Novel 1,4-Asymmetric Induction in Nucleophilic 1,2-Additions to Chiral γ-Amino Enals

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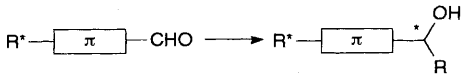
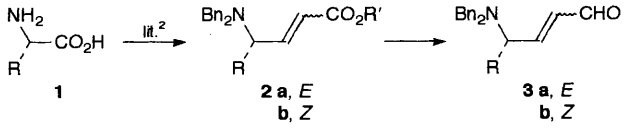
γ-Dibenzylamino enals **3a** with the *E*-configuration derived from amino acids **1** react diastereoselectively with cuprates in an unexpected 1,2-manner, while the analogues **3b** with the *Z*-configuration undergo diastereoselective additions with organolithium reagents.

We are intrigued by the possibility of remote asymmetric induction in nucleophilic addition reactions to prochiral carbonyl functions which are separated from the inducing stereogenic centre by a π-system[1] (Scheme 1). To this end we have prepared the *E*- and *Z*-α,β-unsaturated aldehydes **3a** and **3b**‡ from the corresponding esters **2**[2] which in turn are accessible in enantiomerically pure form from the amino acids **1** (Scheme 2). Whereas Grignard-type and aldol additions to the *Z*-enals **3b** might be expected to show some degree of diastereoslectivity on the basis of proximity, *a priori* predictions in the case of the *E*-analogues **3a** are difficult.

Upon reaction of the *E*-enals **3a** with various alkyllithium and Grignard reagents, essentially stereorandom behaviour was observed (*ca.* 1:1 mixtures of **4** and **5**; Scheme 3). The same applies to the bulky titanium reagent $MeTi(OPr^i)_3$, which is known to perform well in other stereochemically difficult situations.[3] This means that possible electronic and steric effects are not transmitted through or across the alkene π-system. In striking contrast, the reaction of cuprates R_2CuLi in the presence of Me_3SiCl, hexamethylphosphoric triamide (HMPA) and triethylamine[3] (Method A) led to significant levels of 1,4-asymmetric induction and 1,2-regioselectivity in favour of adducts **4**§ (Table 1). Similar results were obtained by adding the additives to a mixture of the cuprate and the enal at low temperatures (Method B). Both regio- and stereoselectivity are novel. The former is particularly surprising,



Scheme 1



Scheme 2

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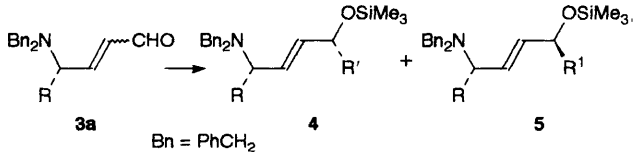
‡ Compounds **2a**[2] were reduced with Bu^i_2AlH–BF_3·OEt_2 at −78 °C for 1 h (70–78%) to the corresponding alcohols, which were oxidized under Swern conditions to the aldehydes **3a** (84–94%). Compounds **2b** were prepared from the corresponding aldehydes using $(CF_3CH_2O)_2P(O)CH_2CO_2Me$–$KN(SiMe_3)_2$–18-crown-6, the *Z*:*E* ratios of the crude products being 80:20 (89%; R = Me), 85:15 (84%; R = $PhCH_2$), and >95:<5 (90%; R = Me_2CHCH_2). Following purification by chromatography they were converted to the enals **3b** by the usual reduction to the corresponding alcohols (58–76%) followed by Swern oxidation (89–91%).

§ The configurational assignment was made, *inter alia*, by desilylation of adduct **4** (R = $PhCH_2$; R′ = Me) and reduction of the double bond and debenzylation using Pd black–H_2, followed by an X-ray structural analysis of the corresponding δ-amino alcohol.

Table 1 Reactions of enals **3a** with cuprates R'_2CuLi

R	R'	Method[a]	1,2-Regioselectivity (%)	**4**:**5**	Yield (%)
Me	Me	B	>98	79:21	83
Me	Bu^n	A	>98	82:18	81
$PhCH_2$	Me	A	>98	80:20	84
$PhCH_2$	Me	B	>98	87:13	81
$PhCH_2$	Me	B[b]	87	92: 8	83
$PhCH_2$	Bu^n	A	>98	90:10	83
Me_2CHCH_2	Me	A	>98	79:21	77
Me_2CHCH_2	Me	B	>98	86:14	77
Me_2CHCH_2	Bu^n	A	>98	84:16	79
Me_2CH	Me	A	>98	80:20	78
Me_2CH	Me	B	>98	89:11	77

[a] Method A: To a stirred solution of R_2CuLi (1.2 mmol) in 5 ml of Et_2O at −78 °C were sequentially added HMPA (1.5 mmol), Et_3N (3.5 mmol), chlorotrimethylsilane (3 mmol) and the enal **3a** (1 mmol) in 25 ml of Et_2O. After 4 h at −78 °C, the mixture was warmed to room temperature and poured onto 100 ml of saturated NH_4Cl and 100 ml of Et_2O. Extractive work-up followed by flash chromatography (SiO_2–light petroleum–ethyl acetate) afforded the products. Method B: To a stirred solution of R_2CuLi (1.2 mmol) in 5 ml of Et_2O at −78 °C was added the enal **3a** (1.0 mmol) in 25 ml of Et_2O. After 4 h at −78 °C the additives HMPA (1.5 mmol), Et_3N (3.5 mmol) and chlorotrimethylsilane (3 mmol) were added. After 4 h at −78 °C, the mixture was warmed to room temperature and worked up in the usual way. [b] In this case a solvent mixture of 5 ml of Et_2O and 25 ml of CH_2Cl_2 was used.



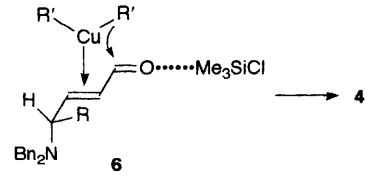
Scheme 3

because the protocol based on R_2CuLi–Me_3SiCl–HMPA–NEt_3 was first used by Normant in cuprate conjugate addition reactions of simple enals.[4] Control experiments show that Me_3SiCl and HMPA are both required for maximum 1,2-regioselectivity, whereas NEt_3 exerts little or no effect except to increase the chemical yields slightly.

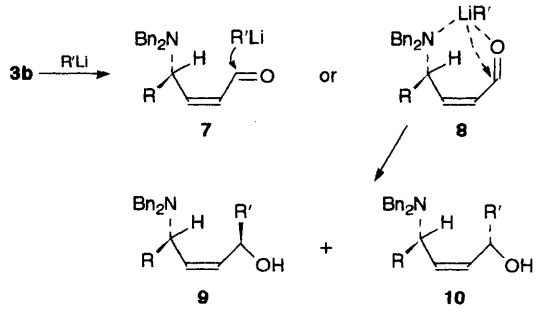
In view of the complexity of the mechanistic problem involved, we restrict any current speculation to the gross features of an admittedly incomplete model. Since the classical 1,2-selective organo-lithium, -magnesium and -titanium reagents (which are known to react *via* a four-centre-type of transition state[5]) show no significant stereoselectivity, the present 1,2-addition reactions of the copper reagents are not likely to proceed by a similar mechanism. Instead, we propose the π-facially selective d,π* complexation **6** (Scheme 4) as the initial step, followed by a 'stereoselective walk' to the terminus of the π-system in the s-*trans* conformation to provide the silylated adducts **7** preferentially.¶ This hypothesis gains some support by the observation that the Me_3SiCl-accelerated conjugate addition of cuprates to the corresponding *E*-esters **2** occurs selectively from the same direction (*Re*-face).[2] π-Complexation as the initial step in conjugate cuprate additions is now generally accepted.[6,7] In certain cases involving chiral alkoxy-substituted carbonyl compounds chelation effects have been postulated.[7] Currently we cannot exclude such a phenomenon in the case of **6**, *i.e.* amine complexation may be occurring. The question as to why the intermediates **6** do not continue along the usual 1,4-reaction path may be answered in part by steric factors. In fact, sterically hindered β-substituted enals react with cuprates under a variety of conditions to form appreciable amounts of 1,2-adducts.[4] In these and other cases of 1,2-additions of copper reagents to enals[8] π-complexation may actually precede Grignard-type addition, as in the present reactions.

Table 2 Reactions of enals **3b** with organolithium reagents R'Li and lithium enolates in ether

R	R'	*T*/°C	*t*/h	**9**:**10**	Yield (%)
Me	Me	−78	7	87:13	79
Me	Me	−100	10	92:8	78
Me	Bu^n	−100	10	88:12	84
Me	CH_2CO_2Me	−100	4	80:20	74
Me	CH_2CO_2Ph	−100	4	95:5	67
Me	CMe_2CO_2Me	−100	4	93:7	68
$PhCH_2$	Me	−78	7	86:14	81
$PhCH_2$	Me	−100	10	92:8	80
$PhCH_2$	Bu^n	−100	10	87:13	80
$PhCH_2$	Ph	−100	10	91:9	84
$PhCH_2$	$CH_2CO_2CH_3$	−78	3	86:14	76
$PhCH_2$	CMe_2CO_2Me	−100	4	89:11	72
Me_2CHCH_2	Me	−100	10	91:9	79
Me_2CHCH_2	Bu^n	−100	10	93:7	82
Me_2CHCH_2	CH_2CO_2Et	−100	4	84:16	71
Me_2CHCH_2	CH_2CO_2Ph	−100	4	91:9	68
Me_2CHCH_2	CMe_2CO_2Me	−100	4	95:5	69



Scheme 4



Scheme 5

The reactions of the aldehydes **3b** with the *Z*-configuration with alkyllithium reagents or lithium enolates provided the adducts **9**** preferentially (Table 2; Scheme 5). In these cases chelation and selective 'intramolecular' delivery of the carbon

¶ The role of HMPA in conjugate cuprate additions to simple enals was not discussed by Normant,[3] and it is not clear why its presence in the present reactions is necessary to ensure 1,2-addition. The mechanistic picture **6** neglects the dimeric nature of many cuprates. HMPA may cause monomer formation.

** The configurational assignment was made by conversion to the deprotected saturated δ-amino alcohols using Pd black–H_2 and comparison with the products obtained previously from the *E*-enals. In the case of the aldol reactions, the adduct obtained by reaction of the Li-enolate of acetic acid methyl ester with **3b** (R = $PhCH_2$) was treated with Pd-black–H_2 in the usual way, providing the corresponding saturated δ-amino alcohol, the relative configuration of which was proven by X-ray structural analysis.

nucleophile to the *Re* side of the aldehyde function (*cf.* **8**) is conceivable. Alternatively, the enal may be conformationally locked (*cf.* **7**) owing to 1,3-allylic strain,[9] selective attack then occurring from the sterically less hindered *Re* side.

The results described here are further examples of the utility of chiral building blocks derived from *N,N*-dibenzyl-protected amino acids.[10]

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References

1 I. Fleming, H. Kühne and K. Takaki, *J. Chem. Soc., Perkin Trans. 1*, 1986, 725.
2 M. T. Reetz and D. Röhrig, *Angew. Chem.*, 1989, **101**, 1732; *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1706.
3 M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Peter, R. Ostarek and S. Maus, *Chem. Ber.*, 1985, **118**, 1421.
4 C. Chuit, J. P. Foulon and J. F. Normant, *Tetrahedron*, 1980, **36**, 2305.
5 E. C. Ashby, *Pure Appl. Chem.*, 1980, **52**, 545; T. Holm, *Acta Chem. Scand, Ser. B*, 1983, **37**, 567; M. T. Reetz and S. Maus, *Tetrahedron*, 1987, **43**, 101.
6 G. Hallnemo, T. Olsson and C. Ullenius, *J. Organomet. Chem.*, 1985, **282**, 133; E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, 1985, **26**, 6019; S. H. Bertz and A. J. Smith, *J. Am. Chem. Soc.*, 1989, **111**, 8276; S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, 1981, **103**, 141.
7 E. J. Corey, F. J. Hannon and N. W. Boaz, *Tetrahedron*, 1989, **45**, 545; see also M. Larchevêque, G. Tamagnan and Y. Petit, *J. Chem. Soc., Chem. Commun.*, 1989, 31; C. Fang, H. Suemune and K. Sakai, *Tetrahedron Lett.*, 1990, **31**, 4751; A. B. Smith III, N. K. Dunlap and G. A. Sulikowski, *Tetrahedron Lett.*, 1988, **29**, 439.
8 G. H. Posner, *An Introduction to Synthesis using Organocopper Reagents*, Wiley-Interscience, New York, 1980; B. H. Lipshutz, *Synthesis*, 1987, 325.
9 R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
10 Review: M. T. Reetz, *Angew. Chem.*, in the press.