NR), 5.10 (3.3–3.5; NR-1), 5.26 (6–7; R-1), 4.56 (3.5; R). Optical rotations of **16**–**22** were all in the range +20–22 ($c = 0.5-1$ in H_2O). Positive-mode LSI-MS (thioglycerol + NaCl/thioglycerol + KF): **16**: *m*/*z*: 2771/2787; **17**: *m*/*z*: 3402/3418; **18** (after cleavage of the levulinoyl group): *m*/*z*: 3934/3950; **19**: *m*/*z*: 4664/4680; **20**: *m*/*z*: not determined/5310; **21**: *m*/*z*: not determined/5940. The ^{1}H NMR spectra of **23**–**28** were very similar in terms of chemical shifts, and, as expected, only the relative intensities of the signals varied between compounds. Resonances for the distinguishable anomeric protons: δ ($J_{1,2}$ [Hz]) = 5.08–5.11 (1–2; NR), 5.38–5.41 (3–4; NR-1), 5.04–5.09 (1–2; CNR), 5.40–5.42 (3–4; CR), 5.05–5.09 (1–2; R-1), 5.10–5.15 (3.5; R). Optical rotations were all in the range +27–34 ($c = 0.4-0.6$ in H_2O); ESI-MS (monoisotopic mass/average mass/experimental mass ± standard deviation): **23**: *m*/*z*: 3603.5/3606.3/3605.13 ± 0.9; **24**: *m*/*z*: 4297.5/4300.7/4296.8 ± 0.9; **25**: *m*/*z*: 4991.4/4995.2/4993.0 ± 2.2; **26**: *m*/*z*: 5685.3/5689.6/5687.6 ± 2.3; **27**: *m*/*z*: 6379.2/6384.1/6381.4 ± 3.2; **28**: *m*/*z*: 7073.1/7078.5/7077.3 ± 3.2.

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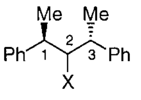
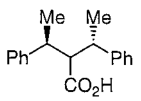
New Chiral Ligands with Nonstereogenic Chirotopic Centers for Asymmetric Synthesis[**]

Claus-Dieter Graf, Christophe Malan, and
Paul Knochel[*]

The design of new chiral ligands for asymmetric synthesis is an active field of research.[1] To obtain an efficient transfer of the stereochemistry the chiral information of the ligand should be as close as possible to the reaction center. This concept led to the development of *P*-chiral phosphanes[2] and to the ingenious design of "chiral pockets"[3] that give impressive enantioselectivities. Alternatively, ligands with chiral secondary organic groups linked to phosphorus or nitrogen atoms have also been used with excellent results in enantioselective reactions.[4] However, many of these ligands involve a challenging synthesis that requires the linkage of a sterically demanding secondary chiral carbon center to a heteroatom (P or N). Stimulated by the work of Mislow and Siegel on local chirality[5] we report the preparation of several new pseudo-C_2-symmetric ligands of type **1** and their utility in asymmetric synthesis. All these ligands avoid the difficulty of controlling the stereochemistry of the C(2) carbon center attached to the heteroatom (P or N).



1 X = PR_2, NR_2, OR, M



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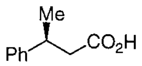

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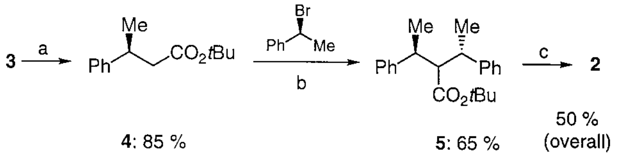
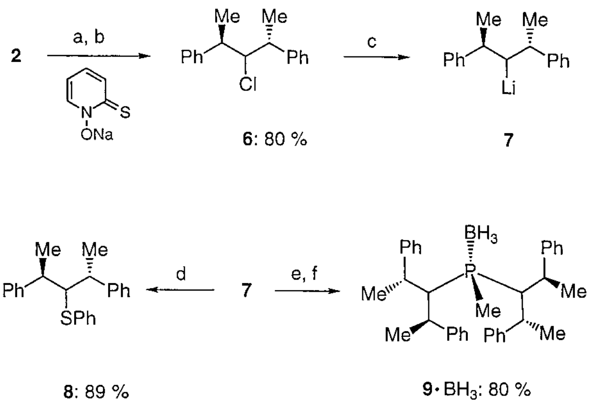
In accordance with the definition of Mislow and Siegel,[5] the center C(2) is not a chiral center, but rather a chirotopic center (a center in a chiral environment). This represents a great synthetic advantage since it avoids the necessity to control the stereochemistry at C(2). We chose the carboxylic acid **2** as the key intermediate for the preparation of ligands of type **1**. The esterification of commercially available (*S*)-3-phenylbutyric acid (**3**) with isobutene provides the *tert*-butyl ester **4**, which was alkylated in a clean S_N2-reaction with (*S*)-1-bromoethylbenzene (88% *ee*)[6] (Scheme 1). Simple recrystallization of (*S*,*S*)-*tert*-butyl ester **5** from pentane/acetone removed the 10% contamination of the *meso* isomers, and provides the pure ester **5** (65% yield). The free carboxylic acid **2** is then obtained by the acid catalysed cleavage of the *tert*-butyl ester **5**. This simple reaction sequence has been performed on a 10-g scale with an overall yield of about 50%.



Scheme 1. a) Isobutene, H_2SO_4 cat., CH_2Cl_2, −15 → 25 °C, 14 h, 85%; b) LDA, THF, −78 °C, 1.5 h, then HMPA (1.0 equiv), (*S*)-PhCH(Br)CH_3 (1.5 equiv), −20 → 25 °C, 65%; c) *p*-TosOH cat., toluene, 110 °C, 14 h, 95%. HMPA = hexamethyl phosphoramide; *p*-TsOH = *para*-toluenesulfonic acid.

The carboxylic acid **2** was readily converted into the corresponding alkyl chloride **6** by a radical decarboxylation.[7] Thus, **2** was converted into its corresponding acid chloride followed by treatment with the sodium salt of 2-mercaptopyridine-*N*-oxide with simultaneous photolysis (Scheme 2).



Scheme 2. a) $SOCl_2$, 90 °C, 3 h; b) NaC_5H_4NOS, DMAP cat., CCl_4, 80 °C, *hν* (300 W), 2 h; c) lithium 4,4″-di-*tert*-butylbiphenylide, THF, −78 °C, 5 min; d) $(PhS)_2$, THF, −78 → 25 °C; e) $MePCl_2$, THF, −78 → 25 °C; f) $BH_3 \cdot SMe_2$. DMAP = 4-dimethylaminopyridine.

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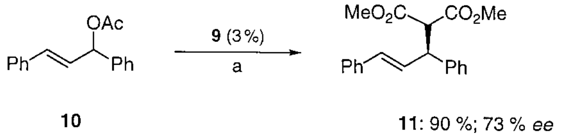
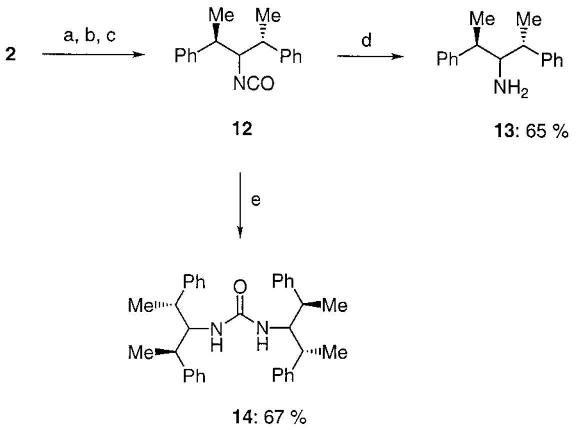
The reductive lithiation of the alkyl chloride **6** forms the optically pure alkyllithium reagent **7** in approximately 90% yield. This compound was trapped with diphenyl disulfide to give the thioether **8** in 89% yield. Interestingly, the chiral organolithium **7** is indefinitely configurationally stable, since an epimerization of the anionic center is impossible for symmetry reasons.

Treatment of **7** with methyldichlorophosphane (−78 °C to 25 °C, 2 h) afforded the chiral phosphane **9**, which was isolated and stored as its oxidation-stable BH_3-complex in 80% yield. After deprotection[8] this free phosphane catalyzed the enantioselective allylation[9] of dimethyl malonate with the allylic acetate **10** in the presence of $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (1.4 mol%) in DMF. This reaction led to the malonate **11** in 90% yield and 73% *ee* under optimized conditions (Scheme 3).[10]

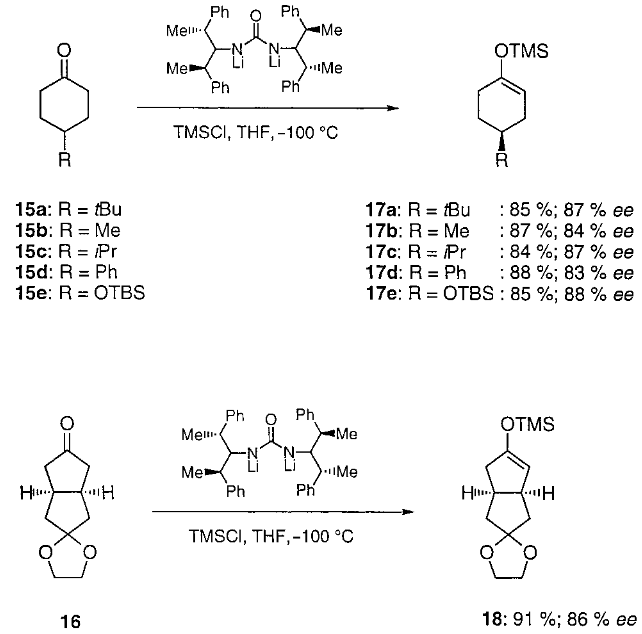


Scheme 3. Palladium catalyzed enantioselective allylation in the presence of **9**. a) $CH_2(CO_2Me)_2$ (3 equiv), *N*,*O*-bis(trimethylsilyl)acetamide (3 equiv), $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (1.4 mol%), KOAc (5 mol%), DMF, 20 °C, 14 h.

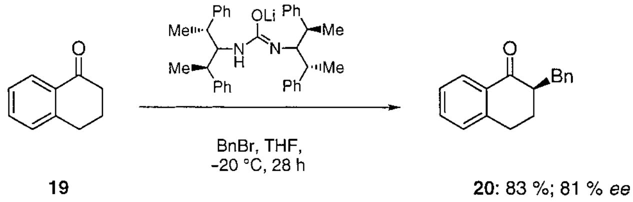
Next, we turned our attention to the preparation of related chiral amines. The carboxylic acid **2** undergoes a straightforward Curtius rearrangement[11] to give the isocyanate **12**, which after purification by flash chromatography furnishes the primary amine **13** in 65% overall yield (Scheme 4). Interestingly, by stirring the isocyanate **12** with silica gel in pentane/diethyl ether (25 °C, 14 h) the chiral urea **14** was obtained reproducibly in 67% yield. The double deprotonation of **14** with *n*BuLi provides a dianion that acts as an excellent base for the enantioselective deprotonation[12] of various prochiral cyclic ketones such as **15a–e** and **16**. These ketones can be transformed into the silylenol ethers **17a–e** and **18** with 83–88% *ee* by using Corey's protocol for in situ quenching[13] (Scheme 5).[14] The new chiral urea derivative **14** is also an excellent auxiliary for the enantioselective alkylation of ketones.[15] Thus, the treatment of α-tetralone **19** with the monoanion of **14** at −78 °C, followed by the addition of an excess of benzyl bromide affords the (*R*)-2-benzyltetralone **20** in 83% yield and 81% *ee* (Scheme 6).



Scheme 4. a) $SOCl_2$, 90 °C, 3 h; b) NaN_3, nBu_4NBr cat., CH_2Cl_2/H_2O, 0 °C, 2 h; c) toluene, 110 °C, 1 h; d) flash chromatography on silica gel; e) stir with silica gel, pentane/diethyl ether, 25 °C, 14 h.



Scheme 5. Enantioselective deprotonation mediated by the dianion of the chiral urea derivative **14**. TMS = trimethylsilyl; TBS = *tert*-butyldimethylsilyl.



Scheme 6. Enantioselective deprotonation mediated by the monoanion of the urea derivative **14**.

We have shown that chiral phosphorus or nitrogen ligands in which the chiral group is attached to the heteroatom by a nonstereogenic chirotopic center can be used for asymmetric synthesis. The new chiral urea derivative **14** proves to be useful in enantioselective deprotonations as well as in enantioselective alkylations. Extension of this concept to cyclic systems is currently underway.

Experimental Section

Typical procedure for the enantioselective allylation: Preparation of **11**: A two-necked flask under argon was charged with the phosphane **9** in CH_2Cl_2 (0.13 mL of a 0.14 M solution, 18 μmol). The solvent was evaporated and the phosphane dissolved in DMF (1.5 mL). After the addition of $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (3.0 mg, 8 μmol), the reaction mixture was stirred for 0.5 h at room temperature to give a yellow solution. 1,3-Diphenyl-1-acetoxy-2-propene (150 mg, 0.60 mmol) was added, and after 0.5 h *N*,*O*-bis(trimethylsilyl)acetamide (366 mg, 1.80 mmol), dimethyl malonate (238 mg, 1.80 mmol), and KOAc (3.0 mg, 0.03 mmol) were added successively. The reaction mixture was stirred for 14 h and was worked up in the usual manner to afford the desired product **11** as a colorless oil (174 mg, 90% yield) after purification by flash chromatography (pentane/ethyl acetate 6/1). The enantiomeric excess (73% *ee*) was determined by HPLC (Daicel Chiralcel OD column, 0.4 $\text{mL}\,\text{min}^{-1}$, heptane/2-propanol 99/1, UV detection at 254 nm).

Typical procedure for the enantioselective deprotonation: Preparation of **17a**: A Schlenk-flask was charged with a solution of **14** (236 mg, 0.47 mmol) in dry THF (10 mL) under argon. The solution was cooled to −78 °C and *n*BuLi (1.60M in hexane, 0.58 mL, 0.94 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C over 15 min, and was stirred for another 15 min at this temperature. The reaction mixture was rapidly cooled to −100 °C and chlorotrimethylsilane (0.24 mL, 1.89 mmol) was added dropwise. After the reaction mixture had stirred for 2 min at this temperature a solution of 4-*tert*-butylcyclohexanone (58 mg, 0.38 mmol) in dry THF (0.8 mL) was added dropwise over 5 min. After 50 min triethylamine (2 mL) was added, followed by a saturated solution of $NaHCO_3$ (2.5 mL). The reaction mixture was warmed to room temperature, extracted with diethyl ether, and the organic phase washed with water (3 × 15 mL). The combined aqueous phase was extracted with diethyl ether (20 mL), and the organic phase was dried over Na_2SO_4. The crude reaction mixture obtained after evaporation of the solvents was subjected to Kugelrohr distillation (150 °C, 10^{-3} bar). This afforded the desired product **17a** (90 mg, 85%) in 87% *ee* (GC analysis: Chirasil-DEX CB (Chrompak), carrier gas H_2 (100 kPa), 80 °C (1 min) →120 °C, T gradient: 2 $^{\circ}\text{C}\,\text{min}^{-1}$: t_R = 20.5 (*S*), 20.8 (*R*) min). Any urea **14** (205 mg, 87%) recovered by distillation was reused in further reactions.

Typical procedure for the enantioselective alkylation: Preparation of **20**: A Schlenk flask was charged with a solution of **14** (505 mg, 1.00 mmol) in dry THF (7 mL) under argon. The solution was cooled to −78 °C and *n*BuLi (1.50M in hexane, 0.67 mL, 1.00 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C over 15 min, and was stirred for another 15 min at this temperature. The reaction mixture was allowed to cool to −40 °C, and a solution of α-tetralone (120 µL, 0.90 mmol) in dry THF (2 mL) was added dropwise over 2 min. The reaction mixture was warmed to room temperature over 20 min and stirred for another 30 min. The reaction mixture was then cooled to −78 °C, and a solution of benzyl bromide (1.20 mL, 10.1 mmol) in dry THF (2 mL) was added dropwise over 15 min. The reaction mixture was allowed to warm to −20 °C and stirred for 28 h at this temperature. The reaction mixture was quenched with aqueous hydrochloric acid (1M, 5 mL), and after warming to room temperature the reaction mixture was extracted with diethyl ether (80 mL) and the organic phase was washed successively with water (2 × 10 mL) and brine (10 mL). The combined aqueous phase was extracted with diethyl ether (10 mL) and the organic phase was dried (Na_2SO_4). Purification by flash chromatography (pentane/diethyl ether 3.5/1) afforded the desired product **20** as a colorless crystalline solid (180 mg, 83%, m.p. 54 °C). The enantiomeric excess was determined by HPLC as 81% *ee* (Daicel Chiralcel OD column, 0.6 $\text{mL}\,\text{min}^{-1}$, heptane/2-propanol 99.5/0.5, UV detection at 254 nm).

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A New Strategy for the Destabilization of Double-Stranded Nucleic Acids by Phenylalkylamine Derivatives[**]

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Hans-Jörg Schneider[*]

The unwinding of double-stranded (ds) nucleic acids is an important process for the biological functions of DNA and RNA. Until now, most of the organic ligands studied stabilize the double-stranded form of nucleic acids,[1] which is characterized by an increase in the thermal denaturation temperature T_m. Only with high concentrations of organic solvents, copper salts,[2] and with some steroidal amines[3] has a decrease in the melting point been reported; stronger destabilization effects are accompanied by DNA precipitation.[4] Kimura et al. found that zinc complexes could desta-

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