been estimated to exceed 100.[11] The largest contribution to the magnitude of *E* factors comes from organic solvents, many of which are ecologically harmful and require costly remediation. In industry, solvents are recycled whenever possible; however, recycling is rarely accomplished with complete efficiency.

One approach to reducing the environmental impact of a reaction is to conduct them under solvent-free conditions.[11−14] Advantages of solvent-free reactions include cost savings, reduced energy consumption, decreased reaction times, and a considerable reduction in reactor size and, therefore, capital investment. These attributes have inspired a substantial research effort directed toward the development of solvent-free reactions.[11−14]

Despite recent progress in solvent-free polymerizations,[12,15] radical additions,[12] ionic reactions,[16] solid-state reactions,[13] and

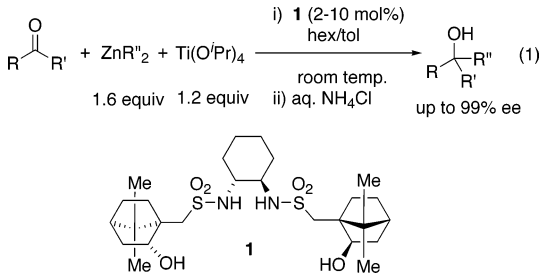
(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.
(2) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1996.
(3) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, Germany, 2003.
(4) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664.
(5) Smith, A. B., III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett.* **2005**, *7*, 1825−1828.
(6) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Proc. Res. Dev.* **2004**, *8*, 122−130.
(7) *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford Science Publications: New York, 1998.
(8) DeSimone, J. M. *Science* **2002**, *297*, 799−803.
(9) Sheldon, R. A. *Chem. Ind.* **1992**, 903−906.
(10) Jacobsen, E. N.; Finney, N. S. *Chem. Biol.* **1994**, *1*, 85−90.
(11) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159−2169.
(12) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975−2978.
(13) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025−1074.
(14) Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.

10.1021/ja052200m CCC: $30.25

photochemical reactions,[13] there have been a limited number of catalytic enantioselective solvent-free reactions,[17−34] excluding those that employ a large excess of one reagent.[35−37] Of these few solvent-free processes, some have not yet been shown to exhibit substrate generality[24,27,29,31,33,34] while others are plagued with enantioselectivities that are either low[26,28,31,32,38] or generally below the useful range (≥90% ee).[23] Examples of highly enantioselective catalysts that exhibit good substrate generality under solvent-free conditions include Jacobsen's kinetic resolution of racemic epoxides, desymmetrization of meso epoxides,[18,20−22] and hetero-Diels−Alder reaction,[39] Ding's hetero-Diels−Alder[25] and carbonyl-ene[40] reactions, and the Hoveyda/Schrock enantioselective ring-closing metathesis route to cyclic amines.[30]

The scarcity of highly enantioselective solvent-free reactions is not surprising. In solution, catalyst enantioselectivity and efficiency can be highly sensitive to the nature of the solvent.[41] For example, instances where a catalyst can generate opposite enantiomers of the product with high levels of enantioselectivity in different solvents are known.[42] Further, asymmetric catalysts can exhibit concentration dependent enantioselectivities. Thus, in solvent-free reactions, two of the most important variables for catalyst optimization, solvent type and concentration, are not available. Further complicating development of solvent-free reactions is that the reaction medium changes significantly as reagents and substrates are converted to products. We believe that these limitations have dissuaded many investigators from considering solvent-free catalytic asymmetric reactions. Although the challenges of solvent-free asymmetric catalysis are significant, the potential environmental and economical benefits have created high demand for such processes. With these considerations in mind, we decided to evaluate our enantioselective catalysts for asymmetric C−C bond formation under solvent-free conditions.

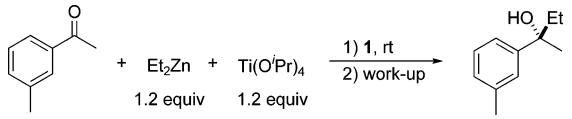
We recently reported a practical and highly enantioselective catalyst for the addition of alkyl groups to ketones (eq 1).[43−45] Unlike the addition of alkyl groups to aldehydes, a reaction that can be catalyzed by a wide variety of highly enantioselective catalysts,[46,47] to date only our catalyst exhibits high enantioselectivity and efficiency for alkyl additions to ketones. This catalyst will also promote the asymmetric addition of phenyl,[48−50] vinyl,[51,52] and dienyl[52] groups to ketones with high enantioselectivities. The enantioenriched tertiary alcohols generated in these reactions are useful chiral building blocks and have been used in natural product synthesis.[53,54]



As outlined in eq 1, the asymmetric addition of alkyl groups to ketones using a solvent mixture of toluene and hexanes required 2−10 mol % of the chiral bis(sulfonamide) diol ligand **1** to achieve the highest levels of enantioselectivity. While 2 mol % ligand loading is low for early transition-metal catalysts, many substrates required 10 mol % **1** to maintain high enantioselectivities and reasonable reaction times. We hypothesized that reducing the amount of solvent employed in the asymmetric addition would have several benefits. First, the corresponding increase in the concentration of the catalyst and reagents could result in greater catalyst turnover frequency, possibly allowing a reduction in catalyst loadings. Second, decreasing the quantity of solvent would make scale-up more attractive by cutting waste generation and reducing costs. Given that titanium tetraisopropoxide and most dialkylzinc reagents are liquids at room temperature, we were optimistic that the asymmetric addition would proceed under solvent-free conditions. We were not able to predict, however, how this dramatic

(15) Komiya, K., Fukuoka, S., Aminaka, M., Hasegawa, K., Hachiya, H., Okamoto, H., Watanabe, T., Yoneda, H., Fukawa, J., Dozono, T. In *Green Chemistry, Designing Chemistry for the Environment*; Anastas, P. T., Williamson, T. C., Eds.; American Chemical Society: Washington, DC, 1996; p 20.
(16) Bram, G.; Decodts, G.; Bensaïd, Y.; Farnoux, C. C.; Galons, H.; Miocque, M. *Synthesis* **1985**, 543−545.
(17) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898.
(18) Tokunaga, M.; Larrow, J. F.; Kakuichi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.
(19) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.
(20) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.
(21) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687−2688.
(22) White, D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633−3638.
(23) Sato, I.; Saito, T.; Soai, K. *J. Chem. Soc., Chem. Commun.* **2000**, 2471−2472.
(24) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688.
(25) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10−11.
(26) Rajagopal, D.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron: Asymmetry* **1996**, *7*, 2189−2190.
(27) Du, H.; Zhao, D.; Ding, K. *Chem. Eur. J.* **2004**, *10*, 5964−5970.
(28) Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349−4352.
(29) Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1070−1072.
(30) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991−6997.
(31) Lu, X.-B.; Liang, B.; Zhang, Y.-J.; Tian, Y.-Z.; Wang, Y.-M.; Bai, C.-X.; Wang, H.; Zhang, R. *J. Am. Chem. Soc.* **2004**, *126*, 3732−3733.
(32) Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Proc. Indian Acad. Sci.* **2001**, *113*, 197−213.
(33) Nozaki, H.; Shibahara, F.; Hiyama, T. *Chem. Lett.* **2000**, 694−695.
(34) Shibahara, F.; Nozaki, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8555−8560.
(35) Shibata, T.; Toshida, N.; Takagi, K. *J. Org. Chem.* **2002**, *67*, 7446−7450.
(36) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.* **2000**, *2*, 2959−2962.
(37) Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J. C.; Cahard, D. *Synthesis* **2001**, 1742−1746.
(38) Graf v. Keyserlingk, N.; Martens, J. *Tetrahedron: Asymmetry* **2001**, *12*, 2213−2222.
(39) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400.
(40) Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5478−5480.
(41) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. 1−3.
(42) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309−1320.
(43) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749−760.
(44) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970−10971.
(45) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455.
(46) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.
(47) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.
(48) Li, H.; García, C.; Walsh, P. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5425−5427.
(49) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641−3644.
(50) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955−1957.
(51) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538−6539.
(52) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355−8361.
(53) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544−9545.
(54) Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745−2748.

Table 1. Diethylzinc Additions to 3′-Methylacetophenone under Solvent-Free and Highly Concentrated Reaction Conditions



entry	**1** (mol %)	time (h)	yield (%)	ee (%)
1	1	4	79	99[a]
2	1	7	78	99[b]
3	0.5	20	80	98[a]
4	0.25	21	62	97[a]
5	0.1	24	58	96[a]

[a] Solvent-free conditions. [b] Two equiv of toluene were added to the reaction.

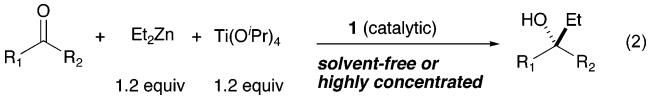
change in reaction medium would impact the catalytic process or the catalyst enantioselectivity.

In this report, we present our study of highly concentrated and solvent-free asymmetric addition of alkyl and functionalized groups to ketones to afford a variety of tertiary alcohols with excellent ee's. Importantly, under these conditions, catalyst loadings can be reduced by up to 40-fold while maintaining enantioselectivity over 90%. We also demonstrate that cyclic enones can be converted to syn epoxy alcohols with three contiguous stereocenters in a one-pot procedure employing the solvent-free asymmetric alkyl addition followed by in-situ epoxidation initiated upon adding *tert*-butyl hydroperoxide (TBHP). The resulting epoxy alcohols can be isolated in >87% yield, >95% ee, and as a single diastereomer, providing access to complex chiral building blocks for enantioselective synthesis. Finally, we have developed a protocol for the reaction workup that uses a minimum amount of environmentally benign solvent.

Results and Discussion

Diethylzinc Additions to Ketones Under Solvent-Free Conditions. In our initial examination of highly concentrated and solvent-free reactions, we employed diethylzinc in the asymmetric addition to 3′-methylacetophenone (Table 1). Under the conditions we originally reported for this addition using toluene and hexane solvents, referred to herein as our "standard conditions", we employed 2 mol % catalyst, and the reaction required 24 h providing 78% isolated yield of the tertiary alcohol with 99% ee.[44] We were pleased to find that the solvent-free reactions exhibited a substantial decrease in reaction time. In the absence of solvent, the same addition reaction was complete in much less time (4 h) at lower catalyst loading (1 mol %) with essentially the same enantioselectivity and yield (Table 1, entry 1). Similar results were obtained under what we will refer to as "highly concentrated conditions", when 2 equiv of toluene (relative to ketone) were added (Table 1, entry 2). In the case of a 1 mmol reaction, this translates to 0.11 mL of toluene added. Given these observations, we investigated the possibility of further decreasing the catalyst loading to as low as 0.1 mol %. In these cases, the addition product was obtained in slightly lower yields and with a small decrease in enantioselectivity (up to 3%). As anticipated, the reactions also required longer times at the lower catalyst loadings (Table 1, entries 3−5). The results in Table 1 indicate that low catalyst loadings can be successfully employed, in part because the catalyst derived from **1** exhibits a high degree of ligand acceleration over the uncatalyzed background reaction of diethylzinc with ketone substrates.[55]

Table 2 shows the scope and limitations in solvent-free and concentrated diethylzinc additions to ketones (eq 2). Like 3′-methylacetophenone, acetophenone and 3′-trifluoromethylacetophenone underwent addition with high enantioselectivities and yields with 0.5 mol % catalyst loading. Using our standard conditions, ethyl addition to 4′-methoxyacetophenone required 111 h at 10 mol % catalyst loading. Under the solvent-free conditions, the reaction was significantly faster, reaching completion in 12 h at 1 mol % catalyst loading. Unfortunately, both the yield and ee of the tertiary alcohol decreased to 50% and 81%, respectively (Table 2, entry 3). By conducting the addition with 2 equiv of toluene, the enantioselectivity increased to 89%. In this case, the methoxy group may be causing a significant change in the polarity of the reaction medium or possibly coordinating to titanium or zinc species. 2′-Acetonaphthone gave high enantioselectivities (98%) with solvent-free and highly concentrated conditions (Table 2, entry 4). Valerophenone exhibited a decrease in reaction times from over 4 days at 2 mol % **1** under standard conditions to 1 day at 1 mol % **1** under solvent-free and highly concentrated conditions. The enantioselectivity dropped, however, to 80% (Table 2, entry 5). These initial results highlight an important difference between our standard conditions and highly concentrated and solvent-free conditions: in the latter cases, the enantioselectivities are more sensitive to substrate structure.



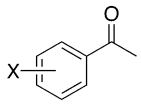
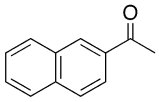
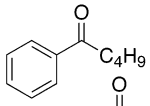
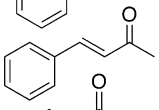
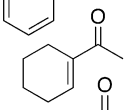
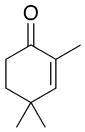
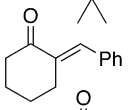
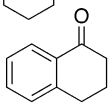
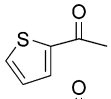
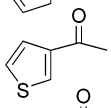
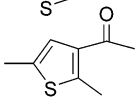
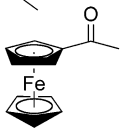
One important class of substrates for these asymmetric addition reactions is enones, because the addition products are tertiary allylic alcohols that can be functionalized at the double bond through hydroxyl directed reactions.[56] As illustrated in Table 2, enantioselectivities >90% were observed with a variety of enones at 1 mol % catalyst loading with 2 equiv of toluene. We were surprised to find that 2,4,4-trimethylcyclohexenone gave only 36% yield of the addition product, with the remainder of the material isolated as byproducts. This is in contrast to the standard conditions, where the product was isolated with 76% yield (Table 2, entry 8). The increased quantity of byproducts under the highly concentrated reaction conditions appears to be substrate dependent.

Certain substrates gave low yields under the standard conditions and, therefore, were evaluated under the concentrated conditions. Unfortunately, both α-tetralone and 2-benzylidene cyclohexanone gave similar yields as compared to the standard conditions, although the enantioselectivities remained very high (Table 2, entries 9 and 10).

We also investigated ketone substrates containing heteroaromatic groups in the asymmetric addition reaction. Thus, using our standard conditions, thiophene derivatives generate corresponding products with good to excellent enantioselectivities and high yields (Table 2, entries 11−13). Under solvent-free reaction conditions, similar yields and enantioselectivities could

(55) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.
(56) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

Table 2. Diethylzinc Additions to Ketones under Solvent-Free, Highly Concentrated, and Standard Conditions

		solvent-free and highly concentrated conditions				standard conditions			
entry	substrates	**1** (mol%)	t (h)	y (%)	ee (%)	**1** (mol%)	t (h)	y (%)	ee (%) (config.)
1	 X = H	1 0.5	4 21	75 78	97[a] 96[a]	2	29	71	96 (*S*)
2	X = 3-CF_3	0.5	17	77	96[a]	2	14	56	98
3	X = 4-OMe	1 1	12 15	50 72	81[a] 89[b]	10	111	85	94
4		0.5 0.5	12 24	74 76	98[a] 98[b]	2	27	90	97
5		1 1	24 24	78 85	80[a] 80[b]	2	102	79	88 (*R*)
6		1	15	71	90[b]	2	26	80	90
7		1	22	53	93[b]	2	46	56	96
8		1	22	36	96[b]	10	40	76	98
9		1	24	30	95[b]	10	38	32	99 (*R*)
10		1	23	35	99[b]	10	22	35	>99
11		1 1	65 72	78 87	80[a] 86[c]	10	40	85	83
12		1 0.5	72 85	85 82	80[a] 80[a]	10	50	85	80
13		1	72	70	96[a]	10	50	75	98
14		1	72	75	89[d]	10	42	86	90

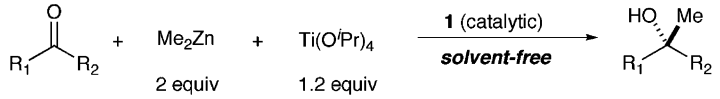
[a] Solvent-free conditions. [b] Two equiv of toluene were added to the reaction. [c] Reaction at −10 °C. [d] Two equiv of toluene were added and 0.6 equiv $Ti(O^iPr)_4$ was used.

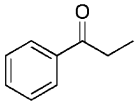
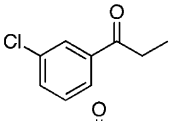
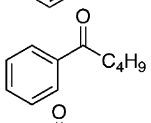
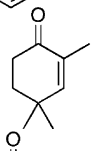
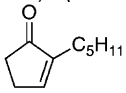
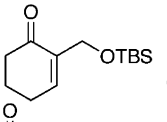
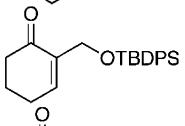
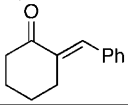
be obtained with reduction of catalyst loadings by up to 20-fold. Higher enantioselectivity was realized at lower temperature (−10 °C) under solvent-free conditions than standard conditions in case of 2-acetylthiophene (Table 2, entry 11). Acetylferrocene was an excellent substrate and underwent addition with 90% enantioselectivity using standard conditions. Our initial attempt with acetylferrocene under solvent-free conditions showed a significant drop in enantioselectivity to 61%. By conducting the addition with 2 equiv of toluene and 0.6 equiv of $Ti(O^iPr)_4$, the enantioselectivity increased to 89% (entry 14). The ketone substrates in entries 4, 6, 9, 12, and 14 of Table 2 are solids. Solids did not present a problem in the asymmetric reactions. No noticeable increase in viscosity was observed, and all reactions were stirred with standard magnetic stir bars and magnetic stir plates.

Solvent-Free Additions of Dimethylzinc to Ketones. The solvent-free asymmetric addition of dimethylzinc to ketones was explored for several reasons. First, it is well-known that dimethylzinc adds to aldehydes around 20 times slower than diethylzinc with amino alcohol-based catalysts.[57] We wanted to determine the difference in turnover frequency under solvent-free conditions with our catalyst. Second, methyl groups are the most common substituents in natural products. Finally, we believed that dimethylzinc would be a superior reagent for

(57) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036.

Table 3. Dimethylzinc Additions under Solvent-Free and Standard Reaction Conditions



		solvent-free conditions				standard condition				
entry	substrates	**1** (mol %)	t (h)	y (%)	ee (%)	**1** (mol %)	t (h)	y (%)	ee (%)	(config.)
1		1 0.5 0.25 0.25	15 48 60 72	85 83 85 87	92 92 80 92[a]	2	45	83	94	(*R*)
2		1 0.5	45 60	95 95	94 94	2	46	90	96	
3		1 0.5	43 45	95 93	83 77	2	48	81	85	
4		1 0.5	45 44	75 83	96 95	10	40	84	99	
5		1 0.5	22 44	77 78	96 97	10	40	62	99	
6		1 0.5 0.25	24 44 70	90 83 84	97 97 92	10	40	81	99	
7		1	60	90	96	10	60	84	98	
8		1	24	43	99	10	38	20	99	

[a] 0.4 equiv $Ti(O^iPr)_4$ was used.

solvent-free reactions, because reduction byproducts occasionally encountered with diethylzinc would not be observed with dimethylzinc because of the absence of β-hydrogens. We were pleased to find that excellent results were obtained in the solvent-free dimethylzinc addition reactions (Table 3).

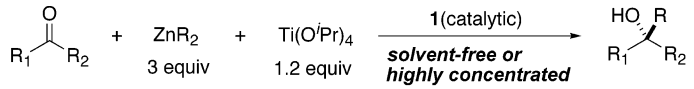
In the dimethylzinc addition reactions, 2 equiv of the dimethylzinc and 1.2 equiv of $Ti(O^iPr)_4$ were generally employed. Propiophenone and 3′-chloropropiophenone gave excellent yields (83−95%) and enantioselectivities (92−94%) using 1.0 or 0.5 mol % **1** (Table 3, entries 1 and 2). The enantioselectivity in the methyl addition to propiophenone decreased to 80% at 0.25 mol % catalyst loading, however. We hypothesized that the background reaction promoted by titanium tetraisopropoxide could be playing a role in the erosion of enantioselectivity at 0.25 mol % catalyst. With this in mind, we employed a substoichiometric amount of titanium tetraisopropoxide under otherwise identical conditions. When the titanium tetraisopropoxide was reduced from 1.2 equiv to 0.4 equiv at 0.25 mol % catalyst loading, the enantioselectivity was restored to 92% (Table 3, entry 1).

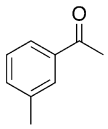
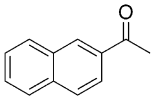
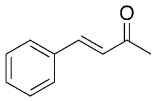
Valerophenone provided an opportunity to directly compare the rates of addition of diethyl- and dimethylzinc with our catalyst in the absence of solvent. Under solvent-free conditions, reaction with dimethylzinc reached completion in about twice the time compared to the reaction with diethylzinc (Table 3, entry 3 vs Table 2, entry 5).

Unlike diethylzinc addition to 2,4,4-trimethylcyclohexenone, which generated mostly byproducts, dimethylzinc addition proceeded smoothly in 75−83% yield with >95% enantioselectivity. Other cyclic enones also proved to be excellent substrates for the solvent-free dimethylzinc additions (Table 3, entries 5−7). Of particular note are the results of addition to 2-pentyl-2-cyclopenten-1-one (entry 5) and the TBS protected enone (entry 6). For these substrates, the catalyst loading could be lowered 20-fold with similar or better enantioselectivity, yield, and reaction time as compared to the standard conditions. Additionally, although the yield of addition to the 2-benzylidene cyclohexanone remained low in the solvent-free reactions, it was double that of the standard solution phase reaction (Table 3, entry 8). Solid substrates also underwent asymmetric dimethylzinc addition smoothly exhibiting high yields and enantioselectivities under solvent-free condition (Table 3, entries 2, 7, and 8).

Addition of Functionalized Dialkylzinc Reagents To Ketones Under Highly Concentrated Conditions. We recently examined the addition of a series of functionalized dialkylzinc

Table 4. Comparison of Solvent-Free, Highly Concentrated, and Standard Reaction Conditions for the Asymmetric Addition of Functionalized Organozinc Reagents to Ketones



entry	substrates	ZnR_2	solvent-free and highly concentrated conditions				standard conditions			
			1 (mol%)	t (h)	y (%)	ee (%)	**1** (mol%)	t (h)	y (%)	ee (%)
1		$Zn((CH_2)_4OTBS)_2$	1	48	68	79[a]	10	72	89	98
			0.5	70	53	80[a]				
			0.25	82	44	69[a]				
			1	40	68	97[b]				
2		$Zn((CH_2)_5Br)_2$	1	46	66	92[a]	10	72	89	96
			0.5	50	41	92[a]				
			1	46	71	97[b]				
3		$Zn((CH_2)_5Br)_2$	1	40	55	94[a]	10	72	55	94
			0.5	76	47	94[a]				
			0.25	84	30	76[a]				
			0.25	90	30	90[a,c]				
			1	38	72	97[b]				
4		$Zn((CH_2)_3CHMe_2)_2$	1	18	56	94[b]	10	72	75	90
5		$Zn((CH_2)_3CHMe_2)_2$	1	27	63	93[b]	10	72	86	93
6		$Zn((CH_2)_4OTBS)_2$	1	21	76	87[b]	10	120	65	90
7		$Zn((CH_2)_5Br)_2$	1	36	65	89[b]	10	48	48	90

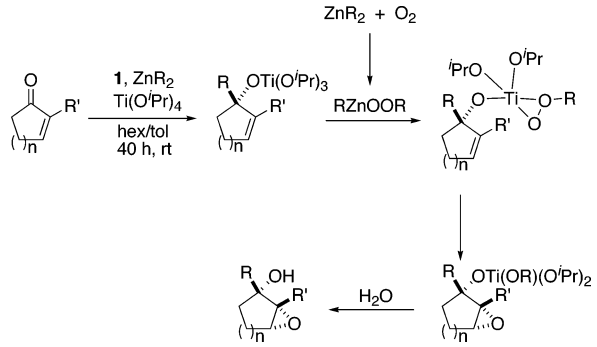
[a] Solvent-free conditions. [b] 2 equiv toluene were added to the reaction. [c] 0.6 equiv $Ti(O^iPr)_4$ was used.

reagents to ketones to generate tertiary alcohols bearing functional groups with high levels of enantioselectivity.[45] In this study, we found that under our standard conditions, 10 mol % loading of ligand **1** resulted in high enantioselectivities but long reaction times (48−120 h). With the goal of reducing the catalyst loading and reaction times, we examined the addition of functionalized diorganozinc reagents to ketones under solvent-free and highly concentrated reaction conditions.

Using the method of Knochel for the preparation of functionalized organozinc reagents,[58−64] we initially employed a dialkylzinc reagent bearing a TBS-protected alcohol in the asymmetric addition to 3′-methylacetophenone under solvent-free conditions. Although we were able to lower the catalyst loadings to 1 mol % and were able to reduce the reaction times, the enantioselectivities were 80% or less under the solvent-free conditions, significantly below the 98% enantioselectivity recorded for the standard conditions at 10 mol % catalyst (Table 4, entry 1). Addition of 2 equiv of toluene, however, restored the enantioselectivity to 97%. Similarly, addition of the bromoalkyl to this substrate exhibited higher yields and enantioselectivity under highly concentrated conditions than with the solvent-free conditions (Table 4, entry 2). Higher enantioselectivities under the concentrated reaction conditions relative to the solvent-free conditions were found to be general for the additions of functionalized organozinc reagents (Table 4, entries 1−3). Surprisingly, with 2′-acetonaphthone, the enantioselectivities with the functionalized organozinc reagents were higher under the concentrated conditions than under the standard conditions with both functionalized organozinc reagents employed. In Table 4, entry 3, reduction of the amount of titanium tetraisopropoxide from 1.2 to 0.6 equiv at 0.25 mol % catalyst resulted in an increase in the enantioselectivity from 76 to 90%. Additions to *trans*-4-phenyl-3-buten-2-one at 1 mol % catalyst loading under concentrated conditions exhibited similar enantioselectivities compared to the standard conditions with significantly reduced reaction times (Table 4,

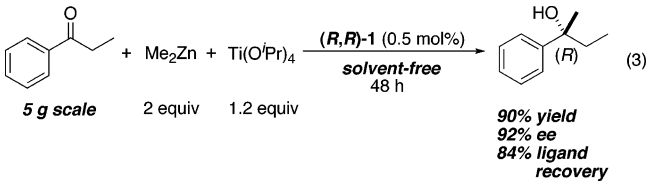
(58) Knochel, P.; Rosema, M. J.; Tucker, C. E.; Retherford, C.; Furlong, M.; AchyuthaRou, S. *Pure Appl. Chem.* **1992**, *64*, 361−369.
(59) Knochel, P. *Chemtracts: Org. Chem.* **1995**, *8*, 205−221.
(60) Knochel, P.; Jones, P. *Organozinc Reagents*; Oxford University Press: Oxford, U.K., 1999.
(61) Langer, F.; Waas, J.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 5261−5264.
(62) Langer, F.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410−412.
(63) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895−7898.
(64) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956−1958.

Scheme 1. One-Pot Asymmetric Addition/Diastereoselective Epoxidation Reaction with Dioxygen



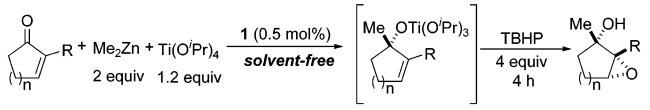
entries 5−7). In general, addition of 2 equiv toluene allows a 10-fold reduction in catalyst loading and reduced reaction times while maintaining high enantioselectivities. At this time, the origin of the beneficial effect of toluene is not understood. The results in Table 4 lead us to hypothesize that the highly concentrated nature of these reactions makes them particularly sensitive to the small changes in the composition of the reaction mixture.

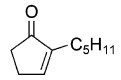
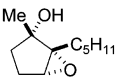
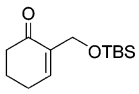
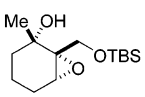
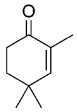
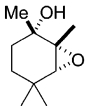
Investigation of the Scalability of the Solvent-Free Asymmetric Additions to Ketones. To test the scalability of our solvent-free procedure for the enantioselective addition of alkyl groups to ketones, the addition of dimethylzinc to propiophenone was examined on larger scale. The reaction of 5 g propiophenone was conducted with 0.5 mol % catalyst loading employing (*R*,*R*)-**1** under solvent-free conditions (eq 3). After 48 h at room temperature, the reaction was diluted with ethyl acetate, quenched with aqueous NH_4Cl, extracted into ethyl acetate, and purified on silica gel to provide 5 g (90% yield) of the addition product with 92% ee. The ligand **1** was recovered in 84% yield. These results highlight the potential scalability of this solvent-free process.



One-Pot Asymmetric Addition/Diastereoselective Epoxidation. We recently reported a one-pot procedure whereby the asymmetric addition to enones could be followed by a directed epoxidation to afford syn epoxy alcohols with three contiguous stereocenters.[53] In this chemistry, the asymmetric addition was conducted under standard conditions, and the resulting tertiary allylic alkoxide product was exposed to dioxygen to initiate the directed epoxidation. As shown in Scheme 1, we propose that the mechanism of this reaction involves insertion of dioxygen into the Zn−C bond to generate a zinc peroxy species. Transmetalation of the peroxide to the titanium allylic alkoxide followed by oxygen atom transfer and workup affords the epoxy alcohol product. In support of this proposal, we have also found that TBHP can be substituted for dioxygen in the directed epoxidation step.[65] Presumably, the TBHP protonates the dialkylzinc to generate a similar zinc peroxide. An advantage of TBHP over dioxygen in the epoxidation is that it is easier to control the rate of addition of the TBHP.

Table 5. One-Pot Epoxidation of Cyclic Enones with TBHP



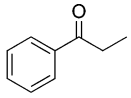
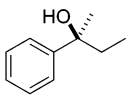
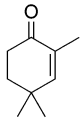
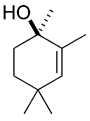
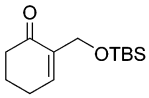
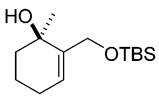
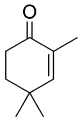
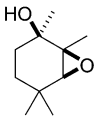
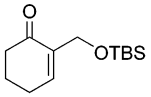
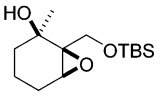
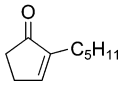
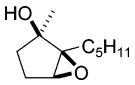
entry	substrates	time (h) addition	time (h) epoxidation	products	yield (%)
1		45	4		87
2		44	4		95
3		44	4		95

Given our experience with these tandem reactions and the fact that epoxy alcohols are very useful chiral building blocks for enantioselective synthesis,[66−69] we turned our attention to development of a one-pot asymmetric addition/diastereoselective epoxidation protocol employing our solvent-free reaction conditions. We chose to employ the addition of dimethylzinc to enones as outlined in Table 3 for the initial asymmetric step. After conducting the addition under the solvent-free reaction conditions, the reaction mixture was cooled to −10 °C, and commercially available 5.5 M TBHP in decane was cautiously added (Table 5). The reaction mixture was then allowed to warm to room temperature, and the progress of the epoxidation was followed by thin layer chromatography (TLC). After 4 h, the reaction was complete, and the epoxy alcohols were isolated in high yields (87−95%) after standard workup and purification (Table 5). These yields are significantly higher than those obtained under standard conditions.[53] Inspired by these results, we examined the one-pot asymmetric addition/diastereoselective epoxidation on a larger scale.

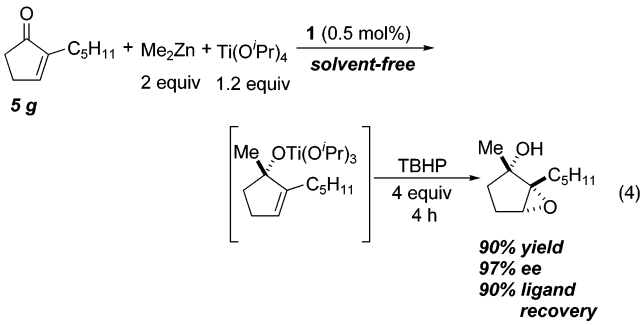
Investigation of the Scalability of the Solvent-Free Asymmetric Addition/Diastereoselective Epoxidation Reactions. To examine the scalability of the solvent-free asymmetric addition/diastereoselective epoxidation reaction, we tested the addition of dimethylzinc to 2-pentyl-2-cyclopenten-1-one using 5 g of the enone, 2 equiv dimethylzinc, and 0.5 mol % ligand **1** as outlined in eq 4. Upon completion of the asymmetric addition, the reaction was cooled to −10 °C, and 24 mL of 5.5 M TBHP (4 equiv) was carefully added. Once evolution of methane ceased, the reaction was warmed to room temperature and was stirred for 4 h. After quenching the reaction mixture, extraction and purification by chromatography resulted in isolation of the epoxy alcohol in 90% yield (5.45 g). Additionally, the ligand **1** was recovered in 90% yield. The 90% yield of the syn epoxy alcohol obtained in this large scale reaction represents a significant improvement over the 67% yield originally reported for the asymmetric addition/diastereoselective epoxidation under standard conditions. Although we have not

(65) Rowley Kelly, A.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 14668−14674.
(66) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5776.
(67) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 621−648.
(68) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, 1.
(69) Bonini, C.; Righib, G. *Tetrahedron* **2002**, *58*, 4981−5021.

Table 6. Yields Obtained Using 1.5 g Ketone Substrate and 15 mL EtOAc for Workup Followed by Distillation

entry	substrates	products	yield (%)
asymmetric additions			
1			86
2			75
3			81
addition/epoxidation			
4			83
5			78
6			80

encountered problems in the reactions outlined in this report, we recommend taking appropriate safety considerations (Experimental Section) when conducting reactions involving concentrated dialkylzinc reagents and either oxygen or TBHP.



Minimization of Solvent Use in the Workup and Purification Steps. The results of Tables 1−5 indicate that use of solvent-free and highly concentrated reaction conditions are advantageous with respect to the standard conditions. The solvent-free and highly concentrated reactions discussed to this point were subjected to traditional workup procedures involving quenching, extraction with ethyl acetate, and purification of the tertiary alcohols by standard chromatographic procedures. In pursuit of a more environmentally friendly asymmetric addition protocol, we focused our attention on minimizing the amount of solvent employed in the workup and purification procedure. For these experiments, the asymmetric addition was conducted with 1.50 g ketone substrate. Attempts to quench reaction mixtures and directly distill the tertiary alcohols were low yielding, most likely because of the nature of solid metal-containing byproducts generated on workup. Thus, after quenching reaction mixtures with saturated ammonium chloride, 10 mL of ethyl acetate was added and the heterogeneous solution was filtered. The solid was then washed with 5 mL ethyl acetate. TLC of this filtrate indicated that it contained substantial amounts of tertiary alcohol. The combined filtrates were dried, the solvent was removed under reduced pressure, and the resulting tertiary alcohol was distilled under reduced pressure to yield the product in 75−86%. This protocol allowed isolation of the product with high levels of purity without loss of ee (Table 6, entries 1−3). An identical workup procedure was applied to the asymmetric addition/diastereoselective epoxidation as outlined in Table 6, entries 4−6, with good yields (78−83% yields).

Summary

The development of truly efficient, practical, and more environmentally friendly catalyst systems is one of the central goals in catalysis and green chemistry. These goals can be approached by drastically reducing or eliminating solvents, which represent the largest contribution to the quantity of waste generated in nearly all chemical reactions. Further, the art of conducting reactions without solvent was described as one of the "grand challenges" facing chemists in the 21st century.[70] There are several benefits to running solvent-free reactions in addition to the decreased environmental impact. As outlined in this study, we have been able to reduce catalyst loading by 4- to 40-fold while maintaining similar yields and levels of enantioselectivity compared to reactions conducted with solvents. In the asymmetric addition of functionalized organozinc reagents to ketones, catalyst loadings have been reduced by a factor of 10 under the highly concentrated reaction conditions.

There is also a significant cost reduction with solvent-free and concentrated reaction conditions. Under our standard asymmetric addition conditions, the catalyst system required the use of high purity toluene and hexanes. Traces of oxygen and water in these solvents were detrimental to the reaction and needed to be removed. Further, both toluene and hexanes pose health risks. Under solvent-free conditions, relatively benign ethyl acetate was used directly out of the bottle in reaction workup. By minimizing the amount of ethyl acetate employed in workup and distillation of the enantioenriched tertiary alcohol, we have substantially reduced the amount of solvent with respect to the standard conditions.

We have also demonstrated that the solvent-free asymmetric additions to ketones can be used in tandem with a diastereoselective epoxidation reaction to provide syn epoxy alcohols with high levels of enantio- and diastereoselectivity. Further, the results outlined here suggest that both the asymmetric alkylation of ketones and the asymmetric addition/diastereoselective epoxidation are amenable to scale-up.

Although the reduced tunability of the catalyst and increased difficulty in controlling heat transfer represent real challenges for the future development of other solvent-free asymmetric reactions, the significant benefits of a successful solvent-free catalytic asymmetric process should inspire additional investigations in this area. The potential utility and scalability of our asymmetric addition of alkyl groups to ketones have been greatly improved under the highly concentrated and solvent-free conditions reported here.

(70) Lippard, S. L. *Chem. Eng. News* **2000**, *78*, 64−65.

Experimental Section

Cautionary Note. Caution must be used in handling dialkylzinc reagents, adding TBHP or oxygen to reaction mixtures containing dialkylzinc reagents, and quenching reaction mixtures.

General Methods. All reactions were carried out under a nitrogen atmosphere with oven-dried glassware. The progress of all reactions was monitored by thin-layer chromatography. All manipulations involving dialkylzinc and titanium(IV) isopropoxide were carried out under a dinitrogen atmosphere using standard Schlenk or vacuum line techniques. Toluene was dried through alumina columns. Titanium(IV) isopropoxide and all liquid ketone substrates were distilled prior to use. Dimethyl- and diethylzinc were used neat and were a gift of Akzo Chemical. All other dialkylzinc reagents were prepared by literature methods and were used without isolation.[45,62,71] The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained at 500 and 125 MHz, respectively. Silica gel (230−400 mesh, Silicycle) was used for air-flashed chromatography. Analysis of enantiomeric excess was performed using chiral GC and HPLC. Chiral tertiary alcohols not reported in the Experimental Section have previously been reported.[44,45,53,72,73]

Enantioselective Addition of Dialkylzinc Reagents to Ketones Under Highly Concentrated and Solvent-Free Conditions. General Procedure A (Solvent-Free Conditions). The bis(sulfonamide) ligand **1** was weighed into the reaction vessel under a nitrogen atmosphere, and the neat dialkylzinc and the titanium(IV) isopropoxide were added at room temperature. After 5 min, the substrate ketone was added neat. The reaction mixture was stirred at room temperature. After completion, as determined by TLC analysis, it was diluted with EtOAc, quenched with a small amount of water (0.5−1 mL) at 0 °C, dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel.

General Procedure B (Highly Concentrated Conditions). To a Schlenk flask under nitrogen was added 2 equiv of toluene before addition of the substrate ketones. The remainder of the procedure is identical to general procedure A.

2-(2,5-Dimethyl-thiophen-3-yl)-butan-2-ol (Table 2, Entry 13). The (*R*,*R*)-bissulfonamide ligand **1** (2.74 mg, 1.0 mol %), dimethylzinc (62 μL, 0.6 mmol), titanium(IV) isopropoxide (178 μL, 0.6 mmol), and 3-acetyl-2,5-dimethylthiophene (72 μL, 0.5 mmol) were added to the Schlenk flask by general procedure A. The reaction mixture was stirred at room temperature for 72 h. After completion, it was diluted with EtOAc (5 mL), quenched with a small amount of water (0.5 mL) at 0 °C, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc:90/10) to give the product (64.5 mg, 70% yield, 96% ee) as an oil: $[\alpha]^{20}_D = -14.1$ (*c* 1.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J = 7.5 Hz, 3H), 1.52 (s, 3H), 1.69 (br, 1H), 1.74−1.86 (m, 2H), 2.36 (s, 3H), 2.49 (s, 3H), 6.53 (s, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 8.95, 15.4, 29.7, 29.8, 36.4, 75.5, 126.4, 131.7, 134.5, 142.7 ppm; IR (neat) 3420, 2967, 2920, 2877, 1452, 1371, 1224 cm^{-1}; HRMS calcd for $C_{10}H_{16}OS$ (M^+): 184.0922, found 184.0931.

2-(*tert*-Butyl-diphenyl-silanyloxymethyl)-1-methyl-cyclohex-2-enol (Table 3, Entry 7). The (*R*,*R*)-bissulfonamide ligand **1** (1.1 mg, 1.0 mol %), dimethylzinc (28 μL, 0.4 mmol), titanium(IV) isopropoxide (71 μL, 0.24 mmol), and 2-(*tert*-butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone (73 mg, 0.2 mmol) were added to the Schlenk flask by general procedure A. The reaction mixture was stirred at room temperature for 60 h. After completion, it was diluted with EtOAc (5 mL), quenched with a small amount of water (0.5 mL) at 0 °C, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc:95/5) to give the product (70 mg, 90% yield, 96% ee) as an oil: $[\alpha]^{20}_D = +30$ (*c* 1.55, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03−1.08 (br, 9H), 1.38 (s, 3H), 1.55−1.61 (m, 2H), 1.74−1.85 (m, 2H), 1.86−1.96 (m, 1H), 2.05−2.12 (m, 1H), 3.34 (br, 1H), 4.06 (d, J = 11.9 Hz, 1H), 4.47−4.52 (m, 1H), 5.62 (t, J = 3.9 Hz, 1H), 7.39−7.52 (m, 6H), 7.68−7.82 (m, 4H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 19.5, 19.6, 26.0, 27.0, 27.3, 28.5, 39.1, 67.3, 70.1, 127.5, 128.1, 128.15, 128.22, 130.0, 130.2, 130.3, 133.3, 133.4, 135.3, 136.1, 139.6 ppm; IR (neat) 3444, 3070, 3049, 2931, 2858, 1959, 1891, 1823, 1470, 1388, 1364 cm^{-1}; HRMS calcd for $C_{24}H_{30}OSi$ $(M-H_2O)^+$: 362.2066, found 362.2088.

Enantioselective Methyl Addition/Diastereoselective Epoxidation with TBHP. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-methyl-cyclohex-2-enol (Table 5, Entry 2). The (*R*,*R*)-bissulfonamide ligand **1** (1.1 mg, 0.5 mol %) was weighted into the flame-dried Schlenk flask, and dimethylzinc (56 μL, 0.8 mmol) and titanium(IV) isopropoxide (124 μL, 0.42 mmol) were added neat. After 5 min, 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclohex-2-enone (100 μL, 0.4 mmol) was added. The reaction mixture was stirred for 44 h at room temperature. After completion, the reaction vessel was cooled to −10 °C. TBHP (292 μL, 5.5 M in decane, 4 equiv) was carefully added at that temperature, and the reaction was stirred for 4 h while warming to room temperature. The reaction mixture was diluted with EtOAc (8 mL), quenched with a small amount of water (0.5 mL) at 0 °C, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc:90/10) to give the product (103.5 mg, 95% yield) as an oil: $[\alpha]^{20}_D = -13.9$ (*c* 1.04, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.23−1.33 (m, 2H), 1.39 (s, 3H), 1.42−1.51 (m, 1H), 1.57−1.65 (m, 1H), 1.73−1.81 (m, 1H), 1.82−1.92 (m, 1H), 3.17 (br, 1H), 3.33 (s, 1H), 3.56 (d, J = 11.5 Hz, 1H), 4.10 (d, J = 11.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ −5.21, −5.13, 18.3, 18.5, 23.2, 25.3, 26.2, 36.3, 58.8, 64.0, 65.7, 71.7 ppm; IR (neat) 2932, 2856, 1468, 1387, 1366, 1254, 1142 cm^{-1}; HRMS calcd for $C_{14}H_{29}O_3Si$ $(MH)^+$: 273.1886, found 273.1893.

Large-Scale One-Pot Epoxidation with TBHP: 2-Methyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (Eq 4). The (*R*,*R*)-bissulfonamide ligand **1** (90 mg, 0.5 mol %) was weighted into the flame-dried Schlenk flask, and dimethylzinc (4.62 mL, 66 mmol) and titanium(IV) isopropoxide (11.7 mL, 39.4 mmol) were added neat. After 5 min, 2-pentylcyclopent-2-enone (5 g, 32.8 mmol) was added. The reaction mixture was stirred for 45 h at room temperature. After completion, the reaction vessel was cooled to −10 °C. TBHP (24 mL, 5.5 M in decane, 4 equiv) was carefully added over 30 min at that temperature and was stirred for 4 h while slowly warming to room temperature. The reaction mixture was diluted with EtOAc (100 mL) and was quenched by careful addition of water to the solution at 0 °C; the organics were extracted into EtOAc (3 × 50 mL), were dried over $MgSO_4$, and were concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc: 80/20) to give the product (5.45 g, 90% yield, 97% ee) as an oil. Eighty-one milligrams (90% yield) of ligand **1** was recovered by subsequent column chromatography using more polar eluting conditions (hexanes/EtOAc: 65/35).

Minimization of Solvent Use in the Workup and Purification Steps. Asymmetric Addition: 2-Phenyl-butan-2-ol (Table 6, Entry 1). The (*R*,*R*)-bissulfonamide ligand **1** (31 mg, 0.5 mol %), dimethylzinc (1.54 mL, 22.4 mmol), and titanium(IV) isopropoxide (3.97 mL, 13.5 mmol) were added to the Schlenk flask by general procedure A. After 5 min, propiophenone (1.5 g, 11.2 mmol) was added. The reaction mixture was stirred for 48 h at room temperature. After completion, the reaction vessel was cooled to −10 °C. Aqueous NH_4Cl (1.2 mL) was carefully added over 30 min at that temperature followed by dilution with 10 mL of EtOAc. The resulting heterogeneous solution was vigorously stirred for 4 h while slowly warming to room temperature, and $MgSO_4$ (0.3 g) was added. The reaction mixture was then filtered, and the solid was washed with EtOAc (5 mL). Solvent

(71) Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 9007−9010.
(72) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117−6128.
(73) Misterkiewicz, B. *J. Organomet. Chem.* **1982**, *224*, 43−47.

was removed under reduced pressure, and vacuum distillation of the resulting liquid afforded the desired product (1.45 g, 86% yield) as an oil (30 °C, 0.9 mmHg).

Addition/Epoxidation: 1,2,5,5-Tetramethyl-7-oxa-bicyclo[4,1,0]-heptan-2-ol (Table 6, Entry 4). The (*R*,*R*)-bissulfonamide ligand **1** (29.8 mg, 0.5 mol %), dimethylzinc (1.50 mL, 21.8 mmol), and titanium(IV) isopropoxide (3.85 mL, 13.1 mmol) were added to the Schlenk flask by general procedure A. After 5 min, 2,4,4-trimethyl-2-cyclohexen-1-one (1.5 g, 10.9 mmol) was added. The reaction mixture was stirred for 44 h at room temperature. After completion, the reaction vessel was cooled to −10 °C. TBHP (7.93 mL, 5.5 M in decane, 4 equiv) was carefully added over 30 min at that temperature and was stirred for 4 h while slowly warming to room temperature. Aqueous NH_4Cl (1.2 mL) was carefully added at 0 °C followed by dilution with 10 mL of EtOAc. The resulting heterogeneous solution was vigorously stirred for 4 h while slowly warming to room temperature, and $MgSO_4$ (0.3 g) was added. The reaction mixture was then filtered, and the solid was washed with EtOAc (5 mL). Solvent was removed under reduced pressure, and vacuum distillation of the resulting liquid afforded the desired product (1.54 g, 83% yield) as an oil (37−38 °C, 0.7 mmHg).

Acknowledgment. This work was supported by the NIH, National Institute of General Medical Sciences (GM58101). We thank Akzo Nobel for a generous gift of dimethyl- and diethylzinc reagents.

Supporting Information Available: Procedures and full characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA052200M