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Enders' SAMP-Hydrazone as Traceless Auxiliary in the Asymmetric 1,4-Addition of Cuprates to Enones

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Dedicated to Prof. Franz Effenberger on the occasion of his 80th birthday.

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Abstract: Conjugate additions of Gilman cyanocuprates to (*S*)-*N*-amino-2-(methoxymethyl)pyrrolidine (SAMP)-hydrazones **4**, **5** derived from cyclic and acyclic α,β-unsaturated ketones were investigated. A protocol utilizing copper(II) sulfate/ammonium chloride was evolved, which allowed cleavage of SAMP (*S*)-**1** under the hydrolysis and work-up conditions, followed by recovery of the auxiliary with ethylenediaminetetraacetic acid (EDTA). The enantioselectivity of cuprate additions was dominated for cyclic SAMP-hydrazones **4** by the cuprate alkyl substituent and the ring size, in the case of acyclic arylidene SAMP-hydrazones **5**, however, by the nature of the aryl substituent. Electron-donating substituents gave poor enantiomeric excesses, whereas electron-withdrawing groups provided excellent *ee* values of 98–99%. The configuration of the new stereocenter was determined to be (*R*). Moreover, a reaction sequence was developed which integrates a tandem 1,4-addition/methylation and traceless hydrolytic cleavage of the auxiliary (*S*)-**1** in a one-pot reaction, resulting in enantiomerically pure methyl ketones **11**–**13**, each of them with > 99% *ee*.

Keywords: asymmetric synthesis; chiral auxiliaries; conjugate addition; cuprates; SAMP-hydrazones

Introduction

Since their introduction in 1976 Enders' (*S*)- and (*R*)-*N*-amino-2-(methoxymethyl)pyrrolidines, SAMP (*S*)-**1** (Scheme 1) and RAMP (*R*)-**1**, belong to the most versatile and successful chiral auxiliaries, which have been employed in asymmetric syntheses.[1,2] Among the broad range of carbonyl compounds forming the corresponding chiral hydrazones with (*S*)- or (*R*)-**1**, enones are much less exploited. For example, Tokoroyama used the stereoselective α′-alkylation of cyclohexenone-derived SAMP-hydrazone **4a** for the preparation of the clerodane diterpenoid (−)-methyl kovalenate.[3] Palacios published the synthesis of α,β-unsaturated hydrazones by Wittig reaction of functionalized ylides and phosphane oxides[4] and Pearson employed α,β-unsaturated hydrazones for the preparation of chiral tricarbonyl iron diene complexes.[5] Besides the use of the C=N bond in **4a** as a dipolarophile in asymmetric [3+2]cycloadditions[6] Enders studied in 1993 conjugate additions of stannyllithium compounds to **4a**.[7] However, to the best of our knowledge 1,4-additions of organometallic carbon nucleophiles such as cuprates to α,β-unsaturated hydrazones have not been reported in the literature. Due to their functional group tolerance and their possible utilization in tandem reactions, stoichiometric cuprate additions are still highly attractive[8–10] despite the tremendous achievements in Cu- and Rh-catalyzed conjugate additions.[11,12] However, the latter do not give reliable yields and enantioselectivities in each case[13] and were only rarely combined with electrophilic trapping of the intermediate enolate.[14] Furthermore, Rh-catalyzed conjugate additions are limited to aryl- and vinylboronic acids,[12] whereas alkyl groups cannot be transferred. These findings motivated us to study the application of Enders' SAMP-hydrazone methodology to conjugate cuprate additions to a variety of α,β-unsaturated carbonyl compounds. The results are reported below.

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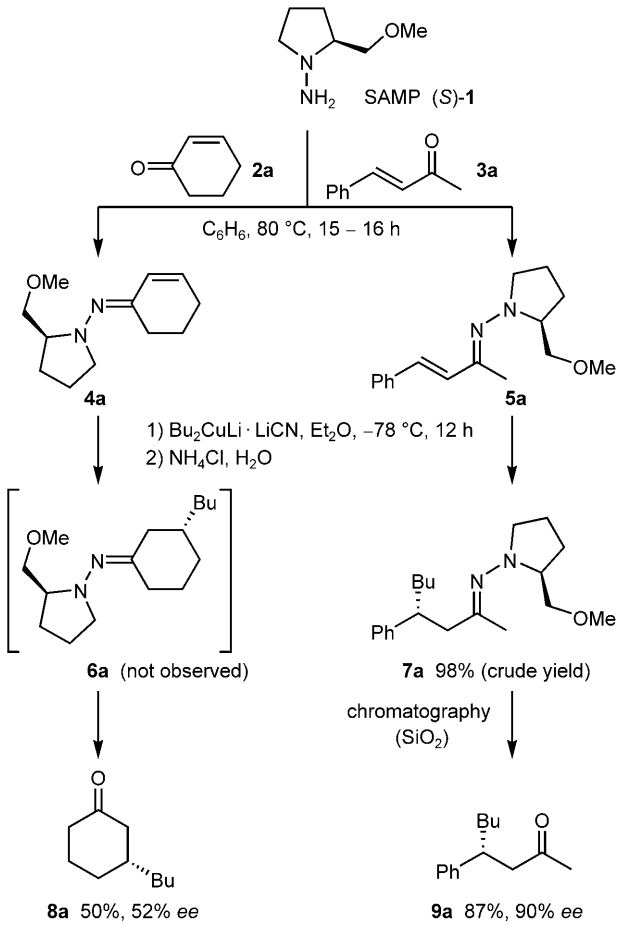

Scheme 1. 1,4-Addition of Gilman cuprate $Bu_2CuLi{\cdot}LiCN$ to SAMP-hydrazones **4a** and **5a**.

Results and Discussion

In a preliminary experiment six-membered ring SAMP-hydrazone **4a**[1c,2f,3] was treated with Gilman cuprate $Bu_2CuLi{\cdot}LiCN$ in Et_2O at −78 °C followed by hydrolysis with a saturated NH_4Cl solution and aqueous work-up (Scheme 1). Surprisingly, the reaction did not give the expected β-substituted hydrazone **6a**, but 3-butylcyclohexanone **8a** was isolated in 50% yield with 52% *ee*. This result suggested that the α,β-unsaturated hydrazone is still intact during the C–C bond formation and thus exerts some stereocontrol on the reaction. The conversion of 4-phenylbut-3-en-2-one (**3a**)-derived SAMP-hydrazone **5a** with the Gilman cuprate under identical conditions yielded the crude β-substituted hydrazone **7a** in 98%.[15] After chromatographic purification on silica gel, however, only (4*R*)-4-phenyloctan-2-one (**9a**) was isolated in 87% with the high enantiomeric excess of 90%.

From these results we anticipated that SAMP (*S*)-**1** might be useful as a "traceless auxiliary" for this kind of asymmetric conjugate additions. The concept of "traceless auxiliaries" has been first introduced by d'Angelo and co-workers in Michael additions of chiral imines to methyl vinyl ketone.[16] Later Hall evolved a synthesis of α-exomethylene-γ-lactones where the auxiliary is either cleaved directly under the reaction conditions or during work-up[17] and Glorius further developed this strategy for catalytic hydrogenations of pyridines.[18] Noteworthy, Enders much earlier used this concept in the SAMP-mediated synthesis of 1,4-dihydropyridines by tandem Michael addition of acetoacetate to benzylidene acetone derivatives and subsequent cyclization, although the term "traceless auxiliary" was never mentioned.[19] Very recently, "traceless auxiliaries" have been applied by Tius for allene ether Nazarov cyclizations[20] and by Kolesinska for peptide couplings.[21] Also *ortho*-diphenylphosphanylbenzoate (*o*-DPPB)-directed allylic substitutions with cuprates developed by Breit can be considered in this category.[22,23]

In order to initiate our studies on SAMP-mediated conjugate additions in more detail, a series of cyclic and acyclic α,β-unsaturated SAMP-hydrazones **4a–c** and **5a–f** were prepared by heating the corresponding enones with (*S*)-**1** in benzene under Dean–Stark conditions (for details see Experimental Section). SAMP-hydrazones **4** and **5**, which were obtained as *E/Z*-mixtures in 73% to 90% and 83% to quantitative yield (Table 1 and Table 2), respectively, were reacted in Et_2O at −78 °C with a slight excess of various Gilman cuprates $R_2CuLi{\cdot}LiCN$ (R = Me, Et, *n*-Bu, *t*-Bu) in the presence of the additive LiBr, and the reaction mixture was allowed to warm to 15 °C overnight. Cleavage of the hydrazone moiety to regenerate the carbonyl functionality depended on the type of SAMP-hydrazone, and thus two different work-up protocols using hydrolytic cleavage conditions have been worked out. Cyclic SAMP-hydrazones **4** were treated with a saturated aqueous NH_4Cl solution at room temperature for 1 h, followed by addition of a 0.4 M $CuSO_4{\cdot}5H_2O$ solution in H_2O/MeOH (1:1) (Table 1). Acyclic SAMP-hydrazones **5** were treated sequentially with a half-saturated aqueous NH_4Cl solution and a 0.4 M $CuSO_4{\cdot}5H_2O$ solution in MeOH for 2 h at room temperature (Table 2).[24] Upon addition of $CuSO_4$ under both conditions an immediate color change from dark yellow to wine red was observed, which is caused by the formation of $(SAMP)_2CuSO_4$ complex **10** ($\lambda_{max} = 260$ nm).[25] The obtained product mixtures were chromatographed on silica gel to yield the β-alkylated ketones **8** and **9** (Table 1 and Table 2), while complex **10** remained as an insoluble residue on top of the column packing. After dissolving complex **10** in DMSO, EDTA was added resulting in the formation of the $(EDTA)_2CuSO_4$ complex ($\lambda_{max} = 243$ nm) as being visible by immediate color change to green. Extraction with Et_2O allowed the recycling of SAMP (*S*)-**1** in 83% isolated yield and >95% purity.

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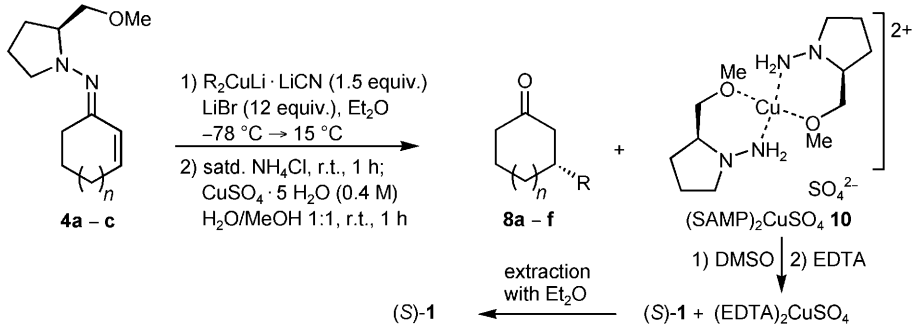
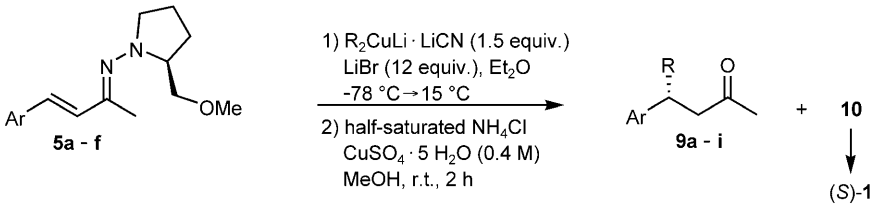
Table 1. Asymmetric 1,4-addition of cuprates $R_2CuLi{\cdot}LiCN$ to α,β-unsaturated SAMP-hydrazones **4**.[a,b]



Entry	Hydrazone	n	*E:Z*	Yield [%]	Product	R	Yield [%]	% *ee*
1	**4a**	1	63:37		**8b**	Me	78	12
2	**4a**	1	63:37		**8c**	Et	97	32
3	**4a**	1	63:37	85	**8a**	*n*-Bu	65	54
4	**4a**	1	63:37		**8d**	*t*-Bu	62	8
5	**4b**	0	63:37	73	**8e**	*n*-Bu	87	18
6	**4c**	2	96:4	90	**8f**	*n*-Bu	92	64

[a] Enantioselectivities were determined by capillary GC on a chiral stationary phase.
[b] The configuration of **8** was assigned to be (*R*) based on comparison with literature data (see Supporting Information).

Table 2. Asymmetric 1,4-addition of cuprates $R_2CuLi{\cdot}LiCN$ to α,β-unsaturated SAMP-hydrazones **5**.[a,b]



Entry	Hydrazone	Ar	*E:Z*	Yield [%]	Product	R	Yield [%]	% *ee*
1	**5a**	Ph	78:22		**9b**	Me	74	85
2	**5a**	Ph	78:22		**9c**	Et	27	93
3	**5a**	Ph	78:22	quant.	**9a**	*n*-Bu	56	98
4	**5a**	Ph	78:22		**9d**[c]	*t*-Bu	88	2
5	**5b**	4-Me-C_6H_4	78:22	99	**9e**	*n*-Bu	69	18
6	**5c**	4-MeO-C_6H_4	62:38	quant.	**9f**	*n*-Bu	65	22
7	**5d**	4-NO_2-C_6H_4	85:15	85	**9g**	*n*-Bu	35	99
8	**5e**	4-Cl-C_6H_4	79:21	83	**9h**	*n*-Bu	80	98
9	**5f**	2-furyl	71:29	quant.	**9i**	*n*-Bu	81	54

[a] Enantioselectivities were determined by HPLC on a chiral stationary phase (entries 1–8) or capillary GC on a chiral stationary phase (entry 9).
[b] The configuration of **9** was assigned to be (*R*) based on comparison with literature data (see Supporting Information).
[c] (*S*)-configuration due to priority rules.

Table 1 reveals for cyclohexenone-derived SAMP-hydrazone **4a** that the cuprate substituent R affected the enantioselectivities of organocuprate additions. With increasing chain length of the alkyl groups the *ee* values increased from 12% *ee* for R = Me to 54% *ee* for R = *n*-Bu (entries 1–3). In contrast, the addition of the branched cuprate (R = *t*-Bu) to **4a** afforded an almost racemic ketone **8d** (entry 4). Additionally, the ring size of hydrazones **4a**–**c** influenced the enantioselectivity, which is enhanced from the five-membered to the seven-membered ring system (entries 3, 5, 6).

Organocuprate addition and subsequent hydrolytic cleavage of auxiliary (*S*)-**1** provided substituted ketones **9** with improved enantioselectivities as compared to **8** (Table 2). The effect of cuprate substituent R on the enantioselectivity is smaller for hydrazone

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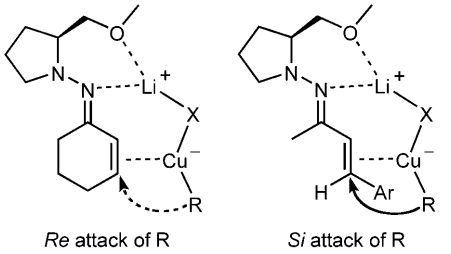
5a than for derivative **4a** (entries 1–3), but again the *tert*-butyl group led to a nearly racemic product (entry 4). With regard to 1,4-additions of *n*-$Bu_2CuLi{\cdot}LiCN$ to various arylidene acetone-derived hydrazones **5b–f**, however, the electronic character of the aryl moiety plays a prominent role. The electron-rich aryl substituents (MeC_6H_4 and $MeOC_6H_4$) decreased the *ee* values significantly, for example, 18% *ee* and 22% *ee* for 4-(methylphenyl)- and 4-(methoxyphenyl)octan-2-one **9e** and **9f** (entries 5 and 6) relative to 4-phenyloctan-2-one **9a** (98% *ee*, entry 3). In agreement with these results the electron-rich furyl substituent in SAMP-hydrazone **5f** caused a decreased enantioselectivity of 54% *ee* for ketone **9i** (entry 9). In contrast, cuprate addition to SAMP-hydrazones **5d** and **5e** with electron-poor aryl moieties afforded the corresponding 4-(nitrophenyl)- and 4-(chlorophenyl)-substituted octanones **9g** and **9h** with excellent selectivities of 98–99% *ee* (entries 7 and 8).

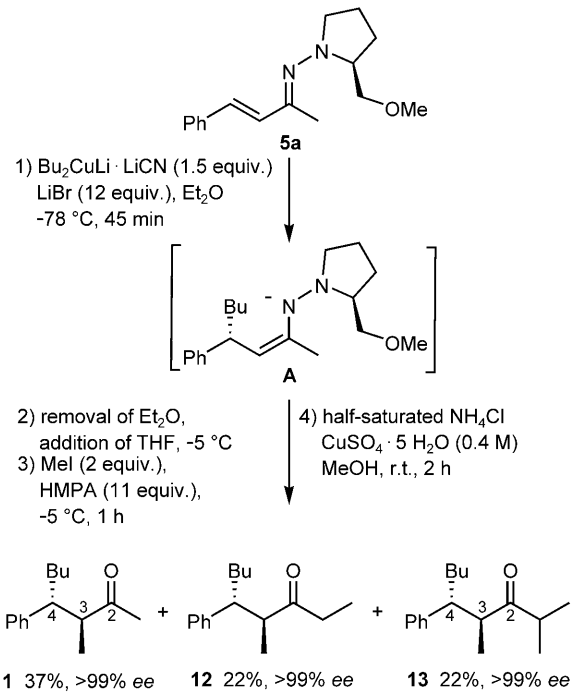
In order to explain the preferred formation of the (*R*)-enantiomers we propose the following mechanistic rationale (Scheme 2). Despite the bimetallic activation *via* Li–N and Cu–C=C interactions, the SAMP auxiliary directs the attack of the cuprate moiety R to the *Re*-face of cyclic hydrazones **4** or the *Si*-face of arylhydrazones **5** leading to the (*R*)-configurated product in both cases.[26]



Scheme 2. Proposed transition states of the cuprate additions. For better visibility the cuprates are shown as monomeric species.

In Cu- and Rh-catalyzed 1,4-additions electrophilic trapping of the intermediate enolate is rarely possible.[14] We were therefore interested to see whether the cuprate addition to SAMP-hydrazones can be combined with an α-alkylation of the formed intermediate azaenolate **A** (Scheme 3).

Thus, we developed a methodology which enabled a sequence of asymmetric cuprate addition to SAMP-hydrazones, α-alkylation and subsequent traceless cleavage of the auxiliary SAMP to liberate the original carbonyl function in one reaction. For this purpose, 2-(methoxymethyl)-*N*-[(1*E*)-1-methyl-3-phenylprop-2-enylidene]pyrrolidin-1-amine (**5a**) was used (Scheme 3). Initial attempts to achieve the α-alkylation of intermediate **A** in Et_2O failed completely. Already in 1979 Smith reported the poor reactivity of cuprate-derived enolates particularly when Et_2O was used as the solvent.[27] Therefore, we considered a solvent exchange prior to the alkylation reaction although this might cause epimerization of the azaenolate and leading to competing α- and α′-alkylation.[27] As shown in Scheme 3, SAMP-hydrazone **5a** was treated with $Bu_2CuLi{\cdot}LiCN$ in Et_2O at −78 °C for 45 min. After removal of Et_2O at −5 °C,[28] residue **A** was redissolved in THF and treated with MeI in the presence of HMPA at −5 °C for 1 h followed by Cu(II)-mediated hydrolytic auxiliary cleavage as described above.



Scheme 3. Cuprate addition to SAMP-hydrazone **5a**, methylation and cleavage of the auxiliary in one reaction.

A mixture of α-methyl-, α,α′-dimethyl- and α,α′,α′-trimethyl-substituted 4-phenyloctan-2-ones **11–13** was isolated in 81% yield in a ratio of **11**:**12**:**13** = 46:27:27. ^1H NMR spectroscopy of compound **13** revealed the *trans* configuration. A characteristic doublet of quartets at $\delta = 2.90$ ppm with coupling constants $J = 10.1$ and 6.9 Hz was found for the signal of the proton at C-4, which is in good agreement with the H-3 proton signal at $\delta = 2.87$ ppm (dq, $J = 10.0$ Hz, 7.0 Hz) reported for the structurally related methyl (2*RS*,3*SR*)-2-methyl-3-phenylbutanoate.[29] In contrast, in the case of derivatives **11** and **12** the H-4 proton signal interfered with that of H-3 and a multiplet was observed. Considering the fact that auxiliary (*S*)-**1** resulted in the (*R*)-configuration at C-4, the newly generated stereogenic center at C-3 should be (*S*). The alkylation

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products **11**–**13** were obtained in high enantioselectivities of >99%, as determined by HPLC in comparison with the corresponding racemic products. In all cases, only one enantiomer was detected, demonstrating that the auxiliary seemed to control also the α-alkylation despite the solvent change.

Conclusions

In summary, we applied successfully Enders' SAMP-hydrazone method to the enantioselective conjugate addition of Gilman cuprates to α,β-unsaturated carbonyl compounds. SAMP-hydrazones **4** and **5**, which were accessible by heating cyclic and acyclic enones with SAMP (*S*)-**1** in benzene, were treated with various cuprates and under Cu(II)-mediated hydrolysis conditions the hydrazone moiety was cleaved to give the β-alkylated ketones **8** and **9** with an (*R*)-configured new stereocenter at C-4. Particularly for aryl-substituted enones high enantioselectivities can be obtained. Recycling of SAMP in 83% yield and >95% purity was realized. It should be emphasized that the hydrolytic cleavage does not require strongly oxidizing conditions such as the recently reported H_2O_2/SeO_2 procedure by Smith.[30] Furthermore, we developed a procedure that combines cuprate addition to acyclic SAMP-hydrazone **5a**, α-alkylation of the formed azaenolate species and traceless cleavage of the chiral auxiliary in one reaction. Also in this case, SAMP acts as a traceless auxiliary, which led to products with high enantioselectivities >99%.

Experimental Section

General

Melting points were measured on a Büchi SMP-20 apparatus and are uncorrected. NMR spectra were recorded on a Bruker ARX 500 spectrometer with TMS as an internal standard. FT-IR spectra were recorded on a Vektor 22 spectrometer (Bruker) with MKII Golden Gate Single Reflection Diamant ATR-System. UV/Vis spectra were recorded on a Lambda 2 spectrometer (Perkin–Elmer) using quartz glass cuvettes. GC was performed on a Hewlett–Packard HP 6890 with HP-5 column (30 m×0.32 mm) and on a Thermo-Finnigan Trace GC Ultra with a Optima-5-MS column (30 m×0.25 mm). Separation of enantiomers: HR-GC Mega 2 series, HT system (Fisons Instruments) with H_2 (0.4 bar) as carrier gas. Chromatography was performed on silica gel 60 (grain size 40–63 μm) (Fluka) using columns of different size. TLC: TLC-plates silica gel 60 F254 (Merck). Glove box: MB 150-GI (M. Braun) with Ar and N_2 as inert gas. MS/HR-MS were measured on MAT 95, MAT 711 and micrOTOF Q (Finnigan and Varian) spectrometers. Analytical HPLC: HPLC apparatus (Shimadzu) with DGU-20 A5 Prominence degasser, LC-20AT Prominence liquid chromatograph, SIL-20 A Prominence auto sampler, SPD-M20 A Prominence diode array detector, ELSD-LT low temperature evaporative light scattering detector, CBM-20 A Prominence communications bus module and CTO-20AC Prominence column oven. Separation of enantiomers: Chiralcel OJ-H (250×4.6 mm) (Chiral Technologies Europe). Optical rotation values $[\alpha]_D^{25}$ were measured on a Polarimeter 241 (Perkin–Elmer). All reactions were performed in dried glassware. Cyclohept-2-enone was prepared according to ref.[31–34] The syntheses of arylidene acetones **3** are described in the Supporting Information.

General Procedure for the Synthesis of SAMP-Hydrazones (4, 5)

A solution of enone **2** or **3** (12.2 mmol) and (*S*)-**1** (1.98 g, 15.2 mmol) in benzene (40.0 mL) was heated at reflux for 5–17 h. The condensate was passed through molecular sieves 4 Å until TLC indicated complete conversion. The reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated. The residue was purified by flash chromatography on SiO_2 and lyophilized under high vacuum. GC analyses were not possible due to decomposition on the HP-5 column.

(+)-(2*S*)-*N*-[(1*E*)-Cyclopent-2-en-1-ylidene]-2-(methoxymethyl)pyrrolidin-1-amine (4b): Chromatography on SiO_2 (EtOAc/MeOH/NEt_3=86:9:5, then MeOH) gave **4b** as an orange oil (*E*/*Z*=63:37 by ^{1}H NMR); yield: 1.73 g (8.91 mmol, 73%); purity: >95% (^{1}H NMR); R_f=0.56; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.49–2.10 (3 m, 5H, 4-H, 5-H, 5′-H_A), 2.10–2.59 (3 m, 5H, 2′-H, 3′-H_A, 4′-H, 5′-H_B), 3.04–3.71 (m, 3H, 3′-H_B, CH_2OCH$_3$), 3.35* (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 6.28 (dt, *J*=5.7 Hz, *J*=2.0 Hz, 1H, 3-H), 6.54–6.75 (m, 1H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=22.5 (C-5), 26.6 (C-4), 28.0 (C-4′), 31.3 (C-3′), 54.0 (C-5′), 59.2 (OCH$_3$), 66.6 (C-2′), 75.7 (CH_2OCH$_3$), 133.0 (C-3), 145.8 (C-2), 171.3 (C-1) [* denotes signal of the (*Z*)-isomer]; FT-IR (ATR): $\tilde{\nu}$=2922 (s), 2872 (s), 2825 (s), 1650 (w), 1458 (m), 1353 (w), 1281 (w), 1196 (m), 1097 (s), 969 (m), 914 (m), 740 (m) cm^{-1}; UV/Vis (acetonitrile): λ_{max}=273.0, 198.0 nm; MS (EI, 70 eV): *m/z* (%)=194 (10) $[M]^+$, 151 (16), 149 (100) $[M-CH_2OCH_3]^+$, 125 (17), 80 (9) [M−pyrrolidine]$^+$; HR-MS (ESI): *m/z*=195.1483, calcd. for $C_{11}H_{18}N_2O$ $[M+H]^+$: 195.1492; anal. calcd. for $C_{11}H_{18}N_2O$ (194.27): C 68.01, H 9.34, N 14.42; found: C 66.60, H 9.56, N 14.45; $[\alpha]_D^{25}$: +212.3 (*c* 1.0, CH_2Cl_2).

(+)-(2*S*)-*N*-[(1*E*)-Cyclohept-2-en-1-ylidene]-2-(methoxymethyl)pyrrolidin-1-amine (4c): Chromatography on SiO_2 (EtOAc/NEt_3=95:5, then MeOH) gave **4c** as a yellow oil (*E*/*Z*=96:4 by ^{1}H NMR); yield: 2.45 g (11.0 mmol, 90%); purity: >95% (^{1}H NMR); R_f=0.62; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.61–2.07 (3 m, 5H, 4-H, 5-H, 5′-H_A), 2.16–2.80 (4 m, 5H, 2′-H, 3′-H_A, 4′-H, 5′-H_B), 3.23–3.50 (m, 7H, 3′-H_B, 6-H, CH_2OCH$_3$, 7-H), 3.34* (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 5.90–6.17 (m, 1H, 3-H), 6.40 (d, *J*=11.5 Hz, 1H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=22.7 (C-5), 24.0 (C-4), 26.7 (C-4′), 26.9 (C-3′), 28.9 (C-6), 36.0 (C-7), 55.6 (C-5′), 59.2 (OCH$_3$), 66.8 (C-2′), 75.8 (CH_2OCH$_3$), 126.7 (C-3), 136.4 (C-2), 161.1 (C-1) [* denotes signal of the (*Z*)-isomer]; FT-IR (ATR): $\tilde{\nu}$=2921 (s), 2851 (s), 1620 (m), 1455 (s), 1384 (w), 1348 (m), 1279 (w), 1194 (m), 1127 (s), 1098 (s), 1067 (m), 1047 (m), 1010 (w), 969 (m), 916 (m), 855 (m), 721 (w) cm^{-1}; UV/Vis (acetonitrile): λ_{max}=308.0, 231.0 nm; MS

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(ESI): $m/z = 223$ $[M+H]^+$, 191, 128, 114 [pyrrolidine]$^+$, 108 [M−pyrrolidine]$^+$, 94; HR-MS (ESI): $m/z = 223.1801$, calcd. for $C_{13}H_{22}N_2O$ $[M+H]^+$: 223.1805; anal. calcd. for $C_{13}H_{22}N_2O$ (222.33): C 70.23, H 9.97, N 12.60; found: C 69.75, H 9.85, N 12.22; $[\alpha]_D^{25}$: +863.8 (*c* 1.0, CH_2Cl_2).

(+)-(2*S*)-2-(Methoxymethyl)-*N*-[(1*E*,2*E*)-1-methyl-3-(4-methoxyphenyl)prop-2-enylidene]pyrrolidin-1-amine (5c): Chromatography on SiO_2 ($CHCl_3$/EtOAc/NEt_3 = 79:16:5, then MeOH) gave **5c** as an orange oil (*E*/*Z* = 62:38 by ^{1}H NMR); yield: 3.52 g (12.2 mmol, quant.); purity: >95% (^{1}H NMR); $R_f = 0.56$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.62$–2.70 (5 m, 6H, 3′-H, 4′-H, 5′-H), 2.11 (s, 3H, 1′-H), 2.17* (s, 3H, 1′-H), 3.05–3.86 (3 m, 3H, 2′-H, CH_2OCH$_3$), 3.35* (s, 3H, CH$_2$OCH_3), 3.36 (s, 3H, CH$_2$OCH_3), 3.81 (s, 3H, OCH_3), 3.82* (s, 3H, OCH_3), 6.81–6.95 (m, 3H, 2-H, 3″-H, 5″-H), 7.21–7.51 (m, 3H, 3-H, 2″-H, 6″-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.7$ (C-1′), 22.9 (C-4′), 27.0 (C-3′), 55.3 (OCH_3), 55.4 (C-5′), 59.2 (CH$_2$OCH_3), 66.8 (C-2′), 75.5 (CH_2OCH$_3$), 114.2 (C-3″, C-5″), 127.1 (C-2″, C-6″), 130.0 (C-1″), 131.7 (C-3), 134.2 (C-2), 158.8 (C-1), 160.2 (C-4″) [* denotes signal of the (*Z*)-isomer]; FT-IR (ATR): $\tilde{\nu} = 2923$ (s), 2873 (s), 2834 (m), 1736 (w), 1666 (w), 1459 (m), 1108 (s), 965 (s) cm^{-1}; UV/Vis (acetonitrile): $\lambda_{max} = 292.0$, 223.0, 192.0 nm; MS (EI, 70 eV): *m/z* (%) = 288 (30) $[M]^+$, 243 (100) $[M-CH_2OCH_3]^+$, 174 (36) [M−pyrrolidine]$^+$, 133 (42); HR-MS (ESI): $m/z = 289.1913$, calcd. for $C_{17}H_{24}N_2O_2$ $[M+H]^+$: 289.1911; anal. calcd. for $C_{17}H_{24}N_2O_2$ (288.38): C 70.80, H 8.39, N 9.71; found: C 70.81, H 8.21, N 9.18; $[\alpha]_D^{25}$: +772.7 (*c* 1.0, CH_2Cl_2).

(+)-(2*S*)-2-(Methoxymethyl)-*N*-[(1*E*,2*E*)-1-methyl-3-(4-nitrophenyl)prop-2-enylidene]pyrrolidin-1-amine (5d): Chromatography on SiO_2 ($CHCl_3$/EtOAc/NEt_3 = 79:16:5, then MeOH) gave **5d** as a red oil (*E*/*Z* = 85:15 by ^{1}H NMR); yield: 2.88 g (9.49 mmol, 85%); purity: >95% (^{1}H NMR); $R_f = 0.64$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.57$–2.70 (5 m, 6H, 3'-H, 4'-H, 5'-H), 2.12 (s, 3H, 1′-H), 2.20* (s, 3H, 1′-H), 2.90–3.62 (3 m, 3H, 2′-H, CH_2OCH$_3$), 3.33* (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 6.79 (d, $J = 16.4$ Hz, 1H, 2-H), 7.04 (d, $J = 16.4$ Hz, 1H, 3-H), 7.57 (d, $J = 8.7$ Hz, 2H, 2″-H, 6″-H), 8.18 (d, $J = 8.8$ Hz, 2H, 3″-H, 5″-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.8$ (C-1′), 23.2 (C-4′), 27.1 (C-3′), 55.9 (C-5′), 59.3 (OCH_3), 66.7 (C-2′), 75.6 (CH_2OCH$_3$), 124.1 (C-3″, C-5″), 129.4 (C-2″, C-6′), 131.1 (C-3), 135.5 (C-2), 143.4 (C-1″), 147.4 (C-4″), 155.1 (C-1) [* denotes signal of the (*Z*)-isomer]; FT-IR (ATR): $\tilde{\nu} = 2968$ (s), 2922 (s), 2874 (s), 2828 (m), 1716 (w), 1643 (w), 1593 (s), 1516 (s), 1447 (m), 1340 (s), 1107 (s), 1094 (s), 966 (m) cm^{-1}; UV/Vis (acetonitrile): $\lambda_{max} = 399.0$, 285.0, 196.0 nm; MS (EI, 70 eV): *m/z* (%) = 303 (13) $[M]^+$, 260 (40), 258 (100) $[M-CH_2OCH_3]^+$, 189 (14) [M−pyrrolidine]$^+$, 183 (24), 125 (18); HR-MS (ESI): m/z = 304.1659, calcd. for $C_{16}H_{21}N_3O_3$ $[M+H]^+$ 304.1656; anal. calcd. for $C_{16}H_{21}N_3O_3$ (303.36): C 63.35, H 6.98, N 13.85; found: C 62.71, H 6.79, N 13.88; $[\alpha]_D^{25}$: +1184.9 (*c* 1.0, CH_2Cl_2).

(+)-(2*S*)-2-(Methoxymethyl)-*N*-[(1*E*,2*E*)-1-methyl-3-(4-chlorophenyl)prop-2-enylidene]pyrrolidin-1-amine (5e): Chromatography on SiO_2 ($CHCl_3$/EtOAc/NEt_3 = 79:16:5, then MeOH) gave **5e** as an orange oil (*E*/*Z* = 79:21 by ^{1}H NMR); yield: 2.63 g (8.98 mmol, 83%); purity: >95% (^{1}H NMR); $R_f = 0.52$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.62$–2.73 (5 m, 6H, 3′-H, 4′-H, 5′-H), 2.10 (s, 3H, 1′-H), 2.17* (s, 3H, 1′-H), 3.16–3.53 (3 m, 3H, 2′-H, CH_2OCH$_3$), 3.36* (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 6.74 (d, $J = 16.5$ Hz, 1H, 2-H), 6.87 (d, $J = 16.4$ Hz, 1H, 3-H), 7.29 (d, $J = 8.6$ Hz, 2H, 2″-H, 6″-H), 7.38 (d, $J = 8.4$ Hz, 2H, 3″-H, 5″-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.9$ (C-1′), 23.1 (C-4′), 27.1 (C-3′), 55.5 (C-5′), 59.3 (OCH_3), 67.0 (C-2′), 75.7 (CH_2OCH$_3$), 128.4 (C-3″, C-5″), 128.9 (C-2″, C-6″), 131.3 (C-3), 133.5 (C-1″), 135.3 (C-4″), 135.4 (C-2), 156.9 (C-1) [* denotes signal of the (*Z*)-isomer]; FT-IR (ATR): $\tilde{\nu} = 2963$ (m), 2920 (s), 2872 (s), 2827 (m), 1715 (m), 1667 (w), 1490 (s), 1446 (m), 1088 (s), 965 (s), 810 (s) cm^{-1}; UV/Vis (acetonitrile): $\lambda_{max} = 346.0$, 276.0, 192.0 nm; MS (EI, 70 eV): *m/z* (%) = 292 (20) $[M]^+$, 249 (32), 247 (100) $[M-CH_2OCH_3]^+$, 178 (24) [M−pyrrolidine]$^+$, 137 (28); HR-MS (ESI): $m/z = 293.1408$, calcd. for $C_{16}H_{21}ClN_2O$ $[M+H]^+$: 293.1415; anal. calcd. for $C_{16}H_{21}ClN_2O$ (292.80): C 65.63, H 7.23, N 9.57, Cl 12.11; found: C 65.68, H 7.11, N 8.76, Cl 12.03; $[\alpha]_D^{20}$: +1094.6 (*c* 1.0, CH_2Cl_2).

(+)-(2*S*)-*N*-[(1*E*,2*E*)-3-(2-Furyl)-1-methylprop-2-enylidene]-2-(methoxymethyl)pyrrolidin-1-amine (5f): Chromatography on SiO_2 (EtOAc/MeOH/NEt_3 = 86:9:5, then MeOH) afforded **5f** as a red-brown oil (*E*/*Z* = 71:29 by ^{1}H NMR); yield: 3.03 g (12.2 mmol, quant.); purity: >95% (^{1}H NMR); $R_f = 0.72$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.62$–2.70 (5 m, 6H, 3′-H, 4′-H, 5′-H), 2.06 (s, 3H, 1′-H), 2.13* (s, 3H, 1′-H), 3.24–3.53 (2 m, 3H, 2′-H, CH_2OCH$_3$), 3.35* (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 6.34–7.43 (m, 3H, 3″-H, 4″-H, 5″-H), 6.62 (d, $J = 16.4$ Hz, 1H, 3-H), 6.82 (d, $J = 16.4$ Hz, 1H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.7$ (C-1′), 23.1 (C-4′), 27.0 (C-3′), 55.4 (C-5′), 59.3 (OCH_3), 66.8 (C-2′), 75.6 (CH_2OCH$_3$), 109.0 (C-3″), 111.7 (C-4″), 119.4 (C-3), 129.1 (C-2), 142.6 (C-5″), 156.9 (C-1), 157.0 (C-2″) [* denotes signal of the (*Z*)-isomer]; FT-IR (ATR): $\tilde{\nu} = 2967$ (m), 2921 (s), 2872 (s), 2827 (m), 1716 (w), 1624 (w), 1447 (m), 1261 (m), 1198 (m), 1095 (s), 1013 (s), 960 (s) cm^{-1}; UV/Vis (acetonitrile): $\lambda_{max} = 343.0$, 299.0, 196.0 nm; MS (EI, 70 eV): *m/z* (%) = 248 (34) $[M]^+$, 203 (100) $[M-CH_2OCH_3]^+$, 134 (49) [M−pyrrolidine]$^+$, 93 (17), 65 (14); anal. calcd. for $C_{14}H_{20}N_2O_2$ (248.32): C 67.71, H 8.12, N 11.28; found: C 67.72, H 8.13, N 11.40; $[\alpha]_D^{25}$: +1339.0 (*c* 1.0, CH_2Cl_2).

General Procedure for the Asymmetric 1,4-Addition of Cuprates to SAMP-Hydrazones with Cleavage of the Auxiliary

***Method for hydrazones* (4):** A solution of the organolithium compound (3.09 mmol) was slowly added dropwise to a suspension of CuCN (138 mg, 1.54 mmol) and LiBr (1.07 g, 12.3 mmol) in Et_2O (16.0 mL) at −78 °C. [In the case of methyllithium, TMSCl (3.09 mmol) was slowly added after 30 min and the reaction mixture stirred further for 40 min]. After stirring for 70 min, a solution of hydrazone **4** (1.03 mmol) in Et_2O (16.0 mL) was added dropwise at −78 °C. Then the reaction mixture was allowed to warm to 10–15 °C overnight. The reaction was quenched with a saturated solution of NH_4Cl (20 mL) and stirred for a further 1 h at room temperature prior to addition of CH_2Cl_2 (15 mL). The reaction mixture was hydrolyzed with H_2O (20 mL), MeOH (20 mL) and $CuSO_4 \cdot 5H_2O$ (4.00 g, 16.0 mmol). After vigorous stirring for 1 h, the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated (40 °C/ > 80 mbar)

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and the crude products were purified by flash chromatography on SiO_2. Traces of SiO_2 were removed by filtration through Celite.

***Method for hydrazones* (5):** A solution of the organolithium compound (2.32 mmol) was slowly added dropwise to a suspension of CuCN (104 mg, 1.16 mmol) and LiBr (807 mg, 9.29 mmol) in Et_2O (16.0 mL) at −78 °C. (In the case of methyllithium, TMSCl (2.32 mmol) was slowly added after 30 min and the reaction mixture stirred further for 40 min). After stirring for 70 min, a solution of hydrazone **5** (0.774 mmol) in Et_2O (16.0 mL) was added dropwise at −78 °C. The stirred reaction mixture was allowed to warm to 10–15 °C overnight prior to addition of CH_2Cl_2 (15 mL) and Et_2O (30 mL). The reaction mixture was concentrated and a half-saturated NH_4Cl solution (40 mL), MeOH (40 mL) and $CuSO_4 \cdot 5H_2O$ (4.00 g, 16.0 mmol) were successively added. After vigorous stirring for 2 h, the reaction mixture was concentrated to the half volume and extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried ($MgSO_4$), concentrated (40 °C/>80 mbar) and the crude products were purified by flash chromatography on SiO_2. Traces of SiO_2 were removed by filtration through Celite.

(+)-(3*R*)-Butylcyclohexanone [(*R*)-8a]:[35] Chromatography on SiO_2 (pentane/Et_2O = 1:1) gave **8a** as a pale yellow oil; yield: 48 mg (0.311 mmol, 65%); purity: 91% (GC); R_f = 0.57; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.8 Hz, 3H, 4′-H), 1.23–1.38 (m, 7H, aliphatic), 1.60–1.70 (m, 1H, aliphatic), 1.71–1.81 (m, 1H, aliphatic), 1.90 (dddd, J = 1.1 Hz, J = 1.1 Hz, J = 4.6 Hz, J = 13.8 Hz, 1H, 2-H_A), 1.96–2.07 (m, 2H, 5-H), 2.25 (dddd, J = 1.1 Hz, J = 6.4 Hz, J = 12.2 Hz, J = 20.1 Hz, 1H, 6-H_A), 2.31–2.38 (m, 1H, 6-H_B), 2.39–2.45 (m, 1H, 2-H_B); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (C-4′), 22.8 (C-2′), 25.4 (C-3'), 28.9 (C-5), 31.4 (C-1′), 36.4 (C-4), 39.1 (C-3), 41.6 (C-6), 48.3 (C-2), 212.3 (C-1); GC (column HP-5, 16 °C min^{-1} gradient from 80–300 °C): t_R = 4.51 min; $[\alpha]_D^{25}$: +40.3 (*c* 0.50, $CHCl_3$) ($[\alpha]_D^{25}$: −74.8 [*c* 1.3, $CHCl_3$) (*S*)-enantiomer[36]]; separation of enantiomers by GC [column Bondex un α (20 m×0.25 mm), 0.4 bar H_2; temperature program: 40 °C, 5 min isothermal, 0.5 °C min^{-1} gradient to 87 °C, then isothermal]: t_{R1} = 89.54 min (major enantiomer), t_{R2} = 90.83 min (minor enantiomer), 54% *ee*.

(−)-(4*R*)-4-Phenyloctan-2-one [(*R*)-9a]:[37,38] Chromatography on SiO_2 (pentane/Et_2O = 2:1) gave **9a** as a pale yellow oil; yield: 85 mg (0.416 mmol, 56%); purity: 97% (GC); R_f = 0.44; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, J = 7.1 Hz, 3H, 8-H), 1.02–1.32 (m, 4H, 6-H, 7-H), 1.50–1.66 (m, 2H, 5-H), 2.01 (s, 3H, 1-H), 2.71 (dd, J = 7.4 Hz, J = 16.2 Hz, 2H, 3-H), 3.06–3.12 (m, 1H, 4-H), 7.13–7.21 (m, 3H, 2'-H, 4′-H, 6′-H), 7.24–7.31 (m, 2H, 3′-H, 5′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (C-8), 22.6 (C-7), 29.6 (C-6), 30.7 (C-1), 36.2 (C-5), 41.3 (C-4), 51.0 (C-3), 126.3 (C-4′), 127.5 (C-2′, C-6′), 128.5 (C-3′, C-5′), 144.6 (C-1'), 208.1 (C-2); GC (column HP-5, 16 °C min^{-1} gradient from 80–300 °C): t_R = 6.37 min; $[\alpha]_D^{25}$: −6.9 (*c* 0.50, CH_2Cl_2); separation of enantiomers by HPLC (column Chiralcel OJ-H, flow 0.2 mL min^{-1}, hexane/2-propanol 98.5:1.5, λ = 220 nm UV): t_{R1} = 38.37 min (minor enantiomer), t_{R2} = 40.42 min (major enantiomer), 98% *ee*, being with utmost probability the (*R*)-enantiomer [comparison with (*R*)-**9c**]; $[\alpha]_D^{26}$: −29.9 (*c* 2.0, $CHCl_3$)[39]).

Recycling of the Auxiliary SAMP (*S*)-1

The Cu(II)-SAMP-complex **10** [from the addition of *n*-$Bu_2CuLi \cdot LiCN$ to **4c** (1.35 mmol); UV/Vis (DMSO): λ_{max} = 260.0, 227.0 nm], which remained on the silica gel, was transferred from the column into a flask, dissolved in DMSO (50 mL) and filtered. With stirring a solution of disodium EDTA dihydrate (3.00 g, 8.06 mmol) in H_2O (150 mL) was added to the filtrate [UV/Vis (DMSO/H_2O 1:2): λ_{max} = 243.0 nm] and the reaction mixture was extracted with Et_2O (2×300 mL). The combined organic layers were washed with H_2O (2×1.0 L) and dried ($MgSO_4$). After removal of the solvent under vacuum (40 °C/>100 mbar), SAMP (*S*)-**1** was isolated as a colorless oil; yield: 146 mg (1.12 mmol, 83%); purity: >95% (^{1}H NMR); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50–1.99 (3 m, 4H, 3-H, 4-H), 2.11–2.47 (2 m, 2H, 5-H), 3.00–3.60 (ABX system, 3H, CH_2OCH_3, 2-H), 3.11 (s, 2H, NH_2), 3.38 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0 (C-3), 26.3 (C-4), 59.2 (OCH$_3$), 60.2 (C-5), 68.4 (C-2), 75.8 (CH_2OCH$_3$); MS (ESI) for $[(SAMP)_2Cu]^{2+}$: *m/z* = 323 $[M]^{2+}$, 297 $[(M-2CH_2)+2H]^{2+}$, 279 $[(M-CH_2OCH_3)+H]^{2+}$, 154, 114. The spectroscopic data are in accordance with those in the literature.[1c]

General Procedure for the Tandem 1,4-Addition/Methylation Reaction

***Method for hydrazone* 5a:** A 1.6 M solution (1.45 mL) of *n*-BuLi (2.32 mmol) in *n*-hexane was slowly added dropwise to a suspension of CuCN (104 mg, 1.16 mmol) and LiBr (807 mg, 9.29 mmol) in Et_2O (16.0 mL) in a dried Schlenk flask at −78 °C. After stirring for 70 min, a solution of hydrazone **5a** (200 mg, 0.774 mmol) in Et_2O (16.0 mL) was added dropwise and the reaction mixture was stirred for a further 45 min, whereby the temperature should not exceed −78 °C. The supernatant solution was placed in a separate Schlenk flask and the solvent was removed in a stream of nitrogen at −5 °C. The residue was dissolved in THF (10.0 mL) and a solution of MeI (0.097 mL, 220 mg, 1.55 mmol) in HMPA (1.5 mL) was added dropwise. After stirring for 1 h at −5 °C, MeOH (0.5 mL) was added. The reaction mixture was then stirred for 22 h at −5 °C and 19 h at room temperature prior to addition of CH_2Cl_2 (15 mL) and Et_2O (30 mL). After concentration (40 °C/>80 mbar), a half-saturated NH_4Cl solution (40 mL), MeOH (40 mL) and $CuSO_4 \cdot 5H_2O$ (4.00 g, 16.0 mmol) were added. After vigorous stirring for 2 h at room temperature, the reaction mixture was concentrated to the half volume and extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated (40 °C/300 mbar). The residue was dissolved in Et_2O (50 mL), washed with H_2O (250 mL) and a 2% solution of $Na_2S_2O_3$ (100 mL). It was dried ($MgSO_4$), concentrated and purified by flash chromatography on SiO_2. Products (3*S*,4*R*)-**11**, (4*S*,5*R*)-**12** and -**13** were isolated in 81% yield in a ratio of **11**:**12**:**13** = 46:27:27.

(+)-(3*S*,4*R*)-3-Methyl-4-phenyloctan-2-one [(3*S*,4*R*)-11]: Chromatography (pentane/Et_2O = 5:1) gave a colorless oil; yield: 63 mg (0.288 mmol, 37%); purity: >95% (^{1}H NMR); R_f = 0.36; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (t, J = 7.5 Hz, 3H, 8-H), 0.80 (d, J = 6.3 Hz, 3H, CH_3), 0.87–1.09 (m, 2H, 6-H), 1.10–1.29 (m, 2H, 7-H), 1.46–1.59 (m, 2H, 5-H), 2.19 (s, 3H, 1-H), 2.68–2.80 (m, 2H, 3-H, 4-H), 7.09–7.15 (m, 2H, 2′-H, 6′-H), 7.18–7.24 (m, 1H, 4′-H), 7.27–7.32

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(m, 2H, 3′-H, 5′-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$ (C-8), 15.8 (CH_3), 22.5 (C-7), 29.2 (C-1), 29.7 (C-6), 34.4 (C-5), 48.6 (C-3), 53.4 (C-4), 126.4 (C-4′), 128.3 (C-2′, C-6′), 128.4 (C-3′, C-5′), 142.5 (C-1′), 213.2 (C-2); $[\alpha]_D^{25}$: +20.3 (*c* 0.30, CH_2Cl_2); separation of enantiomers by HPLC [column Chiralcel OJ-H, flow 0.1 mL min^{-1}, hexane/2-propanol 98:2, $\lambda = 214$ nm (UV), no minor enantiomer]: $t_R = 65.73$ min, >99% *ee*. For a complete characterization see *rac*-**11** (Supporting Information).

(+)-(4*S*,5*R*)-4-Methyl-5-phenylnonan-3-one [(4*S*,5*R*)-12]: Chromatography (pentane/Et_2O = 5:1) gave a colorless oil; yield: 39 mg (0.169 mmol, 22%); purity: >95% (^{1}H NMR); $R_f = 0.56$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.76$ (t, J = 7.5 Hz, 3H, 9-H), 0.78 (d, J = 6.4 Hz, 3H, CH_3), 0.91–1.06 (m, 2H, 7-H), 1.09 (t, J = 7.6 Hz, 3H, 1-H), 1.11–1.28 (m, 2H, 8-H), 1.41–1.55 (m, 2H, 6-H), 2.38–2.60 (m, 2H, 2-H), 2.71–2.82 (m, 2H, 4-H, 5-H), 7.09–7.15 (m, 2H, 2'-H, 6′-H), 7.15–7.25 (m, 1H, 4′-H), 7.25–7.32 (m, 2H, 3′-H, 5′-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 7.7$ (C-1), 13.9 (C-9), 16.2 (CH_3), 22.5 (C-8), 29.8 (C-7), 34.4 (C-6), 35.9 (C-2), 48.7 (C-4), 52.3 (C-5), 126.3 (C-4′), 128.3 (C-2', C-6′), 128.4 (C-3′, C-5′), 142.8 (C-1′), 215.7 (C-3) ppm; $[\alpha]_D^{25}$: +45.1 (*c* 0.30, CH_2Cl_2); separation of enantiomers by HPLC [column Chiralcel OJ-H, flow 0.1 mL min^{-1}, hexane/2-propanol 98:2, λ = 214 nm (UV), no minor enantiomer]: $t_R = 62.92$ min, > 99% *ee*. For a complete characterization see *rac*-**12** (Supporting Information).

(+)-(4*S*,5*R*)-2,4-Dimethyl-5-phenylnonan-3-one [(4*S*,5*R*)-13]: Chromatography (pentane/Et_2O = 5:1) afforded a colorless oil; yield: 42 mg (0.170 mmol, 22%); purity: >95% (^{1}H NMR); $R_f = 0.65$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.75$ (t, J = 7.3 Hz, 3H, 9-H), 0.76 (d, J = 6.4 Hz, 3H, 4-CH_3), 0.97–1.06 (m, 2H, 7-H), 1.12 (d, J = 3.2 Hz, 3H, 1-H), 1.14 (d, J = 3.1 Hz, 3H, 2-CH_3), 1.16–1.29 (m, 2H, 8-H), 1.40–1.53 (m, 2H, 6-H), 2.67–2.82 (m, 2H, 2-H, 4-H), 2.90 (dq, J = 10.1 Hz, J = 6.9 Hz, 1H, 5-H), 7.09–7.16 (m, 2H, 2′-H, 6′-H), 7.18–7.24 (m, 1H, 4′-H), 7.27–7.33 (m, 2H, 3′-H, 5′-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 13.9$ (C-9), 16.8 (4-CH_3), 18.1 (C-1), 18.2 (2-CH_3), 22.5 (C-8), 29.8 (C-7), 34.5 (C-6), 41.2 (C-2), 48.7 (C-4), 50.7 (C-5), 126.3 (C-4′), 128.3 (C-2′, C-6′), 128.4 (C-3′, C-5′), 143.1 (C-1′), 218.7 (C-3); $[\alpha]_D^{25}$: +75.9 (*c* 0.30, CH_2Cl_2); separation of enantiomers by HPLC [column Chiralcel OJ-H, flow 0.1 mL min^{-1}, hexane/2-propanol 98:2, $\lambda = 214$ nm (UV), no minor enantiomer]: t_R = 49.36 min, >99% *ee*. For a complete characterization see *rac*-**13** (Supporting Information).

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