Pergamon

Tetrahedron Vol. 50, No. 8, pp. 2415-2432, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0006-F

Preparation and Reactivity of Chiral β-Amido-Alkylzinc Iodides and Related Configurationally Stable Zinc Organometallics

Rajagopal Duddu, Matthias Eckhardt, Michael Furlong, H. Peter Knoess, Stefan Berger and Paul Knochel*

Philipps-Universität Marburg
Fachbereich Chemie
35032 Marburg, Germany

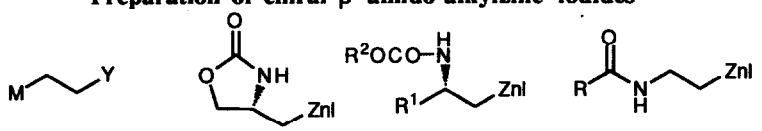
Key words: β-Amido-alkylzinc reagents, configurational stability of zinc organometallics, chiral alkylzinc iodides

Abstract: Several zinc organometallics bearing at the β-position a carbamate or an amido function with an acidic N-H group were prepared using the direct insertion of zinc dust into the corresponding alkyl iodides in THF or THF:DMSO mixtures. Most of the starting iodides were obtained from natural α-amino acids and the resulting zinc species afforded after transmetalation with CuCN·2LiCl and reaction with a selection of relatively reactive electrophiles a variety of polyfunctional 1,2-amino alcohol derivatives and carbamates in optically pure form. Several secondary β-amido alkyl iodides were converted to the corresponding chiral zinc reagents and trapped with electrophiles. The configurational stability of chiral secondary organozinc compounds and the stereochemical course of their reactions were examined.

INTRODUCTION

Zinc organometallics are important nucleophilic reagents having a considerable synthetic potential.[1] Due to their high functional group compatibility, they are ideal intermediates for the elaboration of complex natural products.[2] Furthermore dialkylzincs add in the presence of a chiral titanium catalyst to a variety of aldehydes leading to various classes of secondary alcohols with high enantioselectivity.[3] The excellent tolerance of functional groups by organozinc compounds can be explained by the high covalent character of the carbon-zinc bond (ca. 85%). Recently, we have shown that alkylzinc halides bearing primary or secondary amino or amido groups can be generated by the direct insertion of zinc dust into the corresponding alkyl iodide and further reacted in the presence of CuCN·2LiCl[4] with a range of electrophiles.[5,6] Herein we wish to report two new aspects of this work: (i) the preparation and reactivity of chiral β-amido-alkylzinc halides and (ii) our efforts to prepare configurationally defined zinc organometallic species.

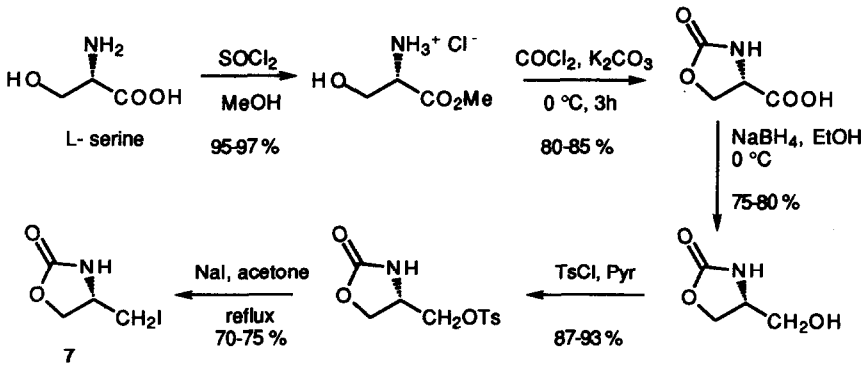
Preparation of chiral β–amido-alkylzinc iodides



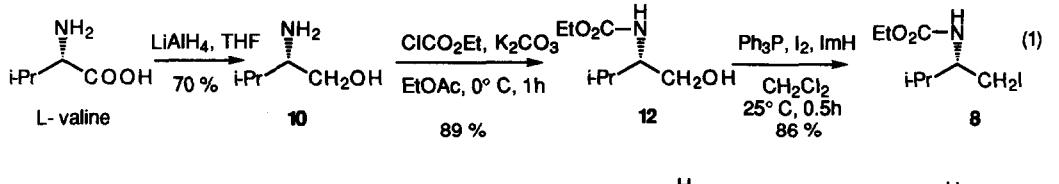
1: M = Li, MgX, ZnX; Y = OR, SR, NR_2 — **2** — **3**: R^1 = i-Pr; R^2 = Et; **4**: R^1 = Bn; R^2 = t-Bu — **5**: R = Me; **6**: R = Ph

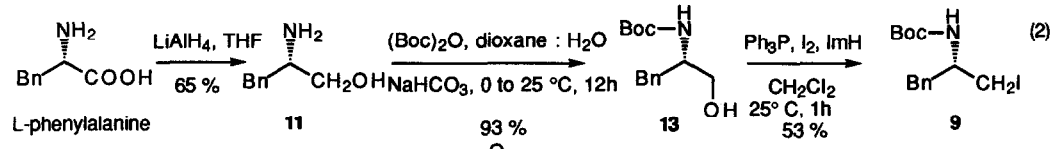
Polar organometallic compounds **1** (M=Li, MgX) bearing a leaving group Y at the β-position (Y=NR_2, OR, SR...) are usually difficult to prepare and readily undergo an elimination reaction.[7] The corresponding zinc reagents **1** (M=ZnX) are considerably more stable.[8] We report in this paper the preparation of various β-amido-

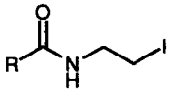
alkylzinc iodides **2-6** obtained from readily available starting materials. Thus the 4-(iodomethyl) oxazolidin-2-one (**7**) was prepared from L-serine using the procedure described by Sibi.[9]



The iodo-carbamates **8** and **9** were obtained in three steps starting from L-valine and L-phenylalanine. After a reduction of these α-amino-acids with lithium aluminium hydride[10] the resulting 1,2-amino-alcohols **10** and **11** were protected as carbamates **12**[11] and **13**[12] and further converted to the corresponding iodides **8** and **9** using triphenylphosphine, imidazole and iodine in CH_2Cl_2 (25 °C, 0.5 - 1h)[13] respectively in 86% and 53% yield (equations 1 and 2). Finally the commercially available N-(2-chloroethyl)acetamide and N-(2-chloroethyl)benza-



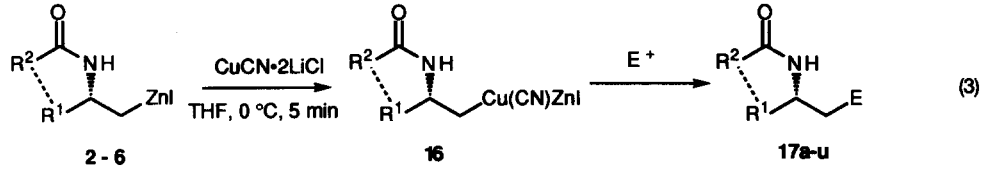




14 : R = Me
15 : R = Ph

mide were heated under reflux with NaI in acetone overnight leading to the β-amido-alkyl iodides **14** (75%) and **15** (94%).[14] The addition of the iodides **7-9** and **14** as a ca. 1.5M THF solution to zinc dust previously activated with 1,2-dibromoethane and TMSCl[4] at 25 °C proceeds smoothly (slightly exothermic to 30-35 °C during the addition). The formation of the zinc reagent is complete after ca. 45 min as judged by GC and ^1H NMR analysis of reaction mixture aliquots. The zinc insertion has been performed at 0 °C in the case of **15** using a THF:DMSO (3:2) solvent mixture leading to a complete insertion within 45 min. After the addition of the THF soluble copper salt CuCN·2LiCl (0 °C, 5 min) the resulting β-amino-copper-zinc reagents **16** react with several classes of electrophiles providing polyfunctional protected amino derivatives of type **17** in 34 -

96% yield (equation 3 and Table 1). Compared to zinc-copper reagents bearing oxygen functionalities, the organometallic species **16** display a reduced reactivity which may the result of intra- or inter-molecular complexation between the donor nitrogen function and the metal center (Zn or Cu). Nevertheless, the reagents **16** can be readily allylated by ethyl α-(bromomethyl)acrylate[15] (entries 1, 9, 14, 18 and 20) or other allylic bromides (entries 2 and 8) in excellent yields (70 - 90%).



2 - 6 **16** **17a-u** (3)

Interestingly, the reaction proceeds with complete S_N2' regioselectivity and 3-phenyl-2-propenyl bromide (entry 2) reacts with **16a** leading only to the allylated product **17b** (> 98% regioselectivity).[4,16] Similarly, propargyl mesylate is substituted by **16a** or **16b** leading cleanly to the corresponding allene[17] (67-84%; entries 3 and 10). A coupling reaction with a 1-iodoalkyne provides an efficient access to chiral homopropargylic amino alcohol derivatives such as **17d** (96% yield, entry 4).[18] Carbometalation of these zinc-copper reagents succeeds only with highly activated alkynes such as diethyl acetylenedicarboxylate leading to the *syn*-addition products with almost complete Z-stereoselectivity (65 - 87%, entries 5, 11 and 15). Ethyl propiolate reacts less readily with **16e** and produces the (E)-δ-benzamido-acrylate **17u** with a low yield of 34%. β-Amino-carbonyl derivatives like **17f** and **17s** (entries 6 and 19) can be prepared by benzoylation (71-51% yield). Whereas Me_3SiCl does not react with the copper-zinc reagents **16**, Me_3SnCl stannylates these organometallics furnishing β-amino-tin derivatives in satisfactory yields (entries 7, 13 and 17). Finally 3-iodo-2-cyclohexen-1-one[19] undergoes a clean addition-elimination reaction with **16b** and **16c** leading to the highly functionalized chiral carbamates **17l** (75%) and **17p** (77%; entries 12 and 16). Michael additions to cyclohexenone or related enones does not proceeds satisfactorily showing the reactivity limitations of these reagents. Interestingly, no appreciable deprotonation of the relatively acidic N-H proton of the carbamate or amide functionalities occurs as indicated by iodolysis experiments of reaction mixture aliquots. However, when the reaction with an electrophile is too slow and requires higher reaction temperatures, then the organometallic **16** is consumed by an unproductive amide or carbamate deprotonation.[5] The remarkable compatibility between an -NH group and a carbon-zinc bond is further demonstrated in the equations 4 and 5. The iodo-amide **18** is rapidly converted to the corresponding zinc reagent under mild conditions (Zn (2-3 equiv), THF, 0 to 25 °C, 15 min). After the addition of CuCN·2LiCl and dimethyl acetylenedicarboxylate (0.7 equiv, -60 °C, 2h), the pure *syn*-carbometalation adduct **19** was obtained in 71% yield (100% Z).The acidic NH_2 group can also be present in the electrophile. Thus the addition of the zinc-copper reagent **20** to propiolamide[20] provides the pure (E)-unsaturated amide **21** in 53% yield.This study shows that a variety of zinc reagents bearing an amide or carbamate function in the β-position to the carbon-zinc bond can be easily prepared. They are stable to β-elimination and react only slowly with the acidic N-H function above 0 °C. The chelation properties of the nitrogen functionalities, however, considerably reduce the reactivity of the copper-zinc **16** and only a selected number of electrophiles react in satisfactory yields. Since the reagents **16a-c** were prepared from optically pure amino-acids, their reaction with electrophiles provides a very convenient access to polyfunctional 1,2-amino alcohol derivatives (**17a-17g**) and to polyfunctional carbamates (**17h-q**) in optically pure form.

Table 1. Polyfunctional protected amino derivatives obtained by the reaction of β-amino-zinc-copper organometallics with electrophiles

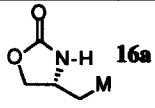
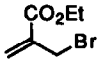
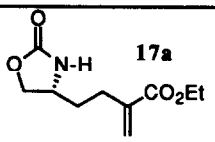
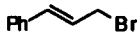
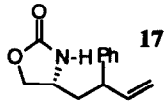
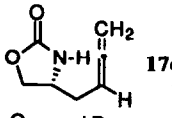
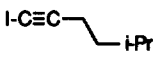
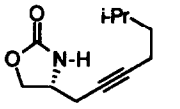
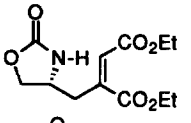
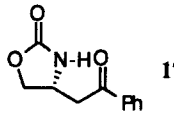
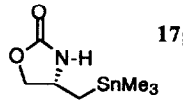
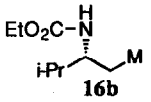
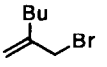
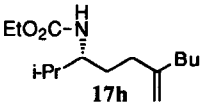
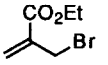
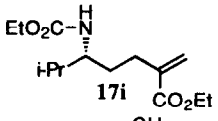
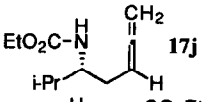
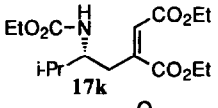
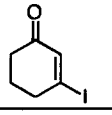
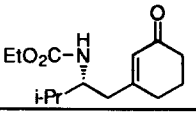
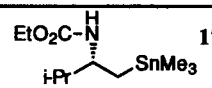
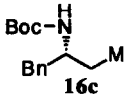
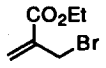
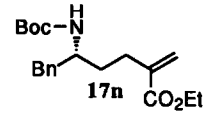
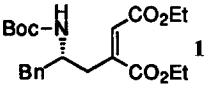
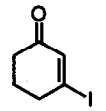
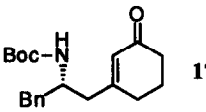
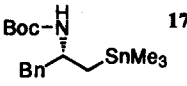
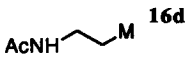
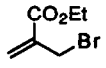
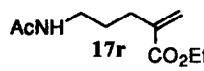
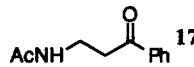
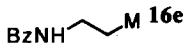
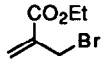
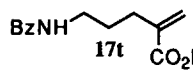
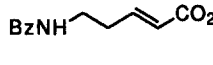
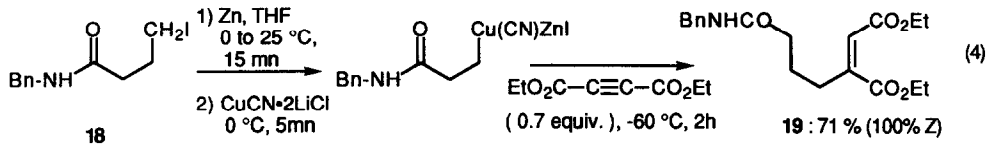
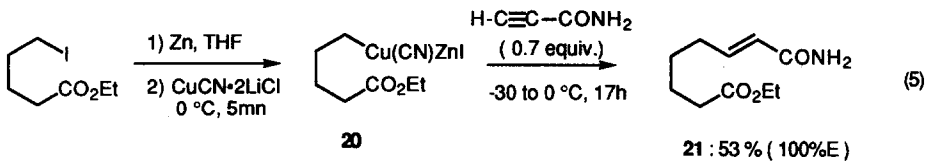
Entry	Zinc-Copper Reagent 16[a]	Electrophile	Product of Type 17	Yield (%)[b]
1	 **16a**		 **17a**	82
2	**16a**		 **17b**	79
3	**16a**	$HC{\equiv}C{-}CH_2OMs$	 **17c**	67
4	**16a**		 **17d**	96
5	**16a**	$EtO_2C{-}C{\equiv}C{-}CO_2Et$	 **17e**	87
6	**16a**	PhCOCl	 **17f**	71
7	**16a**	Me_3SnCl	 **17g**	63
8	 **16b**		 **17h**	70
9	**16b**		 **17i**	74
10	**16b**	$HC{\equiv}C{-}CH_2OMs$	 **17j**	84
11	**16b**	$EtO_2C{-}C{\equiv}C{-}CO_2Et$	 **17k**	68
12	**16b**		 **17l**	75

Table 1 (continued).

Entry	Zinc-Copper Reagent 16[a]	Electrophile	Product of Type 17	Yield (%)[b]
13	**16b**	Me_3SnCl	 **17m**	67
14	 **16c**		 **17n**	90
15	**16c**	$EtO_2C-C\equiv C-CO_2Et$	 **17o**	65
16	**16c**		 **17p**	77
17	**16c**	Me_3SnCl	 **17q**	82
18	 **16d**		 **17r**	82
19	**16d**	PhCOCl	 **17s**	51
20	 **16e**		 **17t**	87
21	**16e**	$EtO_2C-C\equiv C-H$	 **17u**	34[c]

[a] M = Cu(CN)ZnI; [b] All reported yields are yields of isolated compounds being over 98% pure by GC analysis; [c] > 98% E isomer, contamined by 10% of N- ethylbenzamide.

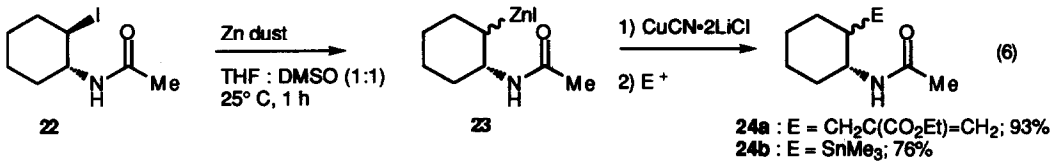


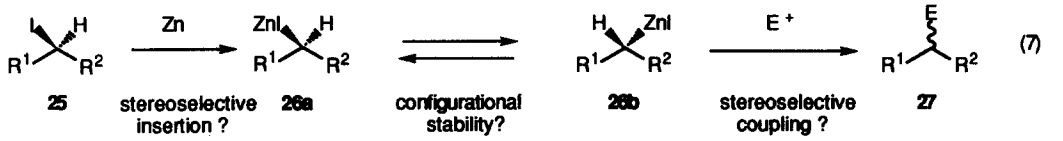


An approach to configurationally stable zinc organometallics

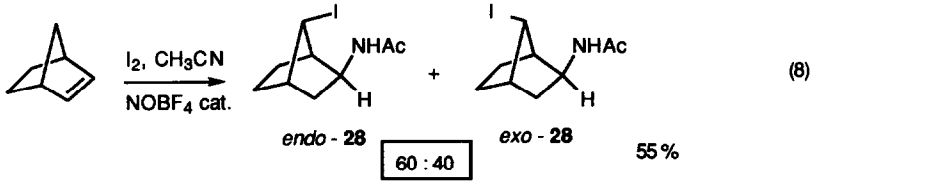
In the course of our studies, we have prepared *trans*-1-acetamido-2-iodocyclohexane[21] **22** and converted it to the corresponding zinc reagent **23** (THF : DMSO 1:1, 25 °C, 1 h). After transmetalation with CuCN·2LiCl and addition of an electrophile (ethyl α-(bromomethyl)acrylate and Me_3SnCl), we obtained the desired products

24a-b in satisfactory yields (respectively 93% and 76%), but as a 1:1 mixture of two diastereoisomers (equation 6).

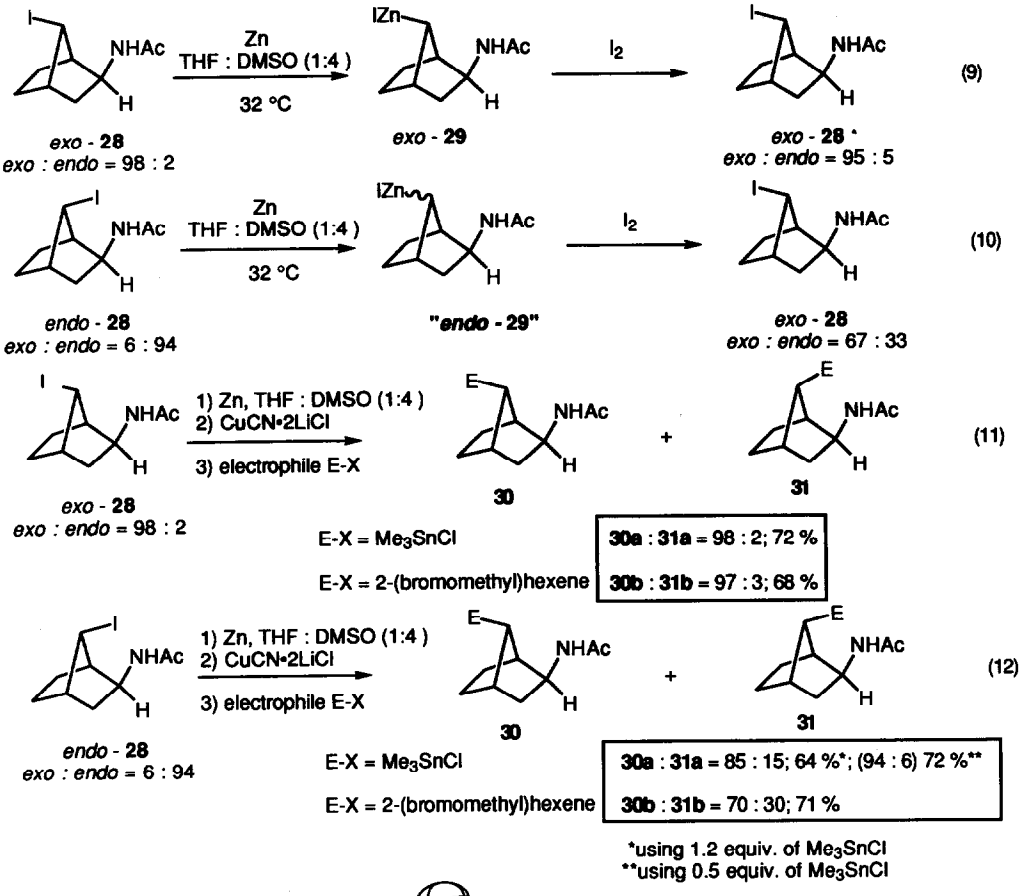




This stereochemical outcome may be due to several reasons: (i) the insertion of the zinc metal into a carbon-iodine bond of an alkyl iodide **25** could be non-stereoselective, (ii) the chiral zinc reagent **26** could be configurationally instable under the reaction conditions used or (iii) the trapping with an electrophile E leading to the product **27** could be non-selective (equation 7). The experiments described below provide some answers to these questions. In order to get some informations concerning the stereoselectivity of the zinc insertion, we have treated 2-norbornene with iodine in acetonitrile in the presence of catalytic amounts of nitrosyl tetrafluoroborate and have obtained a mixture of readily separable *endo* and *exo* 2-acetamido-7-iodobicyclo [2.2.1] heptane **28** (55% yield; *exo*:*endo* = ca. 40:60; equation 8). The zinc insertion occurs at ca. 32 °C for both diastereoisomers



of **28**. In the case of the *endo*-isomer, the reaction can be performed in THF, whereas in the case of *exo*-**28**, the reaction has to be performed in a THF:DMSO mixture (1:4) due to the low solubility of the starting iodide. Iodolysis experiments indicate clearly that the iodide *exo*-**28** (*exo*:*endo* = 98:2) is converted with high stereoselectivity to the *exo*-zinc reagent *exo*-**29** (*exo*:*endo* ratio after iodolysis 95:5; equation 9), whereas the *endo*-**28** (*exo*:*endo* = 6:94) reacts with zinc dust under the same reaction conditions providing after iodolysis a mixture of *exo* and *endo* iodides **28** (*exo*:*endo* = 67:33; equation 10). These results immediately allow some interesting conclusions. First, the zinc insertion does not proceed via a free radical mechanism[22] since this would have led to the same mixture of *exo*- and *endo*-**28** after iodolysis. Second, under our reaction conditions,[23] the iodolysis of a zinc organometallic proceeds with high stereoselectivity (retention of the configuration; equation 9). In order to study the generality of this behavior we have treated the zinc reagents obtained from *exo*-**28** and *endo*-**28** with Me3SnCl and (2-bromomethyl)hexene[24] (equation 11 and 12). We have observed that the zinc reagent prepared from the *exo*-iodide **28** produces after transmetalation with CuCN·2LiCl and stannylation or allylation, the *exo*-coupling products **30a** and **30b** with an excellent selectivity (**30**:**31** ≥ 97:3; 72-68% yield). The structure of the adducts is supported by ^{1}H and ^{13}C NMR spectroscopic data and by the X-ray structure of compound **30a** (Figure 1).



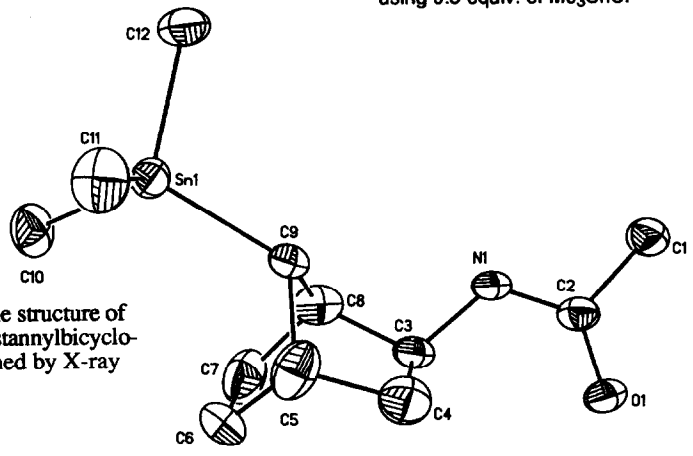
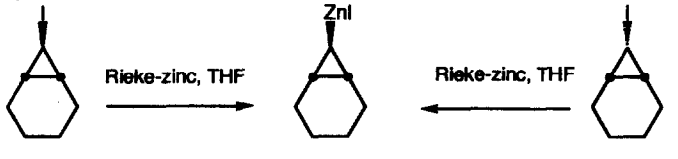


Figure 1
ORTEP Representation of the structure of *exo*-2-acetamido-7-trimethylstannylbicyclo-[2.2.1] heptene **30a** determined by X-ray analysis.

In the case of the *endo*-iodide **28**, like for its iodolysis, the *exo*:*endo* ratios are considerably lower (**30a**:**31a** = 85:15 and **30b**:**31b** = 70:30; 64-71%; equation 12), however, significantly better than for the iodolysis reaction

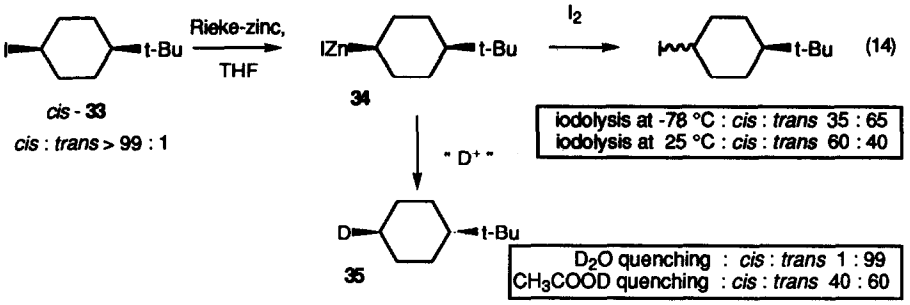
(67:33; equation 10). We attribute this to a preferential reaction with the sterically less crowded *exo*-organozinc-copper reagent. This is supported by the fact that the reaction of 1.2 equiv of Me_3SnCl with the copper-zinc reagent derived from *endo*-**28** produces a 85:15 mixture of *exo* and *endo* products, whereas the same reaction with only 0.5 equivalents of Me_3SnCl provides now the *exo* and *endo* products **30a** and **31a** with the ratio 94:6



(13)

exo - **32** *exo* : *endo* : 95 : 5 as shown by iodolysis *endo* - **32**

(72% yield; equation 12). Although the iodolysis, allylation and stannylation quenching reactions were stereoselective, we have observed that the deuterolysis of the zinc reagents prepared either from *exo*-**28** or *endo*-**28** produce the same deuterated product mixture. These preliminary results show that 7-zincated norbornane derivatives are configurationally stable at room temperature. Related norbornylcopper derivatives have been found by Whitesides to have a high configurational stability.[26] We have briefly investigated the *exo* and *endo*-7-iodonorcarane **32** and have found that in this case both iodides afford the same mixture of the corresponding



endo and *exo* cyclopropylzinc reagents as shown by iodolysis (*exo*:*endo* = ca. 95:5; equation 13). Small but reproducible fluctuations of this ratio were observed depending if the iodolysis was performed at 25 °C or at -15 °C. This was also found in the case of the model compound *cis*-4-*tert*-butylcyclohexyl iodide **33** (100% cis) which afforded after conversion to the corresponding zinc compound and iodolysis the starting iodide **33** as a *cis*:*trans* mixture of 35:65 if the iodolysis is performed at - 78 °C and a *cis*:*trans* mixture of 60:40 if the iodolysis is performed at room temperature. Thus the reaction conditions used for performing quenching reactions influence greatly the steroselectivity of these quenching reactions. Not only is the temperature an important parameter as shown in iodolysis experiments but also the nature of the quenching reagent. Quenching 4-*tert*-butylcyclohexylzinc iodide (**34**) with CH_3CO_2D produces the deuterated cyclohexane **35** as a *cis*:*trans* mixture of 40:60 which is in accord with the low temperature iodolysis results. However a direct quenching of the zinc reagent (**34**) with D_2O produces **35** with a *cis*:*trans* ratio better than 1:99 showing the crucial importance of the reaction conditions for these trapping reactions.

In conclusion we have shown that it is possible in a strained ring system to insert zinc into a secondary carbon-iodine bond with retention of configuration and to trap the corresponding zinc or zinc-copper organometallic with retention of configuration. However this approach is certainly not general and fails for more flexible molecules. This study is also complicated by the strong dependence of the stereoselectivity of the quenching

reactions with the reaction conditions used. Although the nature of the carbon-zinc bond is well suited for leading to configurationally stable secondary alkyl organometallics, the lack of a general method for their stereocontrolled preparation prevents the evaluation of the synthetic potential of these chiral organometallic species.

EXPERIMENTAL

General methods. Unless otherwise indicated, all reactions were carried out under an argon atmosphere. Solvents (THF or DMSO) were dried and freshly distilled over respectively sodium/benzophenone and CaH_2. Zinc dust (-325 mesh) was purchased from Aldrich or Riedel-de Haën (Germany). Reactions were monitored by gas-chromatography (GC) analysis of reaction aliquots. Unless otherwise indicated, the reaction mixtures were worked up as follows: the reaction mixture was poured into a mixture of ethyl acetate and sat. aqueous NH_4Cl. The two phase mixture was filtered to remove insoluble salts and the two layers were separated. The combined organic extracts were washed with water (50 mL) and sat. aqueous NaCl (20 mL), dried over $MgSO_4$ and filtered. The residue obtained after evaporation of the solvents was purified by flash chromatography. Fourier transform infrared spectra (FT-IR) were recorded on a Nicolet 5 DXB spectrometer. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Bruker AC-300 (300 MHz (proton) and 75.5 MHz (carbon)). Mass spectra (MS) and exact mass calculations were recorded on a VG-70-250 S mass spectrometer. The ionization methods used were desorption chemical ionization (CI) and electron impact ionization (EI). All optical rotations have been measured at 25 °C.

Starting materials. The following starting materials were prepared according to literature procedures: (S)-4-(iodomethyl)oxazolidin-2-one **7**,[9] (S)-2-amino-3-methyl-1-butanol **10**,[10] (S)-2-amino-3-phenyl-1-propanol **11**,[10] (S)-2-tert-butoxycarbonyl-3-phenylpropanol,[12] ethyl α-(bromomethyl)acrylate,[15] propargyl mesylate,[27] 3-iodo-2-cyclohexen-1-one,[19] propiolamide,[20] ethyl 4-iodobutyrate,[4] *trans*-1-acetamido-2-iodocyclohexane,[21] (2-bromomethyl)hexene.[24]

(S)-4-(Iodomethyl)oxazolidin-2-one (7):[9] Solid NaI (72.75 g, 425 mmol) was added to a solution of (S)-4-(4-toluenesulfonyloxymethyl)-oxazolidin-2-one[9] (25.0 g, 97 mmol) in dry acetone (250 mL). The reaction mixture was heated under reflux for 16 h. After cooling back to 25 °C, AcOEt (100 mL) was added and the precipitated salts were filtered off and washed again with AcOEt (400 mL). The combined organic layer was evapored and the residue was dissolved in AcOEt (500 mL), washed with sat. aqueous sodium thiosulfate (200 mL), water (200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated to a volume of ca. 100 mL. After the addition of a few mL of hexane, the clear solution became cloudy and was allowed to crystallize overnight in the freezer (ca. -20 °C). The resulting solid was filtered off and dried under vacuum providing the iodide **7** in 72% yield (16.0 g); mp = 52-54 °C. $[\alpha]_D$ = + 12.71 ° (c 3.06, $CHCl_3$). IR (KBr): 3252 (bs), 1761 (s), 1550 (s), ; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.15 (bs, 1H), 4.5 (t, 1H, J = 8.2 Hz), 4.2-4.0 (m, 2H), 3.28 (dd, 1H, J = 4.1, 10.4 Hz), 3.22 (dd, 1H, J = 7.0, 10.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 159.5, 70.4, 52.9, 8.6. MS (EI): 227 (2, M^+), 127 (53), 100 (54), 86 (100). HRMS calcd for $C_4H_6INO_2$: 226.9443; Found: 226.9435.

(S)-2-N-Ethoxycarbonylamino-3-methylbutyl iodide (8):[13] A solution of amino alcohol **12** (5.0 g, 28.5 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a solution of PPh_3 (8.98 g, 34.2 mmol), imidazole (2.33 g, 34.2 mmol) and iodine (8.69 g, 34.2 mmol) in dry CH_2Cl_2 (100 mL). GC analysis of reaction aliquots show that the reaction was complete after 0.5 h. The heterogeneous mixture was filtered and the solid residue was washed with ether (2 x 100 mL). Evaporation of the combined organic layer and flash chromatographical purification (ether:hexane 1:1) afforded a colorless liquid (7.05 g, 86%). $[\alpha]_D$ = -25.37 ° (c 4.26, $CHCl_3$). IR (neat): 3325 (s), 2966 (s), 1694 (s), 1532 (s), ^1H NMR ($CDCl_3$, 300 MHz): δ 4.85 (bd, 1H), 4.05 (q, 2H, J = 7.1 Hz), 3.35 (m, 2H), 3.1 (m, 1H), 1.7 (m, 1H), 1.2 (t, 3H, J = 7.1 Hz), 0.9 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 155.7, 60.4, 56.0, 31.8, 19.0, 17.8, 14.3, 12.0. Mass (CI with NH_3): 303 (100, MNH_4^+), 286 (55, MH^+), 136 (64). HRMS calcd for $C_8H_{16}NO_2IH$: 286.0304. Found: 286.0305.

(S)-2-N-*tert*-Butoxycarbonylamino-1-iodo-3-phenylpropane (9):[13] A solution of the amino alcohol **13**[12] (2.51 g, 10 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a solution of PPh_3 (3.14 g, 12 mmol), imidazole (0.81 g, 12 mmol) and iodine (3.0 g, 12 mmol) in dry CH_2Cl_2 (25 mL). The reaction mixture was stirred at 25 °C for 1 h. The precipitated salts were filtered of and the residual gummy yellow solid obtained after evaporation of the solvents was purified by flash chromatography (ether:hexane 75:25) yielding **9** as a white crystalline solid (1.89 g, 53% yield); mp = 118 °C. $[\alpha]_D$ = 18.87 ° (c 2.93, $CHCl_3$). IR (KBr): 3354 (s), 3032 (s), 2970 (s), 1704 (s), 1655 (s) 1526 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4-7.18 (m, 5H), 4.65 (brs,

1H), 3.6 (m, 1H), 3,4 (dd, 1H, J = 10, 4.4 Hz), 3.15 (dd, 1H, J = 10, 3.9 Hz), 2.85 (m, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 154.7, 136.9, 129.1, 128.5, 126.7, 79.6, 150.9, 40.4, 28.2, 13.9. Mass (CI with NH_3): 379 (20, MNH_4^+), 362 (8, MH^+), 323 (100), 262 (19), 195 (20), 136 (100), 94 (10).

(S)-N-Ethoxycarbonyl-2-amino-3-methyl-1-butanol (12):[11] An aq. solution of K_2CO_3 (3.68 g, 26.6 mmol in 27 mL of water) was added to a solution of (S)-2-amino-3-methyl-1-butanol **10** (5.0 g, 48.5 mmol) in AcOEt (30 mL) and was cooled to 0 °C. Ethyl chloroformate (5.39 g, 49.7 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and diluted with ice-water (100 mL) and brine. The organic layer was separated and the aqueous layer was extracted with AcOEt (2 x 100 mL). The combined organic layer was washed with 1M HCl (50 mL), sat. aqueous $NaHCO_3$ (50 mL) and brine (100 mL). After drying over $MgSO_4$, filtration and evaporation of the solvents, a crude product was obtained which was directly used in the next step (7.51 g, 89% yield). IR (neat): 3332 (bs), 2956 (s), 1694 (s), 1532 (s), ^1H NMR ($CDCl_3$, 300 MHz): δ 5.30 (bd, 1H), 4.05 (q, 2H, J = 7.1 Hz), 3.60 (m, 2H), 3.3 (m, 1H), 1.75 (m, 1H), 1.15 (t, 3H, J = 7.1 Hz), 0.85 (t, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 157.0, 62.6, 60.4, 58.0, 28.8, 19.0, 18.1, 14.1. Mass (CI with NH_3): 176 (25, MNH_4^+), 147 (100), 136 (40). HRMS calcd for $C_8H_{17}NO_3H$: 176.1286. Found: 176.1299.

(S)-N-tert-Butoxycarbonyl-2-amino-3-phenylpropanol (13):[12] To a cooled suspension (0 °C) of (S)-2-amino-3-phenylpropanol **11**[10] (5.3 g, 35.5 mmol) in water (80 mL) was added $NaHCO_3$ (8.9 g, 106 mmol) and $(Boc)_2O$ (9.28 g, 42.5 mmol) in dioxane (80 mL). The reaction mixture was stirrred overnight, diluted with an aqueous saturated solution of $NaHCO_3$ (500 mL) and extracted with AcOEt. The combined organic layer was washed successively with water, brine and dried over $MgSO_4$. After filtration and evaporation of the solvents, the residual solid was triturated with hexane in order to remove the excess Boc_2O. The crude product **13** was 95 % pure by GC analysis (8.28 g; 93 % yield) and was used without purification for the preparation of **9**.

N-(2-Iodoethyl)acetamide 14: A mixture of commercially available N-(2-chloroethyl)acetamide (11.3 g, 92 mmol) and NaI (37.4 g, 250 mmol) was heated in acetone (80 mL) for 4 h at 40 °C. The solvent was evaporated and dry CH_2Cl_2 (200 mL) was added. The resulting precipitate was filtered and the salts washed again with CH_2Cl_2 (2 x 20 mL). The combined organic phase was washed with sat. aqueous sodium thiosulfate and dried over $MgSO_4$. After evaporation of the solvents, a crude yellow oil was obtained 14.72 g (75% yield) which was used directly for the preparation of the zinc reagent. IR (neat): 3287 (s), 3072 (s), 2966 (s), 1743 (s), 1652 (s), 1546 (s). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.85 (bs, 1H), 3.61 (q, 2H, 6Hz), 3.27 (t, 2H, J = 6Hz), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.9, 23.2, 5.07. Mass (CI with CH_4 and NH_3) 231 (10, MNH_4^+), 214 (100, MH^+), 86 (33). HRMS calcd for C_4H_8ONIH: 213.9729. Found: 213.9735.

N-(2-Iodoethyl)benzamide 15. A mixture of commercially available N-(2-chloroethyl)benzamide (15.41 g, 84 mmol) and NaI (37.7 g, 250 mmol) was heated in acetone (80 mL) under reflux for 20 h. The solvent was evaporated and dry CH_2Cl_2 (100 mL) was added. The resulting salts were filtered and washed twice with CH_2Cl_2 (2 x 20 mL). The combined organic phase was washed with sat. aqueous sodium thiosulfate, dried over $MgSO_4$, filtered and concentrated. The resulting pale yellow solid was dried under vacuum (0.1 mm Hg, 25 °C, 60 h) affording 21.70 g (78.9 mmol; 94% yield) of **15**; mp = 107-8 °C. After recrystallization from hot ethanol-water, pale yellow plates were obtained (14.40 g, 63% yield, mp = 108.5-109.5 °C). IR (KBr): 3308 (s), 1643 (s), 1540 (m), 1320 (m), 1291 (m). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.8 (d, 2H, J = 7Hz), 7.5 (m, 3H), 6.5 (bs, 1H), 3.82 (q, 2H, J = 6 Hz); 3.40 (t, 2H, J = 6 Hz). Mass (EI, 70 eV). 275 (1, MH^+), 148 (32), 105 (100), 77 (46). HRMS calcd for $C_9H_{10}NIO$: 274.9807. Found: 274.9822.

Typical procedure for the preparation of an alkylzinc iodide bearing an NHCOR group in β-position (3-6); preparation of (S)-4-(iodozincamethyl)oxazolidin-2-one (2). A dry 50 mL three-necked flask equipped with an argon inlet, a magnetic stirring bar and a low temperature thermometer was charged with zinc dust (0.65 g, 10 mmol) and flushed with argon, 1,2-Dibromoethane (0.2 g) in THF (2 mL) was added via a syringe. The zinc suspension was heated with a heat gun to ebullition and allowed to cool. This cycle was repeated twice. Then Me_3SiCl (0.1 mL) was added and the zinc suspension was stirred 1-2 min at 25 °C. A THF solution of the iodide **7** (1.13 g, 5 mmol in THF (2 mL)) was added dropwise. During the addition, the temperature raised to 30 °C and was maintained for 1 h with a water bath. A GC analysis of a hydrolyzed reaction aliquot shows a complete formation of the zinc reagent **2**. The reaction mixture was diluted with THF (3 mL) and the excess zinc was allowed to settle for 1-2 h at 25 °C and was then ready to use.

Typical procedure for the conversion of the organozinc iodides 2-6 to the corresponding copper derivatives and their reactions with an electrophile. A dry three-necked flask equipped as above was charged with LiCl (0.42 g, 10 mmol previously dried under vacuum at 130 °C for 2 h), CuCN (0.44 g, 5 mmol) and flushed with argon. Dry THF (4 mL) was added and the resulting solution was cooled to -78 °C. The previously prepared THF solution of the zinc reagent was slowly added via syringe. The reaction

mixture was allowed to warm to 0 °C, was stirred for 5 min at this temperature, cooled back to -78 °C and the electrophile (3.5 mmol, 0.7 equiv) was added dropwise. The evolution of the reaction was followed by GC analysis of reaction aliquots. The reaction temperature was raised if no significant reaction was observed (for the specific reaction conditions, see the description of compounds **17a-u**). After completion of the reaction as indicated by GC, the reaction mixture was worked up as described above. The crude product obtained after evaporation of the solvent, was purified by flash chromatography.

Analytical data of the products 17a-u:

(R)-4-(3-Carbethoxy-3-butenyl)oxazolidin-2-one (17a): 970 mg (82% yield). Obtained using **2** (8 mmol) and ethyl α-(bromomethyl)acrylate (1.08 g, 5.6 mmol). Reaction conditions: -30 to 25 °C, 4 h. Chromatography solvent (AcOEt:hexane 1:4). $[\alpha]_D$ = + 0.22 ° (c 1.80, DMSO). IR (neat): 3304 (bs), 2981 (s), 1750 (bs), 1483 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.05 (bs, 1H), 6.1 (s, 1H), 5.5 (s, 1H), 4.4 (t, 1H, J = 8.2 Hz), 4.1 (q, 2H, J = 7.1 Hz), 3.95 (dd, 1H, J = 6.5 Hz), 3.8 (m, 1H), 2.25 (m, 2H), 1.65 (q, 2H, J = 6.3 Hz), 1.2 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 166.5, 159.9, 139.2, 125.5, 169.8, 60.6, 51.8, 34.2, 27.5, 13.9. MS (CI with NH_3): 213 (100, MNH_4^+), 196 (21, MH^+). HRMS calcd for $C_{10}H_{15}O_4N$: 213.1001. Found: 213.1008.

(R)-4-(3-Phenyl-3-butenyl)oxazolidin-2-one (17b): (60:40 mixture of two diastereoisomers); 964 mg (79% yield). Obtained using **2** (8 mmol) and cinnamyl bromide (1.10 g, 5.6 mmol). Reaction conditions: -30 to 0 °C, 12 h. Chromatography solvent (AcOEt:hexane 1:1). IR (KBr): 3239 (bs), 2897 (s), 1729 (s), 1638 (s), 1453 (s), 1418 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.4-7.1 (m, 5H), 6.1-5.85 (m, 1H), 5.5 (brs), 5.1 (m, 4H), 4.5 (t, 1H, J = 8.3 Hz), 4.3 (t, 1H, J = 8.3 Hz), 4.05 (dd, 1H, J = 6.5 Hz), 4.0-3.2 (m, 3H), 3.3 (m, 2H), 2.2-1.9 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 141.0, 140.2, 128.8, 127.4, 127.2, 126.8, 115.4, 114.8, 70.3, 70.3, 52.1, 46.8, 46.7, 41.3, 41.6. MS (EI): 217 (3, M^+), 156 (9), 132 (100), 117 (88), 91 (38), 86 (79). HRMS calcd for $C_{13}H_{15}O_2N$: 217.1102. Found: 217.1103.

(R)-4-(2,3-Butadienyl)-oxazolidin-2-one (17c): 330 mg (67% yield). Obtained using **2** (8 mmol) and propargyl mesylate (0.47 g, 3.5 mmol). Reaction conditions: -30 °C, 12 h. Chromatography solvent (AcOEt:hexane 30:70). $[\alpha]_D$ = + 0.24 ° (c 2.46, $CHCl_3$). IR (neat): 3299 (bs), 2919 (s), 1957 (s), 1751 (s), 1483 (s), 1244 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.9 (bs, 1H), 5.1 (m, 1H), 4.75 (m, 2H), 4.45 (t, 1H, J = 8.5 Hz), 4.1 (dd, 1H, J = 5.6 Hz), 4.0 (m, 1H), 2.3 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 209.0, 159.8, 84.3, 75.6, 69.3, 51.6, 33.6. MS (CI with NH_3): 157 (100, MNH_4^+), 140 (21, MH^+). HRMS calcd for $C_7H_9O_2NH$: 140.0711. Found: 140.0718.

(R)-4-(6-Methyl-2-heptinyl)oxazolidin-2-one (17d): 1.04 g (96% yield). Obtained using **2** (8 mmol) and 1-iodo-5-methyl-1-hexyne (1.25 g, 5.6 mmol). Reaction conditions: - 30 to 0 °C, 6 h. Chromatography solvent (AcOEt:hexane 2:1). $[\alpha]_D$ = 0.13 ° (c 3.0, $CHCl_3$). IR (neat): 3276 (bs), 2952 (s), 1750 (bs), 1420 (s), 1258 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.55 (bs, 1H), 4.45 (t, 1H, J = 8.6 Hz), 4.15 (m, 1H), 3.9 (m, 1H), 2.4 (m, 2H), 2.1 (m, 2H), 1.6 (m, 1H), 1.35 (m, 2H). 0.8 (d, 6H, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 159.5, 83.4, 73.6, 69.1, 51.5, 37.5, 27.0, 25.1, 21.8, 16.4. MS (CI with NH_3): 213 (100, MNH_4^+), 196 (22, MH^+). HRMS calcd for $C_{11}H_{17}NO_2H$: 196.1337. Found: 196.1328.

(Z)-(R)-4-(2,3-Dicarbethoxy-2-propenyl)-oxazolidin-2-one (17e): 1.32 g (87% yield). Obtained using **2** (8 mmol) and diethyl acetylenedicarboxylate (953 mg, 5.6 mmol). Reaction conditions: - 78 to 0 ° C, 6 h. Chromatography solvent (AcOEt:hexane 2:1); mp = 48 °C. $[\alpha]_D$ = +1.86 ° (c 3.46 $CHCl_3$). IR (neat): 3304 (bs), 2988 (s), 1757 (s), 1722 (s), 1652 (s), 1265 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.1 (bs, 1H), 5.95 (s, 1H), 4.5 (m, 1H), 4.25 (q, 2H, J = 7.1 Hz), 4.15 (q, 2H, J = 7.1 Hz), 4.05 (m, 2H), 2.6 (d, 2H, J = 6.3 Hz), 1.4-1.2 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 167.4, 164.0, 158.8, 142.8, 123.9, 68.9, 61.5, 60.7, 50.5, 39.4, 13.7, 13.5. MI (CI with NH_3): 289 (3, MNH_4^+), 213 (100), 196 (7), 136 (10). HRMS calcd for $C_{12}H_{17}NO_6H$: 272.1134. Found: 272.1126.

(R)-4-(Phenacyl)-oxazolidin-2-one (17f): 510 mg (71% yield). Obtained using **2** (5 mmol) and benzoyl chloride (0.49 g, 3.5 mmol); mp = 140 °C. $[\alpha]_D$ = -0.46 ° (c 1.52, DMSO). IR (KBr): 3275 (bs), 2924 (s), 1735 (s), 1682 (s), 1451 (s), 1073 (s). ^1H NMR (DMSO, 300 MHz): δ 7.05 (d, 2H, J = 7.3 Hz), 6.8-6.6 (m, 4H), 3.6 (t, 1H, J = 8.5 Hz), 3.35 (m, 1H), 3.1 (dd, 1H, J = 6.2 Hz), 2.65-2.35 (m, 2H). ^{13}C NMR (DMSO, 75.5 MHz): δ 197.5, 158.3, 136.1, 133.1, 128.4, 127.6, 69.0, 48.0, 43.6. MS (EI): 205 (2, M^+), 120 (63), 105 (100), 77 (46). HRMS calcd for $C_{11}H_{11}NO_3$: 205.0738. Found: 205.0738.

(S)-4-(Trimethylstannyl)-oxazolidin-2-one (17g): 930 mg (63% yield). Obtained using **2** (8 mmol) and trimethyltin chloride (1.11 g, 5.6 mmol). Reaction conditions: -78 to 25 °C, 8 h; mp = 93 °C. $[\alpha]_D$ = -1.79 (c 2.34, $CHCl_3$). Chromatography solvent (AcOEt:hexane 1:4). IR (KBr): 3220 (bs), 2980 (s), 2913 (s), 1765 (s), 1411 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.5 (bs), 4.45 (t, 1H, J = 8.2 Hz), 4.3 (m, 1H), 3.8 (t, 1H, J = 7 Hz), 1.25-1.0 (m, 2H), 0.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 159.6, 72.5, 52.1, 18.1, -9.6. MS

(CI with ammonia): 283 (100, MNH_4^+), 266 (5), 182 (11), 159 (38), 136 (33), 119 (6). HRMS calcd for $C_7H_{15}O_2N^{120}SnH$: 266.0203. Found: 266.0204.

(R)-2-Butyl-5-N-ethoxycarbonylamino-6-methyl-1-heptene (17h): 760 mg (67% yield). Obtained using **3** (5 mmol) and 2-(bromomethyl)hexene (0.62 g, 3.5 mmol). Reaction conditions: -78 to 0 °C, 6 h. Chromatography solvent (AcOEt:hexane 5:95). $[\alpha]_D$ = -9.47 ° (c 2.28, $CHCl_3$). IR (neat): 3364 (s), 2990 (s), 2870 (s), 1691 (s), 1539 (s), 1250 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.65 (d, 2H, J = 3 Hz), 4.45 (d, 1H), 4.05 (q, 2H, J = 7 Hz), 3.45 (m, 1H), 2.0 (m, 4H), 1.8-1.55 (m, 2H), 1.45-1.25 (m, 5H), 1.2 (t, 3H, J = 7 Hz), 0.85 (m, 9H). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 156.6, 149.5, 108.7, 60.4, 56.0, 35.8, 32.5, 32.1, 30.8, 29.9, 22.4, 19.0, 17.5, 14.6, 13.9. MS (CI with NH_3): 273 (3, MNH_4^+), 256 (100, MH^+), 136 (80). HRMS calcd for $C_{15}H_{29}NO_2H$: 256.2276. Found: 256.2272.

(R)-2-Carbethoxy-5-N-ethoxycarbonyl-6-methyl-1-heptene (17i): 1.13 g (74% yield). Obtained using **3** (8 mmol) and ethyl α-(bromomethyl)acrylate (1.08 g, 5.6 mmol). Reaction conditions: -30 to 25 °C, 6 h. Chromatography solvent (AcOEt:hexane 15:85). Mp = 30 °C. $[\alpha]_D$ = -16.22 ° (c 3.31, $CHCl_3$). IR (neat): 3339 (s), 2959 (s), 1715 (s), 1701 (s), 1539 (s), 1244 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.1 (s, 1H), 5.5 (s, 1H), 4.55 (bd, 1H), 4.15 (q, 2H J = 7 Hz), 4.0 (q, 2H, J = 7 Hz), 3.45 (m, 1H), 2.35 (m, 1H), 2.25 (m, 1H), 1.65 (m, 2H), 1.4 (m, 1H), 1.25 (t, 3H, J = 7 Hz), 1.18 (t, 3H, J = 7 Hz), 0.85 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.6, 156.4, 140.3, 124.4, 60.1, 55.5, 31.9, 31.2, 28.7, 18.7, 18.0, 17.4, 14.3, 13.8. MS (CI with NH_3): 289 (13, $(MNH_4)^+$), 272 (100, $(MH)^+$), 243 (91), 177 (11), 136 (32). HRMS calcd for $C_{14}H_{25}NO_4H$: 272.1861. Found: 272.1866.

(R)-5-N-Ethoxycarbonylamino-6-methyl-1,2-heptadiene (17j): 580 mg (84% yield). Obtained using **3** (5 mmol) and propargyl mesylate (0.47 g, 3.5 mmol). Reaction conditions: -30 °C, 12 h. $[\alpha]_D$ = -70.85 ° (c 2.33, $CHCl_3$). Chromatography solvent (AcOEt:hexane 5:95). IR (neat): 3332 (bs). 2961 (s), 1950 (s), 1691 (s), 1537 (s), 1248 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.05 (m, 1H), 4.65 (m, 2H), 4.55 (bd, 1H), 4.1 (q, 2H, J = 7 Hz), 3.55 (m, 1H), 2.2 (m, 1H), 2.1 (m, 1H), 1.8 (m, 1H), 1.25 (t, 2H, J = 7 Hz), 0.9 (m, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 209.3, 156.4, 86.1, 74.4, 60.4, 55.9, 31.7, 31.3, 19.1, 17.6, 14.5. MS (EI): 197 (1, M^+), 144 (100), 116 (22), 98 (13). HRMS calcd for $C_{11}H_{19}O_2N$: 197.1415. Found: 197.1430.

(R)-Ethyl 3-carbethoxy-5-N-ethoxycarbonylamino-6-methyl-2-heptenoate (17k): 1.62 g (68% yield). Obtained using **3** (8 mmol) and diethyl acetylenedicarboxylate (0.95 g, 5.6 mmol). Reaction conditions: -30 to 25 °C, 4 h. Chromatography solvent (AcOEt:hexane 3:1). $[\alpha]_D$ = -7.95 ° (c 4.14, $CHCl_3$). IR (neat): 3339 (bs), 2973 (bs), 1715 (bs), 1652 (s), 1539 (s), 1103 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.85 (s, 1H), 4.65 (bd, 1H), 4.2 (q, 2H, J = 7 Hz), 4.1 (q, 2H, J = 7 Hz), 4.05 (q, 2H, J = 7 Hz), 3.6 (m, 1H), 2.45 (m, 2H), 1.8 (m, 1H), 1.2 (m, 9H), 0.9 (d, 3H, J = 6.8 Hz), 0.85 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.9, 164.4, 156.0, 145.3, 122.6, 70.0, 61.0, 60.3, 54.4, 36.6, 31.5, 18.8, 17.3, 14.2, 13.7, 13.5. MS (CI with NH_3): 347 (22, MNH_4^+), 330 (17, MH^+), 301 (45), 284 (12), 136 (100). HRMS calcd for $C_{16}H_{27}O_6NH$: 330.1916. Found: 330.1908.

(R)-3-[2-(N-Ethoxycarbonylamino)-3-methylbutyl]-2-cyclohexen-1-one (17l): 660 mg (75% yield). Obtained using **3** (8 mmol) and 3-iodo-2-cyclohexen-1-one (0.77 g 3.5 mmol). Reaction conditions. -30 °C, 18 h. Chromatography solvent (AcOEt:hexane 1:4). $[\alpha]_D$ = -57.42 ° (c 1.59, $CHCl_3$). IR (neat): 3325 (brs), 2961 (bs), 1704 (s), 1694 (s), 1664 (s), 1642 (s), 1536 (s), 1412 (s), 1329 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.85 (s, 1H), 4.4 (bd, 1H), 4.05 (q, 2H, J = 7 Hz), 3.9-3.55 (m, 1H), 2.5-1.6 (m, 9H), 1.2 (t, 3H, J = 7 Hz), 0.92 (t, 6H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 199.2, 163.0, 156.3, 127.8, 60.5, 53.8, 41.7, 37.0, 32.2, 29.0, 22.5, 19.0, 17.4, 14.3; Mass (EI, 70 eV): 253 (M^+, 2), 210 (21), 164 (3), 144 (11), 116 (15). HRMS calcd for $C_{14}H_{23}O_3N$: 253.1677. Found: 253.1691.

(S)-3-[2-(N-Ethoxycarbonylamino)-3-methylbutyl]-butyltrimethylstannane (17m): 760 mg (67% yield). Obtained using **3** (5 mmol) and Me_3SnCl (0.69 g, 3.5 mmol). Reaction conditions: -78 to 25 °C, 8 h. Chromatography solvent (AcOEt:hexane 5:95). $[\alpha]_D$ = -3.73 ° (c 2.04, $CHCl_3$). IR (KBr): 3345 (s), 2969 (s), 1693 (s), 1534 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.4 (bd, 1H), 4.15-4.0 (m, 2H), 3.8-3.6 (m, 1H), 1.65 (m, 1H), 1.2 (t, 3H, J = 7 Hz), 1.15-0.9 (m, 2H), 0.89 (t, 6H, J = 7 Hz), 0.09 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 155.8, 60.2, 54.9, 34.8, 18.8, 17.4, 15.7, 14.6, -9.8. Mass (CI with NH_3): 324 (23), 308 (3), 279 (1), 252 (7), 199 (2), 182 (100). HRMS calcd for $C_{11}H_{25}O_2N^{120}SnH$: 324.0985. Found: 324.0987.

(R)-Ethyl 2-(3-*tert*-butoxycarbonylamino-4-phenylbutyl)acrylate (17n): 1.09 g (90% yield). Obtained using **4** (5 mmol) and ethyl α-(bromomethyl)acrylate (675 mg, 3.5 mmol). Reaction conditions: -30 to 25 °C, 6 h. Chromatography solvent (AcOEt:hexane 1:20). $[\alpha]_D$ = +4.57 ° (c 2.32, $CHCl_3$). IR (neat): 3370 (s), 2978 (s), 2932 (s), 1714 (s), 1640 (s), 1580 (s), 1519 (s), 1497 (s), 1453 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.15 (m, 5H), 6.13 (s, 1H), 5.5 (s, 1H), 4.4 (bd, 1H), 4.18 (q, 2H, J = 7.1 Hz), 3.8 (m, 1H), 2.9-2.6 (m, 2H), 2.52-2.2 (m, 2H), 1.75-1.6 (m, 1H), 1.5-1.3 (m, 1H), 1.4 (s, 9H), 1.3 (t, 3H, J = 7 Hz);

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.9, 155.3, 140.1, 138.0, 129.4, 128.2, 126.2, 124.9, 79.0, 60.5, 51.3, 41.4, 33.0, 28.6, 28.3, 14.1; Mass (CI with NH_3): 384 (MH^+, 10), 309 (20), 292 (28), 291 (43), 248 (100), 202 (21), 156 (10), 136 (44); HRMS calcd for $C_{20}H_{29}NO_4H$: 348.2174. Found: 348.2177.

(S)-Ethyl 3-carbethoxy-5-*tert*-butoxycarbonylamino-6-phenyl-2-hexenoate (17o): 0.92 g (65% yield). Obtained using **4** (5 mmol) diethyl acetylenedicarboxylate (0.59 g, 3.5 mmol). Chromatography solvent (AcOEt:hexane 1:9). $[\alpha]_D$ = -13.15 ° (c 1.81, $CHCl_3$). IR (neat): 3430 (bs), 3339 (bs), 3086 (s), 3027 (s), 2977 (s), 2933 (s), 2906 (s), 2872 (s), 1707 (s), 1701 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.1 (m, 5H), 5.9 (s, 1H), 4.5 (bs, 1H), 4.25 (q, 2H, J = 7 Hz), 3.95 (m, 1H), 2.85 (bd, 2H), 2.6-2.5 (m, 2H), 1.4 (s, 9H), 1.32 (t, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.3, 164.5, 154.9, 145.5, 137.5, 129.2, 128.3, 126.4, 122.9, 79.3, 61.4, 60.6, 50.4, 40.4, 38.4, 28.2, 13.9, 13.8. Mass (CI with NH_3): 423 (MNH_4^+, 21), 406 (MH^+, 34), 367 (100), 350 (94), 260 (27), 232 (2), 214 (6), 136 (28). HRMS calcd for $C_{22}H_{31}NO_6H$: 406.2229. Found: 406.2223.

(S)-3-(2-(*tert*-Butoxycarbonylamino)-3-phenylpropyl)-2-cyclohexen-1-one (17p): 880 mg, 77% yield. Obtained using **4** (5 mmol) and 3-iodo-2-cyclohexen-1-one (0.77 g, 3.5 mmol). Reaction conditions: -30 °C, 18 h. Chromatography solvent (AcOEt:hexane 1:9). $[\alpha]_D$ = -15.96 ° (c 1.04, $CHCl_3$): IR (KBr): 3323 (bs), 2946 (bs), 1704 (s), 1654 (s), 1618 (s), 1532 (s), 1494 (s), 1302 (s); 1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.15 (m, 5H), 5.85 (bs, 1H), 4.3 (m, 1H), 4.2-4.05 (m, 1H), 2.95-2.7 (m, 2H), 2.5-2.1 (m, 7H), 2.0-1.9 (m, 1H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 199.2, 162.6, 155.1, 137.4, 129.1, 128.1, 127.9, 126.4, 79.2, 49.4, 43.7, 41.6, 37.1, 29.0, 28.1, 22.5. Mass (CI with NH_3): 347 (MNH_4^+, 100), 330 (MH^+, 16), 291 (96), 274 (21), 230 (7), 167 (7), 138 (13). HRMS calcd for $C_{20}H_{27}O_3NH$: 330.2069. Found: 230.2061.

(S)-(2-N-*tert*-Butoxycarbonylamino-3-phenylpropyl)trimethylstannane (17q): 1.13 g (82% yield). Obtained using **4** (5 mmol) and Me_3SnCl (0.69 g, 3.5 mmol). Reaction conditions. -30 to 0° C, 6 h. Chromatography solvent (AcOEt:hexane 1:9); mp = 76 °C. $[\alpha]_D$ = +4.00 ° (c 1.75, $CHCl_3$). IR (KBr) 3339 (s), 2972 (s), 2955 (s), 2916 (s), 1693 (s), 1681 (s), 1513 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.1 (m, 5H), 4.3 (bs, 1H), 4.0 (m, 1H), 2.65 (d, 2H, J = 6.1 Hz), 1.4 (s, 9H), 1.0 (dq, 2H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 Hz): δ 154.7, 138.4, 129.5, 128.2, 126.1, 79.0, 51.0, 45.2, 28.4, 18.4, -9.6. Mass (CI with NH_3): 400 (MH^+, 13), 384 (10), 361 (5), 348 (24), 344 (88), 343 (39), 342 (70), 340 (45), 326 (22), 282 (17), 208 (11), 182 (100). HRMS calcd for $C_{17}H_{29}NO_2{}^{120}SnH$: 400.1298. Found: 400.1299.

Ethyl 2-(N-acetamidopropyl)acrylate (17r): 0.77 g (94% yield). Obtained using **5** (8 mmol) and ethyl 2-(bromomethyl)acrylate (772 mg, 4 mmol). Reaction conditions: - 40 to 0 °C, 1.5 h. Chromatography solvent (AcOEt:hexane 1:3). IR (neat): 3279 (s), 3080 (m), 2980 (s), 2938 (s), 1714 (s), 1654 (s), 1551 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.17 (s, 1H), 5.70 (bs, 1H), 5.58 (s,1H), 4.20 (q, 2H, J = 6 Hz), 3.23 (q, 2H, J = 6 Hz), 2.33 (t, 2H, J = 6 Hz), 1.97 (s, 3H), 1.69 (m, 2H), 1.30 (t, 3H, J = 6 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170.0, 166.9, 139.7, 124.8, 60.4, 38.6, 28.8, 28.1, 22.8, 13.9. Mass (CI with NH_3): 200 (MH^+, 100), 154 (8), 119 (5), 112 (15). HRMS calcd for $C_{10}H_{17}NO_3H$: 200.1287. Found: 200.1270.

2-(N-acetamido)ethyl phenylketone (17s): 340 mg (51% yield). Obtained using **5** (5 mmol) and benzoyl chloride (490 mg, 3.5 mmol). Reactions conditions: -20 to 0 °C, 12 h. Chromatography solvent (AcOEt:hexane 1:3). IR (KBr): 3297 (m), 1679 (s), 1638 (s), 1597 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.95 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 6.20 (bs, 1H), 3.66 (q, 2H, J = 6 Hz), 3.23 (t, 2H, J = 6 Hz), 1.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.6, 170.1, 136.5, 133.5, 128.7, 128.0, 38.2, 34.3, 23.3. Mass (EI, 70 eV) 191 (M^+, 6), 148 (15), 132 (8), 120 (8), 105 (100). HRMS calcd for $C_{11}H_{13}NO_2$ 191.0946. Found: 191.0944.

Ethyl 2-(N-benzamidopropyl)acrylate (17t): 680 mg (87% yield). Obtained using **6** (4 mmol) and ethyl 2-(bromomethyl)acrylate (610 mg, 3 mmol). Reaction conditions: -60 to 0 °C, 12 h. Purified *twice* by flash chromatography (AcOEt:hexane 1:4). IR (neat): 3323 (m), 2980 (m), 2935 (m), 1715 (s), 1639 (s), 1541 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.77 (m, 2H), 7.43 (m, 3H), 6.6 (bs, 1H), 6.19 (s, 1H), 5.61 (s, 1H), 4.20 (q, 2H, J = 7 Hz), 3.47 (q, 2H, J = 6 Hz), 2.40 (t, 2H, J = 6 Hz), 1.80 (q, 2H, J = 6 Hz), 1.29 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.5, 167.4, 140.1, 134.8, 131.3, 128.5, 126.9, 125.4, 60.8, 39.2, 29.1, 28.8, 14.1. Mass (EI, 70 eV) 261 (M^+, 5), 188 (6), 149 (5), 148 (14), 135 (8), 134 (12), 105 (100). HRMS calcd for $C_{15}H_{19}NO_3$ 261.1365. Found: 261.1352.

(E)-Ethyl 5-N-benzamido-2-pentenoate (17u): 250 mg (34% yield). Contamined by ca. 10 % of N-ethylbenzamide. Obtained using **6** (4 mmol) and ethyl propiolate (0.31 mL, 3 mmol). Reaction conditions: -78 to - 30 °C, 12 h. Chromatography solvent (AcOEt:hexane 15:85). IR (KBr): 3305 (m), 1714 (s), 1637 (s), 1547 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74 (m, 2H), 7.45 (m, 3H), 6.95 (dt, 1H, J = 15.7, 6 Hz), 6.35 (bs, 1H), 5.91 (dt, J = 15.7, 1.5 Hz,1H), 4.18 (q, 2H, J = 7 Hz), 3.59 (q, 2H, J = 6.7 Hz), 2.55 (qd, 2H, J = 1.5, 6.9 Hz), 1.27 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.8, 166.1, 145.1, 134.6, 131.3, 128.4,

126.9, 123.4, 60.2, 38.5, 32.1, 14.1. Mass (EI, 70 eV) 247 (M^+, 1), 134 (27), 105 (100). HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208. Found: 247.1221.

N-Benzyl-4-iodobutanamide (18).

a) N-Benzyl-4-chlorobutanamide: A solution of 4-chlorobutyryl chloride (25.0 g, 177 mmol) in anhydrous ether (125 mL) was cooled to -60 °C. Pyridine (28.0 g, 354 mmol) and benzylamine (19.93 g, 186 mmol) were added and the solution was allowed to warm to 25 °C, then stirred for 2.5 h. The solution was then diluted with ether (150 mL) and filtered. The filtrate was washed successively with aq. 1M HCl, saturated aq. $NaHCO_3$, brine, and then was dried over $MgSO_4$. Evaporation of the solvent followed by recrystallization from ether gave the desired product (24.7 g, 72% yield) as a white solid (unstable to GC analysis); mp = 63-65 °C; IR (KBr): 3297, 3065, 3030, 2966, 2931, 1645, 1539, 1420; ^1H NMR ($CDCl_3$ 300 MHz): δ 7.34-7.22 (m, 5H), 6.31 (brs, 1H), 4.38 (d, 2H, J = 5.8 Hz), 3.56 (t, 2H, J 0 6.2 Hz), 2.36 (t, 2H, J = 7.2 Hz), 2.12-2.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.6, 138.1, 128.4, 127.3, 127.1, 44.3, 43.2, 32.9, 28.1; HRMS (EI) calcd for $C_{11}H_{14}NOCl$: 211.0764. Observed 211.0771.

***b) N-Benzyl-4-iodobutanamide* (18):** A solution of N-benzyl-4-chlorobutanamide (19.25 g, 98.3 mmol), NaI (44.3 g, 295 mmol) in acetone (40 mL) was refluxed for 18 h. The solution was cooled, diluted with ether (500 mL) and filtered. The filtrate was washed with 10 % aq. sodium thiosulfate, brine, then dried over $MgSO_4$. Evaporation of the solvent followed by recrystallization from ether gave **18** (20.85 g, 70% yield) as a yellow solid (unstable to GC analysis); mp = 64-66 °C; IR (KBr): 3438, 3297, 3058, 3030, 2959, 1637; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.18 (m, 5H), 6.87 (brs, 1H), 4.31 (d, 2H, J = 5.8 Hz), 3.13 (t, 2H, J = 6.7 Hz), 2.26 (t, 2H, J = 6.7 Hz), 2.08-1.99 (m, 2H). ^{13}C NNR ($CDCl_3$, 75.5 MHz): δ 171.2, 138.1, 128.5, 127.6, 127.3, 43.5, 36.6, 28.8, 6.4; HRMS (EI): Exact mass calcd for $C_{11}H_{14}NOI$: 303.0120. Observed: 303.0121.

(Z)-N-Benzyl 5.6-dicarbomethoxy-5-hexenamide (19): Yield: 71%; 100% Z Purified by flash chromatography (hexanes:AcOEt, 7:3 to 2:1). IR (neat): 3380, 3301, 3066, 3031, 2952, 1726, 1648, 1541, 1434, 1369; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.27-7.16 (m, 5H), 6.56 (t, 1H, J = 5.6 Hz), 5.73 (d, 1H, J = 0.8 Hz), 4.30 (d, 2H, J = 5.8 Hz), 3.27 (s, 3H), 3.63 (s, 3H), 2.30 (t, 2H, J = 7.5 Hz), 2.16 (t, 2H, J = 7.3 Hz), 1.80-1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 171.7, 168.8, 165.0, 149.3, 138.2, 128.3, 127.4, 127.1, 119.8, 52.1, 51.5, 43.2, 34.7, 33.2, 22.7; HRMS (EI): Exact mass calcd for $C_{17}H_{21}NO_5$: 319.1420. Observed: 319.1417.

(E)-6-Carbethoxy-2-hexamide (21): Yield: 53%. Purified by flash chromatography (AcOEt:hexanes, 3:1). IR (neat): 3332, 3170, 2988, 2952, 1736, 1616; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.77-6.67 (m, 1H), 6.42 (brs, 1H), 6.12 (brs, 1H), 5.82 (d, 1H, J = 15.4 Hz), 4.04 (q, 2H, J = 7.1 Hz), 2.25 (t, 2H, J = 7.4 Hz), 2.19-2.12 (m, 2H), 1.76-1.66 (m, 2H), 1.17 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.0, 168.1, 144.1, 123.8, 60.2, 33.3, 31.0, 23.3, 14.0; HRMS (EI): Exact mass calcd for $C_9H_{15}NO_3H$: 186.1130. Observed: 186.1123.

Analytical data of the products 24a-b obtained by the reaction of the β-acetamidocyclohexylzinc iodide 23 with CuCN·2LiCl and an electrophile. 2-N-Acetamidocyclohexylzinc iodide **23** was prepared according to the general procedure described above. The zinc insertion to N-acetyl-2-iodocyclohexylamine **22**[21] was performed in DMSO and THF (1:1 mixture) at 25 °C and was complete after 1 h.

N-Acetyl-2-trimethylstannylcyclohexylamine (24a): (1:1 mixture of diastereoisomers). 810 mg (76% yield) was obtained as a white solid (mp = 58 °C) using **23** (5 mmol) and Me_3SnCl (690 mg, 3.5 mol). Reaction conditions: -30 ° to 25 °C, 4 h. IR (KBr): 3298 (bs), 3080 (s), 2931 (s), 1651 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.1 (bs, 2H), 4.0 (bs, 1H), 3.55 (m, 1H), 1.82 (s, 3H), 1.78 (s), 1.9-0.9 (m, 8H), -0.05 (s, 9H), -0.05 (s, 9H), -0.09 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 168.6, 168.0, 51.4, 50.1, 35.6, 324, 32.2, 32.1, 29.7, 27.3, 26.9, 26.4, 25.2, 23.2, 23.1. Mass (CI with NH_3): 306 (100, MH^+), 290 (30), 224 (70), 182 (25), 136 (74). HRMS calcd for $C_{11}H_{23}NO^{120}SnH$: 306.0879. Found: 306.0876.

N-Acetyl-2-(2-carbethoxyallyl)-1-cyclohexylamine (24b): (1:1 mixture of diastereoisomers). 1.32 g (93% yield) was obtained using **23** (8 mmol) and ethyl 2-(bromomethyl)acrylate (1.08 g, 5.6 mmol). Reaction conditions: -30 ° to 25 °C, 4 h. IR (neat): 3293 (s), 3075 (s), 2980 (s), 2855 (s), 1716 (s), 1651 (s), 1542 (s), 1446 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.15 and 6.08 (s,1H), 5.8 (bs, 1H), 5.5 and 5.45 (s, 1H), 4.2-4.0 (m, 2H), 3.45-3.35 (m, 1H), 2.7 (m, 1H), 2.3-0.8 (m, ca. 11H), 1.93 (2 s, 3H), 1.28 (t, 3H, J = 7 Hz), 1.26 (t, 3H, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.3, 169.2, 167.07, 167.01, 138.8, 125.7, 60.4, 52.7, 48.1, 41.7, 38.3, 36.0, 33.6, 33.4, 31.0, 29.8, 27.1, 25.4, 24.9, 23.7, 23.1, 21.7. Mass (EI, 70 eV): 253 (4, M^+), 210 (6), 166 (11), 140 (14), 98 (33). HRMS calcd for $C_{14}H_{23}NO_3$: 253.1677. Found: 253.1670.

Preparation of *exo*- and *endo*-2-acetamido-7-iodobicyclo[2.2.1]heptane (28): An oven-dried, 2-L three-necked flask equipped with a gas inlet, an addition funnel, a thermometer and a magnetic stirring bar

was charged with iodine (63.50 g, 0.25 mol, 1.25 equiv.) and acetonitrile. 2-Norbornene (18.80 g, 0.2 mol), water (3.6 mL, 0.2 mol) and nitrosyl tetrafluoroborate (1.30 g, 12 mmol) were successively added. Oxygen was then bubbled in the reaction mixture during 16 h leading to a dark brown-black reaction mixture which was concentrated to 100 mL, then CH_2Cl_2 (200 mL) was added. The mixture was poured in an addition funnel and was washed with sat. aqueous sodium thiosulfate (30 mL), water (200 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated leading to a yellow solid which was further purified by crystallization. The yellow residue was triturated with AcOEt (200 mL). The unsoluble solid was filtered and washed with AcOEt (30 mL) and dried under vacuum for a few hours (25 °C, 0.1 mmHg, 5 h) yielding 10.94 g (39 mmol, 20% yield) of the less soluble white *exo*-**28** (GC analysis shows *exo*-**28**:*endo*-**28** = 98:2). The filtrate was evaporated and the residue was recrystallized from hexanes:ether mixtures and dried similarly under vacuum leading to 18.57 g (67 mmol, 33% yield) of the light yellow *endo*-**28** (GC analysis shows *endo*-**28**:*exo*-**28** = 94:6). The *endo*-iodide **28** (5.0 g) could be further purified by flash chromatography (hexanes:AcOEt 10:1 to 1:1) leading to 4.16 g of white *endo*-**28** (GC purity ≥ 99.5%).

The configurational assignment between *exo*-**28** and *endo*-**28** was performed by 2D-NOESY measurement (Bruker-AMX-500, mixing time 2s). For the endo compound the proton at δ=3.76 (α-iodine)shows strong cross peaks with the bridgehead protons and the multiplet at δ=1.6 belonging to the unsubstituted bridge, whereas the *exo* compound again shows strong cross peaks between the α-iodine proton at δ=3.9 and the bridgehead protons, however, only a rather weak cross peak with the multiplet at δ=1.35.

***Exo*-2-acetamido-7-iodobicyclo[2.2.1]heptane:** mp = 168 °C. IR (KBr): 3274 (s), 2970 (m), 2962 (m), 2939 (m), 1656 (s), 1628 (s), 1546 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.68 (bs, 1H), 3.88 , (s, 1H), 3.75 (m, 1H), 2.32 (m, 2H); 2.00-1.87 (m, 3H), 1.91 (s, 3H), 1.40-1.17 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 50.5, 50.2, 43.7, 38.0, 31.8, 27.1, 25.9, 23.4. Mass (EI, 70 eV): 152 (19), 86 (94), 44 (100). Anal. calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06; N, 5.02. Found: C, 38.92; H, 4.81; N, 5.11.

***Endo*-2-acetamido-7-iodobicyclo[2.2.1]heptane:** mp = 98 °C. IR (KBr): 3262 (s), 2963 (m), 2946 (m), 1627 (s), 1551 (s). ^1H NMR (DMSO-d_6, 500 MHz): δ 7.44 (s, 1H), 3.86 (s, 1H), 3.54 (m), 2.37 (d, 1H, J = 3.9 Hz), 2.30 (bs, 1H), 1.76-1.99 (m, 2H), 1.79 (s, 3H), 1.62-1.51 (m, 2H), 1.22 (dt, 1H, J = 3.6, 10.5 Hz), 1.09 (dt, 1H, J = 2.7, 10.5 Hz). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.4, 53.0, 47.1, 43.2, 37.2, 30.8, 26.5, 24.6, 22.6. Mass (EI, 70 eV): 152 (40), 67 (100). Anal. calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06; N, 5.02. Found: C, 39.00; H, 4.97; N, 5.00. HRMS calcd for $C_9H_{14}NOIH$: 280.0198. Found: 280.0171.

Preparation of the zinc reagents *exo*- and *endo*-29

The zinc reagents *exo*-**29** and *endo*-**29** were prepared under the standard conditions described above. DMSO was used as solvent. The insertion was complete after 2-3 h at 32 °C.

Reactions of the secondary zinc reagents *exo*- and *endo*-29 with electrophiles.

a) Iodolysis: Iodine (400 mg, ca. 1.6 mmol) was dissolved in THF (1 mL) and 0.5 mL of the reaction mixture of *exo* or *endo*-**29** was added at 25 °C. After the addition of ether (3 mL), washing with sat. aqueous sodium thiosulfate and the usual work-up, the ratio between *exo*- and *endo*-**28** was determined by GC analysis. In the case of *exo*-**29** (prepared from *exo*-**28**; *exo*:*endo* ratio = 98:2) the ratio after iodolysis was 95:5. For the iodolysis of the zinc reagent "*endo*-**29**" a ratio *exo*:*endo* of 67:33 was obtained, the original *exo*:*endo* ratio of *endo*-**28** being = 6:94.

b) Stannylation . **Preparation of *exo*-2-N-acetamido-7-trimethylstannylbicyclo [2.2.1] heptane (30a).**

- Starting from the zinc reagent *exo*-**29**. A yield of 1.14 g (72 % yield) of **30a** was obtained starting from *exo*-**29** (5 mmol) and Me_3SnCl (0.5 g, 2.5 mmol; 0.5 equiv.). Reaction conditions: -50 to 25 °C, 4 h. The product was purified by flash chromatography (AcOEt:hexanes 1:1). GC analysis indicates an *exo*:*endo* ratio for **30a**-**31a** of 94:6.
- Starting from the zinc reagent "*endo*-**29**". A yield of 1.01 g (64 % yield) of **30a** was obtained starting from "*endo*-**29**" (5 mmol) and Me_3SnCl (1.19 g, 6 mmol) using the same reaction and purification conditions as indicated above. GC analysis indicates an *exo*:*endo* ratio **30a**:**31a** of 85:15.

30a: mp = 132 °C. IR (KBr): 3270 (s), 2917 (m), 1660 (s), 1630 (s), 1549 (s), 1372 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.4 (bs, 1H), 3.8 (m, 1H), 2.4 (bs, 1H), 2.3 (bs, 1H), 2.05-1.83 (m, 1H), 2.0 (s, 3H), 1.44-1.0 (m, 6H), 0.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.0, 53.6, 46.1, 41.8, 39.5, 34.9, 28.3, 26.9, 23.1, -9.7. Mass (CI with NH_3): 318 (33, MH^+), 136 (100). HRMS calcd for $C_{12}H_{23}NO^{120}SnH$: 318.0879. Found: 318.0901.

c) Allylation with 2-(bromomethyl)hexene. **Preparation of *exo*-2-N-acetamido-7-(2-butyl-2-propenyl)bicyclo [2.2.1] heptane (30b):**

- Starting from the zinc reagent *exo*-**29**. A yield of 590 mg (68% yield) of **30b** is obtained using *exo*-**29** (5 mmol) and 2-(bromomethyl)hexene (620 mg, 3.5 mmol, 0.7 equiv.). Reaction conditions: -50 ° to 25 °C, 4 h. The product was purified by flash-chromatography (AcOEt:hexanes 1:1). GC analysis indicates an *exo*:*endo* ratio of 97:3.
- Starting from the zinc reagent "*endo*-**29**". A yield of 620 mg (71% yield) of **30b** is obtained using "*endo*-**29**" (5 mmol) and 2-(bromomethyl)hexene (620 mg, 3.5 mmol, 0.7 equiv.). Reaction and purification conditions as described above. GC analysis indicates an *exo*:*endo* ratio of 70:30.

30b: IR (KBr): 3301 (s), 2901 (m), 1657 (s), 1548 (s), 1376 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.45 (bs, 1H), 4.7 (d, 2H, J = 4.8 Hz), 3.7 (m, 1H), 2.1-1.7 (m, 8H), 1.98 (s, 3H), 1.7-1.58 (m, 2H), 1.5-1.05 (m, 7H), 0.92 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 169.0, 149.1, 109.1, 53.2, 45.4, 45.2, 40.7, 38.1, 35.8, 33.3, 30.0, 25.6, 24.4, 23.1, 22.3, 13.7. Mass (EI, 70 eV) 249 (11, M^+), 190 (5), 133 (35), 105 (13), 67 (52). HRMS calcd for $C_{16}H_{27}NO$: 249.2092. Found: 249.2103.

Structure determination summary for *exo*-2-acetamido-7-trimethylstannylbicyclo-[2.2.1]heptene (30a):

Crystal Data: empirical formula: $C_{12}H_{23}N_1O_1Sn_1$; formula weight: 316.013 amu; crystal color and habit: colorless rectangular needle; crystal dimensions (mm): 0.20 x 0.20 x 0.68; crystal system: orthorhombic; space group: $Pc2_1b$ (alt. setting #29 $Pca2_1$); Z: 4.

Unit cell dimensions from 35 Reflections ($15.1° \leq 2\theta \leq 30.0°$): a: 6.682(2) Å; b: 9.183(3) Å; c: 23.036(6) Å; α: 90.000°; β: 90.000°; γ: 90.000°; volume: 1413.6(7) $Å^3$; density (calc.): 1.485 gcm^{-3}; F(000): 640 electrons; linear absorption coefficient (μ): 17.90 cm^{-1}

Data Collection: diffractometer: Siemens R3m/v; Radiation type: Mo $K\text{-}\alpha$ λ= 0.71073 Å, Lp corrected, graphite monochromator; temperature: ambient; scan type: θ/2θ scan; 2θ Scan Range: 5-50 degrees; Octants Used: +h, +k, +l (h: 0/8; k: 0/11; l: 0/28) plus Friedel pairs; Scan rate: 1.5-5.0 deg. per min., variable; Scan Width: 0.9° below $K\alpha 1$ to 0.9° above $K\alpha 2$; Background/Scan Ratio: 0.5; Standard Reflections: 3 measured every 97 reflections, linear decay ~5%; number of data collected: 3103; number of unique reflections: 2481, $R_{int.}$ = 0.0170; absorption correction: semi-empirical, psi scans; R merge before/after correction: 0.0358/0.0196; max./min. transmission: 0.662/0.399

Solution and Refinement: system used: Siemens SHELXTL PLUS, VAXStation 3500; solution: Patterson; refinement method: full-matrix least-squares; function minimized: $\Sigma w(|F_O|-|F_C|)^2$; hydrogen atoms: Riding model, d_{C-H} = 0.96 Å, common isotropic U(H) refined to 0.133(6); refined reflections with $(F_O) \geq 0.6\tau(F)$: 2399; number of parameters refined: 138; data/parameter ratio: 17.4; $R = \Sigma(|F_O| - |F_C|) / \Sigma|F_O|$: 0.0323; $R_W = [\Sigma w(|F_O| - |F_C|)^2 / \Sigma w (F_O)^2]^{1/2}$: 0.0480; $w^{-1} = \sigma^2(F_O)+0.000706 (Fo)$; GOF:1.55; mean shift/error: <0.001; maximum shift/error: 0.003; secondary extinction: 4 reflections excluded from refinement; residual electron density: +1.48/-0.95 e/$Å^3$

Synthesis of *exo*- and *endo*-7-iodobicyclo[2.1.0]heptane (32).

Both isomers were prepared from 7,7-dibromobicyclo[2.1.0]heptane[28] in two steps according to literature procedures. The dibromide was reduced with dimethylphosphite in DMSO (25 °C, 2 h; 79% yield) affording *exo*-7-bromobicyclo[2.1.0]heptane[29] (*exo*:*endo* = 99:1). This bromide was treated with n-BuLi (THF, -78 °C, 6 h) and quenched with iodine leading to *exo*-**32** (74%; *exo*:*endo* ratio = 98:2).[30] Similarly 7,7-dibromobicyclo [2.1.0] heptane was reduced to *endo*-7-bromobicyclo[2.1.0]heptane[31] using $LiAlH_4$ in ether in the presence of catalytic amounts of silver perchlorate (71 % yield, *endo*:*exo* = 94:6).[32] After a bromine-lithium exchange performed by using n-BuLi (- 78 °C, 6 h) and iodolysis (I_2, -78 °C), the *endo*-7-iodobicyclo[2.1.0]heptane (*endo*-**32**) was obtained in 74% yield (*endo*:*exo* = 90:10).[30]

Selected analytical data of *exo* and *endo*-32.

Exo-7-iodobicyclo[2.1.0]heptane *exo*-32: bp = 84-88 °C; 15 mmHg. ^{1}H NMR ($CDCl_3$ 300 MHz): δ 2.57 (t, 1H, J = 4 Hz), 1.85-1.62 (m, 4H), 1.29 (m, 2H), 1.23-1.03 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.9, 22.1, 20.7, -8.0. Anal. calcd for $C_7H_{11}I$: C, 37.86; H, 4.99. Found: C, 38.09; H, 5.18.

***Endo*-7-iodobicyclo[2.1.0]heptane (*endo*-32):** bp = 88-91 °C; 15 mmHg. ^{1}H NMR ($CDCl_3$, 300 MHz): d 3.03 (t, 1H, J = 8.1 Hz), 2.1 (m, 2H), 1.42-1.07 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.0, 21.1, 12.1, 10.3. Anal. calcd for $C_7H_{11}I$: C, 37.86; H, 4.99. Found: C, 37.73; H, 5.21.

***Cis*-and *trans*-4-tert-butylcyclohexyl iodide (*cis* and *trans* 33).** Both isomers were prepared from 4-*tert*-butylcyclohexanone. The reduction of this ketone with $LiAlH_4/AlCl_3$ afforded the *trans*-alcohol (*trans*-4-*tert*-butylcyclohexanol) with an excellent selectivity (*cis*:*trans* 0.1:99.9) and 72 % yield[32] which after treatment with N-methyl-N,N'-dicyclohexylcarbodiimidium iodide (THF, 25 °C, 18 h) produces the *cis*-4-*tert*-butylcyclohexanone iodide *cis*-**33** in 60% yield (*cis*:*trans* = 100:0).[33] Similarly, 4-*tert*-butylcyclohexanone was reduced with lithium trisiamylborohydride[34] in THF by -78 °C leading to *cis*-4-*tert*-butylcyclohexanol (84 % yield; *cis*:*trans* = 99.6:0.4). Its reaction with N-methyl-N,N'-dicyclohexylcarbodiimidium iodide produces in

low yields (20%) the desired *trans*-4-*tert*-butylcyclohexyl iodide *trans*-**33** (*cis*:*trans* 28:72). The main product being the elimination product 4-*tert*-butylcyclohexene.

Selected analytical data of *cis*-4-*tert*-butylcyclohexyl iodide *cis*-33: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.83 (m, 1H), 2.10 (m, 1H), 2.05 (m, 1H), 1.61-1.38 (m, 6H), 1.04-1.00 (m, 1H), 0.84 (s, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 47.9, 37.9, 36.9, 32.6, 27.5, 23.4. Anal. calcd for $C_{10}H_{19}I$: C, 45.13; H, 7.20. Found: C, 45.26; H, 7.31.

Preparation of 4-*tert*-butylcyclohexylzinc iodide 34:

Lithium naphthalenide was prepared from lithium (0.29 g, 41.8 mmol) and naphthalene (5.45 g, 42.5 mmol) in dry THF (20 mL). A solution of $ZnCl_2$ (3.0 g, 22 mmol) in dry THF (15 mL) was slowly added. After 10 min of stirring, the active zinc powder[35] was allowed to settle and the solvent was removed with a syringe. Fresh THF (30 mL) was added and removed in the same way after stirring and having allowed the zinc to settle. The active zinc ("Rieke-zinc")[35] was suspended in THF (8 mL) and cooled to -78 °C. 4-*tert*-Butylcyclohexyl iodide (1.07 g, 4.0 mmol) in THF (2 mL) was slowly added and the reaction mixture was allowed to warm up to -50 °C. Complete insertion of zinc had occured at this temperature as indicated by GC analysis of reaction aliquots. The excess of zinc was allowed to settle and the clear solution of the zinc reagent was ready to use.

Iodolysis of 34. The iodolysis was performed at 25 °C as described above leading to a 60:40 mixture of *cis*:*trans* **33** (quantitative conversion). The iodolysis was also performed at -78 °C. In this case a 25 mL three-necked flask equipped with a gas inlet, a septum cap and a low temperature thermometer was charged with iodine (2.5 g, 10 mmol) and THF (10 mL). The solution was cooled to -78 °C and the cooled solution (-70 °C) of the previously prepared **34** was slowly added via cannula. After the usual work-up, the *cis*:*trans* ratio of **33** was determined by GC analysis (*cis*:*trans* = 35:65).

Deuterolysis of 34. a) *Using CH_3COOD:* A three-necked flask equipped with a gas inlet, a septum cap a stirring bar and a thermometer was charged with CH_3COOD (2 mL) in THF (7 mL) and cooled to -70 °C. A solution of the zinc reagent **34** was slowly added. After the usual work-up, the residue was dissolved in hexanes and a ^{2}H NMR spectrum was taken (61 MHz): δ 1.75 ppm (equatorial D 60%), 1.19 ppm (axial D : 40%).

b) *Using D_2O*. By performing the same experiment using D_2O at -75 °C provides the following ^{2}D NMR spectra: δ 1.75 ppm (equatorial D : 100%), 1.19 ppm (axial D : 0%).

Acknowledgments: We thank the Fonds der Chemischen Industrie, the DFG (SFB 260) for generous support of this research, the BASF and Witco Bergkamen for a generous gift of chemicals. H. P. Knoess thanks Okanagan University College, Kelowna, B. C., Canada for a sabbatical leave during 1990-91. We thank Prof. M. P. Sibi for sending us a procedure for the preparation of **7**.

REFERENCES AND NOTES

1. P. Knochel and R. D. Singer *Chem. Rev.* **1993**, *93*, 2117.
2. (a) H. Tsujiyama, N. Ono, T. Yoshino, S. Okamoto and F. Sato *Tetrahedron Lett.* **1990**, *31*, 4481; (b) T. Yoshino, S. Okamoto and F. Sato *J. Org. Chem.* **1991**, *56*, 3205; (c) P. Quinton and T. Le Gall *Tetrahedron Lett.* **1991**, *32*, 4909; (d) T. Tanaka, K. Bannai, A. Hazato, M. Koga, S. Kurozumi and Y. Kato *Tetrahedron* **1991**, *47*, 1861.
3. (a) M. J. Rozema, S. AchyuthaRao and P.Knochel *J. Org. Chem.* **1992**, *57*, 1956; (b) M. J. Rozema, C. Eisenberg, H. Lütjens, R. Ostwald, K. Belyk and P. Knochel *Tetrahedron Lett.* **1993**, *34*, 3115; (c) W. Brieden, R. Ostwald and P. Knochel *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 582; (d) P. Knochel, W. Brieden, M. J. Rozema and C. Eisenberg, *Tetrahedron Lett.* **1993**, *34*, 5881.
4. P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert *J. Org. Chem.* **1988**, *53*, 2390.
5. H. P. Knoess, M. R. Furlong, M. J. Rozema and P. Knochel *J. Org. Chem.* **1991**, *56*, 5974.
6. P. Knochel, M. J. Rozema, C. E. Tucker, C. Retherford, M. Furlong and S. AchyuthaRao *Pure and Appl. Chem.* **1992**, *64*, 361.
7. The conversion of the amino group to a poor leaving group by metalation allows the preparation of β-amido-ethyllithium derivatives: (a) J. Barluenga, F. J. Fananas, M. Yus and G. Asensio *Tetrahedron Lett.* **1978**, 2015; (b) J. Barluenga, F. J. Fananas, J. Villamana and M. Yus *J. Org. Chem.* **1982**, *47*, 1560; (c) J. Barluenga, F. Foubelo, F. J. Fananas and M.Yus *Tetrahedron* **1989**, *45*, 2183; (d) J. Alelmena, F. Foubelo and M. Yus *Tetrahedron Lett.* **1993**, *34*, 1649.
8. (a) R. F. W. Jackson, K. James, M. J. Wythes and A. Wood *J. Chem. Soc., Chem. Commun.* **1989**, 644; (b) R. F. W. Jackson, M. J. Wythes and A. Wood *Tetrahedron Lett.* **1989**, *30*, 5941; (c) R. F. W. Jackson, A. Wood and M. Wythes *Synlett* **1990**, 735; (d) M. J. Dunn and R. F. W. Jackson *J. Chem. Soc., Chem. Commun.* **1992**, 319; (e) R. F. W. Jackson, N. Wishart and M. J. Wythes *J. Chem. Soc., Chem. Commun.* **1992**, 1587; (f) M. J. Dunn, R. F. W. Jackson and G. R. Stephenson *Synlett* **1992**,

905; (g) R. F. W: Jackson, N. Wishart and M. J. Wythes *Synlett* **1993**, 219; (h) R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes *J. Org. Chem.* **1992**, *57*, 3397.
9. (a) M. P. Sibi and P. A. Renhowe *Tetrahedron Lett.* **1990**, *31*, 7407; M. P. Sibi, J. W. Christensen, B. Li and P. A. Renhowe *J. Org. Chem.* **1992**, *57*, 4329.
10. D. A. Dickman, A. I. Meyers, G. A. Smith and R. E. Gawley *Org. Synth. Coll. Vol. 7* **1990**, 530.
11. J. K. Thottathil, J. L. Moniot, R. H. Mueller, M. K. Y. Wong and T. P. Kissick *J. Org. Chem* **1986**, *51*, 3140.
12. M. Bodanszky and A. Bodanszky, The Practice of Peptide Synthesis, Springer Verlag, 1984 p. 20.
13. G. L. Lange and C. Gottardo *Synth. Commun.* **1990**, *20*, 1473.
14. S. Gabriel and S. Stelzner *Chem. Ber.* **1895**, *28*, 2929.
15. J. Villiéras and M. Rambaud, *Synthesis* **1982**, 924.
16. (a) E. Nakamura, S. Aoki, K. Sekiya, H. Oshino and I. Kuwajima *J. Am. Chem. Soc.* **1987**, *109*, 8056; (b) K. Sekiya and E. Nakamura *Tetrahedron Lett.* **1988**, *29*, 5155.
17. H. Ochiai, Y. Tamaru, K. Tsubaki and Z. Yoshida *J. Org. Chem.* **1987**, *52*, 4418.
18. M. C. P. Yeh and P. Knochel *Tetrahedron Lett.* **1989**, *30*, 4799.
19. E. Piers and I. Nagakura *Synth. Commun.* **1975**, *5*, 193.
20. R. B. Vogt U. S. Patent No. 4, 128, 644, Dec. 5, 1978.
21. (a) F. Radner *Acta Chem. Scand.* **1989**, *43*, 902; (b) R. H. Andreatta and A. V. Robertson *Aust. J. Chem.* **1966**, *19*, 161.
22. (a) H. M. Walborsky *Acc. Chem. Res.* **1990**, *23*, 286; (b) H. M. Walborsky and M. Topolski, *J. Am. Chem. Soc.* **1992**, *114*, 3455; (c) H. M. Walborsky and C. Zimmermann *J. Am. Chem. Soc.* **1992**, *114*, 4996; (d) H. M. Walborsky, J. Ollman, C. Hamdouchi and M. Topolski *Tetrahedron Lett.* **1992**, *33*, 761; (e) H. M. Walborsky and C. Hamdouchi *J. Org. Chem.* **1993**, *58*, 1187.
23. The stereoselectivity observed for the iodolysis of carbon-metal bonds depends strongly on the reaction conditions: A. Igau and J. A. Gladysz *Organometallics* **1991**, *10*, 2327.
24. A. Sidduri, M. J. Rozema and P. Knochel *J. Org. Chem.* **1993**, *58*, 2694.
25. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this article.
26. D. E. Bergbreiter and F. M. Whitesides *J. Am. Chem. Soc.* **1974**, *96*, 4937.
27. L. Brandsma in *Preparative Acetylenic Chemistry* Elsevier, Amsterdam **1988**, p. 255.
28. E. V. Dehmlow and M. Lissel *Chem. Ber.* **1978**, *111*, 3873.
29. G. F. Meijs and I. R. Doyle *J. Org. Chem.* **1985**, *50*, 3713.
30. D. T. Longone and W. D. Wright *Tetrahedron Lett.* **1969**, 2859.
31. N. Shimizu, K. Watanabe and Y. Tsuno *Chem. Lett.* **1983**, 1877.
32. E. L. Eliel, R. J. L. Martin and D. Nasipuri *Org. Synth. Coll. Vol. 5* **1973**, 175.
33. R. Scheffold and E. Saladin *Angew. Chem.* **1972**, *84*, 158.
34. H. C. Brown and S. Krishnamurthy *J. Am.Chem.Soc.* **1976**, *98*, 3383.
35. R. D. Rieke *Science* **1989**, *246*, 1260.

(*Received in Germany* 26 *November* 1993; *accepted* 20 *December* 1993)