

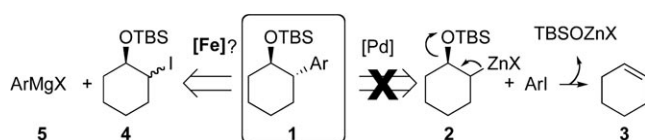
Highly Diastereoselective Iron-Mediated C(sp²)–C(sp³) Cross-Coupling Reactions between Aryl Grignard Reagents and Cyclic Iodohydrine Derivatives**

Andreas K. Steib, Tobias Thaler, Kimihiro Komeyama, Peter Mayer, and Paul Knochel*

Transition-metal-catalyzed cross-coupling reactions have become indispensable tools for C–C bond-forming reactions in modern organic synthesis.^[1] Most of these reactions depend on the use of palladium or nickel complexes as catalysts. Although these metals are used in only catalytic amounts, they have the disadvantage of being toxic^[2] and/or expensive.^[3]

Iron-mediated coupling reactions^[1e,4] were found to be a valuable alternative, since iron is one of the most abundant transition metals and its salts are inexpensive and environmentally benign. Despite spectacular advances^[5] and insights into the role of iron in coupling reactions,^[6] only a few stereoselective versions of iron-mediated or -catalyzed C(sp³) cross-coupling reactions are known.^[5k,1,6f,7]

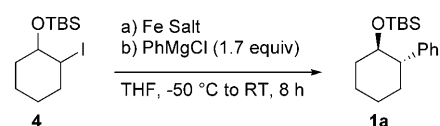
Recently, we developed a diastereoselective palladium-catalyzed cross-coupling of various substituted cycloalkylzinc reagents with (hetero)aryl halides^[8] and bromoalkynes.^[9] However, this coupling reaction could not be used for the preparation of α -arylated cyclohexanol derivatives of type **1**, since the required zinc reagent **2** undergoes fast elimination to give cyclohexene (**3**; Scheme 1).



Scheme 1. Retrosynthesis of 2-arylcyclohexanol derivatives **1**.

Products of type **1** are versatile building blocks for pharmaceuticals,^[10] chiral ligands,^[11] and auxiliaries.^[12] They are usually obtained by the opening of the corresponding epoxides with aryl organometallic compounds. Enantioselective versions of this opening are of limited scope.^[13] In fact, the most efficient procedures for the desymmetrization of oxacycles using aryl Grignard reagents have only been reported for oxabenzonorbornadienes^[14] and 2,3-disubstituted 7-oxabicyclo[2.2.1]hept-5-enes.^[7a,b] These problems can be solved by an alternative retrosynthesis involving the diastereoselective coupling of the readily available iodohydrine derivative **4** with ArMgX **5** (Scheme 1).

In preliminary experiments, we examined the cross-coupling of the TBS-protected (TBS = *tert*-butyldimethylsilyl) iodohydrine **4** with PhMgCl in the presence of various iron salts (Scheme 2). The addition of PhMgCl to the



Scheme 2. Cross-coupling of **4** with PhMgCl in the presence of various iron salts.

cyclohexyl iodide **4** (75:25 *cis/trans*) in the presence of 10% [Fe(salen)Cl]^[5n,15] salen = (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsilylidene)-1,2-cyclohexanediamine resulted in the exclusive formation of protonated product (cHexOTBS; Table 1, entry 1). Further attempts with iron salts, such as [Fe(acac)₃]^[5l] (acac = acetylacetonate) and FeCl₃,^[5l] in catalytic amounts furnished the desired cross-coupling product **1a** in 27% yield at best and with a diastereoselectivity between 76:24 and 96:4 d.r. (entries 2–4). Significant improvements were achieved by using substoichiometric amounts (0.85 equiv) of the complex FeCl₂·2LiCl,^[6d] which is highly soluble in THF; this complex preferentially gave the thermodynamically more stable *trans* isomer^[16] **1a** in 48% yield (59% GC yield) and 96:4 d.r. (entry 5). The addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA)^[5l] led to a deterioration of the diastereoselectivity (83:17 d.r.; entry 6). The use of 4-fluorostyrene as the additive, which is known to facilitate the reductive elimination step in nickel-catalyzed cross-coupling reactions,^[17] resulted in a higher yield of the isolated product (61%; 78% GC yield) with an excellent diastereoselectivity of 96:4 d.r. (entry 7).^[18,19] To elucidate whether traces of other transition metals present in the

[*] A. K. Steib,^[+] T. Thaler,^[+] Dr. P. Mayer, Prof. Dr. P. Knochel
 Department Chemie, Ludwig-Maximilians-Universität München
 Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
 Fax: (+49) 89-2180-77680
 E-mail: paul.knochel@cup.uni-muenchen.de

Prof. Dr. K. Komeyama

Department of Chemistry and Chemical Engineering
 Graduate School of Engineering, Hiroshima University
 Kagamiyama, Higashi-Hiroshima 739-8527 (Japan)

[*] These authors contributed equally to this work.

[**] Funding from the European Research Council under the European Community's Seventh Framework Programme (FP7/2007-2013, ERC grant no. 227763) is acknowledged. We thank the SFB 749 and the Fonds der Chemischen Industrie for financial support, and are grateful to BASF AG, W. C. Heraeus GmbH, Chemetall GmbH, and Solvias AG for the generous gift of chemicals. K.K. thanks the Japan Society for the Promotion of Sciences (JSPS) for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201007187>.

Table 1: Optimization of the conditions for the diastereoselective cross-coupling (Scheme 2).

Entry	Metal mediator	Additive	Yield [%] ^[a]	d.r. ^[a]
1 ^[b]	10% [Fe(salen)Cl] ^[5n,15]	—	0 ^[c]	n.d.
2 ^[d]	10% [Fe(acac) ₃] ^[5]	20% TMEDA 10% HMTA ^[e]	traces	n.d.
3 ^[d]	5% FeCl ₃ ^[5]	TMEDA (1.2 equiv)	17	76:24
4	10% FeCl ₃	10% DPEphos	27	96:4
5	FeCl ₂ ·2 LiCl (0.85 equiv)	—	59 (48)	96:4
6	FeCl ₂ ·2 LiCl (0.85 equiv)	TMEDA (1.2 equiv)	86	83:17
7 ^[f]	FeCl₂·2 LiCl (0.85 equiv)	4-fluorostyrene (0.5 equiv)	78 (61)	96:4
8 ^[g]	FeCl ₂ ·2 LiCl (0.85 equiv)	4-fluorostyrene (0.5 equiv)	73 (57)	96:4
9	10% [Ni(acac) ₂]	10% DPEphos	traces	n.d.

[a] Determined by GC analysis on a capillary column. Tridecane (C₁₃H₂₈) was used as the internal standard. Numbers in brackets indicate yields of isolated products. [b] 2.0 equiv of PhMgCl were used. [c] Only *c*-HexOTBS was obtained. [d] 1.2 equiv of PhMgCl were used. [e] HMTA = hexamethylenetetramine. [f] The use of catalytic amounts of FeCl₂·2 LiCl did not lead to a satisfactory conversion of **4**. [g] With 99.99% Fe (Alfa Aesar). Inductively coupled plasma (ICP) analysis showed that no traces of other transition metals were present in the reaction mixture apart from iron. n.d. = not determined.

reaction mixture were responsible for the cross-coupling we used FeCl₂ with a purity of 99.99% (entry 8). This resulted in **1a** being obtained in a similar yield of 57% (73% GC yield). The use of a combination of 10% [Ni(acac)₂] and 10% bis(2-diphenylphosphanylphenyl)ether (DPEphos)^[20] as catalyst gave **1a** in only trace amounts (< 3%; entry 9).

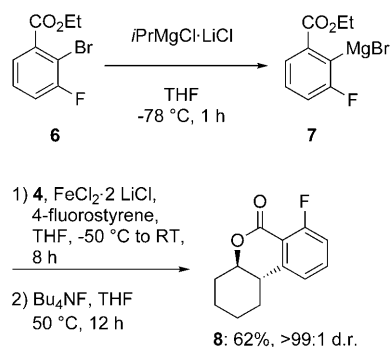
Next, we examined the scope of the diastereoselective iron-mediated cross-coupling of **4** by using various aryl-magnesium reagents (Table 2). These Grignard reagents were prepared either by LiCl-promoted insertion of Mg^[21] or by a Br/Mg exchange using *i*PrMgCl·LiCl.^[22] In all cases, the thermodynamically favored *trans*-1,2-disubstituted cyclohexanols were formed preferentially with ≥ 95:5 d.r.^[16] Aryl-magnesium reagents bearing methyl and trifluoromethyl groups were coupled efficiently with high diastereoselectivity (95:5 to 99:1 d.r.; entries 1–3). The cross-coupling reactions of the bulky naphthalen-1-ylmagnesium bromide^[21] and the sterically congested mesitylmagnesium bromide^[21] with **4** gave the *trans* products **1e** and **1f** in high yields (80 and 90%) and excellent diastereoselectivity (98:2 and > 99:1 d.r.; entries 4 and 5). Grignard reagents bearing sensitive cyano functions underwent smooth coupling reactions with **4** to furnish the respective products **1g** and **1h** in yields of 62 and 65% as single diastereomers (entries 6 and 7). Although a pivaloyloxy function is a well-known leaving group in iron-catalyzed cross-coupling reactions with Grignard reagents,^[5c] the reaction of [4-(pivaloyloxy)phenyl]magnesium bromide (4-PivOC₆H₄MgBr)^[21] with **4** led to the exclusive formation of **1i** (62%; 95:5 d.r.; entry 8). Heteroaryl Grignard reagents, such as 3-quinolinylmagnesium bromide^[21] and 3-pyridinylmagnesium chloride,^[22] were also coupled successfully to give **1j** and **1k** as single diastereomers (entries 9 and 10).

Table 2: Products of the diastereoselective cross-coupling with **4**.

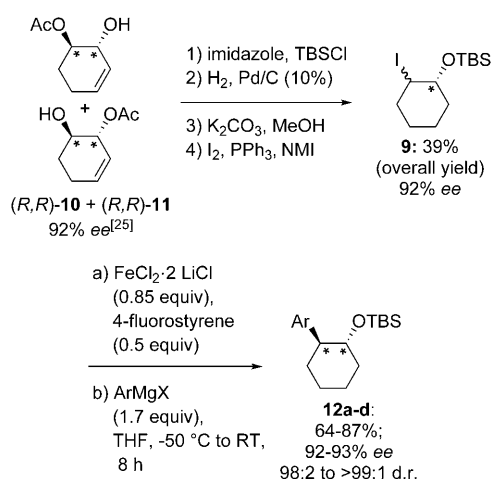
Entry	Product	Yield [%] ^[a] d.r. ^[b]	Entry	Product	Yield [%] ^[a] d.r. ^[b]
1		62 95:5	6		65 > 99:1
2		67 99:1	7		62 > 99:1
3		75 97:3	8		62 95:5
4		90 98:2	9		57 > 99:1
5		80 > 99:1	10		80 > 99:1

[a] Yield of analytically pure isolated product. [b] Determined by GC analysis on a capillary column before and after purification.

Br/Mg exchange on **6** in the presence of *i*PrMgCl·LiCl in THF at –78 °C led to the formation of the Grignard reagent **7**, which bears a sensitive ester function. The arylmagnesium reagent **7** underwent efficient cross-coupling with **4** to give, after desilylation with Bu₄NF, the stereochemically defined 3,4-dihydroisocoumarin **8**^[23] in 62% overall yield and > 99:1 d.r. (Scheme 3). 3,4-Dihydroisocoumarins often dis-



Scheme 3. Preparation of the stereochemically defined 3,4-dihydroisocoumarin **8**.



Scheme 4. Preparation and cross-coupling of the chiral 2-iodocyclohexanol **9**. NMI = *N*-methylimidazole.

play biological activity and their structural motifs occur in a number of natural products.^[24]

To underline its synthetic utility we applied this reaction to the cross-coupling of the enantioenriched 2-iodocyclohexanol derivative **9** which was obtained in four steps from the readily prepared mixture of (*R,R*)-**10** and (*R,R*)-**11**^[25] (92% *ee*) in an overall yield of 39% (Scheme 4). The iron-mediated cross-coupling reactions of **9** with various aryl Grignard reagents produced the *trans* products **12a–d** in a

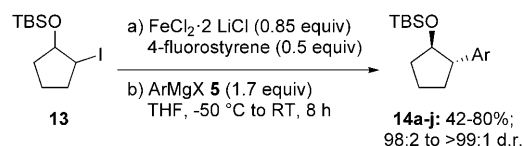
Table 3: Products of type **12** of the iron-mediated cross-coupling with enantioenriched **9** (Scheme 4).

Entry	Product	Yield [%] ^[a] d.r. ^[b]	<i>ee</i> [%] ^[c]
1		87 98:2	92
2		64 > 99:1	92
3		69 > 99:1	93
4		73 > 99:1	92

[a] Yield of analytically pure isolated product. [b] Determined by GC analysis on a capillary column before and after purification. [c] The enantiomeric excess (*ee*) was determined by HPLC on a chiral stationary phase. See the Supporting Information for details.

stereoconvergent manner with no loss of the stereochemical purity (92–93% *ee*) and excellent diastereoselectivities ($\geq 98:2$ d.r.; Table 3). Thus, the reaction is suitable for the efficient propagation of stereoinformation and represents a valuable alternative to the enantioselective opening of symmetrical epoxides.

Finally, we tried this diastereoselective iron-mediated coupling on the TBS-protected 2-iodocyclopentanol **13** in the presence of various (hetero)aryl Grignard reagents (Scheme 5). To our delight, the *trans* coupling products^[26] **14a–j** were obtained with excellent diastereoselectivities of 98:2 to >99:1 d.r. (Table 4). *trans*-2-Arylcyclopentanols are



Scheme 5. Diastereoselective cross-coupling of the 2-iodocyclopentanol derivative **13**.

Table 4: Products of the diastereoselective cross-coupling with **13** (Scheme 5).

Entry	Product	Yield [%] ^[a] d.r. ^[b]	Entry	Product	Yield [%] ^[a] d.r. ^[b]
1		56 98:2	6		68 > 99:1
2		80 > 99:1	7		69 > 99:1
3		65 > 99:1	8		68 > 99:1
4		75 > 99:1	9		42 > 99:1
5		60 > 99:1	10		60 > 99:1

[a] Yield of analytically pure isolated product. [b] Determined by GC analysis on a capillary column before and after purification.

reported to be important building blocks for drugs for the treatment of diabetes^[27] and for chiral phosphine ligands.^[28]

In summary, we have developed a new iron-mediated C(sp²)-C(sp³) coupling of 2-iodocycloalcohol derivatives with (hetero)aryl Grignard reagents. We have verified that iron is truly the mediating transition metal in the coupling. The reaction proceeds in a stereoconvergent manner to give the thermodynamically preferred arylated products. Thus, this method adds to the repertoire of stereoselective iron-mediated C(sp³) coupling reactions, of which only a few examples have been reported. In addition, it provides a convenient access to chiral 2-arylated cyclohexanols, which are difficult to prepare by enantioselective epoxide opening. Extensions of this method to further substrates as well as investigations on the mechanism are currently underway.

Received: November 16, 2010

Published online: February 14, 2011

Keywords: C–C coupling · cross-coupling · diastereoselectivity · iron · synthetic methods

- [1] a) N. Miyaoura, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535; b) E.-i. Negishi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233; c) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; e) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2081; f) A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; g) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147, and references therein.
- [2] a) *Handbook on the Toxicology of Metals* (Eds.: L. Friberg, G. F. Nordberg, V. B. Vouk), Elsevier, Amsterdam, **1986**; b) M. N. Hughes, *Compr. Coord. Chem.* **1987**, *67*, 643; c) *Nickel and the Skin: Absorption, Immunology, Epidemiology, and Metallurgy* (Eds.: J. J. Hostynek, H. I. Maibach), CRC, Boca Raton, **2002**.
- [3] World market prices: Pd: 515 \$ per ounce and Ni: 10 \$ per pound.
- [4] a) E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061; b) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396; c) A. Correa, O. G. Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; e) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; f) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; g) S. M. Neumann, J. K. Kochi, *J. Org. Chem.* **1975**, *40*, 599; h) M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487.
- [5] a) T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono, M. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 10674; b) T. Hatakeyama, S. Hashimoto, K. Ishizuka, M. Nakamura, *J. Am. Chem. Soc.* **2009**, *131*, 11949; c) B.-J. Li, L. Xu, Z.-H. Wu, B.-T. Guan, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 14656; d) W. M. Czaplik, M. Mayer, A. Jacobi von Wangelin, *Angew. Chem.* **2009**, *121*, 616; *Angew. Chem. Int. Ed.* **2009**, *48*, 607; e) G. Cahiez, L. Foulgoc, A. Moyeux, *Angew. Chem.* **2009**, *121*, 3013; *Angew. Chem. Int. Ed.* **2009**, *48*, 2969; f) M. Carril, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 4940; *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; g) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem.* **2007**, *119*, 6641; *Angew. Chem. Int. Ed.* **2007**, *46*, 6521; h) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844; i) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem.* **2007**, *119*, 4442; *Angew. Chem. Int. Ed.* **2007**, *46*, 4364; j) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; k) M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *Synlett* **2005**, 1794; l) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; m) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem. Int. Ed.* **2002**, *41*, 609; n) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856.
- [6] a) S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586; b) J. Kleimark, A. Hedström, P.-F. Larsson, C. Johansson, P.-O. Norrby, *ChemCatChem* **2009**, *1*, 152; c) D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. Nagashima, *J. Am. Chem. Soc.* **2009**, *131*, 6078; d) S. H. Wunderlich, P. Knochel, *Angew. Chem.* **2009**, *121*, 9897; *Angew. Chem. Int. Ed.* **2009**, *48*, 9717; e) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattinig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992; f) A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773.
- [7] a) M. Nakamura, K. Matsuo, T. Inoue, E. Nakamura, *Org. Lett.* **2003**, *5*, 1373; b) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2000**, *122*, 978; for a diastereoselective CoCl₂-catalyzed coupling, see c) H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886.
- [8] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nature Chem.* **2010**, *2*, 125.
- [9] T. Thaler, L.-N. Guo, P. Mayer, P. Knochel, *Angew. Chem.* **2011**, *123*, 2222; *Angew. Chem. Int. Ed.* **2011**, *50*, 2174.
- [10] R. G. Naik, V. N. Mumbaikar, R. Vasumathy, A. D. Lakdawala, M. B. Alreja, B. Lal, J. Blumbach, K. U. Weithmann, R. R. Bartlett, K. S. Joshi, S. Bal-Tembe, S. Raghavan (Hoechst AG), US 6159988, **2000**.
- [11] K. Kumazawa, K. Ishihara, H. Yamamoto, *Org. Lett.* **2004**, *6*, 2551.
- [12] J. K. Whitesell, *Chem. Rev.* **1992**, *92*, 953.
- [13] a) N. Oguni, Y. Miyagi, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 9023; b) S. G. Davies, S. Wollowitz, *Tetrahedron Lett.* **1980**, *21*, 4175.
- [14] R. Millet, L. Gremaud, T. Bernardez, L. Palais, A. Alexakis, *Synthesis* **2009**, 2101.
- [15] R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby, M. Hird, *Chem. Commun.* **2004**, 2822.
- [16] The relative stereoconfiguration of **1i** was determined by X-ray crystallography.
- [17] A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79.
- [18] We assume that a low-valent diaryliron complex is the nucleophilic species in the coupling. A [4-fluorostyrene-Fe(Ar)₂C₆H₁₀OTBS] complex may form. Complexation with the electron-poor 4-fluorostyrene facilitates the reductive elimination process.
- [19] The use of triisopropylsilyl-protected (TIPS-protected) 2-iodocyclohexanol led to the same diastereoselectivity (96:4 d.r.), whereas protection with the bulky *tert*-butyldiphenylsilyl (TBDPS) group resulted in a decreased diastereoselectivity (90:10 d.r.).
- [20] a) L. Melzig, A. Gavryushin, P. Knochel, *Org. Lett.* **2007**, *9*, 5529; b) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, K. Goubitz, J. Fraanje, P. W. N. M. van Leeuwen, *Organometallics* **1995**, *14*, 3081.
- [21] F. M. Piller, A. Metzger, M. A. Schade, B. A. Haag, A. Gavryushin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 7192.
- [22] A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
- [23] The relative stereoconfiguration of **8** was determined by X-ray crystallography.
- [24] a) R. D. Barry, *Chem. Rev.* **1964**, *64*, 229; b) R. C. Larock, C. A. Fellows, *J. Am. Chem. Soc.* **1982**, *104*, 1900; c) R. C. Larock, C. A. Fellows, *J. Org. Chem.* **1980**, *45*, 365 and references therein.

- [25] a) S. Demay, F. Volant, P. Knochel, *Angew. Chem.* **2001**, *113*, 1272; *Angew. Chem. Int. Ed.* **2001**, *40*, 1235.
- [26] The relative stereoconfiguration of **14d** was determined by desilylation. The crystals of the resulting alcohol proved suitable for X-ray crystallography.
- [27] a) E. Sher (Eli Lilly and Company), WO 2002089848, **2002**;
b) T. A. Shepherd, J. A. Aikins, D. Bleakman, B. E. Cantrell, J. P. Rearick, R. L. Simon, E. C. R. Smith, G. A. Stephenson, D. M. Zimmerman, *J. Med. Chem.* **2002**, *45*, 2101.
- [28] B. E. Bosch, A. Monsees, U. Dingerdissen, P. Knochel, E. Hupe (Degussa AG), WO 2002014330, **2002**.
-