Asymmetric Catalysis

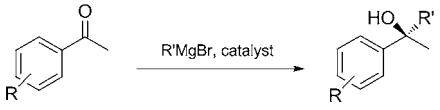
DOI: 10.1002/ange.201109040

Asymmetric Copper-Catalyzed Addition of Grignard Reagents to Aryl Alkyl Ketones**

Ashoka V. R. Madduri, Syuzanna R. Harutyunyan, and Adriaan J. Minnaard**

Tertiary alcohols are ubiquitous in natural products and pharmaceutical compounds. Therefore, methods for the enantioselective preparation of their chiral congeners are a necessity.[1,2] The synthesis of enantiopure secondary alcohols is well established by mature strategies, such as the asymmetric hydrogenation of ketones with transition metals and enzymes[3] followed by dynamic kinetic resolution of the corresponding racemates. However, these strategies do not apply for tertiary alcohols.[4] Even the resolution of racemic tertiary alcohols with lipases or esterases is generally not efficient.[5] The most straightforward method to prepare enantiopure tertiary alcohols would be the catalytic asymmetric addition of organometallic reagents to ketones.[6,1c] For the addition of alkyl groups, this notion has led to several studies in which dialkylzinc and organotitanium reagents were used effectively.[2] In contrast, readily available Grignard reagents have only been used in conjunction with stoichiometric amounts of a chiral ligand.[7] This is not surprising, as the uncatalyzed addition of the Grignard reagent is a formidable competitor.[8] Indeed, catalytic non-asymmetric addition of Grignard reagents to ketones has only recently become possible using Zinc(II) salts as catalysts.[9]

This addition of Grignard reagents to ketones, an archetypical organic chemistry reaction, can now be carried out in a catalytic asymmetric manner (Scheme 1). The use of



Scheme 1. Catalytic asymmetric addition of Grignard reagents to aryl alkyl ketones.

a copper catalyst based on a chiral Josiphos-type diphosphine ligand, in *tert*-butyl methyl ether, provides excellent yields and enantiomeric excesses (>95%) in the addition of branched alkyl Grignard reagents to aryl alkyl ketones.

Very recently, we have shown that, counterintuitively, copper–diphosphine catalysts can be used for the enantioselective 1,2-addition of Grignard reagents to enones.[10] Although the conjugated double bond is thought to play a major role in the course of that reaction, we nevertheless used this catalyst system to study the unprecedented asymmetric addition of Grignard reagents to aryl alkyl ketones.

Initial experiments were carried out using acetophenone as the substrate and $CuBr{\cdot}SMe_2$ as the metal precursor. In the absence of ligand, the reaction with 2-ethylbutylmagnesium bromide in *tert*-butyl methyl ether at various temperatures provided only small amounts of the addition product. The main products were phenethyl alcohol, as a result of Meerwein–Ponndorf–Verley reduction, and unreacted starting material, which is probably due to enolization.[11] A subsequent ligand screening involved a variety of chiral ligands, including monodentate phosphoramidites and bidentate diphosphines.[12] Josiphos-type ligand (S,R_{Fe})-**L1** turned out to be far superior, both in terms of yield and enantioselectivity; a maximum *ee* of 82% with an excellent 96% yield was obtained at −78°C (Table 1, Entry 1). This result indicates that the catalyst has a particularly high turnover frequency and outcompetes the uncatalyzed addition reaction, as well as reduction and enolization, at this temperature.

We were delighted to find that this positive outcome is representative for a broad spectrum of substituted acetophenones (Table 1). Upon addition of the same Grignard reagent, 2-ethylbutylmagnesium bromide, good to excellent enantioselectivities were obtained in combination with high yields of isolated products. Surprisingly, no clear trends were observed that relate the steric and electronic effects of the substituents to the enantioselectivity. *Para* and *meta* substituents have small but significant effects on the *ee*. Also, remarkably, a bromo substituent does not suffer from metal–halogen exchange. Notable results are 3-trifluoromethyl acetophenone **1i** with an excellent *ee* of 96% and 3-methoxyacetophenone **1h** with a decreased yield and an *ee* of 54%. Also remarkable are the excellent enantioselectivities obtained for 3,5-ditrifluoromethyl acetophenone (**1p**, 98%), 3,4-dichloro acetophenone (**1n**, 96%), and 3,5-difluoro acetophenone (**1o**, 92%). An *ortho*-bromo substituent is also well-tolerated (**1m**, 95% *ee*), although the yield is decreased.

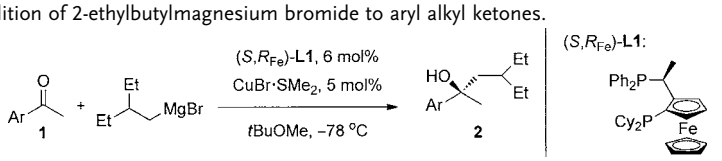
A small extension of the study shows that the reaction is limited neither to methyl-substituted ketones nor to phenyl-substituted ketones. Thus, upon addition, trifluoromethyl propiophenone **1k** gives an *ee* of 84% (Entry 11). This is a result comparable to acetophenone (*ee* 82%, Entry 1), but lower than trifluoromethyl acetophenone **1i** (*ee* 96%, Entry 9). A diminished enantioselectivity was obtained with 2-acetonaphthone **1q**, but 1-acetonaphthone **1r** gave an

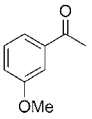
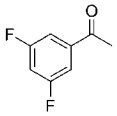
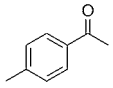
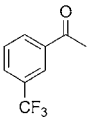
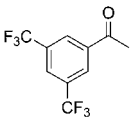
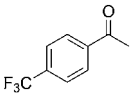
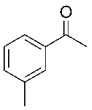
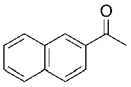
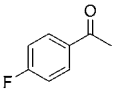
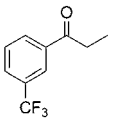
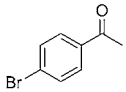
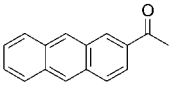
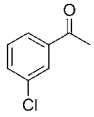
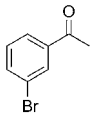
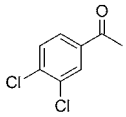
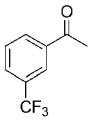
[*] A. V. R. Madduri, Dr. S. R. Harutyunyan, Prof. A. J. Minnaard
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 7, 9747 AG, Groningen (The Netherlands)
E-mail: s.harutyunyan@rug.nl
a.j.minnaard@rug.nl

[**] We thank Dr. B. Pugin (Solvias) for the generous gift of a ligand kit for initial screening.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201109040.

Table 1: Catalytic asymmetric addition of 2-ethylbutylmagnesium bromide to aryl alkyl ketones.



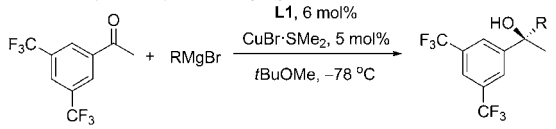
Entry[a]	1	*ee* (yield)[b–d] 2	Entry	1	*ee* (yield)[b–d] 2	Entry	1	*ee* (yield)[b–d] 2
1	 **1a**	**2a**, 82 (96)	8[e]	 **1h**	**2h**, 54 (87)	15	 **1o**	**2o**, 92 (96)
2[e]	 **1b**	**2b**, 76 (85)	9	 **1i**	**2i**, 96 (95)	16[g]	 **1p**	**2p**, 98 (95)
3	 **1c**	**2c**, 76 (93)	10[e]	 **1j**	**2j**, 76 (90)	17[e]	 **1q**	**2q**, 66 (91)
4	 **1d**	**2d**, 76 (95)	11	 **1k**	**2k**, 84 (97)	18	 **1r**	**2r**, 95 (71)
5[e]	 **1e**	**2e**, 86 (91)	12[e]	 **1l**	**2l**, 70 (84)	19[e]	 **1s**	**2s**, 80 (88)
6	 **1f**	**2f**, 84 (97)	13[f]	 **1m**	**2m**, 95 (61)	20	 **1t**	**2t**, 76 (96)
7[e]	 **1g**	**2g**, 90 (96)	14	 **1n**	**2n**, 96 (96)	21[h]	 **1u**	**2u**, rac. (75)

[a] Conditions: $CuBr{\cdot}SMe_2$ (5 mol%), (S,R_{Fe})-**L1** (6 mol%), Grignard reagent (1.25 equiv; 0.1 M in *t*BuOMe), −78 °C, 5–10 h. [b] All conversions > 98% (GC-MS). [c] Regio- and enantioselectivities determined by chiral-phase HPLC analysis. [d] Yield of isolated product. [e] Reaction performed at −60 °C. [f] *i*BuMgBr was used. [g] The reaction was also performed on a 4 mmol scale and resulted in 91% yield and 97% *ee*. [h] Phenylmagnesium bromide was used.

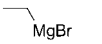
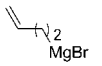
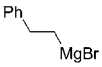
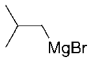
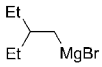
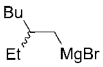
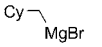
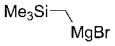
excellent *ee* of 95% (Entries 17 and 18). Even 2-acetoanthracenone **1s** is a suitable substrate for the reaction (80% *ee*, 88% yield). Heteroaromatic substituents are also allowed, as in the case of 2-thiophenyl methyl ketone **1t**. Additions to alkyl alkyl ketones (not depicted) and the addition of phenylmagnesium bromide (**2u**, Entry 21) both afforded racemic product.

The scope in terms of Grignard reagents was then studied (Table 2), using **1p** as the substrate. Although the yields are invariably excellent, bulkier Grignard reagents, such as those with branched alkyl groups, are required to obtain high enantioselectivities. Methylmagnesium bromide is inactive and ethylmagnesium bromide gives only 22% *ee* (Entry 1). With butenylmagnesium bromide the *ee* rises to 44%, with phenylethylmagnesium bromide 68% *ee* is obtained, and the enantioselectivity of the reaction reaches 95% with isobutylmagnesium bromide (Entries 2–4). The addition of 2-ethylbutylmagnesium bromide, 2-ethylhexylmagnesium bromide, and cyclohexylmethylmagnesium bromide were very rewarding as well, each affording the corresponding alcohol in 98% *ee* (Entries 5–7).

Table 2: Catalytic asymmetric addition of Grignard reagents to 3,5-ditrifluoromethyl acetophenone (**1p**).

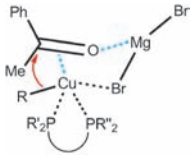


1p **3**

Entry[a]	RMgBr	**3**, *ee* (yield)[b–d]
1		**3a**, 22 (94)
2		**3b**, 44 (92)
3		**3c**, 68 (93)
4		**3d**, 95 (95)
5		**2p**, 98 (95)
6		**3e**, 98 (91)
7		**3f**, 98 (97)
8		**3g**, 74 (86)

[a] Conditions: CuBr·SMe_2 (5 mol%), (S,R_{Fe})-**L1** (6 mol%), RMgBr (1.25 equiv; 0.1 M in *t*BuOMe), −78°C, 5-10 h. [b] All conversions >98% (GC-MS).[c] Regio- and enantioselectivities determined by chiral-phase HPLC analysis. [d] Yield of isolated product. Cy = cyclohexyl.

Trimethylsilylmethylmagnesium bromide is deserving of special note, because the resulting 1,2-addition product is expedient for further functionalization. To our delight, the addition of this reagent was successful, providing the alcohol **3g** in an acceptable 74% *ee* and 86% yield (Table 2, Entry 8).



Scheme 2. Proposed transition state for the reaction.

The working hypothesis for the key alkyl group transfer step is presented in Scheme 2. We surmise that, upon reaction of the Grignard reagent with the chiral copper bromide complex, a new transmetalated species is formed wherein the alkyl moiety is more reactive than in the original Grignard reagent. Furthermore, this species is capable of double activation of the substrate via a pseudo-chair transition state: Lewis acid activation of the carbonyl moiety through the Mg^{2+} and activation of the carbonyl double bond by copper in analogy with the coordination mode of organocopper species reported recently by Bertz et al.[13]

In summary, the first catalytic enantioselective addition of Grignard reagents to aryl alkyl ketones is presented and the scope is shown to be fairly broad, both in substrates and in branched Grignard reagents. Thus, this reaction is especially suitable for use in the synthesis of naturally occurring compounds and pharmaceutically relevant building blocks. Currently, studies to enlarge the scope of the current method by exploring the addition of alkyl alkyl ketones and the use of linear Grignard reagents are ongoing.

Experimental Section

General procedure for the 1,2-addition of Grignard reagents to ketones: CuBr·SMe_2 (0.015 mmol, 3.08 mg, 5 mol%) and ligand (S,R_{Fe})-**L1** (0.018 mmol, 6 mol%) were added to a Schlenk tube equipped with septum and stirring bar. Dry *t*BuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. The ketone (0.3 mmol) in *t*BuOMe (1 mL) was added and the resulting solution was cooled to −78°C. The desired Grignard reagent (0.36 mmol, 1.2 equiv, in Et_2O) was diluted with *t*BuOMe (combined volume of 1 mL) under nitrogen and added to the reaction mixture over 15 min. Once the addition was complete, the reaction mixture was monitored by TLC and GC-MS. After completion, the reaction was quenched by the addition of MeOH (1 mL) and saturated aqueous NH_4Cl (2 mL), and then warmed to room temperature, whereupon it was diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using mixtures of *n*-pentane and Et_2O as the eluent.

Received: December 21, 2011
Published online: February 14, 2012

Keywords: 1,2-addition · aromatic ketones · asymmetric catalysis · chiral tertiary alcohols · copper

[1] a) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778–782; b) H. K. Scott, V. K. Aggarwal, *Chem. Eur. J.* **2011**, *17*, 13124–13132; c) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873.

[2] a) P. I. Dosa, G. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445–446; b) D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 1239–1242; c) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539; d) D. J. Ramón, M. Yus, *Angew. Chem.* **2004**, *116*, 286–289; *Angew. Chem. Int. Ed.* **2004**, *43*, 284–287; e) S.-J. Jeon, H. Li, C. García, L. K. LaRochelle, P. J. Walsh, *J. Org. Chem.* **2005**, *70*, 448–455; f) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669; g) D. K. Friel, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 9942–9951; for reviews, see: h) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; i) C. M. Binder, B. Singaram, *Org. Prep. Proced. Int.* **2011**, *43*, 139–208; j) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647–1675; k) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888.

[3] a) S. Itsuno in *Organic Reactions*, Wiley, Hoboken, **2004**; b) J. C. Moore, D. J. Pollard, B. Kosjek, P. N. Devine, *Acc. Chem. Res.* **2007**, *40*, 1412–1419.

[4] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis, Suppl. 2*, Springer, Berlin, **2004**; b) P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, California, **2009**.

[5] a) R. Kourist, P. Domínguez de María, U. T. Bornscheuer, *ChemBioChem* **2008**, *9*, 491–498; b) M. Paravidino, J. Holt, D. Romano, N. Singh, I. W. C. E. Arends, A. J. Minnaard, R. V. A. Orru, F. Molinari, U. Hanefeld, *J. Mol. Catal. B* **2010**, *63*, 87–92, and references therein.

[6] For examples of Cu^{I}-catalyzed asymmetric 1,2-additions of organoboron and organosilane compounds, see: a) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774–7854; b) K. R. Fandrick, D. R. Fandrick, J. T. Reeves, J. Gao, S. Ma, W. Li, H. Lee, N. Grinberg, B. Lu, C. H. Senanayake,

J. Am. Chem. Soc. **2011**, *133*, 10332 – 10335; c) D. Tomita, M. Kanai, M. Shibasaki, *Chem. Asian J.* **2006**, *1*, 161 – 166; d) D. Tomita, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4138 – 4139.

[7] a) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34 – 55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49 – 69; b) M. R. Luderer, W. F. Bailey, M. R. Luderer, J. D. Fair, R. J. Dancer, M. B. Sommer, *Tetrahedron: Asymmetry* **2009**, *20*, 981 – 998.

[8] For examples of the stoichiometric use of chiral ligands, see: a) J. L. von dem Bussche-Huennefeld, D. Seebach, *Tetrahedron* **1992**, *48*, 5719 – 5730; b) B. Weber, D. Seebach, *Angew. Chem.* **1992**, *104*, 96 – 97; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84 – 86.

[9] For examples of the catalytic non-asymmetric addition of Grignard reagents to ketones, see: a) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.* **2010**, *75*, 5008 – 5016; b) M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998 – 9999; c) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *Chem. Commun.* **2010**, *46*, 2674 – 2676.

[10] A. V. R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Chem. Commun.* **2012**, *48*, 1478 – 1480.

[11] a) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647 – 1675; b) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969 – 5994.

[12] a) J. F. Teichert, B. L. Feringa, *Angew. Chem.* **2010**, *122*, 2538 – 2582; *Angew. Chem. Int. Ed.* **2010**, *49*, 2486 – 2528; b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796 – 2823; c) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, X.-L. Hou, *Acc. Chem. Res.* **2003**, *36*, 659 – 667; d) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824 – 2852; e) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2009**, *38*, 1039 – 1075.

[13] S. H. Bertz, R. A. Hardin, M. D. Murphy, C. A. Ogle, J. D. Richter, A. A. Thomas, *Angew. Chem.* **2012**, DOI: 10.1002/ange.201107060; *Angew. Chem. Int. Ed.* **2012**, DOI: 10.1002/anie.201107060.

