Enantioselective Addition of Dimethylzinc to α-Keto Esters

Gonzalo Blay, Isabel Fernández, Alícia Marco-Aleixandre, José R. Pedro*

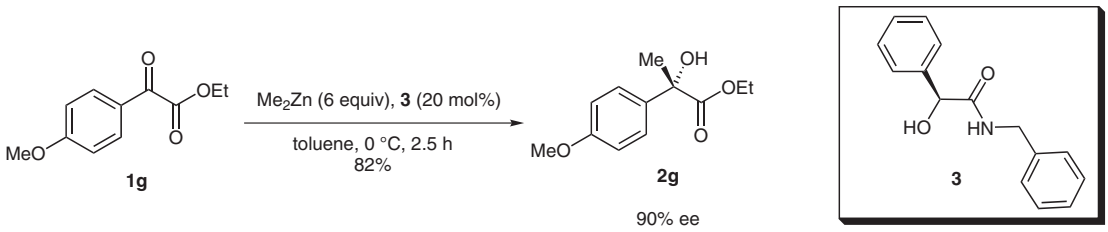
Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100 Burjassot (València), Spain
Fax +34963544329; E-mail: jose.r.pedro@uv.es

Received 16 May 2007

This paper is dedicated to Professor Ramón Mestres on the occasion of his retirement.

Abstract: The readily available (+)-*N*-Benzyl-(*S*)-mandelamide catalyzes the enantioselective addition of dimethylzinc to α-keto esters to give α-methyl-α-hydroxy esters containing stereogenic quaternary centers with moderate to good yields (56–87%). A good enantioselectivity of the reaction is obtained for aryl and heteroaryl keto esters. For these substrates ee values of 75–90% are obtained. The enantioselectivity is somewhat lower for the substrates bearing an aliphatic chain.

Key words: organometallic reagents, asymmetric catalysis, addition reactions, α-keto esters, mandelamides



Scheme 1

Introduction

The addition of organometallic reagents to α-keto esters provides a straightforward synthetic way to α-hydroxy esters containing stereogenic quaternary centers. This kind of compounds are useful intermediates in the synthesis of natural products and biologically active molecules, and many are bioactive themselves.[1] Control over the stereoselectivity of these reactions is an important concern since biological activity of the products may change depending on the absolute stereochemistry. This issue has been mostly approached with the use of chiral esters derived from α-keto acids and chiral alcohols,[2] and with the use of chiral modifiers in stoichiometric amount.[3] The use of organozinc reagents for this reaction shows some advantages with respect to other organometallic reagents: thus, they are compatible with the presence of different functional groups, and also they usually react slowly with carbonyl compounds allowing the use of chiral modifiers in catalytic amount. α-Keto esters are reactive substrates for the addition of organozinc reagents. However, unlike the usual ketones, the uncatalyzed reactions is rather fast, causing difficulties in the development of an enantioselective version, since the substrate itself can act as a chelating ligand, thereby activating the alkylzinc reagent.[4]

The first catalytic enantioselective addition of dialkylzinc reagents to α-keto esters was reported by Kozlowsky et al.[5] These authors use complexes of titanium with bifunctional amine-salen type ligands. Enantiomeric excesses of up to 83% can be attained with these systems for the addition of diethylzinc to methyl oxo(phenyl)acetate (88% ee if 70% titanium isopropoxide is used), although other substituted keto esters give lower enantioselectivities (5–85% ee). Shibashaki et al.[6] have described an enantioselective addition of dimethylzinc to α-keto esters using a proline-derived aminodiol as pre-catalyst. The reaction proceeds with enantioselectivities from fair to excellent (59–96%) although the procedure requires slow addition of the reagent at low temperature (–20 °C) and long reaction times, and diethylzinc is totally unreactive. A third catalytic system has been described by Hoveyda et al.[7] Transformation is promoted by an aluminum complex with amino acid-based ligands. The use of a Lewis base additive leads to a significant improvement in efficiency and enantioselectivity by enhancing the nucleophilicity of the alkylzinc reagent. Diethylzinc reacts to give the expected products with enantiomeric excesses within 56–89% while dimethylzinc addition products are obtained with 56–95% ee.

In previous work, we have introduced mandelamides as chiral ligands for the enantioselective addition of dialkylzinc reagents to carbonyl compounds. Mandelamides are easily prepared in one step starting from mandelic acid and amines. This kind of ligands catalyze the addition of dimethylzinc to aldehydes in the presence of titanium

SYNTHESIS 2007, No. 23, pp 3754–3757
Advanced online publication: 08.08.2007
DOI: 10.1055/s-2007-983851; Art ID: Z12207SS

isopropoxide[8] as well as the addition of mixed methyl-/alkynylzinc reagents to aldehydes to give the corresponding propargyl alcohols.[9]

Mandelamides also catalyze the addition of dimethylzinc to α-keto esters without the need of additional Lewis acid; i.e., Ti(IV) or Al (III) reagents (Scheme 1).[10]

Scope and Limitations

An optimization of the reaction conditions led to the experimental procedure described below. (+)-*N*-Benzyl-(*S*)-mandelamide (**3**) emerged as the best ligand for this reaction that is best carried out in toluene at 0 °C. By using this ligand, products having the *S* configuration in the newly formed quaternary stereogenic center are obtained (Table 1).

Table 1 Addition of Dimethylzinc to α-Keto Esters **1** Catalyzed by **3**[a]

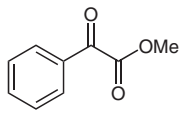
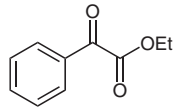
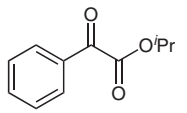
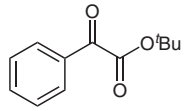
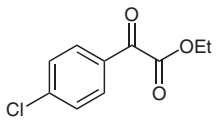
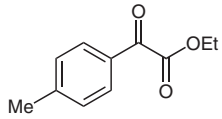
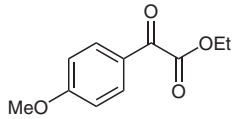
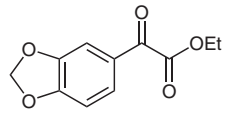
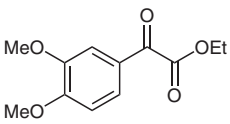
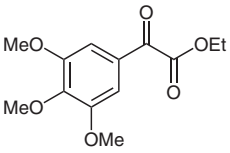
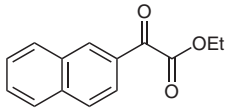
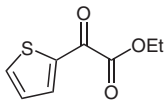
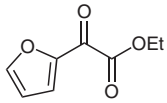
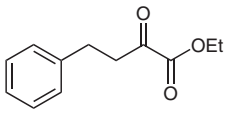
Entry	Substrate		Time (h)	Yield (%)[b]	ee (%)[c]
1		**a**	5	80	65
2		**b**	1.5	80	81
3		**c**	4.5	82	78
4		**d**	6	87	46
5		**e**	4	87	63
6		**f**	3.5	82	81
7		**g**	2.5	82	90
8		**h**	4	87	84

Table 1 Addition of Dimethylzinc to α-Keto Esters **1** Catalyzed by **3**[a] (continued)

Entry	Substrate		Time (h)	Yield (%)[b]	ee (%)[c]
9		**i**	4	82	85
10		**j**	6	83	78
11		**k**	24	70	74
12		**l**	2	66	72
13		**m**	2.5	56	78
14		**n**	2	73	35

[a] Me_2Zn: 6.0 equiv, **3**: 20 mol%, toluene, 0 °C.
[b] Yield of isolated product **2**.
[c] Determined by chiral GLC or chiral HPLC. *S*-configuration.

The reaction requires the use of 20 mol% of ligand and 6.0 equivalents of dimethylzinc. A commercially available 2 M solution of dimethylzinc in toluene is used as the source of the reagent.

The ester group in the substrate has some influence on the enantioselectivity of the reaction. Medium-sized esters, such as ethyl (entry 2) or isopropyl (entry 3) give better results than the small methyl (entry 1) or the bulky *tert*-butyl esters (entry 4).

Substrate generality has been studied with different ethyl α-keto esters. In general, the reaction is complete in less than six hours. Only the more hindered substrate ethyl (2-naphthyl)oxoacetate (**1k**) requires longer times (entry 11). With α-keto esters having aromatic and heteroaromatic substituents (entries 1–13) addition of dimethylzinc takes place with good yields and ee's from moderate (62%) to high (90%). The presence of electron-donating groups on the aromatic ring increases the enantioselectivity of the reaction (entries 7–9). Ethyl (4-methoxyphenyl)oxoacetate (**1g**) gives the best result, the expected product being obtained in 82% yield and 90% ee (entry 7). Remarkably, the addition of dimethylzinc to methyl (4-methoxy)oxoacetate using Shibashaki's system takes place with low yield (42%) and similar enantioselectivity (92%), while Hovey-

da has reported lower yield (71%) and enantioselectivity (84%). Keto ester **1n** bearing an aliphatic chain linked to the ketone carbonyl group reacts readily under the catalytic conditions but with lower enantioselectivity (entry 14).

As with Shibashaki's system, the reaction is also limited to dimethylzinc as the organozinc reagent. Treatment of ethyl oxo(phenyl)acetate (**1b**) with diethylzinc yielded the corresponding racemic reduction product.

In summary, this is an operationally simple and practical procedure for the enantioselective addition of dimethylzinc to α-keto esters. Additional advantages of this procedure are the simplicity and easy preparation of the ligand (also both enantiomers of the ligand are available starting from the proper mandelic acid) and the not requirement for additional Lewis acids. The yields and enantioselectivities with most substrates are comparable to those obtained with other procedures, which require more elaborated ligands and more operationally complicated processes.

Herein we describe the procedure for the preparation of mandelamide ligand **3** and the procedure for the addition of dimethylzinc to ethyl (4-methoxyphenyl)oxoacetate (**1g**) as representative example for the substrates described in Table 1.

All reactions were carried out with a magnetic stirring in oven-dried (120 °C) glassware under N_2. Melting points were measured on a Büchi B-535 apparatus and are uncorrected. Optical rotations were measured on a PerkinElmer 243. NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^{1}H NMR and at 75 MHz for ^{13}C NMR in a Bruker Avance 300 DPX spectrometer, and referenced to the solvent as internal standard. Mass spectra were recorded on a Fisons Instruments VG Autospec GC 8000 series spectrometer (EI, 70 eV). Chiral GLC analyses were carried out in a Thermo Quest Trace GC 2000 series instrument equipped with a flame ionization detector. Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a refraction index detector.

(+)-*N*-Benzyl-(*S*)-mandelamide (3)

To a stirred solution of (*S*)-(+)-mandelic acid (5.0 g, 32.9 mmol) in anhyd THF (140 mL) under N_2 was added benzylamine (3.6 mL, 3.5 g, 32.9 mmol) via a syringe followed by *N*-hydroxysuccinimide (4.2 g, 36.1 mmol).[11] The resulting mixture was cooled to 0 °C and *N*,*N*′-dicyclohexylcarbodiimide (7.5 g, 36.1 mmol) was added. After 15 min, the cooling bath was removed and the solution was stirred at r.t. under N_2 overnight (ca 20 h). After this time, the mixture was filtered through a sintered glass plate and the dicyclohexylurea cake washed with THF (2 × 10 mL). The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (300 mL). The organic layer was washed successively with sat. aq Na_2CO_3 (70 mL), H_2O (70 mL), aq 1 M HCl (70 mL), H_2O (70 mL), and brine (70 mL) and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel eluting with hexane–EtOAc (8:2) to give **3** as a white solid: yield: 6.3 g (80%); mp 134–135 °C (MeOH); $[\alpha]_D^{25}$ +83.2 (*c* 0.54, $CHCl_3$); $[\alpha]_D^{25}$ +45.7 (*c* 0.52, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 8 H), 7.19 (dd, *J* = 7.8, 1.8 Hz, 2 H), 6.60 (s, 1 H, NH), 5.06 (d, *J* = 3.7 Hz, 1 H), 4.43 (AA′ system, 2 H), 3.78 (d, *J* = 3.7 Hz, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2 139.4, 137.7, 128.8, 128.7, 128.6, 127.5, 126.8, 74.2, 43.4.

MS (EI, 70 eV): *m*/*z* (%) = 241 (2, [M$^+$]), 107 (79), 91 (100), 79 (92), 77 (57).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}NO_2$ [M$^+$]: 241.1103; found: 241.1031.

(*S*)-Ethyl 2-Hydroxy-2-(4-methoxyphenyl)propanoate (2g); Typical Procedure

A commercially available 2 M solution of Me_2Zn in toluene (3 mL, 6 mmol) was added to a solution of ligand **3** (48 mg, 0.2 mmol) in anhyd toluene (5 mL), under N_2 at r.t. After stirring for 30 min, the solution was cooled to 0 °C and ethyl (4-methoxyphenyl)oxoacetate (**1g**; 208 mg, 1 mmol) was added. After 2.5 h, aq 1 M HCl (20 mL) was added dropwise while keeping the mixture in the ice bath (***Caution!*** Gas evolution). The mixture was extracted with Et_2O (3 × 20 mL) and the organic layer was washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography eluting with hexane–EtOAc (9:1) gave **2g** as a slightly yellow oil; yield: 184 mg (82%); $[\alpha]_D^{25}$ +39 (*c* 0.51, $CHCl_3$, ee 90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 4.29–4.11 (m, 2 H), 3.78 (s, 3 H), 1.73 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 159.1, 135.0, 126.4, 113.5, 75.2, 62.3, 55.2, 26.6, 14.0.

MS (EI, 70 eV): *m*/*z* (%) = 224 (3, [M$^+$]), 151 (100).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}O_4$ [M$^+$]: 224.1049; found: 224.1055.

Enantiomeric Excess Determination

GLC (Supelco β-dex-225): $T_{injector}$ = 220 °C, $T_{detector}$ = 220 °C, T_{column} = 130 °C, N_2 (1 mL/min), minor enantiomer (*R*) t_R = 81.8 min, major enantiomer (*S*) t_R = 85.3 min.

HPLC (Chiralpack AD-H): Hexane–*i*-PrOH (95:5), 1 mL/min, major enantiomer (*S*) t_R = 11.3 min, minor enantiomer (*R*) t_R = 12.5 min.

Acknowledgment

Support from the Ministerio de Educación y Ciencia (Grant CTQ 2006-14199), Generalitat Valenciana (Grant grupos 03/168) and the Universitat de València (Grant UV-AE-20060244) is acknowledged. A.M-A. thanks the MEC for a pre-doctoral grant (FPU program).

References

(1) (a) Bennet, G. B.; Houlihan, W. J.; Mason, R. B.; Engstrom, R. G. *J. Med. Chem.* **1976**, *19*, 709. (b) Zalkow, L. H.; Glinski, J. A.; Gelbaum, L. T.; Moore, D.; Melder, D.; Powis, G. *J. Med. Chem.* **1988**, *31*, 1520. (c) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org, Chem.* **1994**, *59*, 5120. (d) Senanayake, C. H.; Fang, Q. K.; Grover, P.; Bakale, R. B.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819. (e) Shilova, E. V. *Pharm. Chem. J.* **2000**, *34*, 419. (f) Okumura, Y.; Ando, A.; William Stevens, R.; Shimizu, M. *Tetrahedron* **2002**, *58*, 8729. (g) Sergeeva, N. N.; Golubev, A. S.; Henning, L.; Burger, K. *Synthesis* **2003**, 915. (h) Zha, C.; Brown, G. B.; Brouillette, W. J. *J. Med. Chem.* **2004**, *47*, 6519. (i) Tchilibon, S.; Zhang, J.; Yang, Q.-F.; Eidelman, O.; Kim, H.; Caohuy, H.; Jacobson, K. A.; Pollard, B. S.; Pollard, H. B. *Biochem. Pharmacol.* **2005**, *70*, 381. (j) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T. *Org. Lett.* **2005**, *7*, 5103. (k) Tangirala, R. S.; Antony, S.; Agama, K.; Pommier, Y.;

Anderson, B. D.; Bevins, R.; Curran, D. P. *Bioorg. Med. Chem.* **2006**, *14*, 6202. (l) Xu, Y.; Etgen, G. J.; Broderick, C. L.; Canada, E.; Gonzalez, I.; Lamar, J.; Montrose-Rafizadeh, C.; Oldham, B. A.; Osborne, J. J.; Xie, C.; Shi, Q.; Winneroski, L. L.; York, J.; Yumibe, N.; Zink, R.; Mantlo, N. *J. Med. Chem.* **2006**, *49*, 5649.

(2) (a) Sugimura, H.; Watanabe, T. *Synlett* **1994**, 175. (b) Boireau, G.; Deberly, A.; Abenhaim, D. *Tetrahedron Lett.* **1988**, *29*, 2175. (c) Boireau, G.; Deberly, A.; Abenhaim, D. *Tetrahedron* **1989**, *45*, 5837. (d) Loupy, A.; Monteux, D. A. *Tetrahedron* **2002**, *58*, 1541.

(3) (a) Abenhaim, D.; Boireau, G.; Sabouraoult, B. *Tetrahedron Lett.* **1980**, *21*, 3043. (b) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117. (c) Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301.

(4) Di Mauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668.

(5) (a) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781. (b) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249.

(6) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5489.

(7) Wieland, L. C.; Deng, H.; Snapper, M. L.; Hoveyda, H. *J. Am. Chem. Soc.* **2005**, *127*, 15453.

(8) Blay, G.; Fernández, I.; Hernández-Olmos, V.; Marco-Aleixandre, A.; Pedro, J. R. *Tetrahedron: Asymmetry* **2005**, *16*, 1953.

(9) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *J. Org. Chem.* **2006**, *71*, 6674.

(10) Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Pedro, J. R. *Org. Lett.* **2006**, *8*, 1287.

(11) The flask was opened and the solid reagent rapidly added.