

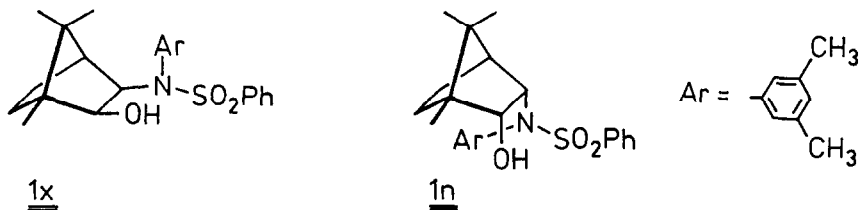
ASYMMETRIC SYNTHESIS OF β -SUBSTITUTED ALCANOIC ACIDS VIA HIGHLY STEREOSELECTIVE
CONJUGATE ADDITIONS OF ORGANOCOPPER COMPOUNDS TO CHIRAL ENOATES¹

Günter Helmchen* and Günter Wegner

Institut für Organische Chemie der Universität Würzburg, Am Hubland, 8700 Würzburg, FRG²

Summary: Conjugate additions of organocopper compounds $\text{RCu}\cdot\text{BF}_3$ to enoates of sulfonamide-shielded alcohols 1x and 1n quite generally proceed with >99 % ee and >90 % yield.

The sulfonamide-shielded alcohols 1x and 1n, introduced by us in 1981³, have proven to be valuable chiral auxiliaries for asymmetric syntheses with esters⁴. According to results obtained with alkylations of propionates of 1x and 1n⁵, the sulfonamide moiety can act as shielding as well as cation coordination site. As a consequence, not only high diastereoface selectivity but in some cases also enhancement of reactivity was found. A striking example is reported in the preceding paper⁶ which records the first successful conjugate additions of preformed trichloromethyl metal compounds to an enoate, the crotonate of 1x. Other crotonates probed, f.i. ethyl crotonate, failed to react. This result has stimulated us to investigate conjugate additions of organocopper compounds to enoates of 1x and 1n. The results achieved are remarkable, even considering that a large number of quite successful asymmetric conjugate additions of C-nucleophiles are described in the literature⁷.



The requisite enoates 2x and 2n (Scheme 1) were readily accessible by Horner-Wittig reaction⁸. Of various types of organocopper compounds the $\text{RCu}\cdot\text{BF}_3$ system developed by Yamamoto and co-workers⁹ was found to be best suited. As precursors of the copper species lithium organyls as well as Grignard compounds could be used, provided that an appropriate solvent (see below) was chosen: ether with the former, THF with the latter. Typical for esters of 1x and 1n, adducts 3 are crystalline and diastereomers are separable by LC so that determinations of diastereoselectivity could be carried out by HPLC. Saponification of 3 (2 N KOH in methanol, reflux) furnished carboxylic acids 4 and the chiral auxiliaries in excellent yield (>90 %).

According to the results listed in table 1 the present method gave exceptionally high degrees of diastereoselectivity. Particularly noteworthy is the fact that excellent results were a-

chieved with the synthetically important but notoriously troublesome methyl copper reagent which possesses a very unfavourable stability/reactivity ratio. This again⁶ demonstrates unusual reactivity towards conjugate additions for α,β -unsaturated esters of 1x and 1n. As was to be expected on the basis of prior experience^{4,5}, esters of 1x and 1n gave products with opposite configurations of their acyl groups (cf. Scheme 1).

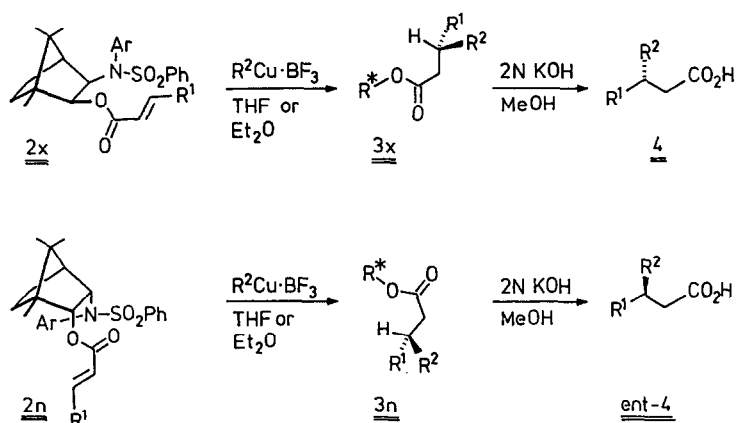
In order to more fully explore properties of the new reagents 2, and to compare organocopper compounds with other metalorganic nucleophiles, additional experiments were carried out (table 2). The following general picture has emerged from these studies:

1. As pointed out above, rate and selectivity of the addition reaction are critically dependent on the solvent. Entries 1-6 of table 2 emphasize the importance of this effect. Solvent effects of this kind are a common feature of organocopper chemistry¹⁰.
2. Experiences with PhLi, PhMgBr, EtLi and EtMgBr indicate that as precursors of the organocopper compounds organolithium reagents are slightly preferable to Grignard reagents (cf. entries 11,12 of table 1, entries 1,4 of table 2).
3. According to results obtained by TLC monitoring preparative runs, the relative reactivity of organocopper compounds in additions to 2 is as follows: Vinyl > Aryl > iPr > Et > Me. Thus, with 4 equiv. of VinylCu·BF₃ (entries 14,15 of table 1) additions were complete at -70 °C within 2 hours, whereas with 10 equiv. of MeCu·BF₃ (entries 5,6 of table 1) at -40 °C 6 hours were required.
4. Comparison of iPrCu and iPrCu·BF₃ (cf. entries 7,8 of table 2) indicates that the Lewis acid BF₃ enhances selectivity but not reactivity.
5. With respect to configurational relationships it is remarkable that PhLi and PhCu·BF₃ yield diastereomeric reaction products (cf. entries 9,10 of table 2), i.e. the sense of asymmetric induction is a function of the metal. This was also found for additions of LiCCl₃ and MgClCCl₃ to 2x (R¹ = CH₃). Presuming applicability of a Prelog type model, these results are rationalized on the basis of syn- and anti-planar reactive enoate conformations for additions of lithium reagents and organocopper species, respectively. Investigations to further substantiate these assumptions are being pursued.



Some of the adducts listed in table 2 yield interesting carboxylic acids upon saponification. Thus, (R)- and (S)-3-methylpentenoic acids (entries 14,15 of table 1) are useful building blocks for natural product syntheses¹¹. Furthermore, the methyl ester and reduction products of 3-ethyl-4-methylpentanoic acid (entries 7,8,11,12 of table 1) have been identified to be pheromones of several ant species¹². Finally, (S)-ar-turmerone can be prepared from (S)-3-p-tolylbutyric acid (entry 18, table 1)¹³.

Scheme 1

Table 1. Conjugate Additions of $R^2Cu \cdot BF_3$ to the Enoates $\underline{2x}$ and $\underline{2n}$ (Scheme 1)[a].

Entry	Enoate	R^1	Precursor of $R^2Cu \cdot BF_3$	Solvent	Diastereoselect. [b] (Conf. Pref. Diast.) [c]	Yield [%] of $\underline{3}$ [d]
1	$\underline{2x}$	Me	EtMgBr	THF	>99 : 1	90
2	$\underline{2n}$	Me	EtMgBr	THF	>99 : 1	84
3	$\underline{2x}$	Me	iPrMgCl	THF	>99 : 1	90
4	$\underline{2n}$	Me	iPrMgCl	THF	98 : 2	97
5	$\underline{2x}$	Et	MeLi	Et ₂ O	99 : 1	86(94)
6	$\underline{2n}$	Et	MeLi	Et ₂ O	>99 : 1	88
7	$\underline{2x}$	Et	iPrMgCl	THF	>99 : 1 (S)	96
8	$\underline{2n}$	Et	iPrMgCl	THF	>99 : 1 (R)	94
9	$\underline{2x}$	iPr	MeLi	Et ₂ O	>99 : 1	92
10	$\underline{2n}$	iPr	MeLi	Et ₂ O	>99 : 1	93
11	$\underline{2x}$	iPr	EtLi	Et ₂ O	99.5 : 0.5 (R)	76(90)
12	$\underline{2x}$	iPr	EtMgBr	THF	98.5 : 1.5 (R)	81(94)
13	$\underline{2n}$	iPr	EtMgBr	THF	>99 : 1 (S)	98
14	$\underline{2x}$	Me	VinylMgBr	THF	>99 : 1 (S)	94
15	$\underline{2n}$	Me	VinylMgBr	THF	>99 : 1 (R)	81
16	$\underline{2x}$	Me	PhLi	Et ₂ O	>99 : 1 (S)	97
17	$\underline{2n}$	Me	PhLi	Et ₂ O	>99 : 1 (R)	94
18	$\underline{2n}$	Me	p-(CH ₃)C ₆ H ₄ Li	Et ₂ O	>99 : 1 (R)	85

[a] Experimental procedure: Suspensions of $R^2Cu \cdot BF_3$ (5 equiv.) in THF or Et₂O were prepared according to Yamamoto (Ref.9). Solutions of esters $\underline{2}$ (0.2 M) were added at -80 °C. After 1 h the temperature was raised to -20 °C and kept at this value until TLC showed complete consumption of $\underline{2}$. [b] Analysis by HPLC: Merck LiChrosorb Si60, 5 μ , 2 or 3 x 20 cm, UV detection (254 nm), hexane/ethyl acetate mixtures of appropriate eluotropicity. Selectivity values are ratios of peak areas. [c] Configurational assignment is based on saponifications which gave carboxylic acids of known absolute configuration. Optical rotations were in good agreement with values reported in the literature (Ref.11-13). [d] All new compounds were characterized by elemental analysis and ¹H NMR spectra. Values in brackets: Yields corrected with respect to recovered $\underline{2}$.

Table 2. Conjugate Additions of Metal Organyls to Crotonates (Scheme 1, R¹=CH₃); Dependence on Reaction Conditions.

Entry	Enoate (R ¹ =CH ₃)	R ² M	Precursor of R ² M	Solvent	Diastereoselect. [a] (Conf.Pref.Diast.) [b]	Yield [%]
1	<u>2n</u>	PhCu·BF ₃	PhLi	Et ₂ O	>99 : 1 (R)	97
2	<u>2n</u>	PhCu·BF ₃	PhLi	THF		[c]
3	<u>2n</u>	PhCu·BF ₃	PhMgBr	Et ₂ O	62 : 38 (R)	82
4	<u>2n</u>	PhCu·BF ₃	PhMgBr	THF	97 : 3 (R)	60
5	<u>2x</u>	EtCu·BF ₃	EtMgBr	Et ₂ O	85 : 15	94
6	<u>2x</u>	EtCu·BF ₃	EtMgBr	THF	>99 : 1	90
7	<u>2x</u>	iPrCu·BF ₃	iPrMgCl	THF	>99 : 1	90
8	<u>2x</u>	iPrCu	iPrMgCl	THF	97 : 3	89
9	<u>2x</u>	PhCu·BF ₃	PhLi	Et ₂ O	>99 : 1 (S)	60
10	<u>2x</u>	PhLi		THF	76 : 24 (R)	72
11	<u>2x</u>	PhMgBr		THF		[c]

[a],[b] Identical to footnotes [b] and [c], respectively, of table 1. [c] Very slow reaction.

Acknowledgements: This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Excellent technical assistance was provided by Miss L. Kemmer.

- This work was presented (G.H.) at "4. Vortragstagung der Arbeitsgemeinschaft Organische Chemie der Gesellschaft Deutscher Chemiker", Bad Nauheim (FRG), October 5, 1984.
- New address: Organisch-chemisches Institut der Universität, Im Neuenheimer Feld 270, D-6900 Heidelberg.
- R.Schmierer, G.Grotemeier, G.Helmchen, A.Selim, *Angew.Chem.* **93**, 209 (1981); *Angew.Chem.Int. Ed.Engl.* **20**, 207 (1981).
- G.Helmchen, R.Schmierer, *Tetrahedron Lett.* **1983**, 1235; G.Helmchen, R.Wierzchowski, *Angew.Chem.* **96**, 59 (1984); *Angew.Chem.Int.Ed.Engl.* **23**, 60 (1984); D.Dorsch, E.Kunz, G.Helmchen, *Tetrahedron Lett.* **1985**, 3319.
- G.Helmchen, A.Selim, D.Dorsch, I.Taufer, *Tetrahedron Lett.* **1983**, 3213.
- G.Wegner, G.Helmchen, *Tetrahedron Lett.* **1985**, preceding paper.
- (a) Early work: J.D.Morrison, H.S.Mosher, *Asymmetric Organic Reactions*, American Chemical Society, Washington D.C. 1976, p. 272; (b) A.I.Meyers, R.K.Smith, C.E.Whitten, *J.Org.Chem.* **44**, 2250 (1979); (c) T.Mukaiyama, N.Iwasawa, *Chem.Lett.* **1981**, 913; (d) K.Koga in E.L. Eliel, S.Otsuka, *Asymmetric Reactions and Processes in Chemistry*, American Chemical Society, Washington D.C. 1982, p. 73; (e) D.Enders, K.Papadopoulos, *Tetrahedron Lett.* **1983**, 4967. (f) J. Mulzer, M.Kappert, G.Huttner, I.Jibril, *Angew.Chem.* **96**, 726 (1984); *Angew.Chem.Int.Ed.Engl.* **23**, 704 (1984); (g) W.Oppolzer, P.Dudfield, T.Stevenson, T.Godel, *Helv.Chim.Acta* **68**, 212 (1985), and lit. cited; (h) G.H.Posner, *Chemica Scripta* **25**, 157 (1985); (i) K.Tomioka, H.Kawasaki, K.Koga, *Tetrahedron Lett.* **1985**, 3027.
- Esterification of 1x or 1n with chloroacetyl chloride (CCl₄, CaH₂, reflux) furnished chloroacetates which were reacted with P(OEt)₃ (170 °C) to give phosphonates in ca. 70 % overall yield. Standard Horner-Wittig reactions with aldehydes yielded (E)-enoates (typical E/Z ratio 97:3) which were purified by standard techniques.
- Y.Yamamoto, S.Yamamoto, H.Yatagai, Y.Ishihara, K.Maruyama, *J.Org.Chem.* **47**, 119 (1982).
- G.H.Posner, *An Introduction to Synthesis Using Organocopper Reagents*, John Wiley, New York 1980.
- K.Mori, T.Umemura, *Tetrahedron Lett.* **1982**, 3391, and lit. cited.
- W.Francke, *Chemiedozententagung 1984 (Konstanz)*, Abstracts p. 48; T.Kaichi, K.Mori, *Nippon Kagaku Kaishi* **1981**, 635; *Chem.Abstr.* **95**, 150895 (1981).
- A.I.Meyers, R.K.Smith, *Tetrahedron Lett.* **1979**, 2749.

(Received in Germany 12 September 1985)