JOC*Article*

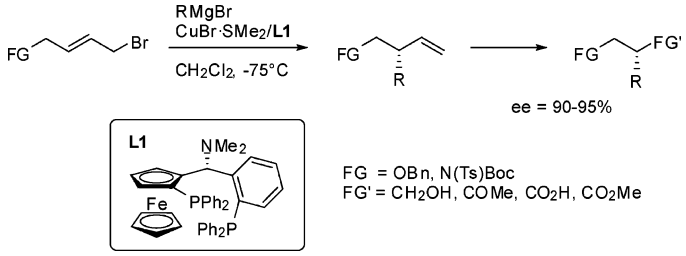
Synthesis of Optically Active Bifunctional Building Blocks through Enantioselective Copper-Catalyzed Allylic Alkylation Using Grignard Reagents

Anthoni W. van Zijl, Fernando López,† Adriaan J. Minnaard, and Ben L. Feringa*

Department of Organic Chemistry and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747AG, Groningen, The Netherlands

B.L.Feringa@rug.nl

Received December 14, 2006



Enantioselective copper-catalyzed allylic alkylations were performed on allylic bromides with a protected hydroxyl or amine functional group using several Grignard reagents and Taniaphos **L1** as a ligand. The terminal olefin moiety in the products was transformed into various functional groups without racemization, providing facile access to a variety of versatile bifunctional chiral building blocks.

Introduction

The complexity of natural and pharmaceutical products currently challenging synthetic chemists provides a major incentive in the design of catalytic methods, which enable access to versatile multifunctional optically active building blocks and starting materials. Retrosynthetic analysis of natural products frequently leads to bifunctional synthons, which contain a single stereogenic center.[1] Among the methods available to prepare these synthons, enantioselective catalysis[2] is particularly attractive due to the ready accessibility of both enantiomers, the potential atom efficiency of such reactions, and the ease with which small variations in the product can be introduced. However, chiral pool or auxiliary-based asymmetric syntheses are still the most widely applied approaches. The fact that the more widespread use of catalytic approaches, the so-called "catalytic switch", over noncatalytic syntheses has not yet happened is due, in part, to the fact that new enantioselective catalytic methods are developed using benchmark substrates and not the building blocks required in actual synthesis. The practicing organic chemists' familiarity with chiral pool strategies and aversion to synthesizing chiral ligands, which must themselves be prepared enantiomerically pure, may be another reason that catalytic asymmetric methods are not routinely used.

Among the enantioselective transition metal-catalyzed C−C bond forming reactions, catalytic allylic substitution has seen significant developments recently,[3] in particular asymmetric allylic alkylations with soft carbon nucleophiles (such as malonates and other stabilized carbanions) using transition metals such as Pd.[4,5] These methods show impressive versatility and have seen numerous applications in total synthesis.[6]

* To whom correspondence should be addressed. Fax: +31 50 363 4296. Phone: +31 50363 4235.

† Current address: Departamento de Química Orgánica, Universidad de Santiago de Compostela, Avda. de las Ciencias, s/n, 15782, Santiago de Compostela, Spain.

(1) (a) Warren, S. *Organic Synthesis: The Disconnection Approach*; Wiley: Chichester, 1982. (b) Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Organic Chemistry Series; Baldwin, J. E., Ed.; Pergamon: Oxford, 1983; Vol. 3. (c) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989. (d) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: Weinheim, 1996. (e) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley-VCH: Weinheim, 2003.

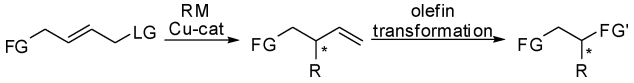
(2) (a) Sheldon, R. A. *Chirotechnology*; Dekker, New York, 1993. (b) *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: Chichester, 1992. (c) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004.

(3) (a) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalysis I-III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, Germany, 1999; Vol. 2, Chapter 24. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(4) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (b) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203−214. (c) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813−5837.

10.1021/jo0625655 CCC: $37.00
Published on Web 03/08/2007

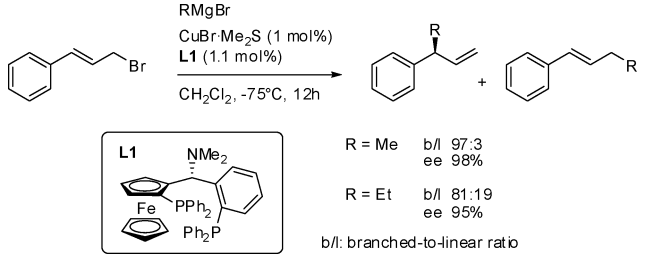
SCHEME 1. Bifunctional Chiral Building Blocks through Catalytic Allylic Alkylation



Copper-based transition-metal catalysts offer the possibility of using hard organometallic nucleophiles, thus enabling the introduction of simple alkyl fragments at the γ-position.[7,8] This provides branched chiral products that contain a terminal olefin functionality, which can be transformed subsequently into a broad range of functional groups, from prochiral monosubstituted allylic substrates (Scheme 1). The inclusion of a functional group in the allylic precursor would offer access to a broad range of synthetically valuable bifunctional chiral building blocks.

Following the first report on asymmetric Cu-catalyzed allylic substitution,[9] major breakthroughs have been realized recently.[10] Several methods have been developed in which either dialkylzinc compounds[11] or Grignard reagents[12,13] can be used with, occasionally, excellent results. Recently, we have applied the catalyst systems developed in our group for the enantioselective Cu-catalyzed 1,4-additions of Grignard reagents[14] to Cu-catalyzed allylic substitutions of allylic bromides.[12] With 1 mol % CuBr·SMe_2 and the commercially available Taniaphos **L1** ligand (1.1 mol %),[15] excellent regioselectivities (branched vs linear products) and enantioselectivities up to 98% (Scheme 2) were achieved. A significant advantage of this new system from a synthetic perspective is the facile introduction of a methyl group with methylmagnesium bromide, one of the most frequently encountered motifs in natural products.

SCHEME 2. Allylic Alkylation of Cinnamyl Bromide with Grignard Reagents



It was also shown that the reaction could be applied to an allylic bromide with a benzyl-protected alcohol at the δ-position, thus providing chiral primary alcohols in high optical purity. Since the terminal olefin can in principle be readily transformed into various other functional groups, the enantioselective reaction of substrates containing functional groups should provide access to a range of valuable chiral bifunctional building blocks.[16] Herein, we report the implementation of this strategy: the enantioselective allylic alkylation of functionalized substrates and the subsequent conversion of the products into highly versatile bifunctional building blocks.

Results and Discussion

To show the compatibility of substrates containing either a protected hydroxyl or amine moiety with the reaction conditions of the allylic alkylation we prepared allylic bromides **1a**−**c** (Table 1). Compounds **1a** and **1b**, subjected to methylmagnesium bromide in CH_2Cl_2 at −75 °C in the presence of 1 mol % catalyst, undergo substitution to provide the products **2a** and **2b**, respectively, in high yields and excellent regioselectivities (Table 1, entries 1 and 2). To demonstrate their synthetic utility, the reactions were also performed on a preparative scale (7.5 mmol). The enantiomeric excesses of **2a** and **2b** were found to be 92 and 95%, respectively, after derivatization (see Experimental Section). The other allylic alkylations were performed on a smaller scale and with 5 mol % catalyst for synthetic convenience. For example substrate **1c**, containing a *tert*-

(5) For examples, see: **Mo**: (a) Hughes, D. L.; Lloyd-Jones, G. C.; Krska, S. W.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Mathre, D. J.; Reamer, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5379−5384. (b) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159−167. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590−4591. **W**: (d) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462−464. **Ru**: (e) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405−10406. **Rh**: (f) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713−1715. **Ir**: (g) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595−4597. (h) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192−17193. (i) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.−Eur. J.* **2006**, *12*, 3596−3609.

(6) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.

(7) (a) Karlström, A. S. E.; Bäckvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH, Weinheim, 2002; Chapter 8. (b) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 6.

(8) There are some examples of asymmetric allylic alkylations with organometallic nucleophiles catalyzed by: **Pd**: (a) Fotiadu, F.; Cros, P.; Faure, B.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 77−80. **Ni**: (b) Nomura, N.; RajanBabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713−1716 and references therein. **Rh**: (c) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569−4572. With a Lewis base: (d) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 15604−15605.

(9) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059−3062.

(10) For recent reviews on Cu-catalyzed enantioselective allylic alkylation, see: (a) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435−4439. (b) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124−130.

(11) (a) Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233−9237. (b) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169−1171. (c) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460. (d) Shi, W.-J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2003**, *14*, 3867−3872. (e) van Zijl, A. W.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2004**, *346*, 413−420. (f) Goldsmith, P. J.; Teat, S. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2235−2237. (g) Piarulli, U.; Daubos, P.; Claverie, C.; Monti, C.; Gennari, C. *Eur. J. Org. Chem.* **2005**, 895−906. (h) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877−6882.

(12) (a) López, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa. B. L. *Chem. Commun.* **2006**, 409−411. (b) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572−15573.

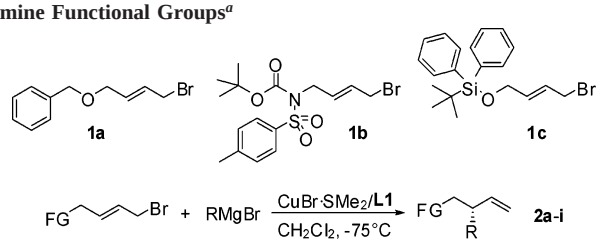
(13) (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426−2428. (b) Okamoto, S.; Tominaga, S.; Saino, N.; Kase, K.; Shimoda, K. *J. Organomet. Chem.* **2005**, *690*, 6001−6007. (c) Falciola, C. A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5995−5998. (d) Cotton, H. K.; Norinder, J.; Bäckvall, J.-E. *Tetrahedron* **2006**, *62*, 5632−5640.

(14) (a) Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834−5838. (b) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784−12785. (c) López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752−2756. (d) Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966−9967. (e) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103−9118.

(15) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212−3215.

(16) A related approach based on a diastereoselective allylic alkylation was recently applied to the synthesis of tertiary alcohols and amines: Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627−4631.

TABLE 1. Cu-Catalyzed Allylic Alkylation with Various Grignard Reagents of Allylic Bromides Containing Protected Hydroxyl and Amine Functional Groups[a]



entry	1	RMgBr	2	yield (%)[b]	*b*/l[c]	ee (%)[d]
1[e,f]	**1a**	MeMgBr	**2a**	94	100:0	92
2[e,f]	**1b**	MeMgBr	**2b**	96	>95:5	95
3	**1c**	MeMgBr	**2c**	72	>95:5	94
4[f,g]	**1a**	EtMgBr	**2d**	98	98:2	94
5	**1b**	EtMgBr	**2e**	83	>95:5	90
6	**1a**	*n*-BuMgBr	**2f**	93	100:0	94
7	**1a**	*n*-PentMgBr	**2g**	87	100:0	94
8	**1a**	3-butenylMgBr	**2h**	89	>95:5	90
9	**1a**	$Ph(CH_2)_2MgBr$	**2i**	86	>95:5	92

[a] Reagents and conditions: RMgBr (1.5 equiv), $CuBr \cdot SMe_2$ (5 mol %), **L1** (6 mol %), CH_2Cl_2, −75 °C. [b] Isolated yield. [c] Established by GC or NMR. [d] Established by chiral GC or HPLC. [e] Reaction performed on preparative scale (7.5 mmol substrate). [f] Reaction performed with 1 mol % cat. and 1.2 equiv RMgBr. [g] See ref 12a.

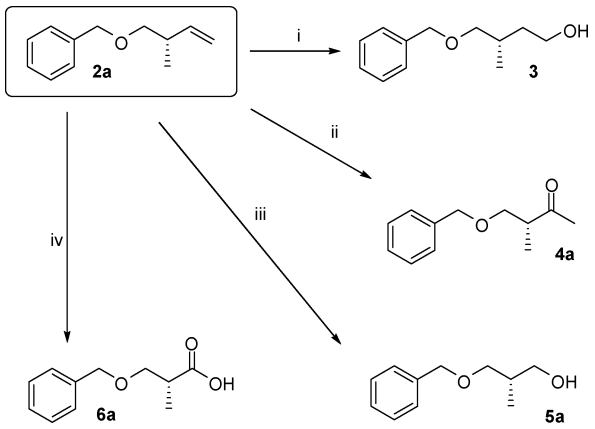
butyldiphenylsilyl ether, could be methylated in high yield, excellent regioselectivity and with an enantiomeric excess of 94% (Table 1, entry 3).

Other linear alkyl Grignard reagents could also be applied to these functionalized substrates, all with similar success. As shown earlier,[12a] substrate **1a** can be ethylated with high regioselectivity and excellent enantioselectivity (Table 1, entry 4). Application of EtMgBr to substrate **1b** led to product **2e** in good yield and high selectivity (Table 1, entry 5). The use of the other Grignard reagents with substrate **1a** gave products **2f-i** also with excellent regio- and enantioselectivities (Table 1, entries 6−9).

A variety of derivatization reactions of **2a** and **2b** were performed to demonstrate their versatility to provide a family of optically active bifunctional synthons (Schemes 3−5). To ensure racemization during the derivatization did not occur, the enantiomeric purity of all bifunctional synthons was determined independently by gas chromatography (GC) or high-performance liquid chromatography (HPLC) analysis.

Hydroboration of **2a** and subsequent treatment with H_2O_2 provides the monoprotected diol **3** (Scheme 3).[17,18] This compound has been used before in the total syntheses of (*E*)-vitamin K_1,[19] vitamin E,[20] and cylindrocyclophane F.[21] The olefin **2a** was converted to methyl ketone **4a** using a catalytic

SCHEME 3. Synthesis of Bifunctional Chiral Building Blocks from Product 2a[a]



[a] Reagents and conditions: (i) 1. 9-BBN, THF, 0 °C, 2. EtOH, aq. NaOH, H_2O_2, 80%; (ii) $PdCl_2$ (10 mol %), CuCl (2 equiv), O_2, DMF/H_2O, room temperature, 86%; (iii) 1. O_3, CH_2Cl_2/MeOH, −78 °C, 2. $NaBH_4$ (5 equiv), room temperature, 52%; (iv) $RuCl_3$ (5 mol %), $NaIO_4$ (4 equiv), MeCN/CCl_4/H_2O, room temperature, 52%.

Wacker oxidation.[22] Thus, treatment of olefin **2a** with $PdCl_2$ (10 mol %) and CuCl (2 equiv) under an O_2 atmosphere provided *β*-hydroxyketone **4a** in 86% yield. This ketone has been applied in the total syntheses of the C_1-C_{25} segment of spirastrellolide A,[23] the octalactins A and B,[24] (+)-miyakolide,[25] (−)-botryococcene,[26] and also (+)-phyllanthocin and (+)-phyllanthocindiol.[27] By carrying out an ozonolysis/$NaBH_4$ reduction protocol, **2a** was converted into the monoprotected 1,3-diol **5a**.[28] This simple building block has been applied in numerous total syntheses. Among the many recent examples are syntheses of potential antitumor agents,[29] antibiotics,[30] MMP inhibitors,[31] and THC analogues.[32] The *β*-hydroxyacid **6a**, which has been used in the synthesis of *clasto*-lactacystin *β*-lactone,[33]

(17) Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.-I.; Tadano, K.-I. *Org. Lett.* **2001**, *3*, 3029−3032.

(18) For a review on hydroboration, see: Smith, K.; Pelter, A. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 3.10.

(19) Schmid, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiser, H. *Helv. Chim. Acta* **1990**, *73*, 1276−1299.

(20) Fuganti, C.; Grasselli, P. *J. Chem. Soc. Chem. Commun.* **1979**, 995−997.

(21) (a) Smith, A. B., III.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423−7424. (b) Smith, A. B., III.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925−5937.

(22) For reviews on the Wacker oxidation, see: (a) Feringa, B. L. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, Chapter 2.8. (b) Takacs, J. M.; Jiang, X.-T. *Curr. Org. Chem.* **2003**, *7*, 369−396.

(23) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125−4128.

(24) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194−2207.

(25) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816−6826.

(26) White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624−1626.

(27) (a) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496−4497. (b) McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984**, *49*, 843−852.

(28) For a review on application of ozonolysis in synthesis, see: Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990−3001.

(29) For examples, see: (a) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973−8982. (b) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546−9547. (c) Deng, L.-S.; Huang, X.-P.; Zhao, G. *J. Org. Chem.* **2006**, *71*, 4625−4635.

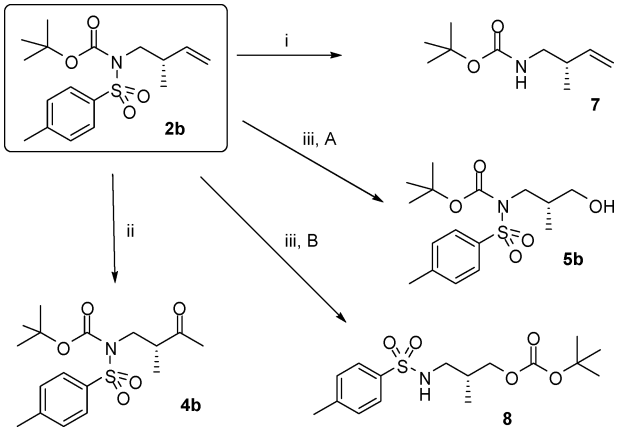
(30) For example, see: Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2259−2276.

(31) For example, see: Ponpipom, M. M.; Hagmann, W. K. *Tetrahedron* **1999**, *55*, 6749−6758.

(32) Huffman, J. W.; Liddle, J.; Duncan, S. G., Jr.; Yu, S.; Martin, B. R.; Wiley, J. L. *Bioorg. Med. Chem.* **1998**, *6*, 2383−2396.

(33) Soucy, F.; Grenier, L.; Behnke, M. L.; Destree, A. T.; McCormack, T. A.; Adams, J.; Plamondon, L. *J. Am. Chem. Soc.* **1999**, *121*, 9967−9976.

SCHEME 4. Synthesis of Bifunctional Chiral Building Blocks from Product 2b[a]



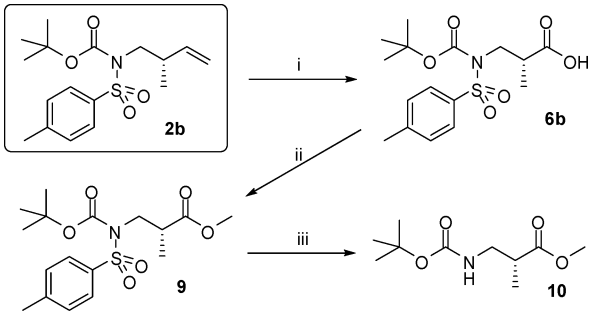
[a] Reagents and conditions: (i) Mg (5 equiv), MeOH, sonication, 90%; (ii) $PdCl_2$ (10 mol %), CuCl (2 equiv), O_2, DMF/H_2O, room temperature, 82%; (iii) 1. O_3, CH_2Cl_2/MeOH, −78 °C, 2. $NaBH_4$ (5 equiv), room temperature, A: direct quenching, 77% B: concentration at 50 °C before quenching, 69%.

was obtained in 52% yield through Ru-catalyzed oxidation of the terminal olefin with $NaIO_4$.[34] From the representative examples shown in Scheme 3 it is evident that the catalytic asymmetric allylic alkylation of **1a** can provide a variety of important difunctionalized synthons in a few steps. All products were shown by chiral GC or HPLC analysis to have retained the high enantiomeric excess (ee, 92%) of the original allylic alkylation product **2a**.

Compound **2b** was detosylated by treatment with magnesium under sonication[35] to yield Boc-protected amine **7** (Scheme 4). As for **4a**, the β-aminoketone **4b** was obtained in 82% yield using the same procedure for a catalytic Wacker oxidation. In an analogous fashion to **5a**, compound **2b** could be transformed using the ozonolysis/reduction protocol into either 1,3-aminoalcohol **5b** or compound **8**, depending on the workup procedure. Direct quenching of the reaction with 1 M aq HCl gave exclusively compound **5b**. In contrast, prior concentration of the reaction mixture at 50 °C (e.g., by removal of solvent in vacuo) led to a 1,5-migration of the Boc-group to the newly formed alcohol,[36] thus yielding compound **8**, which contains a tosyl-protected amine and an alcohol with a Boc-protective group. The full selectivity of either method increases significantly the versatility of this building block precursor.

By use of the same Ru-catalyzed oxidation that furnished **6a**, β^2-amino acid **6b** could be synthesized in 79% yield (Scheme 5). This is especially noteworthy as β^2-amino acids are in general difficult to obtain.[37] The latter product was converted to the respective methyl ester **9** also, using $TMSCHN_2$ and MeOH, and consecutively detosylated with Mg powder and sonication to obtain *N*-Boc-protected β^2-amino acid **10**. This

SCHEME 5. Synthesis of β^2-Amino Acid Building Blocks from Product 2b[a]



[a] Reagents and conditions: (i) $RuCl_3$ (5 mol %), $NaIO_4$ (4 equiv), MeCN/CCl_4/H_2O, room temperature, 79%; (ii) $TMSCHN_2$, MeOH, PhMe, room temperature, 94%; (iii) Mg (5 equiv), MeOH, sonication, 90%.

compound has been applied in the total synthesis of the potent antitumor macrolides cryptophycin A, B, and C.[38] The transformations described in Schemes 4 and 5 show that the allylic alkylation product **2b** is an attractive precursor for (protected) amino alcohols, amino ketones, and β^2-amino acids. Similar transformations are readily accomplished with allylic alkylation products (e.g., compound **2e**) obtained with other Grignard reagents. All derivatives shown in Schemes 4 and 5 were obtained in the same high ee (95%) as product **2b** as determined by GC or HPLC analysis.

In conclusion, we have demonstrated that the Cu-catalyzed allylic alkylation with Grignard reagents can be performed with excellent yield, regioselectivity, and enantioselectivity on allylic bromides bearing protected functional groups on the δ position. The products obtained were shown to be suitable precursors in the synthesis of optically active bifunctional building blocks within one or two steps. This catalytic protocol for a wide variety of versatile bifunctional building blocks provides an important alternative to common approaches using chiral synthons derived from the chiral pool.

Experimental Section

General Procedure for the Preparative Enantioselective Cu-Catalyzed Allylic Alkylation with Methyl Grignard. In a Schlenk tube equipped with septum and stirring bar, CuBr·SMe_2 (75 μmol, 15.4 mg) and ligand **L1** (90 μmol, 61.9 mg) were dissolved in CH_2Cl_2 (15 mL) and stirred under an argon atmosphere at roomtemperature for 10 min. The mixture was cooled to − 75 °C, and the methyl Grignard reagent (9.0 mmol, 3 M solution in Et_2O, 3.0 mL) was added dropwise. Allylic bromide **1a** or **1b** (7.5 mmol) was added dropwise as a solution in 2.5 mL CH_2Cl_2 at that temperature over 60 min via a syringe pump. Once the addition was complete the resulting mixture was further stirred at −75 °C for 24h. The reaction was quenched by addition of MeOH (2.5 mL) and the mixture was allowed to reach rt. Subsequently, aqueous NH_4Cl solution (1 M, 30 mL) and 50 mL Et_2O were added, the organic phase was separated and the resulting aqueous layer was extracted

(34) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(35) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017−1018.

(36) For a review on N-Boc reactivity, see: (a) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701−2724. For examples on Boc-protecting group migration, see: (b) Kise, N.; Ozaki, H.; Terui, H.; Ohya, K.; Ueda, N. *Tetrahedron Lett.* **2001**, *42*, 7637−7639. (c) Bunch, L.; Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Lett.* **2001**, *3*, 433−435. (d) Skwarczynski, M.; Sohma, Y.; Kimura, M.; Hayashi, Y.; Kimura, T.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4441−4444. (e) Mohal, N.; Vasella, A. *Helv. Chim. Acta* **2005**, *88*, 100−119.

(37) (a) Smith, M. B. *Methods of Non-α-Amino Acid Synthesis*; Dekker: New York, 1995. (b) Lelais, G.; Seebach, D. *Peptide Sci.* **2004**, *76*, 206−243. (c) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley: Hoboken, 2005. See also: (d) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700−3701. (e) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359−3362.

(38) (a) Salamonczyk, G. M.; Han, K.; Guo, Z.-W.; Sih, C. J. *J. Org. Chem.* **1996**, *61*, 6893−6900. (b) Ghosh, A. K.; Bischoff, A. *Eur. J. Org. Chem.* **2004**, 2131−2141.

with Et_2O (2 × 25 mL). The combined organic phases were dried and concentrated to yield a yellow oil which was purified by flash chromatography.

(−)-(*S*)-((2-Methylbut-3-enyloxy)methyl)benzene (2a). Purification by column chromatography (SiO_2, 1:99 Et_2O/pentane, R_f = 0.35) afforded **2a** (1.24 g) as a colorless oil. 94% yield, 92% ee, $[\alpha]_D = -5.4$ (*c* 1.3, $CHCl_3$); ref 12a $[\alpha]_D = -6$ (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.32−7.21 (m, 5H), 5.81 (ddd, *J* = 6.9, 10.4 and 17.3 Hz, 1H), 5.11−5.00 (m, 2H), 4.53 (s, 2H), 3.35 (ddd, *J* = 6.7, 9.1 and 23.9 Hz, 2H), 2.54−2.49 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 141.3, 138.6, 128.3, 127.5, 127.4, 114.0, 75.0, 72.9, 37.8, 16.6; MS (EI) *m*/*z* 176 (M^+, 16), 175 (6), 92 (11), 91 (100), 65 (6); HRMS Calcd. for $C_{12}H_{16}O$ 176.1201, found 176.1207. ee determined of derivatized product **3** (vide infra).

(−)-(*S*)-(*N*-2-Methylbut-3-enyl)(*N*-*t*-butoxycarbonyl) *p*-toluenesulfonamide (2b). Purification by column chromatography (SiO_2, 10:90 Et_2O/pentane, R_f = 0.30) afforded **2b** (2.45 g) as a colorless oil. 96% yield, 95% ee, $[\alpha]_D = -7.7$ (c 1.4, $CHCl_3$); ^{1}H NMR δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.73 (ddd, *J* = 8.1, 10.2 and 17.3 Hz, 1H), 5.10−5.00 (m, 2H), 3.82−3.72 (m, 2H), 2.78−2.66 (m, 1H), 2.43 (s, 3H), 1.32 (s, 9H), 1.07 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 151.0, 144.0, 140.7, 137.5, 129.1, 127.9, 115.3, 84.0, 51.9, 38.7, 27.8, 21.5, 17.3; MS (EI) *m*/*z* 283 (9), 216 (20), 185 (6), 184 (64), 155 (42), 91 (39), 68 (7), 65 (11), 57 (100), 56 (5), 55 (13); MS (CI) *m*/*z* 359 (8), 358 (20), 357 ($[M+NH_4]^+$,100), 302 (7), 301 (40), 284 (6). HRMS Calcd. for $[M-Me_2C{=}CH_2]^+$ $C_{13}H_{17}NO_4S$ 283.0878, found 283.0887. ee determined of derivatized product **7**.[39] The absolute configuration was assigned by comparison of the sign of the optical rotation of derivatized product **10** with the literature value.[39]

(+)-(*S*)-4-Benzyloxy-3-methylbutan-1-ol (3). To a cooled solution (0 °C) of **2a** (0.5 mmol, 88 mg) in THF (3.5 mL) a solution of 9-BBN (0.75 mmol, 0.5M in THF, 1.5 mL) was added. The reaction mixture was stirred for 3 h, then it was allowed to reach room temperature, after which sequentially EtOH (2.5 mL), aq NaOH (1 M, 2.5 mL) and aq H_2O_2 (30%, 2.0 mL) were added. The resulting mixture was stirred vigorously overnight at rt, then quenched with aq $Na_2S_2O_3$ (10%, 10 mL). CH_2Cl_2 (20 mL) was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried and concentrated in vacuo. Purification by column chromatography (SiO_2, 40:60 Et_2O/pentane, R_f = 0.25) afforded **3** (77.3 mg) as a colorless oil. 80% yield, 92% ee, $[\alpha]_D = +1.8$ (c 2.9, EtOH), −5.5 (c 2.7, $CHCl_3$), refs 19 and 20 $[\alpha]_D = +2.2$ (*c* 1.1, EtOH), +6.26 (*c* 5.5, $CHCl_3$)[40]; ^{1}H NMR δ 7.39−7.26 (m, 5H), 4.52 (s, 2H), 3.75−3.61 (m, 2H), 3.35 (ddd, *J* = 6.2, 9.1 and 16.5 Hz, 2H), 2.42 (bs, 1H), 1.95 (tq, *J* = 6.9 and 13.8 Hz, 1H), 1.69−1.51 (m, 2H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 138.0, 128.4, 127.7, 76.1, 73.2, 61.2, 38.1, 31.4, 17.7; MS (EI) *m*/*z* 194 (M^+, 7), 108 (11), 107 (37), 105 (6), 92 (28), 91 (100), 85 (12), 79 (7), 77 (8), 65 (15), 55 (8); HRMS Calcd. for $C_{12}H_{18}O_2$ 194.1307, found 194.1309. ee determined by chiral HPLC analysis, Chiralcel OD−H (99% heptane/*i*-PrOH), 40 °C, retention times (min) 57.7 (major) and 64.9 (minor).

(−)-(*R*)-4-Benzyloxy-3-methylbutan-2-one (4a). A suspension of $PdCl_2$ (50 μmol, 8.9 mg) and CuCl (1.0 mmol, 99 mg) in DMF/H_2O (6:1, 5 mL) was stirred vigorously under an O_2 stream for 1.5 h at room temperature. After addition of **2a** (0.5 mmol, 88 mg) vigorous stirring was continued for 32 h under an O_2 atmosphere at room temperature. Then, H_2O (20 mL) was added, and the mixture was extracted with Et_2O/pentane (1:1, 3 × 10 mL). The combined organic layers were washed with H_2O (10 mL), dried, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 10:90 Et_2O/pentane, R_f = 0.20) afforded **4a** (82.4 mg) as a colorless oil. 86% yield, 92% ee, $[\alpha]_D = -14.0$ (*c* 4.0, $CHCl_3$), ref 27b $[\alpha]_D = -16.7$ (*c* 3.91, $CHCl_3$); ^{1}H NMR δ 7.37−7.26 (m, 5H), 4.50 (d, *J* = 1.8 Hz, 2H), 3.63 (dd, *J* = 7.5 and 9.2 Hz, 1H), 3.49 (dd, *J* = 5.5 and 9.2 Hz, 1H), 2.91−2.81 (m, 1H), 2.18 (s, 3H), 1.10 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 211.1, 138.0, 128.4, 127.6, 127.6, 73.2, 72.1, 47.2, 29.0, 13.4; MS (EI) *m*/*z* 192 (M^+, 4), 134 (27), 108 (18), 107 (46), 105 (12), 92 (14), 91 (100), 86 (43), 85 (6), 79 (8), 77 (7), 71 (27), 65 (9); HRMS Calcd. for $C_{12}H_{16}O_2$ 192.1150, found 192.1144. ee determined by chiral HPLC analysis, Chiralcel AS (99.5% heptane/*i*-PrOH), 40 °C, retention times (min) 11.8 (minor) and 16.4 (major).

(−)-(*R*)-3-((*tert*-Butoxycarbonyl)(*p*-toluenesulfonyl)amino)-2-methylpropan-1-ol (5b). Ozone was bubbled for 10 min through a solution of **2b** (0.5 mmol) in CH_2Cl_2/MeOH (1:1, 15 mL) cooled to −78 °C. $NaBH_4$ (2.5 equiv, 2.5 mmol, 95 mg) was added at −78 °C after which the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of aq HCl (1 M, 15 mL). The organic layer was separated, and the resulting aqueous layer extracted with CH_2Cl_2 (2 × 25 mL); the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 Et_2O/pentane, R_f = 0.25) afforded **5b** (132.8 mg) as a colorless oil, which crystallized upon standing. 77% yield, 95% ee, $[\alpha]_D = -3.3$ (*c* 8.1, $CHCl_3$), mp = 59.8−60.4 °C; ^{1}H NMR δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 3.85 (dd, *J* = 9.1 and 14.6 Hz, 1H), 3.72 (dd, *J* = 5.3 and 14.6 Hz, 1H), 3.70−3.63 (m, 1H), 3.51−3.43 (m, 1H), 2.63 (bs, 1H), 2.41 (s, 3H), 2.16−2.04 (m, 1H), 1.29 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 151.9, 144.3, 137.1, 129.2, 127.6, 84.8, 63.6, 49.1, 36.4, 27.7, 21.5, 14.5; MS (EI) *m*/*z* 270 ($[M-t\text{BuO}]^+$, 5), 184 (47), 179 (28), 155 (48), 120 (14), 108 (26), 92 (8), 91 (52), 65 (12), 58 (6), 57 (100), 56 (6); MS (CI) *m*/*z* 363 (8), 362 (22), 361 ($[M+NH_4]^+$, 100), 305 (11). HRMS Calcd. for $[M-t\text{BuO}]^+$ $C_{12}H_{16}NO_4S$ 270.0800, found 270.0787. ee determined by chiral HPLC analysis, Chiralcel AD (98% heptane/*i*-PrOH), 40 °C, retention times (min) 38.6 (major) and 51.0 (minor).

(+)-(*R*)-3-(*p*-Toluenesulfonylamino)-1-(*tert*-butoxycarbonyloxy)-2-methylpropane (8). Ozone was bubbled for 10 min through a solution of **2b** (0.5 mmol) in CH_2Cl_2/MeOH (1:1, 15 mL) cooled to −78 °C. $NaBH_4$ (2.5 equiv, 2.5 mmol, 95 mg) was added at −78 °C, after which the cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h. The solvents were removed from the reaction mixture by rotavap (waterbath at 60 °C), followed by addition of aq HCl (1 M, 15 mL) and Et_2O (25 mL). The organic layer was separated and the resulting aqueous layer extracted with Et_2O (2 × 25 mL); the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 30:70 Et_2O/pentane, R_f = 0.30) afforded **8** (123.8 mg) as a colorless oil. 69% yield, 95% ee, $[\alpha]_D = +0.6$ (*c* 7.9, $CHCl_3$); ^{1}H NMR δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 5.22 (t, *J* = 6.6 Hz, 1H), 4.00 (dd, *J* = 4.7 and 11.2 Hz, 1H), 3.88 (dd, *J* = 6.7 and 11.2 Hz, 1H), 2.95−2.79 (m, 2H), 2.41 (s, 3H), 2.06−1.90 (m, 1H), 1.44 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR δ 153.6, 143.2, 136.9, 129.6, 126.9, 82.2, 68.8, 45.6, 33.2, 27.6, 21.4, 14.4; MS (EI) *m*/*z* 226 (25), 225 (6), 224 (23), 199 (7), 197 (8), 188 (9), 185 (9), 184 (88), 157 (6), 156 (9), 155 (100), 133 (8), 132 (25), 119 (6), 92 (12), 91 (80), 70 (73), 65 (17), 59 (6), 57 (71), 56 (12); MS (CI) *m*/*z* 363 (7), 362 (19), 361 ($[M+NH_4]^+$, 100), 333 (14), 305 (6), 289 (14). HRMS Calcd. for $[M-t\text{BuO}]^+$ $C_{12}H_{16}NO_4S$ 270.0800, found 270.0795. ee determined by chiral HPLC analysis, Chiralcel AS-H (90% heptane/*i*-PrOH), 40 °C, retention times (min) 40.3 (minor) and 43.0 (major).

(−)-(*R*)-3-((*tert*-Butoxycarbonyl)(*p*-toluenesulfonyl)amino)-2-methylpropionic acid (6b). To a biphasic system of **2b** (0.5 mmol) and $NaIO_4$ (2.05 mmol, 438 mg) in CCl_4/MeCN/H_2O (1:1:1.5, 5 mL), $RuCl_3{\cdot}xH_2O$ (25 μmol, 5.2 mg) was added, and the reaction mixture was stirred vigorously overnight. Afterward, 10 mL of CH_2Cl_2 and 5 mL of H_2O were added, and the organic layer was separated, the aqueous layer was further extracted with CH_2Cl_2 (3

(39) See Supporting Information.

(40) The optical rotation in $CHCl_3$ is reported only once but appears to be given in the wrong sign: See ref 19.

× 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in Et_2O (10 mL) and extracted with sat. aq $NaHCO_3$ (3 × 5 mL); the combined aqueous layers were acidified and extracted with CH_2Cl_2 (3 × 10 mL). Drying ($MgSO_4$) and concentrating the combined CH_2Cl_2 layers in vacuo afforded **6b** (140.9 mg) as a white crystalline solid. 79% yield, 95% ee, $[\alpha]_D = -9.5$ (*c* 3.6, $CHCl_3$), mp = 114.4−116.3 °C; ^{1}H NMR δ 10.27 (bs, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.6$ Hz, 2H), 4.14 (dd, $J = 6.8$ and 14.5 Hz, 1H), 3.96 (dd, $J = 7.7$ and 14.5 Hz, 1H), 3.10−3.01 (m, 1H), 2.44 (s, 3H), 1.33 (s, 9H), 1.29 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR δ 180.5, 150.9, 144.3, 137.0, 129.2, 127.9, 84.7, 48.7, 39.7, 27.7, 21.6, 14.5; MS (EI) *m*/*z* 284 ([M-*t*BuO]$^+$, 4), 194 (5), 193 (44), 185 (5), 184 (54), 156 (5), 155 (55), 120 (18), 112 (7), 108 (34), 102 (11), 92 (7), 91 (57), 65 (14), 57 (100), 56 (7); MS (CI) *m*/*z* 377 (8), 376 (19), 375 ([M+NH_4]$^+$, 100), 319 (16), 275 (6), 174 (7). HRMS Calcd. for [M-*t*BuO]$^+$ $C_{12}H_{14}NO_5S$ 284.0592, found 284.0607. ee determined on derivatized product **9**.[39]

Acknowledgment. We thank the NRSC-Catalysis program, The Netherlands Organization of Scientific Research (NWO-CW), the Dutch Ministry of Economic Affairs under the EET scheme (EETK-97107 and 99104), and the European Community's Sixth Framework Programme (Marie Curie Intra-European Fellowship to F. L.) for financial support. The gift of the Taniaphos ligand by Dr. H.-U. Blaser (Solvias, Basel) is gratefully acknowledged. We also thank T. D. Tiemersma-Wegman and A. Kiewiet for technical assistance and Dr. S. R. Harutyunyan for synthesis of Taniaphos ligand.

Supporting Information Available: Experimental procedures, analytical data, and ^{1}H and ^{13}C NMR spectra of all allylic alkylation products and derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0625655