

Preliminary communication

Stereoselective conjugate addition of TMSI-activated butylcopper to 1-(*R*)-endo-(1-naphthyl)bornyl crotonate

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Abstract

Conjugate addition of butylcopper/iodotrimethylsilane to naphthylbornyl crotonate (**1**) at -60°C gives 1-[1-(*R*)-endo-(1-naphthyl)]bornyl [(*S*)-3-methyl]-heptanoate (**2**) in 93% yield and 98% diastereomeric excess. The addition of TMSI-activated butylcopper is faster at -60°C than that of lithium dibutylcuprate (LiBu_2Cu).

Monoorganocopper compounds (RCu) activated with iodotrimethylsilane (TMSI) add rapidly under mild conditions to α,β -unsaturated carbonyl compounds to give trimethylsilyl enol ethers (or ketene acetals) [1,2]. The TMSI-promoted additions of monoorganocoppers are much faster than the TMSCl - or TMSBr -activated reactions [1,2] and can be conducted at low temperature and without additives like HMPA or TMEDA (cf. refs. 3,4).

We have now tested butylcopper activated with TMSI in conjugate addition to the chiral ester **1** at -60°C , and found high diastereoselectivity. Ester **1**, first prepared by Olsson and Stern [5–7] as a substrate for asymmetric synthesis, adopts an *s-cis* conformation in the crystalline state and reacts in this conformation in 1,3-dipolar cycloadditions [6,7]. The ester has given interesting diastereoselectivity in the reaction with lithium dibutylcuprate [5].

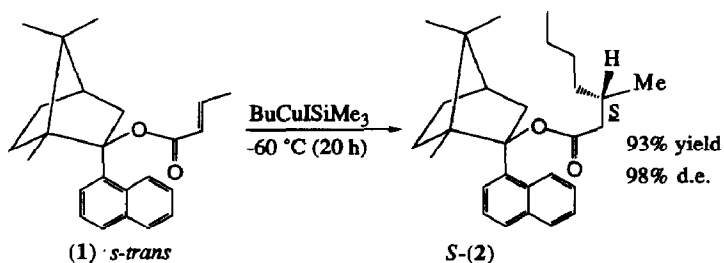


Table 1

Representative conjugate additions to ester 1; substrate (1) was added at -78°C and gave the crystalline ester 2 after work-up

Entry	Reagents	% yield (d.e.) of 2	e.e. of 3 [11*]
A ^a	BuCu : ISiMe ₃ (3.3 mol equiv.)	93 (98%) ^d	98%
B ^a	LiBu ₂ Cu (5.0 mol equiv.)	66 ^c (60%)	—
C ^b	BuCu : ISiMe ₃ (3.3 mol equiv.)	87 (83%)	83%

^a Kept at -78°C for 50 min, then maintained at -60°C for 20 h and quenched. ^b Kept at -78°C for 10 min, temperature then raised to 0°C during ca. 5 min. and then quenched. ^c 25% recovered starting material. ^d M.p. $110-115^{\circ}\text{C}$.

The α,β -unsaturated ester 1 [8*] was added to a mixture of butylcopper and iodotrimethylsilane (1:1) in diethyl ether, containing lithium iodide from the preparation of butylcopper, at -78°C . The temperature was maintained at -60°C for 20 h. The excess of iodotrimethylsilane and remaining organometallics were destroyed at this temperature with dry pyridine followed by moist ether (see experimental section) before work-up to prevent reactions during the warm-up.

We separated the conjugate adducts from side products by chromatography and obtained ester 2 as a crystalline product, in 93% yield (Table 1, entry A). ¹H-NMR spectra before and after chromatography showed that ester 2 was almost diastereomerically pure (98% d.e.); the minor diastereomer was identified at high concentration (Fig. 1). Reduction with lithium aluminium hydride and careful chromatographic separation of the products gave 96% yield of (*S*)-(-)-3-methylheptanol (3), with known absolute configuration [11*,12].

The formation of the *S*-diastereomer indicates that the incoming TMSI-activated butylcopper has added to the *re*-face of an *s-trans* conformer of ester 1 rather than to the *s-cis* conformer expected from the X-ray structure. The *si*-face of the *s-trans*

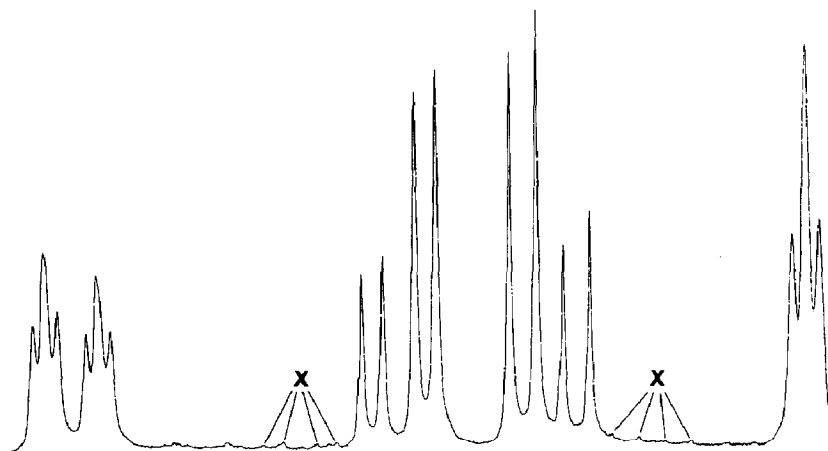
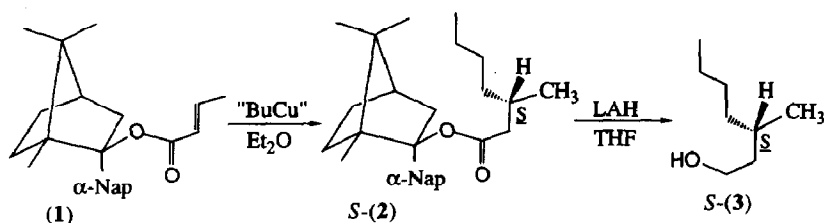


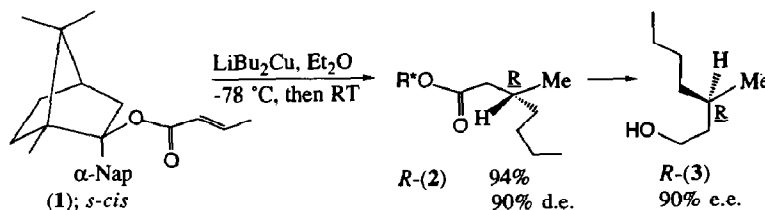
Fig. 1. ¹H-NMR spectrum (400 MHz) in the α -proton region of crude ester (*S*)-2. Signals from the minor diastereomer, (*R*)-2, are indicated with X.

* Reference number with asterisk indicates a note in the list of references.



conformer is efficiently shielded by the naphthyl group. Reaction at higher temperature (entry C) gave lower selectivity (83% d.e.).

The conjugate addition of lithium dibutylcuprate to ester 1 at -60°C was slower and was less selective (60% d.e.) than previously reported [5]. However, when the reaction mixture was warmed rapidly towards room temperature, the addition was fast and gave mainly the other diastereomer, (R)-2, with 90% d.e. according to the $^1\text{H-NMR}$ spectrum [13*], which is identical to the spectrum previously reported for the alleged (S)-2 diastereomer [5]. This surprising result implies an attack on the *si*-face of the *s-cis* conformer at the higher temperature.



The balance between reactions of an *s-cis* or an *s-trans* conformer is probably governed by temperature dependent equilibria involving π -complexation with or without lithium iodide. Lithium iodide is important in determining the product composition from reactions between methylcopper, TMSI and methyl cinnamate; absence of lithium iodide strongly favours formation of the *Z*-silyl ketene acetal [14].

It has been demonstrated that lithium iodide is required for the conjugate addition [15] of methylcopper and also that butylcopper is rather unreactive even in the presence of lithium iodide [16]. We believe that the iodine in TMSI acts as a soft ligand for copper and increases the reactivity of butylcopper towards α,β -unsaturated carbonyl compounds [1]. The nature of monoorganocopper-iodosilane combination is still not clear. We indicate it provisionally as $\text{BuCu}:\text{ISiMe}_3$.

We conclude that the monoorganocopper-iodosilane combination is quite useful, and promising also for asymmetric synthesis since it gives better asymmetric induction and a more rapid reaction than cuprates at low temperature. The naphthylbornyl group [7] also provides a very efficient auxiliary [18] in the reactions of the organocopper-iodotrimethylsilane reagent.

Experimental

Typical procedure: To a light yellow-brown butylcopper slurry (1.67 mmol) in dry ether (10 mL) under argon, prepared from commercial butyllithium (1.67 mmol)

and copper(I) iodide (1.8 mmol), colorless iodotrimethylsilane [17*] (1.67 mmol) was added dropwise at -60°C and the mixture stirred for 5 min. Then, at -78°C , ester 1 (0.5 mmol) in dry ether (10 mL) was added dropwise and the mixture stirred for 50 min. The temperature was raised to -60°C and stirring was continued for 20 h. Dry pyridine: ether (1:9, 10 mL) was added and the mixture stirred for 1 h. Ether, saturated with aqueous $\text{NH}_4\text{Cl}/\text{NH}_3$ (30 mL) was added and the mixture stirred for 4 h at -60°C . The temperature was raised to $+20^{\circ}\text{C}$ and aqueous $\text{NH}_4\text{Cl}-\text{NH}_3$ buffer (20 mL) was added and stirring continued until the aqueous phase turned deep-blue. The solids were filtered off on Celite[®] and washed with several portions of ether. The aqueous layer was extracted with ether (3×30 mL). The combined ether extracts were washed with dilute aqueous copper(II) sulfate, dried over sodium sulfate and the solvent was evaporated. Diastomeric excess (98% d.e.) was determined from the $^1\text{H-NMR}$ spectrum. The crude product was purified with flash chromatography and gave 189 mg (93%) of ester(s) 2 as a colorless solid (m.p. $110-115^{\circ}\text{C}$). The diastomeric excess was identical to that before chromatography confirming that chromatography did not change the optical purity.

Ester 2 was then refluxed (2 h) with lithium aluminium hydride (2 mol equiv.) in THF. Careful separation on a silica gel column gave (*S*)-(-)-3-methylheptanol (3) [11*] (96%) in 98% e.e. and naphthylborneol (94%).

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