Asymmetric chemo- and regiospecific addition of organozinc reagents to Baylis–Hillman derived allylic electrophiles

Christoph Börner,[a] Josep Gimeno,[b] Serafino Gladiali,[c] Paul J. Goldsmith,[a] Daniela Ramazzotti[c] and Simon Woodward*[a]

[a] *School of Chemistry, Nottingham University, University Park, Nottingham, UK NG7 2RD. E-mail: simon.woodward@nottingham.ac.uk; Fax: (+44) 115-9513564; Phone: (+44) 115-9513564*
[b] *Departament de Química, Universitat Autònoma de Barcelona, Bellaterra, 08193 Barcelona, Spain*
[c] *Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy*

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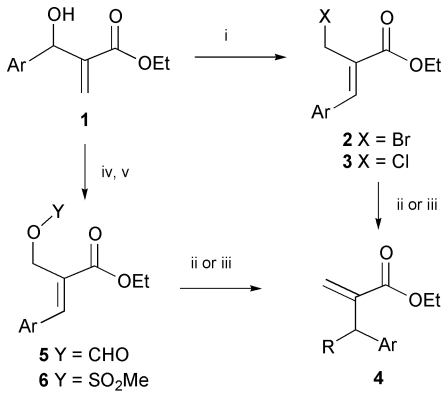
The copper-catalysed S_N2' addition of ZnR_2 to allylic (*Z*)-ArCH=C(CH_2X)(CO_2Et) (X = Br, Cl, OSO_2Me) fashions only ArCH(R)C(=CH_2)(CO_2Et); use of a chiral ligand gives up to 64% ee for this demanding reaction.

The reactions of organometallic nucleophiles, MR, with allylic halide (or pseudohalide) substrates $R^1CH{=}CR^2CH_2X$ often lead to a mixture of S_N2 (attack α to the leaving group X) and S_N2' (attack γ to X) products.[1] This feature causes problems in metal-catalysed asymmetric γ-additions to unsymmetrical allylic electrophiles where the catalyst must control both the regio- and enantioselectivity. Catalysts showing superlative selectivity for both these aspects are rare.[2–6] Pointers in the stoichiometric literature suggested to us that the regiochemical problem might be overcome with substrates where R^2 is an ester function[7] and if an organozinc reagent[8] is used as the terminal organometallic in the catalytic cycle. In particular, we were keen to apply these ideas to enantioselective copper-catalysed S_N2' additions of MR to allylic halides as very few successes have been reported for this otherwise intrinsically useful transformation.[9,10] Aside from controlling the regiochemistry the ester could play two additional roles. Firstly, a more rigorously bound asymmetric transition state might be attained, *via* carbonyl co-ordination. Secondly, the products from such carbonyl containing substrates are present in many compounds of biological interest.

The allylic bromides **2** (Scheme 1) were selected for initial trials with commercial $ZnEt_2$ to demonstrate the viability of this approach. Compounds **2** are attractive as they are available in just two, chromatography-free, steps *via* known Baylis–Hillman chemistry (Scheme 1).[11] Additionally, bromination of **1** proceeds with very high (*Z*)-selectivity[12] to afford solid products which may be crystallised to high chemical and stereochemical purity. Simple mixture of THF solutions of **2** and $ZnEt_2$ in the presence of $[Cu(MeCN)_4]BF_4$[13] (3 mol%) at −20 °C leads to rapid formation of **4** (R = Et) as apparently the



a Ar = Ph; **b** Ar = 4-$C_6H_4NO_2$; **c** Ar = 4-C_6H_4Cl
d Ar = 4-C_6H_4Me; **e** Ar = 1-$C_{10}H_7$

Scheme 1 *Reagents and conditions*: i, conc. HX/H_2SO_4, 16–24 h, rt; ii, ZnR_2, THF, −20 °C, cat. $[Cu(MeCN)_4]BF_4$; iii, $ZnEt_2$, THF, −20 °C, cat. $[Cu(MeCN)_4]BF_4/(S_a)$-**7**; iv, for **5** NEt_3–HCO_2H reflux; v, for **6** treatment of **5** with aq. HCl in MeOH followed by mesylation ($MeSO_2Cl$–NEt_3) of the derived alcohol.

Table 1 Reaction of allylic electrophiles **2**–**6** with organometallics (RM) in the presence of $[Cu(MeCN)_4]BF_4$†

Halide	RM	Cu^I/mol%	Ligand/ mol%	Temp./°C	Time/min	Yield/%[a]	ee/%[b]
2a	$ZnEt_2$	3	None	−20	40	100 (78)	—
2a	$ZnEt_2$	0.5	None	−20	40	100 (73)	—
2b	$ZnEt_2$	3	None	−20	40	100 (63)	—
2c	$ZnEt_2$	3	None	−20	40	100 (80)	—
2d	$ZnEt_2$	3	None	−20	40	86	—
2e	$ZnEt_2$	3	None	−20	40	84	—
2a	$Zn(CH_2TMS)_2$[c]	7	None	0	180	47 (25)	—
2a	$ZnEt_2$	10	**7** 20	−20	20	100 (80)	3 (+)
2a	$ZnEt_2$	10	**7** 20	−40	40	(44)	13 (+)
3a	$ZnEt_2$	10	**7** 20	−20	40	56 (35)	36 (−)
3a	$ZnEt_2$	10	**7** 20	−40	40	(19)	34 (−)
3a	$AlEt_3$	10	**7** 20	0	40	12 (< 5)	8 (−)
3b	$ZnEt_2$	10	**7** 20	−20	40	100 (76)	60 (−)
3b	$ZnEt_2$	10	**7** 20	−40	40	64	64 (−)
3d	$ZnEt_2$	10	**7** 20	−20	40	25 (19)	30 (−)
3e	$ZnEt_2$	10	**7** 20	−20	40	27 (14)	22 (−)
5	$ZnEt_2$	10	**7** 20	−20	20	< 5	—
6	$ZnEt_2$	10	**7** 20	−20	20	100 (90)	2 (+)

[a] Based on NMR conversion, isolated yields in parentheses. [b] Determined by HPLC on a Chiracel OD column, predominant stereoisomer in parentheses. [c] Used in the presence of $MgCl_2$.

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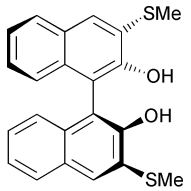
sole product (Scheme 1). Extremely high chemo- and regioselectivity, technical simplicity, and high rate ($\sim$50 TON h^{-1}) characterise these reactions (Table 1).† The reactions can be run at even lower copper loadings, for example, **2a** gives a near quantitative yield of **4a** (R = Et) at 0.5 mol% Cu^{I} (>290 TON h^{-1}). In the absence of Cu^{I} polar co-solvents are necessary to provide high chemical yields[7] (in the absence of any copper, yields of <12% were attained in our control reactions). The new catalytic protocol is superior to use of classical Gilman cuprates. For example, reaction of **2a** with $LiCuMe_2$·LiI in THF affords only a 8:1 $S_N2':S_N2$ mixture. Compounds **4** (R = Et) are the intimate precursors of a number of biologically active molecules showing, for example, inhibition of *angiotensin-converting* and *epithelial neutral endopetidase* enzymes[14] or those showing molluscicidal activity against endoparasite carrying *Biomphalaria glabrata*.[15]

Preliminary approaches to rendering these reactions viable as catalytic asymmetric syntheses are also reported in Table 1.† Relatively high copper and ligand loadings were used to maximise the asymmetric induction obtained as this is noted to be a problematic area.[9,10] Ligand **7** was selected as an initial



(S_a)-**7**

candidate based on its efficacy in asymmetric conjugate addition.[16] Varying the leaving group indicated chloride to be the best leaving group with respect to enantioselectivity, although the chemical yield suffered somewhat in this case. Very high chemical yields were realised with the mesylate **6**, but the product **4a** is essentially racemic, while the formate **5** does not participate in the reaction. Ligand **7** was confirmed as the optimal structure by screening a small library of compounds against a test reaction of **3a** with $ZnEt_2$; none of the other structures lead to very active catalysts. Similarly, changing to a terminal $AlEt_3$ organometallic source is not tolerated.

In conclusion, a new type of efficient catalytic S_N2' chemistry has been developed. The degree of stereocontrol realised in these reactions appears to be due more to electronic than steric factors, however, more experiments are required before the details of the asymmetric transition state become clear. These studies together with applications of the compounds **4** to the synthesis of biologically active compounds are underway in our laboratories.

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Notes and references

† *Representative procedures and compound data.* An argon-protected solution of $[Cu(MeCN)_4]BF_4$ (6.3 mg, 0.02 mmol, 3 mol%) in THF (0.7 cm^3) at −20 °C was treated sequentially with solid **2b** (211 mg, 0.67 mmol) and $ZnEt_2$ (1.0 cm^3 of 1.0 M hexane solution, 1.0 mmol). After 40 min the pale yellow solution was quenched with aqueous HCl (2 M, 3 cm^3), the product was extracted with diethyl ether, and the organic fraction dried ($MgSO_4$). The solvent was removed and the product assayed directly by ^1H NMR spectroscopy. In all cases the spectra were consistent with a >20:1 $S_N2':S_N2$ selectivity.

For asymmetric runs, ligand **7** (38 mg, 0.10 mmol, 20 mol%) and $[Cu(MeCN)_4]BF_4$ (15.7 mg, 0.05 mmol, 10 mol%) in dry THF (1 ml) were stirred at −20 °C in the presence of $ZnEt_2$ (0.10 mmol). Solutions of the allylic chloride **3b** (140.2 mg, 0.52 mmol) in THF (0.55 cm^3) and $ZnEt_2$ (0.77 ml of a 1.0 M hexane solution, 0.77 mmol) were added by syringe pump over 20 min and the reaction stirred for a further 20 min at −20 °C. The reaction was worked up as above. In cases (Table 1) where the reaction was not complete unreacted allylic chloride was removed by flash chromatography or treatment with DABCO.

(−)-Ethyl 2-methylene-3-(4-nitrophenyl)pentanoate **4b** (R = Et) Yield 76% (60% ee); $[\alpha]_{546}^{21}$ −84 (c = 0.33, in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, J = 7.3, $CHCH_2$*Me*), 1.21 (3 H, t, J = 7.1, OCH_2*Me*), 1.79 (1 H, ddq, J = 13.4, 8.8, 7.3, $CHCH_{2\alpha}$Me), 1.78 (1 H, ddq, J = 13.4, 6.3, 7.3, $CHCH_{2\beta}$Me), 3.84 (1 H, dd, J = 8.8, 6.3, *CH*CH_2), 4.11 (2 H, m, OCH_2Me), 5.76 (1 H, s, $=CH_{2\alpha}$), 6.41 (1 H, s, $=CH_{2\beta}$), 7.39 (2 H, d, J = 8.7, C_6H_4), 8.14 (2 H, d, J = 8.7, C_6H_4); δ_C (67.8 MHz, $CDCl_3$) 12.0 ($CHCH_2$*Me*), 13.8 (OCH_2*Me*), 26.9 ($CHCH_2$), 47.8 (CH), 60.6 (OCH_2), 123.3 (Ar-H), 124.5 ($=CH_2$), 128.8 (Ar-H), 142.4 (Ar-*i*), 146.3 (=*C*CO), 150.7 (Ar-*i*), 166.2 (CO); ν_{max}(thin film)/cm^{-1} 2967m, 2936m, 2876 (3 × C-H), 1714s (C=O), 1520s, 1347s (2 × N=O), 1254m, 1152m, 851m; *m/z* (FAB) 264 ([M + H]$^+$, 13%), 221 (14), 207 (16), 147 (38), 77 (13), 73 (100). [Found (HRMS, FAB): [M + H]$^+$, 264.1244. $C_{14}H_{18}NO_4$ requires *M* + *H*, 264.1236].

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