Chiral Allylic Cyanohydrins as Versatile Substrates for Diastereoselective Copper(I)-mediated S_N2' Allylic Substitutions

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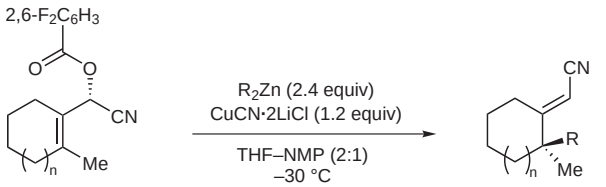
Abstract: 2,6-Difluorobenzoated derivatives bearing a protected cyanohydrin function undergo highly stereoselective copper(I)-mediated S_N2' allylic substitution reactions with diorganozinc reagents leading to chiral unsaturated nitriles.

Key words: asymmetric synthesis, allylic substitution, cyanohydrins, copper, zinc, unsaturated nitriles

Cyanohydrins occupy a unique place at the interface between chemistry and biology.[1] They are readily prepared by a number of synthetic methods,[2] and their stereoselective synthesis can be achieved either by chemical[3] or enzymatic procedures.[4] Herein, we wish to report a highly stereoselective S_N2' allylic substitution reaction[5–8] on chiral difluorobenzoated allylic cyanohydrins with diorganozinc reagents in the presence of CuCN·2LiCl that produces α,β-unsaturated nitriles bearing a new stereogenic center in the γ-position.

Tetrasubstituted allylic difluorobenzoated cyanohydrins of type **1** bearing a methyl group in the γ-position undergo highly regio- and stereoselective S_N2' substitutions and afforded exclusively the S_N2'-substituted product of type **2** with perfect transfer of chirality (Scheme 1 and Table 1).



1a: n = 1, 96% ee
1b: n = 0, 90% ee

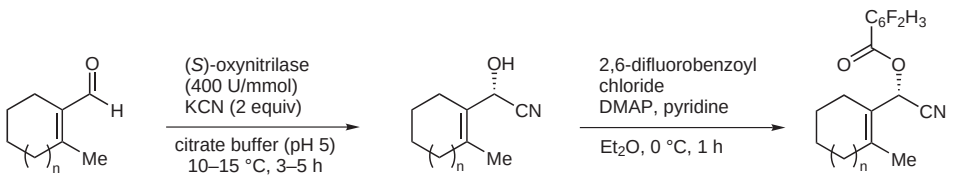
2: up to 96% ee
40–91% yield

Scheme 1

Cyanohydrin derivatives like **1** were synthesized in their enantiomerically enriched form starting from the corresponding carbaldehydes **3a** and **3b** (Scheme 2). The enantioselective (*S*)-oxynitrilase-catalyzed addition of KCN (2 equiv) in a citrate buffer[9] gave the chiral cyanohydrins (*S*)-**4a** (58%, 96% ee) and (*S*)-**4b** (55%, 90% ee). Subsequent esterification with 2,6-difluorobenzoyl chloride afforded (*S*)-**1a** in 83% and (*S*)-**1b** in 73% yield without racemization.

The substitution of the allylic cyanohydrin derivative **1a** with $Pent_2Zn$ (2.4 equiv) in the presence of CuCN·2LiCl [1.2 equiv, THF–NMP (2:1), –30 °C to 0 °C, 5 h) afforded the γ-substituted unsaturated nitrile **2a** as a single regioisomer in 75% yield and 96% ee (entry 1 of Table 1). No traces of the S_N2 product was detected and the substitution afforded only the *E*-isomer.[10]

The substitution with Et_2Zn led to the expected product **2b** (65%, 96% ee, entry 2). Similarly, a functionalized zinc reagent like $[PivO(CH_2)_3]_2Zn$ gave the chiral pivalate **5c** in 65% yield and 96% ee (entry 3). Although the substitution occurred in excellent diastereoselectivity, it was limited to primary alkyl substituents. Indeed, reactions with more sterically demanding groups like *i*-Pr_2Zn or *c*-Hex_2Zn were not selective. However, the cyclopentyl cyanobenzoate derivative **1b** did not suffer from these limitations and reacted with a wide range of diorganozincs. Thus, the substitution of **1b** with $Pent_2Zn$ as well as with Et_2Zn in the presence of CuCN·2LiCl afforded the corresponding α,β-unsaturated nitriles **2d** (91%, 90% ee, entry 4) and **2e** (80%, 90% ee, entry 5) with an optimum transfer of chirality. The substitution proceeded with excellent diastereoselectivity with secondary diorganozincs like *i*-Pr_2Zn and *c*-Hex_2Zn to furnish the sterically hindered substituted cyclopentane derivatives **2f** (75%, 90%



3a: n = 1
3b: n = 0

(*S*)-**4a**: 58%, 96% ee
(*S*)-**4b**: 55%, 90% ee

(*S*)-**1a**: 89%
(*S*)-**1b**: 73%

Scheme 2

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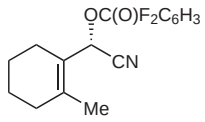
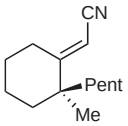
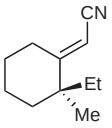
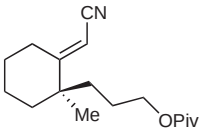
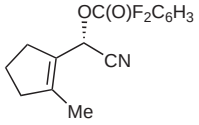
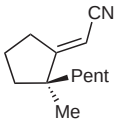
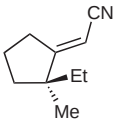
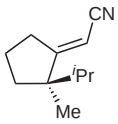
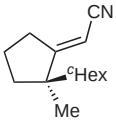
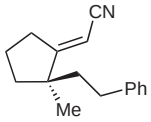
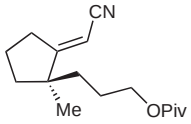
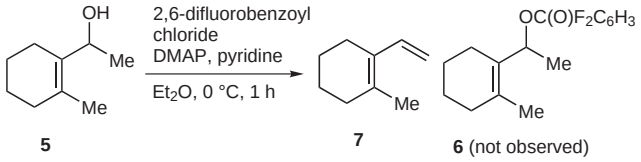
Table 1 Copper(I)-Mediated S_N2' Allylic Substitution of 2,6-Difluorobenzoated Allylic Cyanohydrins **1a**,**b**

Entry	Allyl substrate (ee, %)[a]	R^2Zn (*R*)	α,β-Unsaturated nitrile of type **1**	Yield (%)[b]	ee (%)[a]
1	 **1a** (96)	Pent	 **2a**	75	96
2	**1a**	Et	 **2b**	65	96
3	**1a**	$PivO(CH_2)_3$	 **2c**	65	96
4	 **1b** (90)	Pent	 **2d**	91	90
5	**1b**	Et	 **2e**	80	90
6	**1b**	*i*-Pr	 **2f**	75	90
7	**1b**	*c*-Hex	 **2g**	60	90
8	**1b**	$Ph(CH_2)_2$	 **2h**	40	90
9	**1b**	$PivO(CH_2)_3$	 **2i**	71	90

[a] The ee was determined by GC analysis of the pure product on Chirasil-Dex CB column. In each case the racemic product was used for calibration.
[b] Isolated yield of analytically pure product.

ee, entry 6) and **2g** (60%, 90% ee, entry 7). Diorganozincs like $[Ph(CH_2)_2]_2Zn$ (entry 8) or $[PivO(CH_2)_3]_2Zn$ (entry 9) reacted similarly with **1b** and afforded, respectively, **2h** in 40% yield and 90% ee and **2i** (71% and 90% ee).

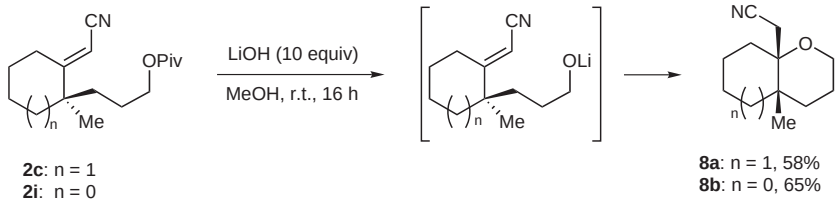
Interestingly, we could demonstrate that in this sequence the presence of the cyano group was essential. Indeed, any attempts to derivatize the cyclic allylic alcohol **5**, in which the cyano group is replaced by a methyl group, into the corresponding benzoated ester **6** provided only the elimination product **7** (Scheme 3).



Scheme 3

In addition, we explored the transformation of the resulting α,β-unsaturated nitriles of type **2**. We found that **2c** and **2i** underwent a diastereoselective cyclization when treated with LiOH leading to the fused bicycles **8a** and **8b** (Scheme 4).

In summary, we have shown that enantiomerically enriched difluorobenzoated cyanohydrin derivatives constituted substrates of choice for the copper(I)-mediated S_N2' allylic substitution. They reacted with diorganozinc reagents in the presence of CuCN·2LiCl leading to α,β-unsaturated nitriles bearing a new stereogenic center in the γ position with an excellent transfer of chirality.[11]



Scheme 4

Acknowledgment

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(10) The stereochemistry of the double bond was confirmed by 2D ^{1}H NMR spectroscopy.

(11) **Typical Procedure for the S_N2' Substitution: Preparation of (2*S*,*E*)-2-(2-Methyl-2-pentylcyclopentylidene)acetonitrile (2d)**

A flame-dried flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with CuCN·2LiCl solution (2.6 mL, 1.0 M in THF, 2.64 mmol, 1.2 equiv), anhyd NMP (2.6 mL, overall ratio of solvents THF–NMP = 2:1). The mixture was cooled at –30 °C. To this solution was added dropwise dipentylzinc solution (1.1 mL, 4.8 M in THF, 5.28 mmol, 2.4 equiv). The resulting mixture was stirred at –30 °C for 45 min, and then (2*S*)-cyano(2-methylcyclopent-1-enyl)methyl 2,6-difluorobenzoate (**1b**, 610 mg, 2.2 mmol, 90% ee) was added dropwise as a solution in THF (1.5 mL). The reaction mixture was stirred at –30 °C to 0 °C for 2 h and sat. aq NH_4Cl solution (5 mL) was added. The quenched reaction mixture was poured into 25% aq NH_3 (2 mL), aq sat. NH_4Cl (100 mL) and Et_2O (100 mL) and stirred at 25 °C until the copper salts had dissolved then extracted with Et_2O (3 × 100 mL). The combined extracts were washed with H_2O, brine and dried over Mg_2SO_4. Evaporation of the solvents and purification by column chromatography (silica gel, pentane–Et_2O, 9:1) afforded the unsaturated nitrile **2d** (382 mg, 2.0 mmol, 91%, 90% ee) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (t, ^3J = 2.55 Hz, 1 H), 2.81–2.56 (m, 2 H), 1.78–1.66 (m, 2 H), 1.66–1.53 (m, 2 H), 1.34–1.16 (m, 8 H), 1.04 (s, 3 H), 0.87 (t, ^3J = 6.75 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9, 117.9, 89.9, 47.6, 40.4, 38.9, 34.0, 32.6, 26.1, 24.4, 22.7, 22.1, 14.3. MS (EI, 70 eV): *m/z* (%) = 191 (8) [M^+], 176 (11), 162 (8), 148 (12), 121 (89), 120 (100), 106 (12), 93 (23), 79 (25). HRMS: *m/z* calcd: 191.1674; found: 191.1651. $[\alpha]_D^{20}$ –15.9 (*c* 1.49, $CHCl_3$). GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/min to 140 °C; t_R(min) = 23.45 (*R*), 23.93 (*S*).

(2*R*,*E*)-(-2-Methyl-2-phenethylcyclopentylidene)acetonitrile (2h)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.14 (m, 5 H), 5.09 (t, ^3J = 2.55 Hz, 1 H), 2.91–2.46 (m, 4 H), 1.88–1.58 (m, 6 H), 1.14 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4, 142.2, 128.7, 128.4, 126.2, 117.8, 90.3, 47.7, 42.5, 38.9, 34.0, 31.3, 26.1, 22.2. MS (EI, 70 eV): *m/z* (%) = 225, 121 (16), 134 (9), 105 (100), 104 (63), 91 (64), 79 (18), 77 (18), 65 (15). HRMS: *m/z* calculated: 225.1517; found: 225.1487. $[\alpha]_D^{20}$ –5.8 (*c* 0.69, $CHCl_3$). GC (Chirasil-Dex CB), 100 °C (5 min), ramp of 2 °C/min to 160 °C; $t_{R(}$min) = 49.21 (*R*), 50.24 (*S*).

{4a-Methyl-hexahydro-cyclopenta[*b*]pyran-7a-yl}acetonitrile (8b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81–3.74 (m, 1 H), 3.53–3.43 (m, 1 H), 2.85 (d, ^2J = 16.8 Hz, 1 H), 2.35 (d, ^2J = 16.8 Hz, 1 H), 2.19–2.00 (m, 2 H), 1.94–1.58 (m, 5 H), 1.45–1.17 (m, 3 H), 0.85 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.8, 82.8, 61.8, 42.5, 36.5, 34.8, 30.2, 25.5, 21.3, 20.8, 18.9. MS (EI, 70 eV): *m/z* (%) = 180, 162 (2), 150 (2), 139 (100), 111 (15), 93 (15), 81 (12), 68 (36). HRMS: *m/z* calcd: 180.1388; found: 180.1390.