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COMMUNICATIONS

Published on Web 09/21/2004

Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to Acyclic Enones

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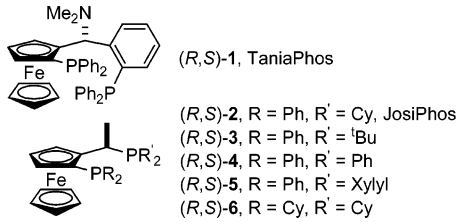
The conjugate addition (CA) of organometallic reagents to enones is one of the most widely used synthetic methods for carbon−carbon bond formation.[1] Enantioselective metal-catalyzed versions of this key transformation have been studied extensively with cyclic enones and chalcones using dialkylzinc,[2] organoboron, and silicon reagents.[3] However, despite the versatility and ready availability of Grignard reagents for organic synthesis, enantioselectivities in asymmetric CA reactions rarely reached the 90% ee level.[4] Recently, we showed that enantioselective Cu-catalyzed CA of Grignard reagents to cyclic enones can be achieved using chiral ferrocenyl diphosphines.[5] Here we report the Cu-catalyzed addition of Grignard reagents to the challenging class of acyclic aliphatic enone substrates with high regio- and enantioselectivity to provide optically active β-substituted ketones.

Aliphatic β-substituted linear ketones are common subunits in biologically active molecules and are important building blocks for natural product synthesis. However, highly enantioselective catalytic procedures for their preparation are rare, and enantioselectivities are usually substrate- and ligand-dependent.[6] Notable exceptions are the Cu-catalyzed CA of dialkylzinc reagents using peptidic phosphine ligands described by Hoveyda[7] and a complementary approach by Lipshutz that relies on a CuH-catalyzed asymmetric conjugate reduction of β,β-disubstituted enones.[8] Nevertheless, despite more than two decades of intensive research, a general method based on asymmetric CA of organomagnesium reagents to acyclic enones is still lacking.[9]

We started our investigation with the screening of TaniaPhos ligand **1**,[10] recently found to be effective in the asymmetric addition of Grignard reagents to cyclic enones (Figure 1).[5] In the present study, the catalyst prepared in situ from **1** and CuCl provides good regioselectivity in the Cu-catalyzed addition of EtMgBr to the model substrate (*E*)-3-nonen-2-one (**7a**), although the product is obtained with low enantioselectivity (Scheme 1, Table 1, entries 1 and 2). Noteworthy is that the use of JosiPhos ligand **2**[11] dramatically enhanced the selectivity of the addition, providing **8a** in 80% ee (entry 3). Optimization of solvent, Grignard halide, and copper source (entries 4−7) resulted in a further improvement in the selectivity of this process, providing **8a** in 94% isolated yield and 90% ee (entry 6).[12] Interestingly, ligand **2** proved to be clearly superior to any of the structurally related ferrocenyl diphosphines studied (**3**−**6**), with different alkyl and aryl residues at phosphorus (entries 8−11).

Having established an optimal protocol, the addition of different Grignard reagents as well as a variety of aliphatic linear enones was examined. The results are summarized in Table 2. Gratifyingly, the optimal conditions found for EtMgBr and the model substrate **7a** resulted in high selectivities when Grignard reagents with different linear alkyl chains were employed.

Thus, the CA of RMgBr reagents (R = Me, Et, *n*-Pr, *n*-Bu) to (*E*)-nonenone, octenone, or heptenone (entries 1−7) occurred smoothly at −75 °C within 2 h to give the corresponding chiral β-substituted ketones with excellent yields (62−91%), regio- (>94:6), and enantioselectivities (90−98%). High enantioselectivities were also observed in the formation of **8h**,**i** despite the small β-Me substituent in enone **7d** (entries 8−10). In all cases, the 1,2-addition products **9** were obtained as racemates. Particularly noteworthy is the addition of MeMgBr (e.g., to octenone and heptenone, entries 3 and 7), which provides **8d** and **8g** with 97−98% ee. The influence of the catalyst loading was examined for the addition of MeMgBr to heptenone. With only 1 mol % of catalyst, ketone **8g** was obtained with good regioselectivity and in equal enantioselectivity (97% ee) (entry 17). To the best of our knowledge, these values constitute the highest enantioselectivities thus far reported in the addition of alkylmetals to acyclic aliphatic enones. Furthermore, the versatility of this procedure is illustrated by the fact that opposite enantiomers for a particular ketone can be obtained just by judicious selection of complementary enones and Grignard reagents, without changing the configuration of the chiral diphosphine (entries 3, 9 and 4, 5).



(*R*,*S*)-**1**, TaniaPhos

(*R*,*S*)-**2**, R = Ph, R' = Cy, JosiPhos
(*R*,*S*)-**3**, R = Ph, R' = ^{t}Bu
(*R*,*S*)-**4**, R = Ph, R' = Ph
(*R*,*S*)-**5**, R = Ph, R' = Xylyl
(*R*,*S*)-**6**, R = Cy, R' = Cy

Figure 1. Chiral ferrocenyl-based diphosphines.

Scheme 1

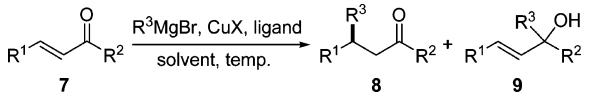


Table 1. Enantioselective CA of EtMgBr to *(E)*-3-Nonen-2-one **7a** (R^1 = *n*-Pent, R^2 = Me, R^3 = Et)[a,b]

entry	ligand	CuX	solvent	temp (°C)	**8a**:**9a**[c]	ee[c] (*R*/*S*)
1	**1**	CuCl	Et_2O	0	84:16	1
2	**1**	CuCl	Et_2O	−75	70:30	48 (*R*)
3	**2**	CuCl	Et_2O	−75	86:14	80 (*R*)
4	**2**	CuI	Et_2O	−75	83:17	72 (*R*)
5	**2**	CuBr·SMe_2	Et_2O	−75	91:9	86 (*R*)
6	**2**	**CuBr·SMe_2**	**^{t}BuOMe**	**−75**	**99:1**	**90** (*R*)[d]
7[e]	**2**	CuBr·SMe_2	^{t}BuOMe	−75	77:23	74 (*R*)
8	**3**	CuBr·SMe_2	^{t}BuOMe	−75	86:14	44 (*R*)
9	**4**	CuBr·SMe_2	^{t}BuOMe	−75	95:5	57 (*R*)
10	**5**	CuBr·SMe_2	^{t}BuOMe	−75	80:20	21 (*R*)
11	**6**	CuBr·SMe_2	^{t}BuOMe	−75	71:29	27 (*R*)

[a] Conditions: EtMgBr (1.15 equiv) added to a solution of the enone (0.1 M), 5 mol % CuX, and 6 mol % ligand unless otherwise noted. [b] All conversions >98% (GC−MS) after 2 h. [c] Regio- and ee's determined by chiral GC. [d] 94% isolated yield (**8a**). [e] EtMgCl (1.15 equiv) was employed.

10.1021/ja046632t CCC: $27.50

Table 2. Enantioselective CA of Grignard Reagents (R^3MgBr) to Aliphatic Methyl Linear Enones (R^2 = Me, Scheme 1)[a,b]

entry	R^1 (**7**)	Grignard (R^3)	regio (**8**: **9**)[c]	yield (**8**) (%)[d]	ee (%);[c] (*R*/*S*)[e]
1	*n*-pent (**7a**)	*n*-PrMgBr	98:2	84 (**8b**)	90
2	*n*-Bu (**7b**)	EtMgBr	96:4	91 (**8c**)	90
3	*n*-Bu (**7b**)	MeMgBr	99:1	86 (**8d**)	98 (*R*)
4	*n*-Bu (**7b**)	*n*-PrMgBr	94:6	88 (**8e**)	91
5	*n*-Pr (**7c**)	*n*-BuMgBr	95:5	91 (**8e**)	95
6	*n*-Pr (**7c**)	EtMgBr	95:5	66 (**8f**)	91 (*R*)
7	*n*-Pr (**7c**)	MeMgBr	99:1	62 (**8g**)	97
8	Me (**7d**)	EtMgBr	95:5	54 (**8h**)	93 (*S*)
9	Me (**7d**)	*n*-BuMgBr	95:5	78 (**8d**)	93 (*S*)
10	Me (**7d**)	Cl−BuMgBr	95:5	63 (**8i**)	94
11	*n*-Pr (**7c**)	*i*-Pr$(CH_2)_2$MgBr	95:5	90 (**8j**)	93
12	Me (**7d**)	*i*-Pr$(CH_2)_2$MgBr	96:4	64 (**8k**)	93
13[f]	*n*-Bu (**7b**)	*i*-BuMgBr	97:3	89 (**8l**)	84
14[f]	Me (**7d**)	*i*-BuMgBr	98:2	58 (**8m**)	86 (*S*)
15	*n*-pent (**7a**)	*i*-PrMgBr	96:4	83 (**8n**)	48
16	*n*-Pr (**7c**)	PhMgBr	81:19	75 (**8o**)	76
17[f,g]	*n*-Pr (**7c**)	MeMgBr	83:17	**8g**	97

[a] Conditions: 5 mol % CuBr·SMe_2, 6 mol % **2**, 1.15 equiv of R^3MgBr, 0.1 M in ^{t}BuOMe, −75 °C, 2 h. [b] All conversions >98% (GC−MS). [c] Regio- and enantioselectivities determined by chiral GC.[13] [d] Isolated yields of **8**. [e] Absolute configuration was established by comparison with known compounds.[6c,13] [f] A solution of the enone was added to the mixture of catalyst and R^3MgBr over 1 h. [g] 1 mol % CuBr·SMe_2, 1.12 mol % **2**.

The effect of the steric hindrance in the organometallic reagent was examined in γ [*i*-Pr$(CH_2)_2$], β (*i*-Bu), and α (*i*-Pr) alkyl-substituted Grignard reagents. Branching at the γ position is tolerated, providing the ketones with excellent regioselectivities and 93% ee (entries 11 and 12). Substitution at the β position required, however, a small modification of the experimental conditions to achieve high enantioselectivities: enones were slowly added to the mixture of catalyst and RMgBr reagent over 1 h. Thus, ketones **8l** and **8m** can be obtained with excellent regio- and enantioselectivities (84−86%, entries 13 and 14).[14] With α-branched reagents as *i*PrMgBr the reaction occurred with only 48% ee (entry 15). Finally, the use of PhMgBr was also examined, providing the ketone **8o** in 75% yield and 76% ee (entry 16).

Table 3. Acyclic Enones in the Cu-Catalyzed Asymmetric CA of Grignard Reagents (Scheme 1)[a]

entry	enone (R^1, R^2), (**7**)	Grignard (R^3)	regio (**8**:**9**)	yield **8** (%)[b]	ee (%) (*R*/*S*)
1	*i*-Pr, Me (**7e**)	MeMgBr	90:10	52 (**8p**)	94
2	(*t*-Bu)CH_2, Me (**7f**)	MeMgBr	90:10	81 (**8q**)	97 (*R*)
3	(*t*-Bu)CH_2, Me (**7f**)	*n*-BuMgBr	90:10	86 (**8r**)	93
4[c]	Me, *n*-Bu (**7g**)	*n*-PrMgBr	98:2	83 (**8s**)	95
5	*n*-pent, *t*-Bu (**7h**)	MeMgBr	77:23	56 (**8t**)	40
6	Ph, Me (**7i**)	MeMgBr	85:15	73 (**8u**)	97 (*S*)
7[d]	2-thienyl, Me (**7j**)	MeMgBr	83:17	72 (**8v**)	97
8[d,e]	2-furyl, Me (**7k**)[f]	EtMgBr	93:7	89 (**8w**)	90
9[d]	2-furyl, Me (**7k**)[f]	MeMgBr	87:13	80 (**8x**)	96

[a] Conditions: see Table 2. All conversions >98% (GC−MS). [b] Isolated yields of **8**. [c] A solution of the enone was added to the mixture of catalyst and Grignard reagent over 1 h. [d] Reaction time: 12 h. [e] EtMgBr (1.0 M in Et_2O) was added dropwise over 3 h. [f] (*Z*) geometry.

We next studied the influence of the enone structure on the efficiency of the asymmetric CA. The results are summarized in Table 3. Bulky substituents (*i*-Pr or *t*-Bu) at the β or γ positions of the enone did not affect the enantioselectivity of the process. Thus, ketones **8p**−**8r** were obtained from enones **7e** and **7f** with enantioselectivities ranging from 93 to 97% (Table 3, entries 1−3). Enone **7g** reacted smoothly with *n*-PrMgBr reagent to give the corresponding ketone (**8s**) with excellent yield and enantioselectivity (entry 4). Not unexpected, with the sterically hindered *t*-Bu ketone **7h** a drastic decrease in enantioselectivity was observed (40% ee, entry 5).

The scope of the Cu-catalyzed asymmetric CA includes both β-substituted aliphatic and aromatic enones. Benzylideneacetone (**7i**) and thienyl and furyl derivatives **7j** and **7k** react smoothly in ^{t}BuOMe at −75 °C with RMgBr reagents to give the corresponding enones in good yields and high regioselectivities and enantioselectivities of 90−97% (entries 6−9). It is noteworthy that the scope of the Cu-catalyzed CA reactions presented here is not limited to (*E*)-enones. The versatility of the present method is illustrated in the reactions of (*Z*)-4-furyl-3-en-2-one **7k**, providing chiral ketones **8w** and **8x** in 80−89% yield and with excellent enantioselectivities (90−96% ee) (entries 8 and 9).

In summary, we have developed a general and efficient catalytic CA of Grignard reagents to achiral acyclic enones to provide optically active β-substituted acyclic ketones with high yields and enantioselectivities. Studies toward the elucidation of the mechanism of this transformation are currently in progress.

Acknowledgment. We thank T. D. Tiemersma-Wegman for technical support (GC). F.L. thanks the Spanish Ministry of Education and Culture (M.E.C.D.) for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series 9; Pergamon: Oxford, 1992.
(2) (a) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002, pp 224−258. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (c) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Vol. 3, pp 1105−1120.
(3) (a) Yamasaki, K.; Hayashi, T. *Chem. Rev.* **2003**, *103*, 2829−2844. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (c) Oi, S.; Taira, A.; Honna, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97−99 and references therein.
(4) (a) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175−3182. (b) van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J.; Grove, D. M.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135−6138. (c) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467−4478. (d) Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503−16510. (e) Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3843−3854. (f) Pichota, A.; Pregosin, P. S.; Valentini, M.; Wörle, M.; Seebach, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 153−156.
(5) Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834−5838.
(6) (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236 and references therein. (b) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508−11509. (c) For an addition of $AlMe_3$ to linear aliphatic enones (ee's = 76−93%, 20 mol % catalyst), see: Frase, P. K.; Woodward, S. *Chem.−Eur. J.* **2003**, *9*, 776−783.
(7) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781.
(8) (a) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789−4792. (b) For a related approach for the reduction of linear unsaturated esters, see: Apella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474.
(9) Promising results (ee < 82%) limited to benzylideneacetone were reported in refs 4b and 4d.
(10) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212−3215.
(11) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3−16 and references therein.
(12) Other solvents (THF, ^{n}Bu_2O, ^{i}Pr_2O, DME, toluene) and Cu sources (CuBr, CuTC, $Cu(OTf)_2$, $CuCl_2$) evaluated provided lower selectivities.
(13) See Supporting Information for more details.
(14) Standard conditions gave **8l** in 62% ee (90:10 regio). The use of ^{t}BuOMe was crucial (the reaction in Et_2O provided **8l** with 42% ee, 78:22 regio).

JA046632T