Asymmetric Synthesis

Highly Enantioselective Preparation of Tertiary Alcohols and Amines by Copper-Mediated Diastereoselective Allylic S_N2' Substitutions**

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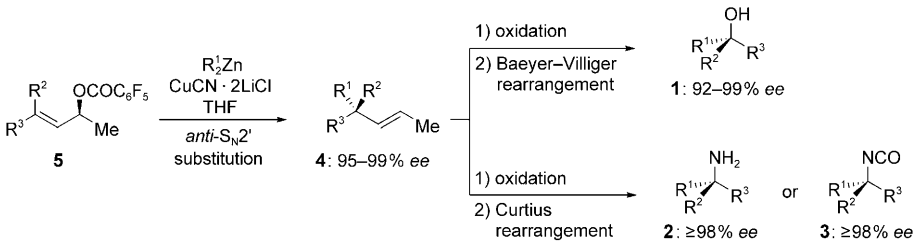
The asymmetric preparation of tertiary alcohols and amines is an important synthetic problem that has been the subject of numerous studies.[1,2] Copper-catalyzed S_N2' substitutions are an excellent method for setting up chiral centers in cyclic and acyclic systems.[3–5] Only a few of these reactions can be applied to the construction of quaternary carbon centers.[6] We have recently reported an efficient *anti*-S_N2' allylic substitution reaction with pentafluorobenzoates of trisubstituted allylic alcohols that produces quaternary centers with almost complete transfer of the chiral information.[7] Herein, we report applications of this method for preparing chiral tertiary alcohols **1** and amines and isocyanates such as **2** and **3**, which bear a tertiary chiral center, with high enantioselectivity starting from the chiral allylic substitution products **4**, which were obtained from the allylic pentafluorobenzoates **5** (Scheme 1).



Scheme 1. Enantioselective preparation of tertiary alcohols **1**, amines **2**, and isocyanates **3** bearing a tertiary chiral carbon center.

In a typical procedure the *E* pentafluorobenzoate **5a** (97% *ee*, entry 1 of Table 1) was treated with $Pent_2Zn$ (2 equiv) and CuCN·2 LiCl (1 equiv) in THF at −30 to −10 °C for 14 h to afford the expected *anti*-S_N2' substitution product **4a** (70%, 96% *ee*) with an almost perfect transfer of chiral information. Functionalized diorganozinc reagents such as $(EtO_2C(CH_2)_3)_2Zn$[8] reacted in a similar way providing the corresponding chiral esters **4b** (68%, 96% *ee*) and **4c** (58%, 96% *ee*) with the same level of enantioselectivity. In all these substitutions, allylic pentafluorobenzoates were used as substrates. Other allylic alcohol derivatives such as 2,6-difluorobenzoate **5c** (99% *ee*) underwent the allylic substitution with optimum enantioselectivity leading to the *E* alkene **4d** in 85% yield and 98% *ee* (entry 4). These substrates also gave excellent results with purely alkyl-substituted allylic reagents such as **5d** (99% *ee*, entry 5). In this case, the substitution with Et_2Zn provided the *E* alkene **4e** (80%, 96% *ee*) bearing a quaternary center with three different alkyl substituents. Although allylic acetates react only sluggishly with diorganozinc reagents, in the case of the allylic acetate **5e** (97% *ee*), which bears small substituents (Me and Et) at the double bond, an efficient substitution with $Pent_2Zn$ took place providing the *E* alkene **4f** in 60% yield and 95% *ee*.

This substitution reaction proceeded with a reliable transfer of chirality (entries 7 and 8) and was also performed with secondary diorganozinc reagents like iPr_2Zn to furnish the sterically hindered alkene **4i** (73%, 95% *ee*; entry 9). Interestingly, functionalized allylic pentafluorobenzoates such as **5i** (99% *ee*) and **5j** (99% *ee*) provided useful chiral building blocks like **4j** (69%), **4k** (90%), and **4l** (80%) in enantiomerically pure form (99% *ee*; entries 10–12).

With the chiral alkenes of type **4** in hand, we then developed a straightforward oxidation sequence for the conversion of chiral alkenes **4** to either the corresponding aldehydes **12** or carboxylic acids **13** (Scheme 2). The former intermediate undergoes stereoselective Baeyer–Villiger rearrangement[9] to afford the chiral tertiary alcohol **1**, and the latter undergoes stereoselective Curtius rearrangement[10] leading to the isocyanates **3**, which can be converted to the corresponding amines **2**. In this way the ozonolysis of the alkene **4d** followed by a reductive workup (PPh_3, −78 to 25 °C, 2 h) provided the aldehyde **12a** in 85% overall yield and 98% *ee*. Treatment of **12a** with MCPBA (3 equiv, Na_2HPO_4, CH_2Cl_2, RT, 2 h) furnished, after saponification of the intermediate formyl ester, the tertiary alcohol **1a** (70%, 97% *ee*) with perfect retention of configuration (entry 1 of Table 2). Alternatively, the conversion of **4d** to the corresponding carboxylic acid **13a** (entry 2) was achieved when the ozonolysis was followed by a Jones oxidation. Heating **13a** with $(PhO)_2P(O)N_3$ in toluene for 1 h in the presence of Et_3N afforded an intermediate isocyanate, which was converted to the corresponding chiral amine **2a** (20% HCl, reflux, 18 h, 65%, 98% *ee*) with very high retention of the configuration for the chiral tertiary center.

These reaction sequences proved to be general, and the alkenes **4e** (96% *ee*) and **4g** (98% *ee*) afforded the alcohols **1b** (76%, 92% *ee*; entry 3) and **1c** (68%, 93% *ee*; entry 4), respectively, and the isocyanate **3a** (68%, 98% *ee*). Polyfunc-

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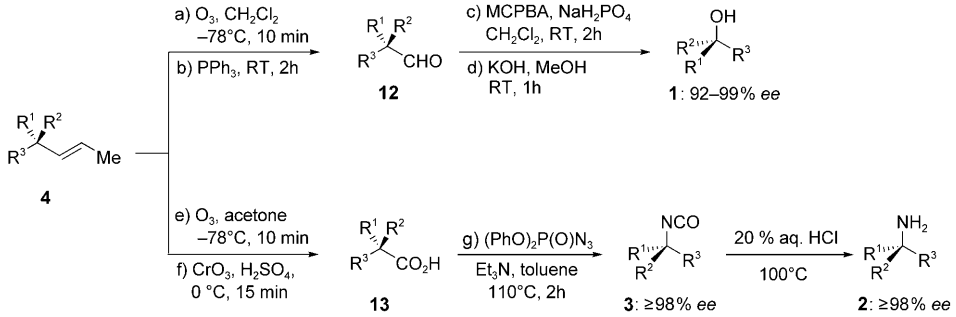
Table 1: Products **4** resulting from the copper-mediated *anti*-S_N2' substitution of pentafluorobenzoates **5** with diorganozinc reagents.

Entry	Allyl substrate (*ee* [%][a])	Product	Yield [%][b]	*ee* [%][a]	Entry	Allyl substrate (*ee* [%][a])	Product	Yield [%][b]	*ee* [%][a]
1	**5a** (97)	**4a**: R = Pent	70	96	7	**5f** (99)	**4g**	88	98
2	**5a** (97)	**4b**: R = $(CH_2)_3CO_2Et$	68	96					
3	**5b** (98)	**4c**	58	96	8[c]	**5g** (97)	**4h**	90	95
4	**5c** (99)	**4d**	85	98	9	**5h** (99)	**4i**	73	95
5	**5d** (99)	**4e**	80	96	10	**5i** (99)	**4j**: R = Et	69	99
					11	**5i** (99)	**4k**: R = Pent	90	99
6	**5e** (97)	**4f**	60	95	12	**5j** (99)	**4l**	80	99

[a] The enantiomeric excess was determined by HPLC or GC analysis. In each case the racemic product was also prepared for HPLC or GC calibration. [b] Yield of analytically pure product. [c] In this case the reaction was performed in a 2:1 THF/*N*-methylpyrrolidinone.

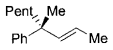
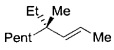
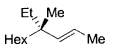
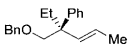
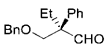
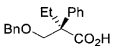
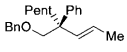
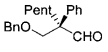
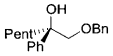
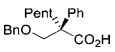
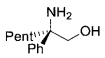
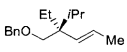
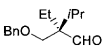
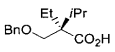


Scheme 2. Oxidation–rearrangement sequence for the preparation of chiral tertiary alcohols.

tional products such as selectively protected 1,2-diols bearing a tertiary hydroxyl group can be readily prepared starting from the chiral homoallylic benzyl ethers **4j** (99% *ee*), **4k** (99% *ee*) and **4l** (99% *ee*). After ozonolysis, the intermediate aldehydes **12d** (62%, 99% *ee*; entry 6), **12e** (66%, 99% *ee*; entry 8), and **12f** (71%, 99% *ee*; entry 10) were submitted to the Baeyer–Villiger reaction to provide the mono-protected diols **1d** (70%, 99% *ee*), **1e** (77%, 98% *ee*), and **1f** (93%, 96% *ee*), respectively. By performing the Curtius rearrangement on the corresponding carboxylic acids **13c** (65%, 99% *ee*; entry 7), **13d** (60%, 99% *ee*; entry 9), and **13e** (85%, 99% *ee*; entry 11), we obtained the amino alcohols **2b** (60%, 99% *ee*), and **2c** (88%, 99% *ee*), respectively, as well as the isocyanate **3b** (79%, 99% *ee*).

As an application of this methodology, we prepared the chiral 1,2-diol **14**, which is a key intermediate in the synthesis of the combined NK_1 and NK_2 tachykinin receptor antagonist (Scheme 3).[11] Thus, the S_N2' substitution of **5i** with $(PivO(CH_2)_3)_2Zn$ in the presence of CuCN·2 LiCl provided the chiral alkene **15** in 60% yield and 98% *ee*. The ozonolysis of **15** followed by reductive workup afforded the chiral aldehyde in 76% yield and 98% *ee*. Baeyer–Villiger oxidation of **16** in the presence of NaH_2PO_4 in CH_2Cl_2 followed by the saponification of the two ester functions gave the diol **17** in 70% yield. Quantitative protection of the remote primary hydroxy function as a TBDMS-silyl ether provided an intermediate alcohol, which underwent hydrogenolysis over Pd/C in 2-propanol (H_2 (1 atm), 25°C, 1 h) to furnish the

Table 2: Tertiary alcohols **1** obtained by oxidation followed by Baeyer–Villiger rearrangement and chiral isocyanates **3** and amines **2** obtained by oxidation followed by Curtius rearrangement.

Entry	Alkene	Intermediate	Yield [%][b]	*ee* [%][a]	Product	Yield [%][b]	*ee* [%][a]
1	 **4d**	 **12a**	85	98	 **1a**	70	97
2	**4d**	 **13a**	79	98	 **2a**	65	98
3	 **4e**	 **12b**	63	96	 **1b**	76	92
4	 **4g**	 **12c**	65	98	 **1c**	68	93
5	**4g**	 **13b**	68	98	 **3a**	68	98
6	 **4j**	 **12d**	62	99	 **1d**	70	99
7	**4j**	 **13c**	65	99	 **2b**	60	99
8	 **4k**	 **12e**	66	99	 **1e**	77	98
9	**4k**	 **13d**	60	99	 **2c**	88	99
10	 **4l**	 **12f**	71	99	 **1f**	93	96
11	**4l**	 **13e**	85	99	 **3b**	79	99

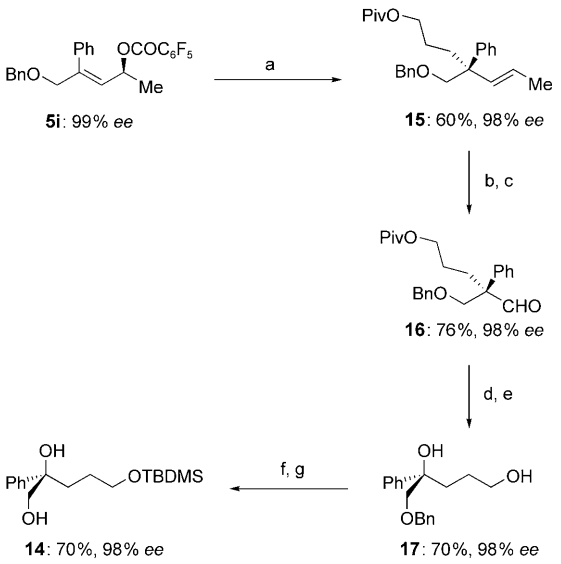
[a] The enantiomeric excess was determined by HPLC or GC analysis. In each case the racemic product was also prepared for HPLC or GC calibration. [b] Yield of isolated analytically pure product.

expected product **14**, an intermediate in the synthesis of a tachykinin receptor antagonist.

In summary, we have developed a straightforward sequence for the synthesis of tertiary alcohols with high enantioselectivity. We have shown that a Curtius rearrangement on the corresponding chiral carboxylic acids provides a stereoselective approach to amines bearing a tertiary center and to amino alcohol derivatives. Further applications of this method to the preparation of polyfunctional chiral building blocks are currently underway in our laboratories.

Experimental Section

Typical procedure for the copper(I)-mediated allylic substitution of fluorobenzoates with dialkylzinc reagents: **4d**:[7a]: $Pent_2Zn$ (2.35 mL, 11.3 mmol, 2.4 equiv) was added at −30 °C to a solution of CuCN·2-LiCl (5.6 mL, 5.6 mmol, 1.2 equiv, 1 M in THF) stirred under argon. The resulting mixture was stirred for 0.5 h at −30 °C, then **5c** (4.7 mmol in THF (2 mL), 1.0 equiv) was added dropwise. The reaction mixture was allowed to warm to −10 °C within 1.5 h and was stirred at −10 °C for 14 h. The reaction mixture was quenched by addition of aq. sat. NH_4Cl (5 mL) and was then poured into 25% aq. ammonia (2 mL), aq. sat. NH_4Cl (100 mL), and Et_2O (100 mL). After extraction with Et_2O (3 × 100 mL), the combined extracts were washed with brine (100 mL) and dried ($MgSO_4$). The solvents were



Scheme 3. Preparation of the diol **14**, an intermediate in the synthesis of the tachykinin receptor antagonist. a) $(PivO(CH_2)_3)_2Zn$, CuCN·2 LiCl, THF, −30→−10 °C, 16 h; b) O_3, CH_2Cl_2, −78 °C; c) PPh_3, RT, 2 h; d) MCPBA, NaH_2PO_4, CH_2Cl_2, RT, 2 h; e) LiOH, MeOH, RT, 5 h; f) TBDMSCl, imidazole, DMF, RT, 5 h; g) 1 atm H_2, Pd/C, *i*PrOH, RT, 1 h. MCPBA = *meta*-chloroperbenzoic acid, TBDMS = *tert*-butyldimethylsilyl.

removed by evaporation and the residue purified by column chromatography to yield alkene **4d** (855 mg, 3.96 mmol, 85 %) as a colorless liquid.

Typical procedure for the oxidation[12] and Baeyer–Villiger rearrangement[9] sequence: **1a**: Ozone was passed through a solution of alkene **4d** (260 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at −78 °C under N_2 until the solution turned blue (3–10 min); excess O_3 was removed with a stream of N_2. PPh_3 (408 mg, 1.5 mmol, 1.3 equiv) was added in one portion, and the mixture was warmed to 20 °C within 2 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with water and brine, and then dried ($MgSO_4$). The solvents were removed by evaporation in vacuo, and the residue was purified by column chromatography to give **12a** (194 mg, 0.95 mmol, 85 %, 98 % *ee*) as a colorless liquid. The enantiomeric excess was determined by GC analysis (column: Chiraldex B-PH; 100 °C (30 min), 0.5° min^{-1} until 120 °C: t_R = 78.3 (*R*), 79.7 min^{-1} (*S*)). To a solution of aldehyde **12a** (163 mg, 0.80 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added anhydrous MCPBA (260 mg, 1.2 mmol, 1.5 equiv). The reaction was stirred at room temperature for 24 h before it was quenched with water and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (pentane/Et_2O = 98:2). (2*S*)-2-phenylheptan-2-yl formate (123 mg, 70 %) was obtained as a colorless liquid. To a solution of (2*S*)-2-phenylheptan-2-yl formate (123 mg, 0.56 mmol, 1.0 equiv) in MeOH (2 mL) was added KOH (62 mg, 1.12 mmol, 2.0 equiv). The reaction mixture was stirred at 20 °C for 1 h, then diluted with Et_2O (10 mL), washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (pentane/Et_2O = 9:1) yielded **1a** (75 mg, 0.39 mmol, 70 %, 97 % *ee*) as a colorless oil. The enantiomeric excess was determined by GC analysis (column: chiraldex B-PH; 100 °C (30 min), 0.5° min^{-1}, 120 °C (60 min)): t_R = 78.3 (*S*), 79.7 min^{-1} (*R*)). Na_2HPO_4 (1 equiv) can be used as a buffer in order to enhance the rate of the reaction (reaction time reduced to 2 h at 20 °C) and to improve the *ee* value. See the Supporting Information for the preparation of compounds **1b** and **1c**.

Typical procedure for the oxidation[12] and Curtius rearrangement:[10] **2a**: Ozone was passed through a solution of alkene **4d** (432 mg, 2.00 mmol, 1.0 equiv) in acetone (10 mL) at −78 °C under N_2 until the solution turned blue (3–10 min); excess O_3 was removed by a stream of nitrogen. The reaction mixture was cooled to 0 °C, and Jones reagent (2.0 mL, 2.67 M, 5.4 mmol, 2.7 equiv) was added dropwise until the orange color persisted. The mixture was stirred for 1 h at 20 °C, then *i*PrOH (8 mL) was added until the mixture turned green. The solvents were removed by evaporation, and the residue was dissolved in water/ (100 mL, 1:4). After acid–base workup[12c] the desired carboxylic acid **13a** (348 mg, 1.58 mmol, 79 %) was obtained as a colorless liquid. A mixture of **13a** (124 mg, 0.56 mmol, 1.0 equiv), $(PhO)_2P(O)N_3$ (231 mg, 0.84 mmol, 1.5 equiv) and NEt_3 (85 mg, 0.84 mmol, 1.5 equiv) in toluene (5 mL) was heated at reflux for 2 h. After removal of the solvent by evaporation in vacuo, the residue was taken up in ether (50 mL) and washed with water (3 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (pentane/Et_2O = 98:2). 1-((2*S*)-2-Isocyanatoheptan-2-yl)benzene (120 mg, quant., 98 % *ee*) was obtained as a colorless liquid. The enantiomeric excess was determined by GC analysis (column: Chiraldex B-PH; 100 °C const.: t_R = 57.8 (*S*), 61.9 min^{-1} (*R*)). 1-((2*S*)-2-isocyanatoheptan-2-yl)benzene (50 mg, 0.23 mmol) was heated at reflux in 20 % aq. HCl (5 mL) for 24 h. The reaction mixture was partitioned in Et_2O and water (4:1), and the layers were separated. The aqueous layer was treated with NaOH (20 %) and extracted with Et_2O (3 × 80 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated in vacuo to give **2a** (30 mg, 0.16 mmol, 65 %, 98 % *ee*) as a colorless oil.

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