ChemComm
www.rsc.org/chemcomm

Facile protocol for the highly regioselective and stereodivergent synthesis of substituted bishomoallylic alcohols from esters

Martin Oestreich* and Fernando Sempere-Culler
Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität, Albertstrasse 21, D-79104 Freiburg im Breisgau, Germany. E-mail: martin.oestreich@orgmail.chemie.uni-freiburg.de; Fax: +49(0)761/203-6100

Received (in Cambridge, UK) 3rd December 2003, Accepted 26th January 2004
First published as an Advance Article on the web 13th February 2004

Regio- and diastereoselective preparation of bishomoallylic alcohols was realized by a facile four-step protocol including α,α′-selective zinc-mediated bispropargylation of unactivated esters and stereoselective reduction of the resulting bishomopropargylic alcohols.

The α-regioselective formation of homoallylic alcohols from carbonyl compounds and γ-monosubstituted allyl metals has remained a major challenge in organic synthesis.[1] In addition, controlling the double bond geometry within such a transformation is oftentimes as intricate as the problematic α/γ-selectivity. The sole method of some generality is the use of stereogenic allylic barium reagents which transfer the allyl group onto carbonyl compounds with excellent regioselectivity as well as diastereospecificity.[2] Additionally, high regioselectivities are also achieved using acylsilanes yet being intrinsically restricted to monoallylations.[3]

Within the scope of a total synthesis project,[4] we required a reliable methodology for the selective preparation of several bishomoallylic alcohols starting from simple esters (**1** → **2**, Scheme 1). Unfortunately, it appeared extremely delicate to control both regio- and diastereoselectivity in the direct bisallylation of esters **1** using allylic metal (zinc) reagents.

Interestingly, allylic zinc reagents[5] exhibit a markedly anomalous behaviour since their monoaddition to carbonyl compounds is a *reversible* process.[6]

In our hands, initial bisallylation[7] of **1** with **4** gave a mixture of α- and γ-isomers which were thermally isomerized providing the α,α′-adducts **2** exclusively. However, **2** was invariably formed in *E*,*Z* ratios which precluded further synthetic transformations.[8]

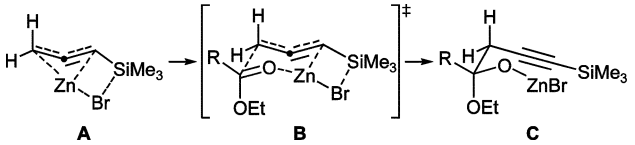
These investigations led us to consider an alternative approach to the selective preparation of alcohols **2**. We envisaged a strategy in which the issues of regio- (**1** → **3**) and diastereoselectivity (**3** → **2**) are divided into two separate synthetic steps.

In principle, propargylation of carbonyl compounds is generally afflicted with the same regiochemical problems (alkyne *vs.* allene formation) as allylation.[1] However, if the γ-substituent R′ of the propargylic zinc reagent **5** is a trimethylsilyl group (**5a**), propargylation exhibits surprisingly high α-selectivity.[9,10]

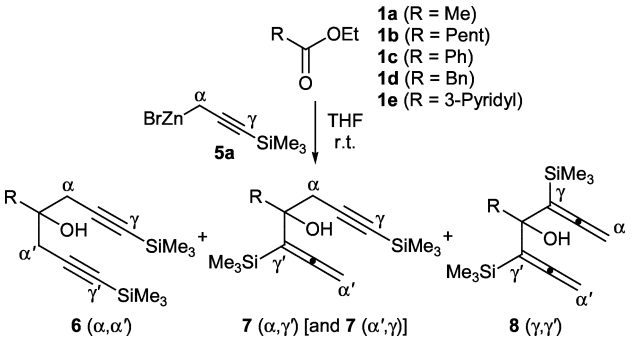
Recently, this 'directing' effect of the trimethylsilyl group has been rediscovered and mechanistically rationalized for the indium-mediated *mono*propargylation.[11] Analogously, the mechanism of the zinc-mediated *bis*propargylation might also involve coordination of the silyl group by bromide which in turn is coordinated by zinc (**A**, Scheme 2). Transfer of the propargylic moiety onto the carbonyl carbon atom of the ester might proceed through the six-membered transition state **B** providing the α-adduct **C** (Scheme 2). After collapse of the tetrahedral intermediate **C**, this process is reiterated once.

Preparation of propargylic zinc reagent **5a** is accomplished on a large scale (50 mmol) by insertion of activated zinc dust[12] into the carbon–bromine bond of the corresponding 3-bromo-1-trimethylsilyl-1-propyne.[13] We were pleased to find that **5a** smoothly reacts with esters **1** without any further activation under very mild conditions (Scheme 3).† The desired bishomopropargylic alcohols **6** were isolated in excellent α,α′-regioselectivities and excellent yields except for **1c** (Table 1, Entries 1–5). Even easily enolizable substrate **1d** (Table 1, Entry 4) and ethyl nicotinate (**1e**) (Table 1, Entry 5) performed well.

Minor quantities of the undesired regioisomer **7** were removed by flash chromatography on silica providing regioisomerically pure **6** (Scheme 3, Table 1).



Scheme 2 Plausible mechanistic rationale for the α-directing effect of the trimethylsilyl group: first step of the bispropargylation of esters.

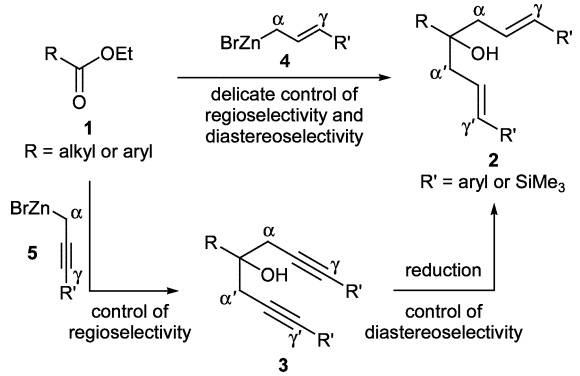


Scheme 3 Bispropargylation of versatile esters **1**.

Table 1 Yields and regioselectivities for bishomopropargylic alcohols **6**

				Regioselectivity[a]			
Entry	Ester	R	Product	α,α′ (**6**)	α,γ′/ α′,γ (**7**)	γ,γ′ (**8**)	Yield for **6** (%)[b]
1	**1a**	Me	**6a**	> 98	1	< 1	94
2	**1b**	Pent	**6b**	> 98	1	< 1	96
3	**1c**	Ph	**6c**	> 98	1	< 1	56
4	**1d**	Bn	**6d**	> 97	2	< 1	72
5	**1e**	3-Pyridyl	**6e**	> 98	1	< 1	85

[a] Determined from the ^{1}H NMR spectra of the crude products. [b] Isolated yield of analytically pure product **6** after flash chromatography.



Scheme 1 Strategies for the regio- and diastereoselective synthesis of bishomoallylic alcohols employing allylic or propargylic zinc reagents.

DOI: 10.1039/b315758j

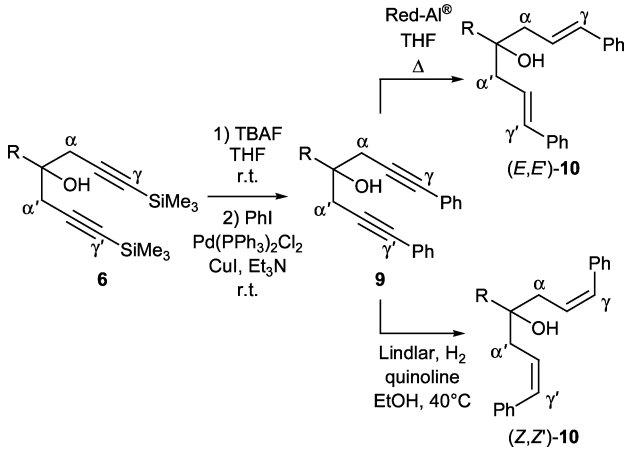
Although the procedure is initially limited to the trimethylsilyl group as the terminal substituent, it allows for further functional group manipulation in this position. The terminal alkynes were liberated by treatment of **6** with substoichiometric amounts of TBAF (0.15 equivalents per alkyne). Subsequent arylation was accomplished by Sonogashira coupling[14] without protection of the tertiary alcohol (**6** → **9**, Scheme 4).[15] The modified bishomopropargylic alcohols **9** were isolated regioisomerically pure in good overall yields (Table 2, Entries 1/2 and 3/4).

In the second step of our strategy, we intended to control the configuration of both double bonds in the bishomoallylic alcohols (**3** → **2**, Scheme 1). Simple reduction of diynes **9b** and **9d** with Red-Al® (7.0 equiv.) at elevated temperature gave the corresponding (*E*,*E*′)-dienes **10** in good yields and diastereoselectivities (Scheme 4). The reasonable overall diastereoselectivity of *E*/*Z* = 96 : 4 is slightly diminished due to the presence of two reducible branches (Table 2, Entries 1 and 3). In order to demonstrate the potential stereodivergency of our approach, we also performed *Z*-selective reductions and subjected **9b** and **9d** to Lindlar conditions (Scheme 4). Overreduction was fairly problematic but, after some optimization, (*Z*,*Z*′)-**10** were isolated in good yields and excellent overall diastereoselectivities of *E*/*Z* = 1 : 99 (Table 2, Entries 2 and 4).

In summary, we have elaborated a preparatively straightforward and scalable four-step protocol for the regio- and diastereoselective synthesis of bishomoallylic alcohols **10**. Within this reaction sequence, the α,α′-selective bispropargylation of esters using zinc reagent **5a** plays the decisive role.

Application of this methodology in total synthesis as well as the use of bishomoallylic alcohols in desymmetrization reactions are currently being investigated in our laboratories.[4]

The research was supported by the Fonds der Chemischen Industrie and the Wissenschaftliche Gesellschaft in Freiburg im Breisgau. M. O. is indebted to the Deutsche Forschungsgemeinschaft for an Emmy Noether fellowship (2001–2005). The authors thank Ilona Hauser and Engelbert Redel for skilful technical assistance, Sebastian Rendler for orientating experiments, and Professor Reinhard Brückner for his continuous support.



Scheme 4 Terminal modification of bishomopropargylic alcohols **6** and diastereoselective formation of bishomoallylic alcohols **10**.

Table 2 Yields for desilylation/Sonogashira coupling sequence (**6** → **9**) and for reduction (**9** → **10**), respectively, and diastereoselectivities for bishomoallylic alcohols **10**

Entry	Alkyne	R	Yield for **9** (%)[b]	Diastereoselectivity[a] *E*,*E*′	*E*,*Z*′/*E*′,*Z*	*Z*,*Z*′	Yield for **10** (%)[b]
1	**6b**	Pent	72	93	6	1	65
2	**6b**	Pent	(2 steps)	0	2	98	75
3	**6d**	Bn	61	93	6	1	65
4	**6d**	Bn	(2 steps)	0	2	98	80

[a] Ratio of diastereoisomers was determined from the ^{1}H NMR spectra of the crude products by integration. [b] Isolated yield of analytically pure product **9** or **10** after flash chromatography.

Notes and references

† *Representative experimental procedure*: A flask equipped with an argon inlet and a reflux condenser was charged with zinc dust (2.27 g, 34.7 mmol, 6.00 equiv.) and flame-dried until sublimation of zinc occurred. The thermally activated zinc was suspended in dry THF (45 mL) and subsequently treated with 1,2-dibromoethane (693 mg, 3.69 mmol, three cycles) followed by refluxing and Me_3SiCl (149 mg, 1.37 mmol, three cycles) without external heating. After cooling to ambient temperature, 3-bromo-1-trimethylsilyl-1-propyne[13] (3.31 g, 17.3 mmol, 3.00 equiv.) was carefully added dropwise *via* syringe in order to maintain a gentle reflux. Upon complete addition, the reaction mixture was maintained at room temperature for 12 h providing the propargylic zinc reagent **5a** in almost quantitative yield. A solution of ester **1a** (R = Me) (509 mg, 5.78 mmol) and dry THF (5 mL) was added *via* syringe in one portion. After 12 h at room temperature, saturated aqueous NH_4Cl (50 mL) was added, the organic phase was separated and the aqueous phase was extracted with *t*-butyl methyl ether (TBME) (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The yellow residue was purified by flash chromatography on silica gel (cyclohexane : TBME = 30 : 1) furnishing **6a** (1.05 g, 94%) as a white solid. R_f = 0.27 (CH : TBME = 10 : 1). Mp 54–55 °C (CH). IR ($CDCl_3$): 3016, 2401, 1521, 1214, 929 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 18H), 1.35 (s, 3H), 2.19 (s, 1H), 2.49 (d, *J* = 16.8 Hz, 1H), 2.52 (d, *J* = 16.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.0, 25.8, 33.0, 71.0, 88.2, 102.8 ppm. LRMS (CI): *m*/*z* = 267 [(M + H)$^+$]. Anal. Calcd for $C_{14}H_{26}OSi_2$ (266.53): C, 63.09; H, 9.83; Found: C, 63.22; H, 9.82%.

1 A. Yanagisawa and H. Yamamoto, in *Advances in Carbanion Chemistry*, Ed. V. Snieckus, JAI Press, London, 1996, Vol. 2, pp. 87–110 and references cited therein.
2 A. Yanagisawa, S. Habaue and H. Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 8955–8956.
3 A. Yanagisawa, S. Habaue and H. Yamamoto, *J. Org. Chem.*, 1989, **54**, 5198–5200.
4 M. Oestreich and F. Sempere-Culler, submitted for publication.
5 Z. Zha, Z. Xie, C. Zhou, M. Chang and Z. Wang, *New J. Chem.*, 2003, **27**, 1297–1300 and references cited therein.
6 C. Bouchoule and P. Miginiac, *Bull. Soc. Chim. Fr.*, 1968, 4675–4676. For a synthetic application of this phenomenon, see: P. Jones and P. Knochel, *J. Org. Chem.*, 1999, **64**, 186–195.
7 For zinc-promoted bisallylation of acid chlorides, see: Y. Ishino, M. Mihara and M. Kageyama, *Tetrahedron Lett.*, 2002, **43**, 6601–6604.
8 Thermal isomerization of **2** (R′ = Ph) as a mixture of all regioisomers (α,α′/α,γ′/α′,γ/γ,γ′) strongly favored the α,α′-adducts yet with mediocre diastereoselectivity (*E*,*E*′/*E*,*Z*′/*E*′,*Z*/*Z*,*Z*′) and in deteriorated yields. For an extensive study disregarding diastereoselectivity, see: F. Barbot, J. Laduranty, C. H. Chan and P. Miginiac, *Bull. Soc. Chim. Fr.*, 1989, 864–871.
9 For references reporting the observation of this effect, see: (*a*) D. Mesnard and P. Miginiac, *J. Organomet. Chem.*, 1990, **397**, 127–137; (*b*) D. Mesnard and P. Miginiac, *J. Organomet. Chem.*, 1990, **397**, 139–146.
10 A substantial decrease of the regioselectivity was observed when R′ = Me_3Si (**5a**) was replaced by H (**5b**) and Ph (**5c**), respectively.
11 M.-J. Ming and T.-P. Loh, *J. Am. Chem. Soc.*, 2003, **125**, 13042–13043.
12 P. Knochel, M. J. Rozema and C. E. Tucker, in *A Practical Approach – Organocopper Reagents*, Ed. R. J. K. Taylor, Oxford University Press, Oxford, 1993, pp. 85–104.
13 R. B. Miller, *Synth. Commun.*, 1972, **2**, 267–272.
14 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467–4470.
15 Since alkylation or carboxylation of the alkyne would demand protection of the tertiary alcohol functionality, we have exemplarily chosen an arylation protocol which tolerates the hydroxyl group.