

Enantioselective Preparation of β,β -Disubstituted α -Methylenepropionates by MAO Promotion of the Zinc Schlenk Equilibrium**

Paul J. Goldsmith, Simon J. Teat, and Simon Woodward*

Dedicated to Dr. John M. Brown, FRS on the occasion of his 65th birthday

In the copper-catalyzed reactions of organometallic nucleophiles (RM) with allylic halides $R^1CH=CR^2CH_2X$, two reaction pathways are possible: either direct S_N2 displacement at the α carbon or S_N2' displacement γ to the leaving group. Recently, considerable progress has been made towards the development of asymmetric processes that result from copper-catalyzed S_N2' addition of organozinc or Grignard reagents.^[1] These studies have generally used allylic halides that lack functional groups and have focused largely on (*E*)-cinnamyl halides or equivalent phosphate esters ($R^1 = Ph$, $R^2 = H$). Reactions with ester-functionalized electron-deficient allylic halides ($R^2 = CO_2R$, $R^1 =$ various, **1**) would offer rapid access to highly useful chiral β,β -disubstituted α -methylenepropionates **2** (see Table 1). Highly selective additions of ZnR_2 to the regioisomers of **1** have been demonstrated,^[2] but the former substrates themselves have proved highly resistant to effective asymmetric catalysis.^[3]

Stoichiometric groundwork by Xu and Kündig showed the viability of addition of organozinc reagents to halides of type **1**.^[4] Using Baylis–Hillman chemistry (to obtain suitable allylic halides **1**), we developed a first-generation catalytic system for the addition of ZnR_2 to allylic chloride **1a** by employing a chiral thioether ligand.^[5] However, only low levels of enantioselectivity were observed, and the system was resist-

ant to further optimization. With high-throughput screening, the chiral secondary amines **3** were identified as alternative ligands for the transformation of **1a** to **2a** in the presence of CuI (Table 2). A number of the other 80 species tried produced significant ligand-accelerated catalysis (LAC)^[6]

Table 1: Synthesis of chiral β,β -disubstituted α -methylenepropionates **2**.

1	Ar	3	R ¹	R	2	Ar
a	Ph	a	Ph	H	a	Ph
b	4-(MeO)C ₆ H ₄	b	Ph	Me	b	4-(MeO)C ₆ H ₄
c	4-MeC ₆ H ₄	c	Ph	CHO	c	4-MeC ₆ H ₄
d	1-Naphthyl	d	<i>c</i> -C ₆ H ₁₁	H	d	1-Naphthyl
e	2-BrC ₆ H ₄	e	1-Naphthyl	H	e	2-BrC ₆ H ₄
f	4-FC ₆ H ₄	f	4-FC ₆ H ₄	H	f	4-FC ₆ H ₄
g	4-(CF ₃)C ₆ H ₄	g	4-MeC ₆ H ₄	H	g	4-(CF ₃)C ₆ H ₄
h	4-(NO ₂)C ₆ H ₄	h	4-(MeO)C ₆ H ₄	H	h	4-(NO ₂)C ₆ H ₄
		i	3-(MeO)C ₆ H ₄	H		
		j	2-(MeO)C ₆ H ₄	H		
						 2aa

Table 2: Addition of $ZnEt_2$ to allylic chloride **1a** using CuI and (*S,S*)-**3**.^[a]

Entry	Ligand	R ¹	R	Yield 2a [%]	ee 2a [%]
1	3a	Ph	H	50	65
2	3a ·HCl	Ph	H	50	51
3	3b ·HCl	Ph	Me	10	< 5
4	3c ·HCl	Ph	CHO	18	< 5
5	3d ·HCl	<i>c</i> -C ₆ H ₁₁	H	41	< 5
6	3e ·HCl	1-Naphthyl	H	18	15
7	3f ·HCl	4-FC ₆ H ₄	H	28	47
8	3g ·HCl	4-MeC ₆ H ₄	H	60	72
9	3h	4-(MeO)C ₆ H ₄	H	70	78
10	3h ·HCl	4-(MeO)C ₆ H ₄	H	69	74
11	3i ·HCl	3-(MeO)C ₆ H ₄	H	56	53
12	3j	2-(MeO)C ₆ H ₄	H	53	6

[a] Addition of $ZnEt_2$ (0.7 mL of a solution in toluene (1.1 M), 0.77 mmol) to **1a** (0.5 mmol) in THF (1 mL) at -20°C in the presence of (*S,S*)-**3** (10 mol%) and CuI (5 mol%). Yield and ee values determined after 1 h by chiral-GC analysis (see Supporting Information).

effects (see Supporting Information), but only compound **3** gave ee values over 35%. Subsequent investigation revealed that the presence of C_2 symmetry is vital for efficient stereoselection; for example, use of (*S*)-PhCH(Me)NHBn gave **2a** in high yield, but with less than 20% ee. The presence of the secondary amino group is also crucial as either its alkylation or formylation (Table 2, entries 3 and 4, respectively) dramatically reduced the activity and selectivity of the catalyst. Finally, it was noted that the presence of an aryl function in the ligand **3** was also vital as **3d**·HCl showed no enantioselectivity and poor conversion of **1a** (entry 5). The

[*] P. J. Goldsmith, Dr. S. Woodward
School of Chemistry
The University of Nottingham
Nottingham NG7 2RD (UK)
Fax: (+44) 115-951-3564
E-mail: simon.woodward@nottingham.ac.uk

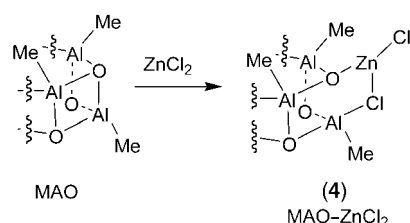
Dr. S. J. Teat
Diamond Light Source Ltd.
Rutherford Appleton Laboratory
Chilton, Didcot
Oxfordshire OX11 0QX (UK)

[**] This work was supported in part by the European Union COST-D24 Program (W6-D24-0003) and by the EPSRC (Grant GR/S56054). P.J.G. is also grateful for the support of the Grundy Educational Trust. MAO = methylaluminoxane.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

role of the ligand aryl group was further investigated by increasing the range of substituents in **3** (Table 2). These were mostly screened as their HCl salts as these are more convenient to handle than the free amines. A strong detrimental steric effect was noted for ligands with a 2-substituent (entries 6 and 12), but a favorable electronic effect (either +I or +M) existed at the 4-position (entries 8–10). Through these studies the 4-methoxy ligand **3h** was determined to be optimal (Table 2, entry 9).

These studies also highlighted that the free amines **3** outperformed their corresponding salts **3**·HCl in terms of product stereoselectivity (compare entries 1 and 9 versus 2 and 10, respectively; Table 2). Alongside this, kinetic studies had shown that the enantioselectivity of the reaction in THF was time-dependent: When substrate **1a** was treated with ZnEt₂ using ligand **3h**·HCl, the *ee* value fell from 80% at the onset of the reaction to 74% after one hour (69% yield, the mass balance being **1a**). Coupled together these facts indicated that EtZnCl, whose concentration increases as the reaction evolves, impairs the selective transition state. This could be confirmed by deliberate addition of EtZnCl (prepared from a 1:1 mixture of ZnEt₂ and ZnCl₂) [7] which led to an immediate and catastrophic collapse in the catalyst selectivity (30% *ee*, 12% yield at 1 h.). We therefore reasoned that if we could promote the forward reaction (*k*₁) of the zinc Schlenk equilibrium [Eq. (1)], the enantioselectivity of the reaction should improve with the lower concentration of EtZnCl. Conditions under which ZnCl₂ is scavenged from the reaction mixture should fulfil this requirement. After screening several additives, including crown ethers, we found that the addition of methylaluminoxane (MAO; [−Al(Me)O−]_n) which is known to strongly scavenge halides^[8] led to the desired effect (83% *ee*, 48% yield of **2a** at 1 h, −20°C). It has been speculated that MAO can act as a “latent Lewis acid” and sequester chlorides as shown in structure **4**. ZnMe₂



showed similar benefit, presumably through formation of unreactive MeZnCl, though catalyst turnover was reduced (84% *ee*, 35% yield of **2a** at 1 h, −20°C).^[9]



To the best of our knowledge, attempted manipulation of the zinc Schlenk equilibrium as a synthetic route to alkyl ZnR₂ species has not been reported before.^[10] Alongside these additive trials, stronger coordinating solvents were screened, and we found that DME

(1,2-dimethoxyethane) as solvent (with no additive) leads to a significant increase in enantioselectivity (88% *ee*, 47% yield of **2a** at 1 h, −20°C). A combination of the use of MAO and DME and lowering the temperature led to the attainment of synthetically useful levels of enantioselectivity in the preparation of **2a**. Use of excess MAO led to *ee* values greater than 95%, but with low yields of **2a**. These results could be generalized across the range of substrates **1** (Table 3), with

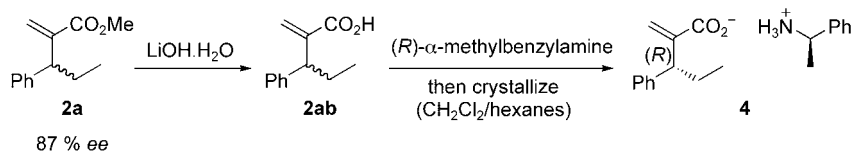
Table 3: CuTC/(*S,S*)-**3h**-catalyzed addition of ZnR₂ (R = Et, Bu) to allylic chlorides **1** under conditions that promote Schlenk equilibration.^[a]

Entry	Product	Ar	Yield [%]	[α] _D ^{23[b]}	<i>ee</i> [%] (stereoisomer) ^[b]
1	2a	Ph	92	−92.8	87 (<i>R</i>)
2	2aa	Ph	81	−76.2	78 (<i>R</i>) ^[c]
3	2b	4-(MeO)C ₆ H ₄	80	−96.4	90 (<i>R</i>)
4	2c	4-MeC ₆ H ₄	95	−94.4	89 (<i>R</i>)
5	2d	1-Naphthyl	53	−63.3	86 (<i>R</i>)
6	2e	2-BrC ₆ H ₄	95	−82.7	80 (<i>S</i>) ^[d]
7	2f	4-FC ₆ H ₄	95	−90.0	87 (<i>R</i>)
8	2g	4-(CF ₃)C ₆ H ₄	93	−80.3	83 (<i>R</i>)
9	2h	4-(NO ₂)C ₆ H ₄	95	−97.0	76 (<i>R</i>)

[a] Addition of ZnEt₂ (1.0 mL of a solution in toluene (1.1 M), 1.1 mmol) to **1** (0.5 mmol) in DME (1 mL) at −40°C in the presence of (*S,S*)-**3h** (10 mol%), CuTC (5 mol%), and MAO (0.5 mL, 15 wt % solution in toluene). Yields of isolated products quoted. [b] (*c* 1.0, CHCl₃) for [α]_D²³ in all cases. The absolute configuration of (−)-**2a** was confirmed crystallographically as *R*, and the products **2aa–h** were assumed to show the same sense of stereoselection. [c] The reaction was performed using Zn(*n*Bu)₂ (1.0 mL of a solution in heptane (1 M), 1.0 mmol). [d] Yield from NMR spectroscopic studies based on isolation of a mixture of **1e** and **2e**. The absolute configuration has changed owing to a change in assignment priority of the aryl substituent.

optimal results attained when CuTC (copper(i) thiophene-2-carboxylate)^[11] was used as the source of copper(i). The origin of the enantioselectivity attained in this reaction unusually depends critically on electronic effects. Electron-rich substrates give products with higher enantioselectivities than electron-poor substrates (compare entry 3 versus 9, Table 3), which implicates a π-stacking interaction in the transition state.

The sense of the enantioselectivity in the addition of ZnEt₂ to the halide **1a** could be determined by X-ray crystallographic analysis of the carboxylic acid **2ab**, which resulted from the hydrolysis of **2a**, when crystallized as its (*R*)-α-methylbenzylamine salt (Scheme 1). Single recrystallizations of the acids derived from **2** and further derivatization with α-methylbenzylamine improved the enantioselectivity to > 99% *ee* for the catalytic addition. This enrichment was considerably easier and more efficient than direct resolution of racemic **2ab**. The product **2ab** of the S_N2' reaction is of



Scheme 1.

direct use in the preparation of combined ACE–NEP (angiotensin-converting enzyme and neutral endopeptidase) inhibitors.^[12]

In conclusion, we have described the first method for the copper-catalyzed enantioselective alkylation of Baylis–Hillman-derived electron-deficient allylic chlorides with organozinc reagents thorough the use of a simple chiral secondary amine and promotion by MAO of the zinc Schlenk equilibrium. Further intensive studies are underway to identify the nature of the π -stacking interactions responsible for the ordered transition state.

Experimental Section

General procedure for the CuTC-catalyzed alkylation of allylic chlorides **1**: A dried Schlenk tube was charged with chloride **1** (0.50 mmol), CuTC (4.8 mg, 0.025 mmol), and (S,S)-**3h** (14.3 mg, 0.05 mmol). Dry DME (1 mL) was introduced, the stirred mixture was cooled to -40°C , and MAO (0.5 mL of a 15 wt% solution in toluene; Aldrich) was added. The yellow reaction mixture was stirred for 5 min at -40°C , and then ZnR_2 (for $\text{R}=\text{Et}$: 1 mL of a 1.1 M solution in toluene, 1.1 mmol; for $\text{R}=n\text{Bu}$: 1 mL of a 1 M solution in heptane, 1.0 mmol) was added. Stirring was continued for 45 h at -40°C , then the reaction was quenched by cautious addition of 2 M HCl (2 mL). The aqueous layer was extracted with Et_2O (2×5 mL), then the organic extracts were dried (MgSO_4), and the solvent was evaporated. The products were isolated by flash chromatography using mixtures of Et_2O /hexanes as eluent.

Received: December 22, 2004

Published online: March 10, 2005

Keywords: allylation · asymmetric catalysis · copper · zinc

conceptual purposes only. For lead overviews, see: a) E. Zurek, T. Ziegler, *Prog. Polym. Sci.* **2004**, 29, 107–148; b) P. L. Bryant, C. R. Harwell, A. A. Mrse, E. F. Emery, Z. Gan, T. Caldwell, A. P. Reyes, P. Kuhns, D. W. Hoyt, L. S. Simeral, R. W. Hall, L. G. Butler, *J. Am. Chem. Soc.* **2001**, 123, 12009–12017; c) H. Hanawa, N. Abe, K. Marouka, *Tetrahedron Lett.* **1999**, 40, 5365–5368.

- [9] The preparation of PhZnEt (from ZnPh_2 and ZnEt_2) has been reported by the groups of Fu and others, see: a) M. Fontes, X. Verdaguer, L. Solà, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2004**, 69, 2532–2543; b) J. Rudolph, N. Hermanns, C. Bolm, *J. Org. Chem.* **2004**, 69, 3997–4000; c) P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, 120, 445–446; d) P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, 62, 444–445. We are unaware of any work on the equivalent halide equilibrium.
- [10] a) NMR spectroscopic evidence indicates a value of $k_1/k_{-1} < 0.002$ under unpromoted conditions: D. F. Evans, G. V. Fazakerley, *J. Chem. Soc. A* **1971**, 182–183; b) Very recently, Knochel has demonstrated exchange of ArZnI species: F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem.* **2004**, 116, 1032–1036; *Angew. Chem. Int. Ed.* **2004**, 43, 1017–1021.
- [11] G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, 118, 2748–2749.
- [12] N. Inguibert, P. Coric, H. Poras, H. Meudal, F. Teffot, M.-C. Fournie-Zaluski, B. P. Roques, *J. Med. Chem.* **2002**, 45, 1477–1486.

- [1] a) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem.* **2004**, 116, 2480–2482; *Angew. Chem. Int. Ed.* **2004**, 43, 2426–2428; b) A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, 126, 11130–11131; c) U. Piarulli, P. Daubos, C. Claveric, M. Roux, C. Genari, *Angew. Chem.* **2003**, 115, 244–246; *Angew. Chem. Int. Ed.* **2003**, 42, 234–236; d) W.-J. Shi, L.-X. Wang, Y. Fu, S.-F. Zhou, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2003**, 14, 3867–3872; e) H. Malde, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, 3, 1169–1171; f) F. Dubner, P. Knochel, *Tetrahedron Lett.* **2000**, 41, 9233–9237.
- [2] a) K. E. Murphy, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, 125, 4690–4691; b) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, 126, 10676–10681.
- [3] The addition of $\text{Zn}(\text{CH}_2\text{tBu})_2$ to **1a** (62% yield, 12% ee, 6.8:1 $\text{S}_\text{N}2'/\text{S}_\text{N}2$) has been reported in a patent: P. Knochel, F. Dübner (Avecia Ltd., UK), PCT Int. Appl. WO2000012449, **2000** [*Chem. Abstr.* **2000**, 132, 222063].
- [4] L.-H. Xu, E. P. Kündig, *Helv. Chim. Acta* **1994**, 77, 1480–1484.
- [5] C. Börner, P. J. Goldsmith, S. Woodward, J. Gimeno, S. Gladiali, D. Ramazzotti, *Chem. Commun.* **2000**, 2433–2434.
- [6] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, 107, 1159–1171; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1059–1070.
- [7] a) J. Boersma, J. G. Noltes, *Tetrahedron Lett.* **1966**, 1521–1525; The limited data that exists suggests that under MAO-free conditions $k_1/k_{-1} < 0.01$, see: b) D. F. Evans, I. Wharf, *J. Chem. Soc. A* **1968**, 4, 783–787.
- [8] The structure of MAO is not known (linear, ring, and cage structures have all been proposed). Structure **4** is given for