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Diastereoselective carbozincation of propargylic amines

Hadi Rezaei,[a] Ilan Marek[b] and Jean F. Normant[a,*]

[a]*Laboratoire de Chimie des Organoéléments, Université P. et M. Curie, 4 Place Jussieu, Tour 44-45, Boite 183, 75252, Paris Cedex 05, France*

[b]*Department of Chemistry and Institute of Catalysis, Science and Technology. Technion-Israel Institute of Technology, Technion City, 32000 Haifa, Israel*

Dedicated to Henri B. Kagan on the occasion of his Tetrahedron Prize award

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Abstract—The carbometalation of propargylic amines derived from methylbenzylamine takes place with good 1,3-diastereoselection in the presence of Lewis acids. © 2001 Elsevier Science Ltd. All rights reserved.

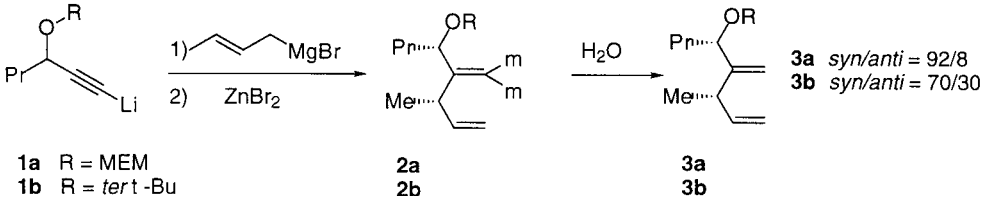
1. Introduction

We have recently shown that the carbometalation by crotylzinc bromide of a metalated propargylic alcohol, blocked by a methoxyethoxymethyl (MEM) group, occurred with a good diastereoselectivity[1] (Scheme 1), whereas a *tert*-BuO protection of the alcohol led to a d.r. of only 70/30.

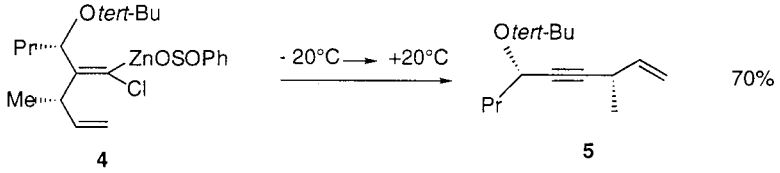
We also observed that when bismetallic reagent **2b** is monochlorinated into **4**,[2] the formed zinc carbenoid undergoes a clean Fritsch–Buttenberg–Wiechell (FBW) rearrangement.[1] Such rearrangement was so far restricted mostly to cases where the migration of hydrogen, or of an aryl group occurred. We could check that zinc had a predominant role in so far as the lithio analog of **4** did not rearrange to the corresponding alkyne **5** (Scheme 2).

Even more, the migration step from **4** takes place with retention of configuration,[1] leading to a formal 1,4-induction in **5**.[1,3]

In this paper we disclose our results in the nitrogen series, and our efforts to obtain an appreciable diastereoselectivity in the carbozincation of a propargylic amino derivative. Since an array of enantiopure amines are commercially available, such an approach should lead to nitrogen analogs



Scheme 1.



Scheme 2.

Keywords: diastereoselection; zinc derivatives.

* Corresponding author. Tel.: +33-1-44-27-55-72; fax: +33-1-44-27-75-67; e-mail: normant@ccr.jussieu.fr

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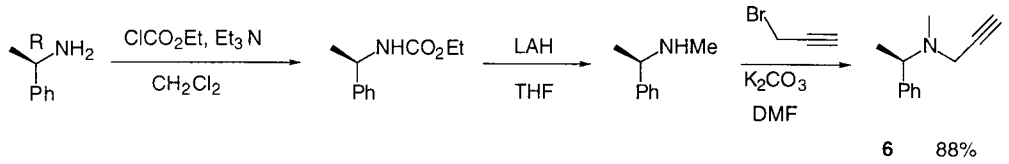
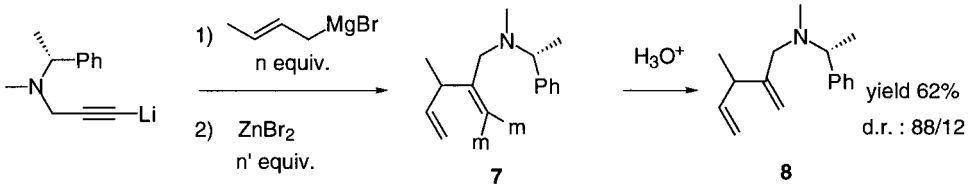


Scheme 3.



Scheme 4.

Table 1. Influence of the ratio of crotylGrignard and zinc salts on the diastereoselection

Entry	CrotylMgBr (equiv.)	$ZnBr_2$ (equiv.)	% d.e. of **8**
1	1.5	1	20
2	3	2	40
3	3	3	30
4	2	3	40

of **3a** in non-racemic form. However, until now, reports on such diastereoselective carbometalation reactions are scarce,[4] in spite of their increasing interest. This is due to the difficulties associated with the enantio facial differentiation of unactivated alkynes.[5]

We chose the methylbenzylamino moiety as a cheap source, available in (*R*) or (*S*) form. The starting derivative **6** is prepared according to Scheme 3.

The carbometalation by crotylzinc bromide of lithiated **6** affords the dienylamine **8**.

The diastereoselectivity depends highly on the ratio of $MgBr_2$ and $ZnBr_2$ present in the reaction mixture. At the outset of this study, we carried out the reaction of Scheme 4 with racemic *N*-methylbenzylamine, and the corresponding influence of added salts is quoted in Table 1.

Use of an excess of zinc bromide is beneficial, although diastereoselectivity remains low. We were then much surprised to observe that, by using non-racemic 1-methylbenzylamine, under the conditions of entry 4, the d.e. raised to 76%! This result can be tentatively explained by considering that the bis metallic reagent **7** is in fact a di-, tri- or tetra-mer (whose stabilities are much higher than that of the monomer, as established computationally for saturated gem biszinca compounds by Nakamura et al.[6]). The carbozincation process being reversible,[7] it is then possible that a homochiral tri- or tetramer be better matched than one of its diastereomers.[8] This point awaits further study.

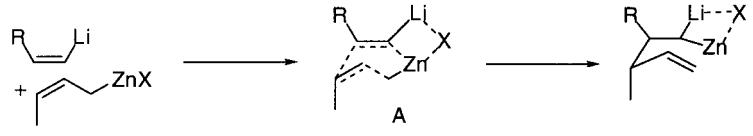
Our choice for methyl benzylamine was dictated by a previous study of the crotyl zincation of an analogous vinyl metal substrate[9] where we postulated a π-stacking between the zinc center and the aromatic residue. In order to check this coordination, we performed the reaction of Scheme 4 using (*S*)-(+)-methylcyclohexylamine, under the same reaction conditions. In this case the dienyl amine is indeed obtained in 69% yield but with a d.r. of 1/1.

The (*S*)-(−)-methyl-1-naphthylamine was then tried, in order to improve the π-stacking, but the reaction required a higher temperature, and the diastereoselectivity was not better (d.r.=87/13).

The hypothesis was to consider the transition state as a 'late' one with a C-metal bond of high sp^2 character. Indeed, computational methods[6,10] in the case of the carbometalation of a vinylmetal show the formation of a precomplex A (Scheme 5) with a square planar Li–C–Zn–X arrangement which is extremely stable as compared to the starting organometallics (ΔH~40 kcal).

If such was the case with the acetylenic reagent, nitrogen chelation and π stacking bring the benzylic methyl in close vicinity with the aromatic and propargylic hydrogens in **B**, whereas in the other possible TS (**C**) this methyl is equatorial and stays apart from these hydrogens (Fig. 1). In order to accentuate this difference of staggering between **B** and **C** the *N*-Me group in **6** was replaced by a more bulky *N*-Et group prepared according to Scheme 6

When **9** was submitted to the crotyl zincation in the optimal conditions described above, the amine **10** was formed with a



Scheme 5.

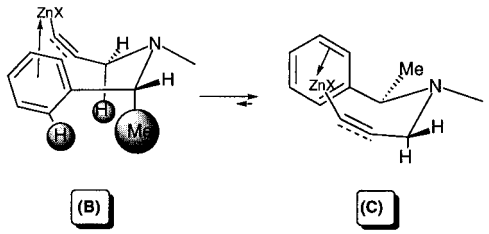
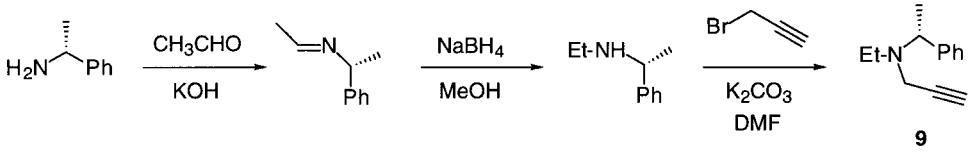


Figure 1. Face selection in a late transition step.

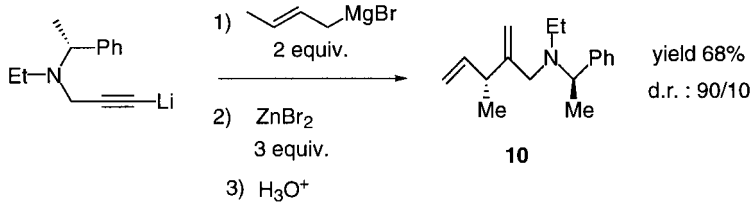
d.r. of 90/10 (Scheme 7) thus only slightly better than the one obtained from **6**.

The geometry of **10** could be ascertained by an X-ray pattern of its crystalline hydrochloride (Fig. 2).

However, if the ethylamino group is replaced by an isopropylamino group, the diastereoselection drops to 75/25. In this case, it is possible that, due to the bulkiness of the nitrogen substituent, π-stacking is no more efficient.



Scheme 6.



Scheme 7.

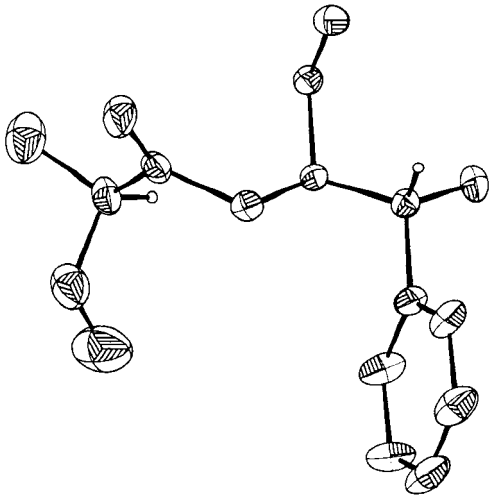


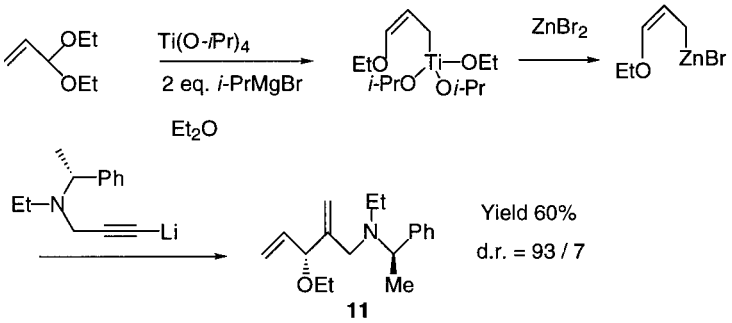
Figure 2. X-Ray crystallographic structure of the hydrochloride of **10**.

When the electron donating ability of the amine is lowered, as is the case with amides, the diastereoselectivity also drops significantly: when the *N*-Me group in **6** is replaced by a *N*-Boc, or a *N*-Tos group, the carbometallation takes place, although at a higher temperature, but the d.r. is almost 1/1.

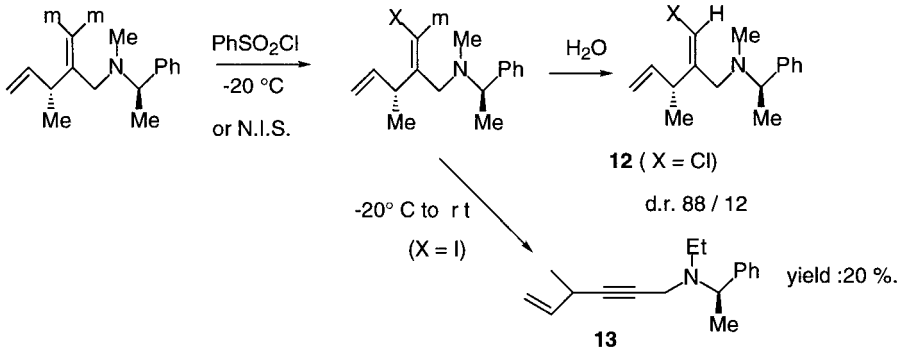
The allylic zinc reagent derived from titanated allyl ethyl ether[11] reacts in the same way, and leads to **11** which was thus obtained with an appreciable d.e. (Scheme 8). Its stereochemistry is attributed by analogy to **10**.

Having at hand a reasonable 1,3-diastereoselection, we then tried the FBW rearrangement.[1]

First **7** was submitted to monochlorination at −20°C and hydrolyzed. NOE experiments showed that the unique monochloroderivative thus obtained was indeed the *E* one, **12** (Scheme 9). However, by warming up the intermediate chloro-zincio carbenoid we could detect no alkyne derived



Scheme 8.



Scheme 9.

from FBW rearrangement. We attribute this failure to a stabilization of the carbenoid by electron donation from the amine to the metal. Already in the oxygen series, the chloro carbenoid derived from **2a**, where oxygen to zinc coordination is important, rearranged much slower than its analog derived from **2b**. This coordination of nitrogen, although helpful for the diastereoselection of the addition step, now turns to hamper dramatically the rearrangement. We tried several ways to circumvent this difficulty, namely the addition of an excess of Lewis acids to coordinate nitrogen:$ZnBr_2$, $ZrCl_2Cp_2$, BF_3–Et_2O, BH_3–THF, as well as transmetalation of zinc to Al ($AlCl_3$, $AlMe_2Cl$), to Ti ($TiCl_2(OiPr)_2$, to Cu (CuCN), or to Co ($CoBr_2$),… were of no help. We also tried the formation of a zincate complex from the intermediate chloro-zincio carbenoid by addition of *tert*-BuOK, PrSLi, or BuLi… but in no case did the rearrangement take place.When the bismetallic **7b** is transformed to an iodozinciocarbenoid, (via NIS), the FBW derived alkyne **13** is formed, however, but in only 20% yield (Scheme 9).

In summary, the carbometalation of propargylamines derived from methylbenzylamine can be realized with a good 1–3 diastereoselection in the presence of excess Lewis acid. The zinc carbenoid, derived from monochlorination of the bismetallic thus obtained is however extremely stabilized, and is not prone to the FBW rearrangement.

2. Experimental

2.1. General

Experiments involving organometallics were carried out under a positive pressure of dry nitrogen. Liquid nitrogen was used as a cryoscopic fluid. A four-necked round bottom flask was equipped with an internal thermometer, a septum cap, a nitrogen inlet and a mechanic stirring, was used. Ether and THF were distilled from sodium-benzophenone ketyl. IR spectra were recorded on a PERKIN-ELMER 1420. NMR spectra have been recorded on either a BRUKER ARX 400 or a BRUKER AC 200, in $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS. The NMR shift corresponding to the major diastereoisomer is indicated with an asterisk (*).

2.1.1. (+)-(*R*)-Ethyl-*N*-(1-phenylethyl)-carbamate[12] (15). To a solution of *R*-(+)-1-phenyl-ethylamine (24.2 g, 200 mmol) in dichloromethane (100 mL) under nitrogen were added triethylamine (6.3 mL, 1.1 equiv.) and, at −30°C, dropwise, ethyl chloroformate (21 mL, 1.1 equiv.), then the mixture was allowed to warm to rt. When no starting material was left (TLC), the reaction mixture was poured into a solution of 0.1 M HCl. The aqueous layer was extracted with dichloromethane (2× 50 mL) and washed with a saturated solution of $NaHCO_3$. The organic layers were dried over $MgSO_4$ and concentrated in vacuo. Yield: 39.8 g (~100%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.18 (t, 3H, J=6.8 Hz), 1.41 (d, 3H, J=6.9 Hz), 4.07 (m, 2H), 4.86 (m, 2H), 7.21–7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.0, 22.9, 50.9, 61.2, 126.3, 127.7, 129.0, 143.8, 156.2. IR (neat): ν=3340, 3010, 2990, 1700 cm^{-1}. $[\alpha]_D^{20}$=+70 (0.86, $CHCl_3$).

2.1.2. (+)-(*R*)-*N*-methyl-1-phenylethylamine.[13] A round bottom flask (500 mL) under nitrogen was charged with lithium aluminium hydride (22.8 g, 3 equiv.) in dry THF (150 mL). A solution of carbamate **15** (200 mmol) in THF (50 mL) was added slowly at 0°C and the mixture was refluxed for 4 h. After cooling down at 0°C, the reaction was diluted with Et_2O (100 mL) and quenched sequentially, dropwise, under vigorous stirring with: H_2O (12 mL), NaOH 15% (22 mL) and H_2O (25 mL). The resulting precipate was stirred for 30 min at rt, filtrated, washed with hot AcOEt, and the filtrate was concentrated in vacuo. Yield: 25.11 g (93%); colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.32 (d, 3H, J=6.6 Hz), 1.45 (s, 1H), 2.28 (s, 3H), 3.60 (q, 1H, J=6.6 Hz), 7.18–7.34 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ=24.2, 34.8, 60.5, 126.8, 127.0, 128.5, 145.5. $[\alpha]_D^{20}$=+74.9 (1.02, $CHCl_3$).

2.1.3. (*R*)-(+)-*N*-methyl-*N*-propargyl-1-phenylethylamine 6. A round bottom flask (250 mL) under nitrogen was charged with (*R*)-*N*-methyl-1-phenylethylamine (25.11 g, 186 mmol) and potassium carbonate (28.2 g, 1.1 equiv.) in DMF (100 mL). Propargyl bromide (15.4 mL, 1.1 equiv.) was added slowly at 0°C and after 2 h stirring at rt, 100 mL water was added and the aqueous layer was extracted with (cyclohexane/dichloromethane: 90/10) (3×70 mL). The joined organic layers were washed with brine (3×20 mL), dried over $MgSO_4$, and concentrated in vacuo. The product can be purified by flash chromatography using cyclohexane/ether: 70/30 or by distillation under low pressure. Yield: 31.2 g (97%); colorless oil. $bp_{20\ mmHg}$= 180°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.38 (d, 3H, J=6.6 Hz), 2.26 (t, 1H, J=2.2 Hz), 2.33 (s, 3H), 3.24 (dd,

1H, J=14.9, 2.2 Hz), 3.47 (dd, 1H, J=14.9, 2.2 Hz), 3.53 (q, 1H, J=6.6 Hz), 7.27–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.6, 39.9, 44.0, 62.3, 73.5, 78.9, 127.2, 127.5, 128.6, 144.8. IR (neat): ν=3250, 3020, 1600, 700 cm^{-1}. $[\alpha]_D^{20}$=+135 (2.4, $CHCl_3$).

2.1.4. *N*-methyl-*N*-(3-methyl-2-methylene-pent-4-enyl)-(*R*)-1-phenylethylamine 8. To a cooled (−30°C) solution of (*R*)-(+)-*N*-methyl-*N*-propargyl-1-phenylethylamine (346 mg, 2 mmol) in dry ether (10 mL) was added dropwise *n*-butyllithium (1.6 M solution in hexane, 1.3 mL, 2 mmol, 1.05 equiv.). The reaction mixture was allowed to warm to rt. After 10 min of further stirring a pale yellow solution was obtained. To this solution were added at rt a solution of crotylmagnesium bromide (1.2 M solution in ether, 3.3 mL, 2 equiv.) (the reaction mixture turned gray) and at −25°C a 1 M ethereal solution of zinc bromide (6 mL, 3 equiv.). The resulting mixture was stirred at −25°C for 6 h and a yellow paste was obtained. The reaction was then hydrolyzed with an aqueous solution of NH_3/NH_4Cl: 1/2. The mixture was then allowed to warm to rt and 0.5 mL of ethanolamine is added. After stirring at rt for 30 min the aqueous layer was extracted with ether (2×20 mL). The combined organic layer was washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and the solvents were evaporated in vacuo. Flash chromatography on SiO_2 (cyclohexane/AcOEt: 90/10) of the crude product yielded: 394 mg (86%) of a clear liquid. d.r.=88/12. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.11/1.14* (d, 3H, J=6.9 Hz), 1.37 (d, 3H, J=6.8 Hz), 2.10 (s, 3H), 2.76 (d, 1H, J=13.4 Hz), 3.05 (m, 2H), 3.06 (q, 1H, J=6.9 Hz), 4.97(m, 4H), 5.57 (m, 1H), 7.24–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=18.1, 19.0, 38.2, 40.6, 59.6, 63.5, 111.3, 113.3, 126.9, 127.9, 128.3, 143.1, 144.3, 151.3. IR (neat): ν=3090, 2980, 1640, 1645, 1010, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N$ (229.12):C, 83.78%; H, 10.11%. found: C, 83.71%; H, 10.15%.

2.1.5. *N*-methyl-*N*-(3-methyl-2-chloromethylene-pent-4-enyl)-(*R*)-1-phenylethylamine 12. The typical procedure described for **8** was followed without hydrolysis. At −20°C was added $PhSO_2Cl$ (3 equiv. 0.77 mL), and the mixture was stirred 1 h at −20°C then warmed to rt. The mixture was then hydrolyzed with a solution of NH_3/NH_4Cl: 1/2. After the usual work-up, flash chromatography on SiO_2 (cyclohexane/AcOEt: 95/5) of the crude product yielded: 432 mg (82%) of a clear liquid. d.r.=88/12. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.14/1.17* (d, 3H, J=7.1 Hz), 1.37 (d, 3H, J=6.7 Hz), 2.09 (s, 3H), 2.87–2.93 (m, 2H), 3.60 (m, 2H), 4.97–5.09 (m, 2H), 5.88–5.92 (m, 1H), 6.14*/6.15 (s, 1H), 7.24–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.9/17.1*, 17.9/18.0*, 38.1, 38.4, 56.4/56.6, 63.6, 114.1/114.2*, 114.8/114.9*, 127.0, 127.7, 128.3, 143.8, 140.4, 142.3/142.4*.

2.1.6. (*S*)-(+)-*N*-methyl-1-cyclohexylethylamine. The typical procedure described for (*R*)-*N*-methyl-1-phenylethylamine was followed using (*S*)-(+)-1-cyclohexylethylamine (5 g, 39.3 mmol). Yield: 3.54 g (64%), colorless oil. ^{1}H NMR (100 MHz, $CDCl_3$) δ=0.95 (d, 3H, J=7.3 Hz), 0.95–1.73 (m, 11H), 2.35 (m, 4H). $[\alpha]_D^{20}$=+9 (6.3, $CHCl_3$).

2.1.7. (*S*)-(+)-*N*-methyl-*N*-propargyl-1-cyclohexylethylamine. The procedure described for **6** was followed from (*S*)-(+)-*N*-methyl-1-cyclohexylethylamine (1 g, 7.1 mmol). Yield: 1.0 g (78%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.93 (d, 3H, J=6.6 Hz), 0.95–1.89 (m, 11H), 2.2 (s, 1H), 2.30 (s, 3H), 2.41 (qt, 1H), 3.30 (dd, 2H, J=14.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.6, 26.5, 26.8, 29.0, 29.8, 31.0, 37.7, 40.9, 43.2, 61.6, 71.6, 80.9. $[\alpha]_D^{20}$=+11 (2.9, $CHCl_3$).

2.1.8. *N*-methyl-*N*-(3-methyl-2-methylene-pent-4-enyl)-(*S*)-1-cyclohexylethylamine. The typical procedure described for **10** was followed using (*S*)-(+)-*N*-methyl-*N*-propargyl-1-cyclohexylethylamine (180 mg, 1 mmol). The reaction mixture was hydrolyzed after stirring for 5 h at −25°C. Flash chromatography on SiO_2 (cyclohexane/AcOEt: 90/10) of the crude product yielded: 141 mg (60%) of a clear liquid. d.r.=50/50. ^{1}H NMR (200 MHz, $CDCl_3$) δ=0.82 (d, 3H, J=6.7 Hz), 1.08 (d, 3H, J=6.9 Hz), 1.12–2.30 (m, 12 H), 1.96 and 2.00 (s, 3H), 2.85–3.00 (m, 3H), 4.80–5.03 (m, 4H), 5.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=9.4/9.6, 18.9/19.1, 26.9, 27.2, 31.1, 31.4, 35.3, 36.2, 40.5, 40.6, 41.8/42.0, 59.4/60.1, 62.9/63.5, 110.8, 113.3, 143.5, 151.9/152.0.

2.1.9. (+)-(*R*)-*N*-ethyl-1-phenylethylamine. To the pure (*R*)-(+)-1-phenyl-ethylamine at 0°C, under nitogen was added dropwise acetaldehyde (11.2 mL, 2 equiv.). After stirring for 4 h potassium hydroxyde (2 g) was added and the solution was stirred for 5 h at rt (the solution became red). Et_2O (50 mL) was added and the organic layer was separated from potassium hydoxide. The etheral solution was dried on potassium hydroxide and concentrated in vacuo to give a crude imine. The crude imine was dissolved in methanol (60 mL) and at +10°C sodium borohydride (6 g, 1.6 equiv.) was added slowly. The reaction was over after 2 h stirring at rt as shown by TLC. The mixture was hydrolyzed with an aqueous solution of NH_3/NH_4Cl: 1/2 (20 mL). Water (20 mL) was added and the aqueous layer was extracted with AcOEt (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the crude product witch can be purified by chromatography on SiO_2 using saturated ammoniacal Et_2O, or by distillation under low pressure. Yield: 11.51 g (77%); colorless oil. $Bp_{15\ mmHg}$=140°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.10 (t, 3H, J=7.1 Hz), 1.38 (m, 4H), 2.52 (m, 2H), 3.79 (q, 1H, J=6.6 Hz). $[\alpha]_D^{20}$=+41 (2.0, MeOH).

2.1.10. (*R*)-(+)-*N*-ethyl-*N*-propargyl-1-phenyl-ethylamine 9. The procedure described for **6** was followed from (*R*)-(+)-*N*-ethyl-1-phenyl-ethylamine (11.51 g, 77.3 mmol). Yield: 12.88 g (90%); colorless oil. $bp_{1\ mmHg}$=80°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.03 (t, 3H, H_4, J=7.2 Hz), 1.38 (d, 3H, H_2, J=6.6 Hz), 2.20 (t, 1H, H_7, J=2.2 Hz), 2.56 (m, 2H, H_3 and $H_{3'}$), 3.39 and 3.63 (2 dd, 2H, H_5 and $H_{5'}$, J=17.7 and 2.2 Hz), 3.72 (q, 1H, H_1), 7.27–7.39 (m, 5H, H_{ar}). ^{13}C NMR (50 MHz, $CDCl_3$) δ=12.9 (C_4), 21.2 (C_2), 38.2 (C_5), 44.5 (C_3), 61.1 (C_1), 72.5 (C_7), 79.2 (C_6), 126.9–127.4–128.4–145.4 (C_{ar}). $[\alpha]_D^{20}$=+102 (2.4, $CHCl_3$).

2.1.11. *N*-ethyl-*N*-(3-methyl-2-methylene-pent-4-enyl)-(*R*)-1-phenylethylamine 10. The typical procedure described for **8** was followed using (*R*)-(+)-*N*-ethyl-*N*-propargyl-1-phenyl-ethylamine (374 mg, 2 mmol). The

reaction mixture was hydrolyzed after stirring 8 h at −25°C. Flash chromatography on SiO_2 (cyclohexane/AcOEt: 95/5) of the crude product yielded: 427 mg (89%) of a clear liquid. d.r.=90/10. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.99 (t, 3H, H_4, J=7.1 Hz), 1.10 (d, 3H, H_{11}, J=7.0 Hz), 1.35 (d, 3H, H_2, J=6.8 Hz), 2.38–2.59 (m, 2H, H_3), 2.92–3.06 (m, 3H, H_5 and H_8), 3.91 (q, 1H, H_1), 4.88–5.07 (m, 4H, H_7 and H_{10}), 5.73–5.82 (m, 1H, H_9), 7.24–7.41 (m, 5H, H_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.4 (C_4), 15.1/16.0* (C_{11}), 18.8 (C_2), 40.3 (C_8), 43.1 (C_3), 54.5 (C_5), 57.6/57.9* (C_1), 110.9 and 113.1 (C_7 and C_{10}), 126.6–128.0–128.1 (C_{ar}), 143.1 (C_9), 144.4 (C_{ar}), 152.1 (C_6). IR (neat): ν=3090, 3020, 2990, 2850, 1680, 1595, 700 cm^{-1}.

2.1.12. Crystal structure of the hydrochloride of 10. Crystal data: $C_{17}H_{26}N_1Cl_1$, AcOEt, M_w=279.86, orthorhombic, space group $P2_12_12_1$, Z=4, a=7.192 (3), c=13.376 (6), c=17.933 (9) Å, V=1725 (1) Å^3, d_{calc}=1.08 g cm^{-3}, λ (MoKα)=0.71069 Å, μ=2.09 cm^{-1}. 1973 collected reflexions, 1950 unique of which 994 were considered as observed having $I \geq 1.7\ \sigma(I)$. Hydrogen atoms fitted the theorical positions. A molecule of AcOEt was not observed. Refinement minimizing the function $\sum \|F_o| - |F_c\| / \sum F_o$, R=0.067 and R_w=0.073, goodness of fit=0.82. The residual electron density in the final difference map was located between −0.31 and 0.38 e Å^{-3}.

2.1.13. *N*-ethyl-*N*-(3-ethoxy-2-methylene-pent-4-enyl)-(*R*)-1-phenylethylamine 11. According to Sato et al.[11] to a cooled (−50°C) solution of diethylacrolein acetal (520 mg, 4 mmol) and titanium tetraisopropoxide (1.2 ml, 4.1 mmol) in dry ether (10 mL) was added a 1.4 M ethereal solution of isopropylmagnesium chloride (4.1 mL, 8.2 mmol). After 2 h of further stirring at −40°C, a red–black solution was obtained. At −40°C a solution of lithiated **6** (2 mmol), prepared as for**8**, was added followed by an ethereal solution of zinc bromide (1 M, 6 mL, 6 mmol). After stirring for 8 h at −10°C, the resulting mixture was hydrolyzed with a solution of NH_3/NH_4Cl: 1/2. After the usual work-up described for **8**, Flash chromatography on SiO_2 (cyclohexane/AcOEt: 95/5) of the crude product yielded: 302 mg (58%) of a clear liquid. d.r.=93/7. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.99 (t, 3H, J=7.2 Hz), 1.16 (t, 3H, J=7.2 Hz), 1.33 (d, 3H, J=6.8 Hz), 2.39 and 2.58 (2m, 3H), 2.98 (s, 2H), 3.33–3.45 (m, 2H), 3.88 (q, 1H), 4.27 (d, 1H), 5.10–5.21 (m, 4H), 5.74 (m, 1H), 7.20–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=12.6*/13.0, 15.8, 16.7, 43.4, 52.3, 57.6/58.2*, 64.3, 81.6, 113.2/113.5*, 116.3/116.5*, 126.9, 128.2, 128.3, 144.4, 138.3, 146.9/147.7*.

2.1.14. *N*-ethyl-*N*-(4-methyl-hex-5-en-2-ynyl)-(*R*)-1-phenylethylamine. The typical procedure of carbometalation described for **9** was followed using (*R*)-(+)-*N*-ethyl-*N*-propargyl-1-phenylethylamine (375 mg, 2 mmol). After 8 h stirring at −25°C, pure NIS was added at −25°C. The mixture was then warm to rt, stirred overnight and hydrolyzed with a solution of NH_3/NH_4Cl: 1/2. After the usual work-up, flash chromatography on SiO_2 (cyclohexane/AcOEt: 90/10) offered: 97 mg (20%) of a pure product as a clear liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.03 (t, 3H, J=7.1 Hz), 1.31 (d, 3H, J=7.0 Hz), 1.38 (d, 3H, J=6.6 Hz), 2.50–2.61 (m, 2H), 3.22 (m, 1H), 3.40 (dd, 1H, J=17.4, 1.8 Hz), 3.58 (dd, 1H), 3.72 (q, 1H, J=6.7 Hz), 5.08 (dt, 1H, J=10.1, 1.5 Hz), 5.33 (dt, 1H, J=16.9, 1.5 Hz), 5.86 (m, 1H), 7.27–7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.2, 21.6, 22.1, 30.1, 38.9, 44.6, 61.4, 77.4, 86.8, 114.2, 127.2,127.8, 128.7, 145.9, 140.2.

2.1.15. (*S*)-*N*-isopropyl-1-phenylethylamine. To a solution of *S*-(−)-1-phenyl-ethylamine (5 g, 41.3 mmol) in methanol (40 mL), was added acetone (7.6 mL 2.5 equiv.) and platinium (IV) oxide (120 mg). The mixture was stirred under atmospheric pressure of hydrogen for 11 h. After a filtration on celite with Et_2O, the solvents were evaporated to give a pure product. Yield: 6.7 g (~100%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.98 and 1.01 (2d, 6H, J=6.3 Hz), 1.32 (d, 3H, J=6.6 Hz), 2.62 (hept, 1H), 3.87 (q, 1H), 7.17–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=22.4, 24.2, 25.1, 45.6, 55.2, 126.5, 126.8, 128.5, 146.3.

2.1.16. (*S*)-(−)-*N*-isopropyl-*N*-propargyl-1-phenylethylamine. The procedure described for **9** was followed from (*S*)-(−)-*N*-isopropyl-1-phenyl-ethylamine (6.7 g, 41.3 mmol). Yield: 7.1 g (86%); colorless oil. $Bp_{10\ mmHg}$=125°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.08 (m, 6H), 1.42 (d, 3H, J=6.6 Hz), 2.19 (t, 1H, J=2.4 Hz), 3.09 (m, 1H), 3.32 (dd, 1H, J=18.2 Hz), 3.48 (dd, 1H), 4.07 (q, 1H), 7.24–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=18.8, 20.7, 21.4, 34.0, 49.0, 58.3, 72.1, 83.3, 127.0, 127.5, 128.5, 146.1. $[\alpha]_D^{20}$=− 77 (2.4, $CHCl_3$).

2.1.17. *N*-isopropyl-*N*-(3-methyl-2-methylene-pent-4-enyl)-(*S*)-1-phenylethylamine. The typical procedure described for **10** was followed using (*S*)-(−)-*N*-isopropyl-*N*-propargyl-1-phenylethylamine (402 mg, 2 mmol). The reaction mixture was hydrolyzed after stirring 6 h at −25°C. Flash chromatography on SiO_2 (cyclohexane/AcOEt: 95/5) of the crude product yielded: 293 mg (57%) of a clear liquid. d.r.=75/25. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.86*/0.89 (d, 3H, J=6.6 Hz), 0.99 (d, 3H, J=6.6 Hz), 1.05* and 1.13 (d, 3H, J=7.0 Hz), 1.35 (d, 3H, J=6.8 Hz), 2.96–3.18 (m, 4H), 3.94 (q, 1H), 4.91–5.24 (m, 4H), 5.83 (m, 1H), 7.23–7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=18.6, 18.9, 19.0, 20.7, 40.8, 47.6/47.8*, 49.5, 57.2/57.6*, 110.5, 113.1, 126.4, 127.7, 128.1, 145.9, 143.2, 153.3.

2.1.18. (*S*)-*N*-methyl-1-naphth-1-yl-ethylamine. The typical procedure described for **6** was followed using (*S*)-(−)-1-naphth-1-yl-ethylamine (5 g, 29.2 mmol). Yield: 3.4 g (63%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.54 (d, 3H, J=6.6 Hz), 1.88 (s, 1H), 2.45 (s, 3H), 4.55 (q, 1H), 7.49–8.21 (m, 7H).

2.1.19. (*S*)-(−)-*N*-methyl-*N*-propargyl-naphth-1-yl-ethylamine. The procedure described for **9** was followed from (*S*)-*N*-methyl-1-naphth-1-yl-ethylamine (1.53 g, 8.27 mmol). Yield: 1.48 g (81%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.51 (d, 3H, J=6.6 Hz), 2.29 (t, 1H, J=2.4 Hz), 2.40 (s, 3H), 3.41 (dd, 1H, J=17.2 Hz), 3.66 (dd, 1H, J=17.2 Hz), 4.37 (q, 1H), 7.45–8.48 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=20.5, 40.1, 44.1, 59.5, 73.4, 79.2, 124.9, 125.5, 125.7, 128.8, 127.6, 128.9, 131.6, 134.2, 140.8. $[\alpha]_D^{20}$=−110 (4.0, $CHCl_3$).

2.1.20. *N*-methyl-*N*-(3-methyl-2-methylene-pent-4-enyl)-

(*S*)-naphth-1-yl-ethylamineThe typical procedure described for **10** was followed using (*S*)-(−)-*N*-methyl-*N*-propargyl-naphth-1-yl-ethylamine (223 mg, 1 mmol). The reaction mixture was hydrolyzed after stirring 5 h at −15°C. Flash chromatography on SiO_2 (cyclohexane/AcOEt: 90/10) of the crude product yielded: 165 mg (60%) of a clear liquid. d.r.=82/18. ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.95*/1.01 (d, 3H, J=6.9 Hz), 1.50 (d, 3H, J=6.7 Hz), 2.19*/2.20 (s, 3H, H_3), 2.90 (m, 2H, H_4 and H_7), 3.05 (d, 1H, $H_{4'}$, J=13.3 Hz), 4.33 (q, 1H, H_1), 4.85–5.01 (m, 4H), 5.65–574 (m, 1H), 7.43–8.45 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=16.3, 18.7, 38.2*/38.71, 38.7, 58.9/59.6*, 111.1, 113.0, 124.1, 124.8, 125.3, 125.4, 127.5, 128.7, 132.0, 134.2, 140.8, 143.0, 151.4.

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