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HIGHLY DIASTEREOSELECTIVE ADDITIONS OF ORGANOCOPPER REAGENTS TO 2-*EXO*-BORNYL CROTONATES[1]

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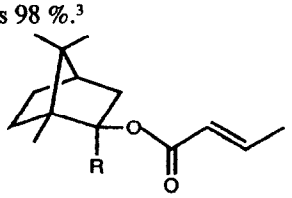
Abstract. *Iodotrimethylsilane-activated butylcopper adds to the chiral bornyl crotonates* ***1-3*** *in high yields and with good to excellent diastereoselectivities. In the present investigation, these reactions are compared with additions of lithium butylcuprates of various composition to the same esters. The cuprate additions show a remarkable dependence on the exact composition of the reagent, with the diastereoselectivity on addition to 1-naphthyl substituted ester* ***1*** *ranging from 57 % d.e. of the (S)-product using the reagent "$LiBu_3Cu_2$" to 90 % d.e. of the (R)-product using "Li_2Bu_3Cu". Diastereoselectivities of up to 98% can be obtained using BuCu•TMSI.*

INTRODUCTION

Asymmetric conjugate additions with organocopper reagents have long been a goal for several groups.[2] Chiral ester auxiliaries in substrates have been used where bulkiness or chelation could provide sufficient diastereofacial selectivity.

This paper focuses on asymmetric conjugate additions of two different organocopper reagents to substituted bornyl crotonates: butylcopper activated with iodotrimethylsilane (BuCu•TMSI) and lithium butylcuprates ($Li_mBu_{m+n}Cu_n$). Comparative experiments using the copper reagents in conjugate additions to *exo*-bornyl crotonates substituted in the 2-position with 1-naphthyl, phenyl, or methyl groups (**1-3**), respectively, reveal that both reagents give excellent diastereoselectivities and that one can control the stereochemical outcome of the reaction by selecting the appropriate reagent. Depending on the composition of the lithium cuprates, products of opposite configuration at C3 of the side chain are obtained when the reagent is added to the ester **1**. The addition of lithium cuprates to crotonate **2** also shows a composition-dependence where a preference of 4:1 (60 % d.e.) for one diastereomer can be obtained with the reagent "Li_2Bu_3Cu" while almost no selectivity is obtained when a reagent with excess CuI is used. Addition of BuCu•TMSI to naphthylbornyl crotonate **1** at low temperature gives a diastereomeric excess of as much as 98 %.[3]



1 R = 1-Naphthyl
2 R = Phenyl
3 R = Methyl

The esters **1** and **2** give good results in 1,3-dipolar cycloadditions of nitrile oxides to yield enantiomerically pure isoxazolines after separation of the initially produced diastereomers and cleavage of the ester bond.[4] Additions of nitrones to the corresponding acrylates also give excellent diastereoselectivities.[5] The absolute configurations of the cycloadducts, as determined by X-ray analysis and optical rotations, are in accordance with the esters reacting in an *s-cis* conformation with the *si*-face of the double bond shielded by the bornyl substituent.[4] Furthermore, X-ray analysis of bornyl crotonate **1** clearly shows that the ester moiety adopts an *s-cis* conformation in the crystalline state (Fig. 1a).[5] Molecular mechanics calculations show that the lowest-energy *s-cis* conformation (Fig. 1b) is only a few kJ/mol higher in energy than the corresponding *s-trans* conformer.[4]

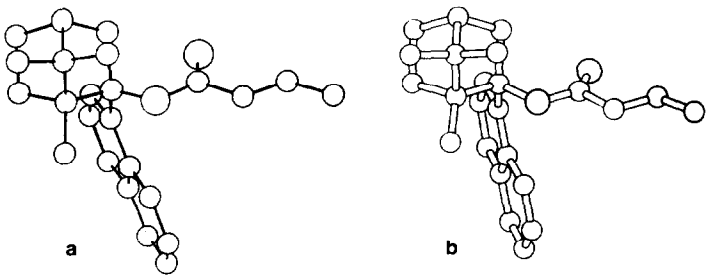
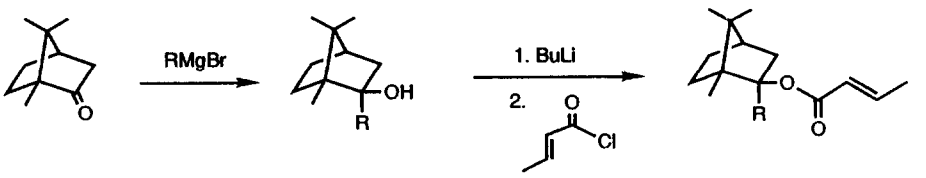


Figure 1. *(a) Lowest-energy* s-cis *conformation of ester* ***1*** *as determined by molecular mechanics. (b) X-Ray structure of 1-naphthyl-substituted bornyl crotonate* ***1****.*

We rationalized the early results for cuprate additions to esters **1-3** by suggesting that the cuprates mainly add to the lowest-energy *s-trans* conformation of the esters.[6] As the diastereoselectivities of the cuprate additions were excellent and a new method for adding monoorganocopper reagents directly to α,β-unsaturated carbonyl compounds merely by the addition of iodotrimethylsilane has been developed by some of us,[7] we were eager to investigate TMSI-activated organocopper additions to the substituted bornyl esters. We were also interested in comparing *s-cis versus s-trans* modes of addition of monoorganocopper compounds[8] by comparing the absolute configurations of the products from these reactions. However, we were confused when we found that the ^{1}H-NMR spectrum obtained on addition of BuCu•TMSI to naphthyl bornyl crotonate **1** showed the opposite diastereomer to be the major product as compared to the major product in the published spectrum for $LiBu_2Cu$ addition to the same ester. However, the sign of the optical rotation of the 3-methylheptanol **4**, obtained after reduction of the product, was the same as that reported for the cuprate adduct! This prompted us to reinvestigate the cuprate additions carefully and we found a remarkable dependence of the exact composition of the reagent for the reactions of lithium butylcuprates with esters **1** and **2** (cf. Tables 1 and 2).

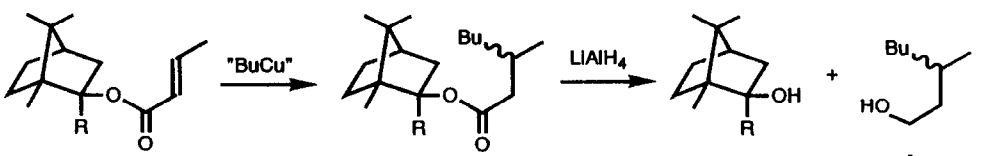
RESULTS AND DISCUSSION

The chiral esters used in this investigation are readily prepared in two steps from (+)-camphor. The appropriate borneol is first prepared by a Grignard reaction. Esterification with butyllithium and crotonyl chloride in THF yields the desired bornyl ester as described by Kaiser and Woodruff[9] (Scheme 1).



Scheme 1. Preparation of substituted bornyl crotonates.

In the reaction of butylcopper/iodotrimethylsilane or lithium butylcuprates with any of the substituted bornyl crotonates **1-3**, two possible diastereomers with the *(R)*- or *(S)*-configuration on C3 of the side chain can be formed. Reduction of the addition products with lithium aluminum hydride gives *(R)*- or *(S)*-3-methylheptanol **4**, along with recoverable borneol. The reaction sequence is shown in Scheme 2.



5 R = 1-Naphthyl
6 R = Phenyl
7 R = Methyl

Scheme 2. Addition of organocopper compounds to substituted bornyl crotonates followed by reduction of the addition products 5-7 to yield the initial chiral auxiliary and 3-methylheptanol 4.

The 1-naphthyl-substituted crotonate **1**, in which rotation of the crotonyl moiety is prevented by the large naphthyl group, gave the best results in nitrile oxide[4] and nitrone[5] additions as well as in the previously reported cuprate additions.[6] The iodotrimethylsilane-activated monoorganocopper reagent also gave the highest stereoselectivities in the reaction with ester **1**[3], and the results for lithium butylcuprates and BuCu•TMSI additions are summarized in Table 1.

Table 1. *Addition of butylcopper/TMSI and lithium butylcuprates to naphthylbornyl crotonate* ***1***.

Entry	Copper reagent[a]	Reaction temp. (time)	Yield **5** (%)[b]	d.e. (%)[c]	configuration[d]
1	$BuCu{:}ISiMe_3$	-60 °C(20 h)	93	98	S[f]
2	$BuCu{:}ISiMe_3$	3 °C(10 min)	87	83	S
3	$LiBu_3Cu_2$	-60 °C(20 h)	33	57	S
4	$BuCu{:}ClSiMe_3$	-60 °C(20 h)	0		
5	$BuCu{:}ISiMe_3$(-LiI)	-60 °C(20 h)	0[g]		
6	$BuCu{:}ISiMe_3$(-LiI)	0 °C(10 min)	45	70	S
7	$LiBu_2Cu$[e]	-60 °C(20 h)	>95	84	R
8	$LiBu_2Cu$[e]	-60 °C(20 h)	94	50	R
9	$LiBu_2Cu$[e]	20 °C(10 min)	>95	18	S
10	$LiBu_2Cu$[e]	-30 °C(2 h)	>95	43	S
11	$LiBu_2Cu$[e]	-30 °C(1 h)	>95	54	S
12	$Li_{1.5}Bu_{2.5}Cu$	-40 °C(<1 h)	>95	85	R
13	$Li_{1.75}Bu_{2.75}Cu$	-40 °C(<1 h)	>95	83	R
14	Li_2Bu_3Cu	-60 °C(1 h)	>95	86	R
15	BuLi + cat. CuI	-78 °C(2 h)	54	67	R
16	BuLi	-78 °C(2 h)	88	0	

[a]Formal reagent composition, not actual verified species. [b]Isolated yields. [c]Obtained from the ^{1}H-NMR spectra before chromatographic purification. [d]At C3 of the side chain, major product, determined from optical rotation after $LiAlH_4$ reduction of **5**. [e]Reported in ref. 6: $LiBu_2Cu$ addition to ester **1** at -78 °C; yield 74 %; d.e. 95 %; configuration *S* (*R* according to the major diastereomer in the published spectrum). At -25 °C; yield 75 %; d.e. 87 %. [f]White solid; mp 110-115 °C. [g]87 % recovered starting material.

In table 1, entry 1, ester **1** was added to TMSI-activated butylcopper (3.3 mol eq.) at -78 °C and the mixture stirred for 20 hours at -60 °C to give addition product **5** with 98 % d.e. as a crystalline material (mp. 110-115 °C). Reduction of this ester gave a 96 % yield of *(S)*-(−)-3-methylheptanol with an optical purity of 98 % e.e. A rapid rise of the reaction temperature to +3 °C (Table 1, entry 2) led to a decrease in stereoselectivity, as expected. The reactions of naphthylbornyl ester **1** with lithium dibutylcuprate at -60 °C were at first very difficult to reproduce and the results were inconsistent. The formation of the *(S)*-diastereomer implies an attack of the copper reagent on the *re*-face of an *s-trans* conformation of crotonate **1** rather than on the *si*-face of an *s-cis* conformer (Fig. 2). The *si*-face of the *s-trans* conformer and the *re*-face of the *s-cis* conformer are both efficiently shielded by the naphthyl group.

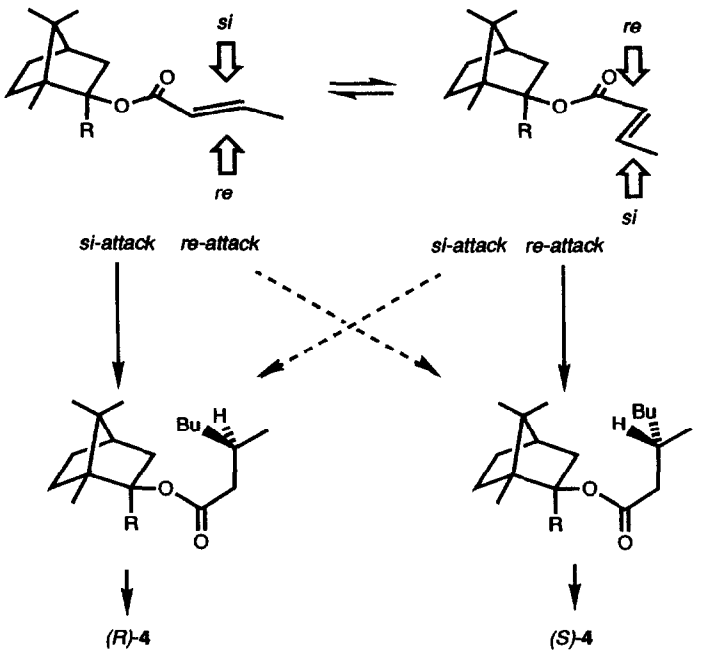


Figure 2. *Diasteromers (and enantiomers) produced as the result of attack on different faces and different conformations of chiral enoates.*

The exceptional difficulties to reproduce the results from ref. 6 when reacting $LiBu_2Cu$ and ester **1** prompted us to reinvestigate this reaction. We found that using what we considered to be $LiBu_2Cu$, we obtained inconsistent results (Table 1, entries 7-11). The yields were generally high, but the rate of the reaction as well as the diastereoselectivity varied drastically. When the exact composition of the cuprate was deliberately varied from the "exact" 1:1 Cu/Li ratio these inconsistent results could be rationalized. A "cuprate" having less than one equivalent Li (Table 1, entry 3) reacts very slowly and gives the *(S)*-diastereomer, as the BuCu-reagents do. On the other hand, cuprates with more than one equivalent Li (Table 1, entries 12-14) all react fast and give high diastereomeric excess of the *(R)*-diastereomer. Even butyllithium with only a catalytic amount of CuI gives a reasonable excess of the *(R)*-diastereomer while butyllithium itself, although giving a 1,4-addition, gives negligible diastereoselectivity (Table 1, entries 15-16). Formation of the *(R)*-diastereomer corresponds to an addition to the *si*-face of the *s-cis* conformation of ester **1**. Similar results were observed on addition of lithium butylcuprates to phenyl-substituted crotonate **2** (Table 2). The *(R)*-diastereomer of addition product **6** dominates using a higher than 1:1 Li/Cu ratio while the (S)-diastereomer is obtained using BuCu•TMSI. For the reagent "$LiBu_3Cu_2$" the reaction is slow and the selectivity poor, thus for this substrate representing the "turnover" composition.

Table 2. Addition of butylcopper/TMSI and lithium butylcuprates to phenylbornyl crotonate 2.

Entry	Copper reagent[a]	Reaction temp. (time)	Yield 5 (%)[b]	d.e. (%)[c]	configuration[d]
1	$BuCu{:}ISiMe_3$	-60 °C(20 h)	91	70	S
2	$BuCu{:}ISiMe_3$	-15 °C	94	45	S
3	$LiBu_3Cu_2$	-45 °C(15 min)	low	low	
4	$LiBu_2Cu$	0 °C(30 min)	94	50	R
5	$LiBu_2Cu$	-78 °C(50 min)	82[e]	37[e]	R[e]
6	$LiBu_2Cu$	-20 °C(5 h)	79	24	R
7	$LiBu_2Cu$	-60 °C(20 h)	80	15	R
8	Li_2Bu_3Cu	-60 °C(10 min)	33[f]	60	R

[a]Formal reagent composition, not actual verified species. [b]Isolated yields. [c]Obtained from ^{1}H-NMR spectra before chromatography. [d]At C3 of the side chain, major product, determined from optical rotation after $LiAlH_4$ reduction of 6. [e]Reported in ref. 6: $LiBu_2Cu$ addition to ester 2 at -25 °C; yield 77 %; d.e. 60 %. [f]54 % recovered starting material.

The unusual reactivity of bornyl esters 1 and 2 towards different organocopper reagents can be explained if we assume different transition states giving the two diastereomers. Two such transition states are shown in Fig 3. The transition state giving the *(S)*-configuration at C3 involves a Lewis acid (LiI or TMSI) coordinating to the carbonyl oxygen and thus stabilizing the *s-trans* conformation. The transition state giving the *(R)*-configuration probably occurs via the *s-cis* conformation in which the organocopper reagent can coordinate to both the π-bond and the carbonyl oxygen.

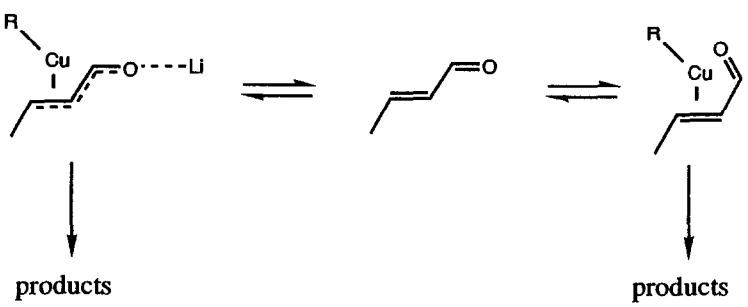


Figure 3. Possible transition states giving different diastereomers.

The additions of butylcopper/TMSI to crotonate 2 closely followed the results obtained in the corresponding experiments with naphthyl-substituted ester 1. The additions to phenylbornyl ester 2 (Table 2, entries 1 and 2) were less stereoselective, as expected, due to the limited occupation of space by the phenyl group as compared to the naphthyl group. The *(S)*-configuration was obtained at the new chiral center regardless of temperature and substrate for esters 1 or 2, in accordance with attack by the incoming butyl group on the *re-face* of *s-trans* conformations of the esters. The preferred *s-trans* con-

formation of the esters in the reactions with TMSI-activated BuCu is probably due to coordination of the carbonyl group with lithium iodide. When the addition to naphthyl bornyl ester **1** was performed with butylcopper washed with ether to remove LiI (Table 1, entries 6-7), no reaction was obtained for 20 h at -60 °C and a yield of 45 % with 70 % d.e. of the *(S)*-product was obtained at 0 °C. This difference in reactivity is in agreement with a Lewis acid (possibly LiI) coordinating to the carbonyl group, and thus lowering the energy of the LUMO by withdrawing electrons from the system. The lower stereoselectivity obtained without LiI could be due to more facile rotation within the α,β-unsaturated carbonyl moiety in the absence of a Lewis acid. The total lack of reactivity when TMSCl is used instead of TMSI (Table 1, entry 4) indicates that all three components BuCu, LiI, and TMSI are involved in these reactions.

With a decrease of the bulk of the bornyl substituent, like in methyl-substituted ester **3**, an excess of the *(R)*-diastereomer was obtained with both copper reagents (Table 3). The yields and stereoselectivities of BuCu•TMSI addition to crotonate **3** were about the same, independent of temperature. To discuss the results of addition to bornyl ester **3** in terms of *s-trans* or *s-cis* conformations is difficult, as the crotonyl moiety rotation around the ester-bornyl bond is not efficiently hindered by the small 1-*endo*-methyl substituent. The diasteromeric excess of addition product **7** was not measured as it gave a complex ^{1}H-NMR spectrum. The d.e. was therefore only determined from the optical rotation of the reduction product **4**. Excess *(R)*-(+)-3-methylheptanol was obtained in all experiments (Table 3).

Table 3. *Addition of butylcopper/TMSI and lithium dibutylcuprate to methylbornyl crotonate 3.*

Entry	Copper reagent	Reaction temp.	Yield **7** (%)[a]	d.e. (%)[b]	configuration[b]
1	$BuCu{:}ISiMe_3$	-60 °C	79	37	R
2	$BuCu{:}ISiMe_3$	-35 °C	77	43	R
3	$LiBu_2Cu$	-25 °C	80[c]	37[c]	R

[a]Isolated yields. [b]Major product, determined from optical rotation after $LiAlH_4$ reduction of **7**. [c]Reported in ref. 6: $LiBu_2Cu$ addition to ester **3** at -25 °C; yield 81 %; d.e. 50 %.

$LiBu_2Cu$ was previously reported[6] to add fast and completely to naphthyl bornyl crotonate **1** at -78 °C, but much slower to esters **2** and **3**. Our results show that both the rate of the reactions and the diastereoselectivity are dependent of the exact composition of the cuprate. The reactivity and selectivity of the RCu•TMSI reagent compared to organocopper reagents activated by TMSCl or other Lewis acids and this unusual composition dependence of the cuprate reactions offer several new possibilities for organic synthesis.

ACKNOWLEDGMENTS

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EXPERIMENTAL

General Methods. All organocopper reagents were prepared from copper(I) iodide and butyllithium at -78 °C. To guarantee total consumption of butyllithium, the temperature was raised to approximately -50 °C and the mixture stirred for at least 30 min. The solution of lithium dibutylcuprate ($LiBu_2Cu$), under these conditions, was nearly homogeneous and colorless and was also stable at higher temperatures. Addition of butyllithium at higher temperature (-45 °C) always gave a heterogeneous and black mixture. Butylcopper (BuCu) was prepared by adding one equivalent of butyllithium to copper(I) iodide at -78 °C and then slowly raising the temperature to -60 °C and stirring for 50 min. To the heterogeneous mixture of BuCu was added one equivalent of TMSI, the mixture stirred an additional 5 min and then cooled to -78 °C again. The appropriate bornyl crotonate (1-3) was then added to the copper reagent, usually at a low temperature (-78 °C). The temperature was then raised to the appropriate reaction temperature and maintained there.

We used different work-up methods depending on temperature and copper reagent. All copper reagents were quenched with moist ether, saturated with ammonium chloride and ammonia, to prevent reactions at higher temperatures. In the BuCu reactions, excess TMSI was destroyed with dry pyridine. In the absence of pyridine, the yields decreased, probably due to hydrolysis of the esters by hydriodic acid, formed from TMSI and water. TMSI is often used to cleave ethers and esters[10] but these cleavage reactions seem to require higher temperatures.

The diastereomeric excess (d.e.) in most experiments could then be determined from the ^{1}H-NMR spectra of the crude addition products. The d.e. was checked again with ^{1}H-NMR after flash chromatography of the reaction mixtures to ensure that the optical purity was not enhanced in the purification process. The diastereomeric excess (d.e.) could then be measured in the α-proton region (2.0-2.4 ppm) of the ^{1}H-NMR spectra of products **5** and **6**. It was also possible to determine the d.e. of naphthyl-substituted addition product **5** in the aliphatic region. Ester *(S)*-**5** gave a doublet at 0.85 ppm and *(R)*-**5** a doublet at 0.68 ppm from the 3-methyl group of the ester moiety. The ^{1}H-NMR spectrum of methyl-substituted bornyl ester **7** was more complex, however, and measurement of the optical rotation of the 3-methylheptanol produced after reduction of the diastereomeric mixture was therefore used to determine the d.e. of the reaction. The addition products in all entries were subjected to lithium aluminum hydride reduction and after careful separation 3-methylheptanol was isolated. The amount and sign of the optical rotation confirmed the absolute configuration and diastereoselectivity obtained for each entry.

Equipment and instruments. All reactions were performed in septum-capped reaction flasks under argon. All glass equipment was flame- or oven-dried and was cooled in a desiccator. Liquid samples were transferred and introduced dropwise with syringes. All reaction mixtures were purified by flash chromatography using Merck silica gel 60 (230-400 mesh), usually with diethyl ether/pentane as eluent. ^{1}H-NMR spectra were obtained on either Varian XR-5000 (400 MHz) or Bruker WH-270 (270 MHz) instruments with TMS as internal standard. Mass spectra were recorded on a Finnigan 1020 (GC-MS, 70 eV, capillary column). IR spectra were recorded on a Perkin Elmer 1600 FT-IR instrument with only the structurally most important peaks noted here. Optical rotations were measured on a Perkin Elmer 241 polarimeter using the sodium D-line. Melting points were determined on either a Reichert Thermovar apparatus or a Gallenkamp digital heater using capillary (cap.) for the substituted borneols.

Chemicals. Copper(I) iodide was recrystallized from dimethyl sulfide and hexane, crystals collected, pumped until constant weight and stored in a light-protected bottle.[11] Diethyl ether and tetrahydrofuran (THF) were distilled under argon from sodium-benzophenone and were collected when the solution become deep blue. Pyridine was distilled over CaH_2 under nitrogen pressure and stored over 4Å molecular sieves under argon. (+)-Camphor was recrystallized from 95% EtOH-water, filtered, dissolved in diethyl ether, washed with brine, dried over sodium sulfate, filtered and dried under reduced pressure.[12] Butyllithium (1.6 M in hexane) was purchased from Aldrich and titrated prior to use.[13] Iodotrimethylsilane (Jansen) was stored at -25 °C under argon with copper chips in a light-pro-

tected septum bottle before use.

1-*(R)*-*Endo*-(1-naphthyl)borneol. The procedure of Bredt and Dussier[14] was used with modifications as follow: (+)-Camphor (3.04 g, 20 mmol) dissolved in THF (15 mL) was added dropwise to a solution of 1-naphthylmagnesium bromide (60 mmol, 1.7 M) in THF (35 mL) at 40 °C. The mixture was heated at 55 °C for 15 h, then poured out on an ice-cold mixture of ether (100 mL) and ammonia/ammonium chloride buffer (100 mL, pH 8). The organic layer was separated and the aqueous phase was extracted with ether (4 x 50 mL). The combined ether extracts were washed with brine (50 mL) and dried with sodium sulfate. After removal of the solvent, the solid residue was purified through the removal of unreacted camphor and naphthalene by sublimation (0.1 mm/20 °C). After sublimation, naphthylborneol was recrystallized from triethylamine and pentane. The colorless crystals were collected and dried until constant weight to give 2.64 g (47%) of colorless needles; mp 123-124 °C (cap.) ; $[\alpha]^{20}_D$ -42.4° (*c*=2.0, benzene) (Lit.[14] mp 122-124 °C; $[\alpha]^{15}_D$ -42° (c=15, benzene)). MS: *m/Z*=280(M+, 8%), 262(M-H_2O, 95%), 219(85%), 170(100%). IR(KBr): ν=3450, 800 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 328K) : δ= 8.76 (bm, H8, 1H), 7.82 (dd, H5, *J*= 7.5, 2.8 Hz, 1H), 7.70 (2d, H2 and H4, *J*= 7.5 Hz, 2H), 7.44 (bm, H6 and H7, 2H), 7.34 (t, H3, *J*= 7.5 Hz, 1H), 2.74 (bd, H3exo, *J*= 13.7 Hz, 1H), 2.37 (bd, H3endo, *J* 13.7 Hz, 1H), 2.10 (s, ROH, 1H), 1.88 (bt, H4, $J_{H4\text{-}3exo}$=$J_{H4\text{-}5exo}$ 4.4 Hz, 1H), 1.80 (bm, H5endo, 1H), 1.70 (bm, H5exo, 1H), 1.48 (bm, H6exo, 1H), 1.34, 1.28 (2s, CH_3, 3H each), 1.06 (bm, H6endo, 1H), 0.96 (s, CH_3, 3H). ($C_6D_5CD_3$, 363K), 2.77 (bdt, H3exo, *J*=13.7, 4.4 Hz, 1H), 2.48 (bd, H3endo, *J*=13.7 Hz, 1H), 1.94 (bt, H4, *J* 4.4 Hz), 1.81 (bm, H5exo, 1H).

$C_{20}H_{24}O$	calc.	C	85.67	H	8.63
(280.41)	found		85.85		8.59

1-*(R)*-*Endo*-phenylborneol. The procedure of Coxon *et al.*[15] was used with modifications as follow: To a solution of phenylmagnesium bromide (70 mmol, 2.3 M) in THF (30 mL) at 0 °C, (+)-camphor (2.28 g, 14.8 mmol) in THF (20 mL) was added dropwise. The mixture was refluxed under argon for 8 h, then quenched with an ammonia/ammonium chloride buffer (50 mL, pH 8), stirred an additional 1 h and filtered through Celite. The aqueous phase was extracted with ether (2x50 mL), the combined ether extracts were washed with brine (50 mL) and dried over sodium sulfate. After evaporation of the solvent the crude mixture was purified with flash chromatography (10% diethyl ether/pentane, R_f=0.3) and gave 2.34 g (68%) of a colorless syrup. The ^{1}H-NMR spectrum was nearly identical to that reported.[15] $[\alpha]^{20}_D$ -41.3° (*c*=1.0, benzene) (Lit.[15] mp 41-42 °C; $[\alpha]^{25}_D$ -34° (c=0.99)). MS: *m/Z*=230(M+, 24%), 212(M-H_2O, 42%), 169(78%), 120(100%), 95(62%). IR(neat): ν=3450, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=7.53 (m, Hortho, *J*= 8, 1.5 Hz, 2H), 7.30 (m, Hmeta+ Hpara, 3H), 2.33 (bd, H3endo, *J*= 14 Hz, 1H), 2.19 (bdt, H3exo, *J*=14, 3.5 Hz, 1H), 1.91 (bt, H4, *J*= 3.5 Hz, 1H), 1.80-1.65 (m, CH_2, 2H), 1.27 (s, CH_3, 3H), 1.25-1.10 (m, CH_2, 2H), 0.91 (s, 2xCH_3, 6H).

$C_{16}H_{22}O$	calc.	C	83.43	H	9.63
(230.35)	found		83.28		9.60

1-*(R)*-*Endo*-methylborneol was prepared according to the procedure of Dimmel and Fu.[16] The crude product was purified with flash chromatography (using 20% diethyl ether in pentane, R_f= 0.4) and gave 8.80 g (80%) of colorless solid; mp 165-167 °C (cap.) ; $[\alpha]^{22}_D$ -15.7° (c=1.0, 99.5% EtOH) (Lit.[16] mp 167-168 °C; $[\alpha]^{25}_D$ -14.8° (c=4%, abs. EtOH)). MS: *m/Z*=168(M+, 4%), 150(M-H_2O, 22%), 135(33%), 107(100%). IR(KBr): ν=3500 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=2.08 (bdt, H3exo, *J*=13, 3.5 Hz, 1H), 1.72 (bt, H4, *J*= 3.5 Hz, 1H), 1.41 (m, CH_2, 2H), 1.38 (d, H3endo, *J*=13 Hz, 1H), 1.25, 1.11 (2s, CH_3, 3H each), 1.10-0.90 (m, CH_2, 2H), 0.87, 0.85 (2s, CH_3, 3H each).

1-*(R)*-*Endo*-(1-naphthyl)bornyl *E*-butenoate (1). Butyllithium (1.53 mL, 2.35 mmol) was added dropwise to 1-*(R)*-*endo*-(1-naphthyl)borneol (600 mg, 2.14 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 45 min at 0 °C and an additional 10 min at room temperature. Freshly distilled crotonyl chloride (450 mg, 4.28 mmol) in THF (10 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 27 h and the reaction quenched with water (20 mL) at 0 °C. The mixture was transferred to a separation funnel, the aqueous phase extracted with ether (5 x 20 mL) and the

combined organic phases dried over sodium sulfate. After removal of the solvent, the crude product was flash-chromatographed on a silica gel column (30 x 3 cm) with 10% diethyl ether in pentane (R_f= 0.2) to give 510 mg (68%) of **1** as colorless crystals; mp 156-157 °C; $[\alpha]^{23}_D$ -224° (*c*=1.0, CH_2Cl_2) (Lit.[6] mp 139-141 °C; $[\alpha]^{22}_D$ -139° (*c*=0.67, CH_2Cl_2). MS: *m/Z*=262(M-$C_4H_6O_2$, 100%), 247(42%), 234(52%), 219(76%). IR(KBr): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$). δ= 8.57 (bdd, H8, *J*= 8, 2 Hz, 1H), 7.79 (dd, H5, *J*= 8, 2 Hz, 1H), 7.74 (bd, H2 and H4, *J*= 8 Hz, 2H), 7.43 (t, H3, *J*= 8 Hz, 1H), 7.34 (m, H6 and H7, 2H), 6.84 (dq, Hβ, *J*= 15.5, 7 Hz, 1H), 5.86 (dq, Hα, *J*= 15.5, 1.5 Hz, 1H), 2.96 (bd, H3endo, *J*= 15.5 Hz, 1H), 2.53 (bdt, H3exo, *J*= 15.5, 4 Hz, 1H), 1.95 (bt, H4, *J* 4 Hz, 1H), 1.85 (dd, CH_3, *J*= 7, 1.5 Hz, 3H), 1.81-1.71 (m, H5exo, 1H), 1.49-1.40 (m, H5endo, 1H), 1.28 (s, CH_3, 3H), 1.24-1.12 (m, H6exo, partly hidden, 1H), 1.18 (s, CH_3, 3H), 1.06-0.98 (m, H6endo, partly hidden, 1H), 0.97 (s, CH_3, 3H).

$C_{24}H_{28}O_2$	calc.	C	82.72	H	8.10
(348.48)	found		82.87		8.03

1-*(R)-Endo*-phenylbornyl *E*-butenoate (2). Freshly distilled crotonyl chloride (3.11 g, 29.8 mmol) in THF (20 mL) was added dropwise at 20 °C to a solution of the lithium salt of 1-*(R)-endo*-phenylborneol (5.70 g, 24.7 mmol) in THF (40 mL). The mixture was refluxed for 1.5 h and the reaction quenched with water (10 mL) at 20 °C. The aqueous phase was extracted with ether (5 x 50 mL) and the combined ether extracts dried over sodium sulfate. Evaporation of the solvent gave a yellowish oil that was purified with flash chromatography (5% diethyl ether in pentane, R_f= 0.2). The white residue obtained was recrystallized from ethanol and dried until constant weight to give 6.24 g (85%) of **2** as colorless crystals; mp 78.5-79.5 °C, $[\alpha]^{23}_D$ -177° (*c*=1.0, CH_2Cl_2). MS: *m/Z*=212(M-$C_4H_6O_2$, 65%), 197(58%), 184(74%), 169(100%), 91(52%). IR(KBr): ν=1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 293K): δ=7.60-7.20 (b, aromatic, 5H), 6.88 (dq, Hb, *J*= 15.5, 7 Hz, 1H), 5.82 (dq, Ha, *J*= 15.5, 1.5 Hz, 1H), 2.61 (bd, H3endo, *J*= 15 Hz, 1H), 2.48 (bdt, H3exo, *J*= 15, 3.5 Hz, 1H), 1.90 (bt, H4, partly hidden, *J*= 3.5 Hz, 1H), 1.85 (dd, CH_3, *J*= 7, 1.5 Hz, 3H), 1.80-1.65 (bm, H5exo, 1H), 1.40-1.15 (bm, H5endo and H5exo, 2H), 1.17, 1.00, 0.95 (3s, CH_3, 3H each), 0.95-0.80 (bm, H6endo, 1H).

$C_{20}H_{26}O_2$	calc.	C	80.50	H	8.78
(298.42)	found		80.53		8.70

1-*(R)-Endo*-methylbornyl *E*-butenoate (3). To a solution of 1-*(R)-endo*-methylborneol (2.50 g, 14.9 mmol) in dry THF (20 mL) at 0 °C, butyllithium (10.3 mL, 16.4 mmol) was added dropwise. After slowly raising the temperature to 20 °C, the solution was stirred an additional 30 min followed by the addition of a solution of freshly distilled crotonyl chloride (1.87 g, 17.9 mmol) in THF (10 mL). The mixture was refluxed and the reaction quenched after 1 h with an ammonia/ammonium chloride buffer (10 drops, pH 8) at 0 °C. After removal of THF the residue was extracted with diethyl ether (100 mL) and water (50 mL). The organic layer was separated and the aqueous phase extracted with ether (3 x 50 mL). The combined ether extracts were washed with brine (50 mL) and dried over sodium sulfate. After evaporation of the solvent, the mixture was purified with flash chromatography (5% diethyl ether in pentane, R_f= 0.3) and gave 2.49 g (71%) of **3** as a colorless oil; $[\alpha]^{20}_D$ -60.5° (*c*=1.30, CH_2Cl_2). MS: *m/Z*= 236(M+, 0.2%), 150(M-$C_4H_6O_2$, 33%), 135(40%), 107(100%). IR(neat): ν=1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=6.84 (dq, Hb, *J*= 15.5, 7 Hz, 1H), 5.76 (dq, Ha, *J*= 15.5, 2 Hz, 1H), 2.56 (bdt, H3exo, *J*= 14.5, 4 Hz, 1H), 1.84 (dd, CH_3, *J*= 7, 2 Hz, 3H), 1.70 (bm, H4, 1H), 1.63 (bd, H3endo, *J*= 14.5 Hz, 1H), 1.48 (s, CH_3, 3H), 1.45-1.35, 1.12- 1.00 (2bm, CH_2, 2H each), 1.00-0.85 (3s, CH_3, 3H each).

Conjugate additions. General procedures.

Addition of $LiBu_2Cu$. Butyllithium (6.1 ml, 9.9 mmol, 1.6 M) was added dropwise to a stirred slurry of copper(I) iodide (950 mg, 5.0 mmol) in diethyl ether (10 mL) at -78 °C. The temperature was raised to -45 °C and the mixture stirred for 30 min to give a homogeneous solution, often clear to pale violet. The temperature was lowered to -78 °C and a solution of bornyl ester **1**, **2**, or **3** (0.5-1.5 mmol) in diethyl ether (10-15 mL) was added dropwise (2mL/min) The mixture immediately become pale yellow and slightly heterogeneous. At -60 °C the reaction mixture became completely homogeneous.

The reaction was quenched with diethyl ether containing ammonia/ammonium chloride buffer at the appropriate time and temperature. The aqueous phase was extracted with ether (3 x 50 mL) and the combined ether extracts washed with brine (25 mL). The organic layer was dried over sodium sulfate and the solvent evaporated. The crude material was purified with flash chromatography using 5-10% diethyl ether in pentane as the eluent. The same procedure was followed for the non-stoichiometric cuprates only using different ratios butyllithium/copper(I) iodide.

Addition of BuCu:ISiMe$_3$. Butyllithium (3.1 mL, 5.0 mmol, 1.6 M) was added dropwise to a slurry of copper(I) iodide (1.05 g, 5.5 mmol) in diethyl ether (10 mL) at -78 °C. The slurry was stirred for 40 min at -60 °C. Colorless iodotrimethylsilane (0.71 mL, 5.0 mmol) was added dropwise and the slurry stirred for 5 min. The temperature was lowered to -78 °C and a solution of bornyl ester **1**, **2**, or **3** (0.5-1.5 mmol) in diethyl ether (10-15 mL) was added dropwise (2 mL/min). The reaction was quenched with dry pyridine: dry ether (1:9; 10 mL) and the suspension stirred (1-2 h) at low temperature. Diethyl ether saturated with ammonia/ammonium chloride buffer was added and the mixture stirred an additional 4 h. The temperature was raised to +20 °C and aqueous ammonium chloride/ammonia (5 mL) was added. The excess heterogeneous material was filtered off over Celite, washed with several portions of ether and the organic layer separated. The aqueous phase was extracted with ether (3 x 50 mL) and the combined ether extracts washed with dilute copper(II) sulfate, brine, dried over sodium sulfate and the solvent evaporated. Flash chromatography (5-10 % diethyl ether/pentane) gave pure products **5-7**.

Spectroscopic data for the addition products **5-7**:

1-*(S)*-*Endo*-(1-naphthyl)-bornyl (3-*(S)*-methyl)heptanoate (*(S)*-5). MS: *m/Z*=262(M-$C_8H_{16}O_2$, 63%), 247(42%), 234(44%), 219(100%), 203(57%), 165(52%). IR(KBr): ν = 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$). δ 8.60 (bd, H8, *J*= 8 Hz, 1H), 7.80 (bd, H5, *J*= 8 Hz, 1H), 7.74 (2bd, H2 and H4, *J*= 8 Hz, 2H), 7.42 (bt, H3, *J*= 8 Hz, 1H), 7.37 (bm, H6 and H7, 2H), 2.96 (bd, H3$_{endo}$, *J*= 15 Hz, 1H), 2.48 (bdt, H3$_{exo}$, *J*= 15, 4 Hz, 1H), 2.25 (bdd, Hα to carbonyl, *J*= 15, 6 Hz, 1H), 2.14 (bdd, Hα to carbonyl, *J*= 16, 8 Hz, 1H), 1.95 (bt, H4, *J*= 4 Hz, 1H), 1.84-1.70 (bm, H5$_{exo}$ and methine, 2H), 1.48-1.38 (bm, H6$_{exo}$, 1H), 1.28 (s, CH_3, 3H), 1.25-0.90 (m, 3xCH_2 alkyl chain, H5$_{endo}$, H6$_{endo}$, 8H), 1.16, 0.96 (2s, CH_3, 3H each), 0.85 (d, CH_3, *J*= 7 Hz, 3H), 0.78 (t, CH_3, *J*= 7 Hz, 3H).
Recrystallization three times from aqueous ethanol gave white cotton-like needles of the pure diastereomer *(S)*-**5**; mp 118-120 °C, $[\alpha]^{24}_D$ -116° (c=0.63, CH_2Cl_2).

$C_{28}H_{38}O_2$	calc.	C	82.71	H	9.42
(406.61)	found		82.50		9.24

1-*(R)*-*Endo*-(1-naphthyl)-bornyl-(3-*(R)*-methyl)heptanoate; (*(R)*-5). MS: *m/Z*=262(M-$C_8H_{16}O_2$, 72%), 247(45%), 234(41%), 219(100%), 203(59%), 165(52%). IR(neat): ν =1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$). δ 8.60 (bm, H8, 1H), 7.80 (bd, H5, *J*= 8 Hz, 1H), 7.74 (2bd, H2 and H4, *J*= 8 Hz, 2H), 7.42 (bt, H3, *J*= 8 Hz, 1H), 7.37 (bm, H6 and H7, 2H), 2.96 (bd, H3$_{endo}$, *J*= 15.5 Hz, 1H), 2.49 (bdt, H3$_{exo}$, *J*= 15.5, 4 Hz, 1H), 2.32 (bdd, Hα to carbonyl, *J*= 15.5, 6 Hz, 1H), 2.06 (bdd, Hα to carbonyl, *J*= 15.5, 7.5 Hz, 1H), 1.94 (bt, H4, *J*= 4 Hz, 1H), 1.85-1.70 (bm, H5$_{exo}$ and methine, 2H), 1.48-1.35 (bm, H6$_{exo}$, 1H), 1.28 (s, CH_3, 3H), 1.25-0.90 (m, 3xCH_2 alkyl chain, H5$_{endo}$, H6$_{endo}$, 8H), 1.16, 0.96(2s, CH_3, 3H each), 0.86 (t, CH_3, *J* 7 Hz, 3H), 0.68 (d, CH_3, *J*= 7 Hz, 3H).

1-*(R)*-*Endo*-phenyl-bornyl-(3-methyl)heptanoate (6). (Mixture of diastereomers). MS: *m/Z*=212(M-$C_8H_{16}O_2$, 100%), 197(62%), 184(71%), 169(95%), 91(39%). IR(neat): ν = 1730 cm^{-1}.

1-*(R)*-*Endo*-methyl-bornyl-(3-methyl)heptanoate (7). (Mixture of diastereomers). MS: *m/Z*=294(M^+, 0.2%), 150(M-$C_8H_{16}O_2$, 42%), 135(47%), 107(100%). IR(neat): ν =1720 cm^{-1}.

Reductions:

***(S)*-(-)-3-Methylheptanol (*(S)*-4).** A solution of the addition product from table 1, entry 1 (*(S)*-5; 98% d.e.) in dry THF (10 mL) was added to a slurry of lithium aluminum hydride (2 equiv) in THF (10 mL) at 0 °C. The mixture was refluxed and the reaction was quenched after 2 h, using a standard method.[17] The heterogeneous material was filtered off over Celite, and washed with diethyl ether. After removal of the solvent, the crude mixture was purified on a silica gel column (2 x 15 cm) and gave, after flash chromatography with 30% diethyl ether in pentane, 94% recovered naphthyl borneol and as a second fraction 96% of *(S)*-4. $[\alpha]^{25}_D$ -3.02° (98% e.e.) (c=1.45, CH_2Cl_2) (Lit.[18] $[\alpha]_D$ -3.07°, neat). MS: *m/Z*=129 (M-1, 1%), 112(M-H_2O, 2%), 84(27%), 70(40%), 55(100%). IR(neat): ν = 3300, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ= 3.68 (m, CH_2, 2H), 1.71-1.50 (m, 2H), 1.50-1.05 (m, 8H), 0.90 (d and t, 2x CH_3, *J*= 7 Hz, 6H).

***(R)*-(+)-3-Methylheptanol (*(R)*-4).** A solution of the addition product from table 1, entry 14 (*(R)*-5; 86% d.e.) in dry THF (10 mL) was treated as described above and gave after work-up 97% of recovered naphthylborneol (R_f = 0.75) and a second fraction with a 90% yield of *(R)*-4 (R_f = 0.2) as a colorless oil. $[\alpha]^{25}_D$ +2.64° (86% e.e.) (*c*=1.45, CH_2Cl_2).

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