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The Preparation of Nonracemic Secondary α-(Carbamoyloxy)alkylzinc and Copper Reagents. A Versatile Approach to Enantioenriched Alcohols

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Chiral α -(carbamoyloxy)alkyllithium reagents, prepared using Hoppe's sBuLi/(–)-sparteine methodology, were transmetalated with ZnCl₂. Further transmetalation with CuCN with overall retention of configuration gave chiral species that reacted with various electrophiles to give enantiomerically pure alcohols after deprotection. A short, highly efficient synthesis of an industrially relevant pheromone, japonilure, illustrates the value of the methodology.

ABSTRACT

1. sBuLi/(-)-sparteine

2. ZnCl

3. CuCN.2LiCl 4. Allyl bromide

Efforts to design asymmetric routes to secondary alcohols have been considerable as a result of their usefulness as building blocks and their widespread occurrence in natural products. Nucleophilic addition to aldehydes and hydrogenation or hydride addition to ketones are routine procedures to prepare secondary alcohols, and a number of efficient asymmetric variants have been developed. Enantioenriched epoxides also make attractive precursors to secondary alcohols, particularly given recent progress made in their preparation. An alternative process, which has been much less studied, is the reaction between a nucleophilic α -alkoxyalkylmetal reagent and an electrophile. The first convenient preparation of α -alkoxyalkyllithium species, using α -alkoxyalkylstannane precursors, was reported by Still.¹ Later, the groups of Linderman² and Fuchs³ reported the conjugate addition of α -alkoxyorganocopper reagents. Importantly, Still and Sreekumar also showed that enantioenriched α -alkoxyalkylstannanes could be transmetalated with *n*-butyllithium with retention of configuration. The α -alkoxyalkyllithium

reagents thus formed were shown to be configurationally stable below -40 °C in ethereal solvents.⁴ McGarvey et al. demonstrated the stabilizing influence of oxygen upon the carbanionic center⁵ and provided examples of the utility of these anions in stereoselective synthesis.⁶ These findings prompted several other groups to study the synthesis of the α -alkoxyorganostannane precursors in enantioenriched form.⁷ Falck and co-workers have reported the successful stereoselective cross-couplings of α -alkoxytributylstannanes with organohalides, using copper⁸ or copper/palladium⁹ catalysis.

11 examples

Yield 0-83%

e.e. > 96%

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Calter and Bi recently reported a successful stereoselective conjugate addition of a chiral mixed higher-order α -alkoxy-cuprate reagent.¹⁰

A spectacular development in this field was achieved by Hoppe et al., who demonstrated that the complex *s*BuLi/ (–)-sparteine could induce the enantioselective deprotonation of achiral alkyl carbamates.^{11,12} The chiral lithium species thus formed can be alkylated with retention of configuration to give the protected secondary alcohols in high ee's. The use of these lithium species has so far been limited as a result of their configurational lability above -70 °C, although Hoppe¹³ and others¹⁴ have reported various applications of this methodology.

However, examples of the utilization of chiral nonracemic α -alkoxyorganometallic compounds in synthesis have been scarce. It seemed to us that transmetalation of Hoppe's species could lead to thermally and configurationally stable compounds and thus open up interesting synthetic possibilities. As far as we were aware when we commenced this study, the only examples of transmetalation of the lithiated carbamate prepared using Hoppe's methodology had been reported by Hoppe himself.^{11,15} His group prepared α -(carbamoyloxy)alkyl tin and silicon derivatives, although no attempt at utilizing these species in cross-coupling reactions has been reported. We were hopeful that the transmetalation from the chiral lithium reagents to the alkylzinc derivatives would be stereoselective.¹⁶ A handful of reports have shown that chiral alkylzinc halides are configurationally stable, even at room temperature.^{16,17} Moreover, Knochel has demonstrated that the transmetalation of alkylzinc reagents with copper cyanide gives reagents that react with a broad range of electrophiles while showing excellent chemoselectivity.¹⁸ His group has also prepared racemic α -alkoxyalkylzinc

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^{*a*} (a) (i) *s*BuLi (1.5 equiv), (–)-sparteine (1.5 equiv), Et₂O, -78 °C, 5 h, (ii) ZnCl₂ (0.8 M in THF, 1.3 equiv), -78 °C to rt, (iii) CuCN·2LiCl (1.0 equiv) in THF, -40 to 0 °C, (iv) electrophile **3–13**, -40 to 0 °C.

cuprates and showed that they are efficient nucleophiles.¹⁹

Our synthetic strategy is illustrated in Scheme 1. The carbamate 1, prepared using the literature procedure,^{11b} was deprotonated at -78 °C for 4-5 h using 1.5 equiv of (–)-sparteine and 1.5 equiv of *s*BuLi. A 0.8 M solution of ZnCl₂ in THF²⁰ was then added, followed by CuCN•2LiCl in THF and finally the electrophile.²¹ The results are summarized in Table 1 (all yields are unoptimized).

The coupling of the chiral organometallic species $2c^{22}$ derived from 1 with allyl bromides proceeded in good yields (entries 1–3). In the case of 1-bromocyclohex-2-ene the reaction gave a 1:1 mixture of diastereomers (entry 2). The reagent 2c also displayed excellent reactivity toward alkynyl bromide 6 and gave the protected propargylic alcohol 17 in 72% yield (entry 4). The propargylic mesylate 7 reacted exclusively in an S_N2' fashion to give the allene 18 in 75% yield (entry 5). Activated vinyl iodide 8 (entry 6) and vinyl triflate 9 (entry 7) reacted in modest yields and provided further examples of the chemoselectvity of these types of organometallic species.

The reactivity of **2c** toward Michael acceptors was very poor, and reaction with cyclohexenone or methyl acrylate

(20) We found it convenient to quench the lithiated carbamate 2a with a freshly prepared solution of anhydrous $ZnCl_2$ in THF. Using $ZnCl_2$ in Et₂O gave a heterogeneous mixture that was difficult to stir.

(21) Representative Experimental Procedure. sBuLi (2.0 mL, 1.32 M in hexane, 2.64 mmol) was added dropwise to a stirred solution of 1 (0.40 g, 1.78 mmol) and (-)-sparteine (0.62 g, 2.65 mmol) in anhydrous ether (5 cm^3) at -78 °C. After 4 h at -78 °C, zinc chloride (0.8 M in THF, 2.9 mL, 2.32 mmol) was added dropwise at -78 °C over 10 min, and the mixture was stirred for a further 20 min at this temperature. The mixture was warmed to room temperature over 15 min and recooled to -40 °C, and a solution of copper cyanide (99%, 0.16 g, 1.78 mmol) and lithium chloride (dried at 150 °C under 0.2 mmHg for 4 h, 0.15 g, 3.56 mmol) in anhydrous THF (3 cm³) was added rapidly. The yellow slurry was warmed to 0 °C over 15 min and recooled to -40 °C. The electrophile (1.78 mmol) was added dropwise, either neat if liquid or in a minimum volume of anhydrous THF if solid. The mixture was allowed to warm to 0 °C over 1.5 h, whereupon it was quenched with dropwise addition of a 10% solution of NH₄OH in saturated aqueous NH₄Cl. Ether was added, and the mixture was vigorously stirred for 20 min and filtered through Celite. The organic layer was washed with saturated aqueous Na₂CO₃, water, and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography to give the carbamates as colourless oils.

(22) The formula RCu(CN)ZnCl merely represents the stoechiometry of the reagent; see ref 18.

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Table 1.	Electrophilic Trappi	ng of 2	2c					
entry	electrophile		product		yield (%) ^{a, b}	e.e. ^c	yield of alcohol (%)	
1	Br	3	OCby	14	83	> 99	> 90 ^d	25
2	Br	4	OCby	15	54 (65) ^e	n.a.	83^d \sim	26
3	Br MeO ₂ C	5	CO ₂ Me	16	60 (81)	96	$< 10^{d,f}$, $co_2 Me$	27
4	Br─ ── C ₅ H ₁₁	6	C ₅ H ₁₁	17	72	> 99	98 ^d	28
5	■ ^{OMs}	7	OCby	18	75 (85)	n.d. ^g	n.d.	
6		8		19	42 (55)	97	61 ^{<i>d</i>, <i>h</i>}	29
7		9	MeO ₂ C NO MeO ₂ C NO MeO	20	50	n.d. ⁱ	69 ^{f, i}	30
8	\bigcirc	10	осьу С	21	< 10	n.d.	n.d.	
9	CO ₂ Me	11		22	0 ^{<i>i</i>}	n.a.	n.a.	
10	≡−CO ₂ Me	12	OCby CO ₂ Me	23	< 10	n.d.	n.d.	
11	≡ -C₅H ₁₁	13		24	0 ⁱ	n.a.	n.a.	

^{*a*} The yield refers to isolated product. ^{*b*} The figure in brackets gives the yield based on recovered starting carbamate. ^{*c*} The ee's were measured by HPLC analysis; see Supporting Information. ^{*d*} The carbamate was hydrolyzed using: (i) cat. MeSO₃H, MeOH, reflux, overnight, (ii) Ba(OH)₂, MeOH, reflux, 2 h. ^{*e*} The product was obtained as a 1:1 mixture of inseparable diastereomers. ^{*f*} The carbamate was hydrolyzed using: (i) cat. MeSO₃H, MeOH, reflux, 2 h, (ii) HSiCl₃, Et₃N, THF, reflux, 3 h. ^{*s*} Despite extensive efforts to measure the ee, we were unsuccessful using HPLC chiral columns Chiralcel OD, OJ, OJ-R and Chiralpak AD; $[\alpha]^{20}_{D} + 18.4$ (*c* 4.45, CHCl₃). ^{*h*} Complete racemization occurred upon deprotection. ^{*i*} Only one diastereomer was detected by ¹H NMR spectroscopy. ^{*j*} The starting carbamate was recovered quantitatively. Abbreviations: n.d. = not determined, n.a. = not applicable, Ms = methylsulfonyl, Tf = trifluoromethylsulfonyl, Cby = 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl.

gave at best traces of product (entries 8 and 9). An attempted carbometalation with 1-heptyne was also unsuccessful (entry 11).

The alkylated carbamates were obtained in excellent ee's, similar to those described by Hoppe in the case of the simple alkylation of **2a**, indicating that the transmetalation to the mixed copper–zinc species **2c** is stereoselective. The alkylation takes place with overall retention of configuration, as shown by comparison between the optical rotation of (*R*)-1-hepten-4-ol obtained by deprotection of **14** { $[\alpha]^{20}_{D} + 13.2$ (*c* 2.4, CHCl₃)} with the value described in the literature { $[\alpha]^{20}_{D} + 12.7$ (*c* 0.54, CHCl₃)}.²³ Attempts to directly transmetalate the lithium species **2a** with CuCN and subsequent reaction with allyl bromide afforded **14** in only 38% yield and 88% ee,²⁴ which is in sharp contrast with the results obtained from similar experiments carried out with *N*-Boc-2-lithiopyrrolidine.¹⁵

The hydrolysis of the carbamates was carried out using the conditions described by Hoppe (Table 1, entries 1-7).^{11b} The carbamates **14**, **15**, and **17** afforded the corresponding alcohols in very good yields, whereas **19** racemized and **16** and **20** decomposed upon treatment with Ba(OH)₂ in refluxing methanol. However, after opening the tetramethyl oxazolidine group of **20** under standard conditions, we found that the carbamate could be cleaved with trichlorosilane (6 equiv) in the presence of triethylamine (6 equiv) in refluxing THF²⁵ to give the alcohol **30** in 69% yield (Scheme 2). This new method for the deprotection of Hoppe's carbamate was ineffective with **16**.

We have applied this methodology to the synthesis of the Japanese beetle sex pheromone, japonilure. The Japanese beetle, *Papillia Japonica*, is a pest causing damage to crops, and japonilure has been used in traps to attract the males.²⁶ It is particularly important that the synthetic pheromone is

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 a (a) MeSO₃H cat., MeOH, reflux, 24 h; (b) HSiCl₃ (6.0 equiv), Et₃N (6.0 equiv), anhydrous THF, reflux, 3 h.

enantiomerically pure, since as little as 0.5% of the unnatural (S)-enantiomer reduces the male response to the pheromone by a third.²⁶ Given the industrial importance of japonilure. a large number of syntheses have been reported.²⁷ Our synthesis starts from 4-pentenol, which is converted into the carbamate 33 in 95% yield (Scheme 3). The derived chiral zinc cuprate is reacted with decynyl bromide²⁸ to give the alkyne 34 in 90% yield. Standard hydrolysis of the carbamate and careful ozonolysis followed by triphenylphosphine workup gave the lactol, which was immediately oxidized to the lactone **36** using nBu_4NI/NIS^{29} in 86% overall yield. The enantiomeric excess of 36 was found to be superior to 99%.³⁰ Reduction of **36** over Lindlar catalyst^{27b} afforded japonilure **37** in 94% yield { $[\alpha]^{21}_{D}$ -69.4°, (c 0.74, CHCl₃); lit.^{27b} $[\alpha]^{21} - 70.4^{\circ}$, (c 1.08, CHCl₃); lit.^{27a} $[\alpha]^{21} - 69.7$ (c 1.0, CHCl₃). This constitutes a particularly efficient synthesis of japonilure (6 steps, 61% overall yield, and ee > 99%).

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^{*a*} (a) (i) NaH, Et₂O, rt, 30 min, (ii) CbyCl, Et₂O, rt, 3 days; (b) (i) *s*BuLi (1.5 equiv), (–)-sparteine (1.5 equiv), Et₂O, -78 °C, 5 h, (ii) ZnCl₂ (0.8 M in THF), -78 °C to rt, (iii) CuCN•2LiCl in THF, -40 to 0 °C, (iv) decynyl bromide,²⁸ -40 to 0 °C; (c) (i) MeSO₃H cat., MeOH, reflux, 15 h, (ii) Ba(OH)₂•8H₂O, MeOH, reflux, 2 h; (d) (i) O₃, DCM, -78 °C, (ii) PPh₃ (1.2 equiv), DCM, -78 °C to rt, 2 h; (e) *N*-iodosuccinimide (5.0 equiv), *n*Bu₄NI (1.0 equiv), rt, 15 min; (f) Lindlar catalyst, H₂, quinoline, pentane, 0 °C, 4 h.

In conclusion, we have demonstrated that Hoppe's lithiated alkyl carbamates can be transmetalated with zinc chloride and further reacted with copper cyanide without loss of chirality. These species react with various electrophiles to afford, after hydrolysis of the carbamate, chiral alcohols of enantiomeric purity superior to 96%.

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Supporting Information Available: Analytical data for compounds 14-20, 25, 26, 28-30, and 33-37 and experimental procedures for compounds 30 and 33-37. This material is available free of charge via the Internet at http://pubs.acs.org.

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