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High Diastereoselectivity in the Conjugate Addition of Functionalized Alcohols to a Chiral (E)-Nitroalkene

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Abstract: Modest to high diastereoselectivites have been observed in the conjugate addition of functionalized alcohols to chiral (E)-nitroalkene 1 depending on the presence of metal catalysts at low temperature. The results indicated that the anti-form had been preferred in all cases.

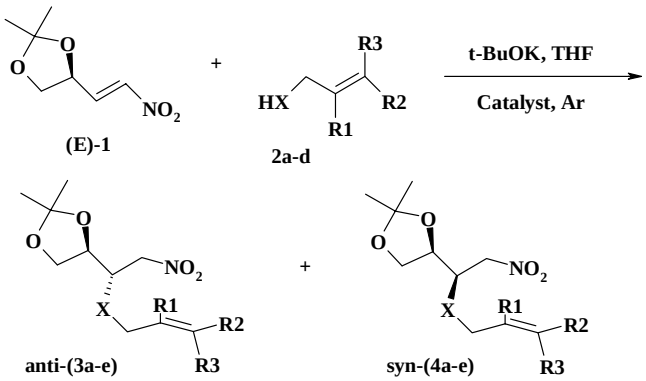
Key words: Diastereoselectivity, michael addition, alcohols, catalysts.

Nitroalkenes are versatile synthetic intermediates as powerful electron-deficient reactants in cycloaddition and conjugate addition reaction to produce a large variety functionalized carbocyclic rings[1]. Furthermore, the nitro group can be converted into a wide range of functionalities[2]. Alough Diels-Alder reaction[3] and cyclopropanation of functionalized carbon nucleophiles[4] to γ-chiral nitroalkene have been reported recently. So far the detailed research of the conjugate additions of functionalized alcohols to chiral nitrokenes has not been reported. Here we wish to report our studies on stereoselective additions of several functionalized alcohols **2** with γ-chiral-(E)- nitroalkene **1** derived from (R)-2,3-isopropylidene glyceraldehyde prepared according to literature[5] in our ongoing project on the asymmetric synthesis of the functionalized carbocyclic and heterocyclic compounds (**Scheme 1**).

The most siginificant data among the different catalysts and reaction conditions tested have been collected in **Table 1**. For example, reaction of nitroalkene **1** with alcohol **2** proceeds with a diastereomeric excess of 58-70% in the presence of CuCN or CuI (entry 1-6). This stereocontrol was slightly improved by using an excess of CuI (entry 11). The stereoselectivities of reaction performed in the absence of catalyst were comparatively lower (entry 7-8) and the catalyst DMAP had little effect on the diastereomeric ratio (entry 9-10). However, the best results (de 84-90%) of this reaction have been obtained by using a mixture of CuCN and CuI or CuI and ZnI_2 as catalysts (entry 12-15). The major anti-isomers of adducts were afforded preferably in all cases, as were expected from the model proposed by Leonard[6] and other workers[7] for conjugate additions of organometallics to enones. According to their proposal, an electron-donating group in the anti-position of the corresponding transition structure is favored, based on

the preferred conformations of acceptor and steric models as well the non-chelating reagents should afford mainly anti-isomers in conjugate addition.

Scheme 1



3a, R1=R2=R3=H, X=O; 3d. R1=R3=H, R2=CH_3, X=O
3b, R1=R2=R3=H, X=S; 3e. R1=R2=H, R3=CH_3, X=O
3c. R1=CH_3, R2=R3=H, X=O

Table 1. Conjugate additions of Chiral Nitroalkene 1 to Functionalized Alcohols 2[a]

Entry	Alcohols 2 (a-e)	Catalyst[b]	Reaction conditions	Anti:Syn[c] 3 (a-e): 4 (a-e)	Yield[d] (%)
1	CH_2=$CHCH_2OH$	CuCN (1.2)	-98℃/THF	82:18	76
2	(E)-CH_3CH=$CHCH_2OH$	CuCN (1.2)	-98℃/THF	80:20	80
3	CH_2=$CHCH_2OH$	CuBr (1.2)	-98℃/THF	80:20	79
4	CH_2=$CHCH_3CH_2OH$	CuI (1.2)	-98℃/THF	85:15	81
5	CH_2=$CHCH_2SH$	CuI (1.2)	-98℃/THF	78:22	74
6	(Z)-CH_3CH=$CHCH_2OH$	CuI (1.2)	-98℃/THF	85:15	82
7	CH_2=$CHCH_2OH$	None	-98℃/THF	70:30	64
8	CH_2=$CHCH_3CH_2OH$	None	-98℃/THF	72:28	72
9	CH_2=$CHCH_2OH$	DMAP (1.2)	-98℃/THF	73:27	86
10	CH_2=$CHCH_3CH_2OH$	DMAP (1.2)	-98℃/THF	75:25	82
11	(E)-CH_3CH=$CHCH_2OH$	CuI (3.0)	-98℃/THF	87:13	81
12	CH_2=$CHCH_2OH$	CuCN (1.2), CuI (1.2)	-98℃/THF	92:8	84
13	(E)-CH_3CH=$CHCH_2OH$	CuCN (1.2), CuI (1.2)	-98℃/THF	93:7	83
14	CH_2=$CHCH_2OH$	CuI (1.2), ZnI_2 (1.2)	-98℃/THF	95:5	87
15	(Z)-CH_3CH=$CHCH_2OH$	CuI (1.2), ZnI_2 (1.2)	-98℃/THF	95:5	85

a. All reagents were performed using nitroalkene (1.0 eq), alcohol (1.0 eq) and t-BuOK (2.0 eq) under argon for 1 h. **b.** Numbers in parentheses are the relative quantities with respect to substrate (1.0 eq). **c.** The ratio of diastereoisomers was measured by ^{1}H-NMR (500 MHz) on the crude reaction mixture. **d.** Yield of products after isolation by flash chromatography.

The struture and stereochemistry of products[8] were assigned by ^{1}H-NMR spectroscopic and computational studies on the geometry optimization of diastereomers using method **PM3**[7, 9], which exhibited a significant preferential conformation for both

diastereomeric products. The coupling constants between C_β and C_γ protons were higher for the anti-isomers such as 10.5 Hz for anti-isomers **3** and 3.5Hz for syn-isomers **4**, which were in agreement with the theoretical data (10Hz for anti-, 3.4Hz for syn-)[10] and allowed the assignment of anti- and syn-products.

In summary, it can be concluded that nitroalkene **1** is quite efficient as Michael acceptor both in terms of chemical yield and stereoselectivity. The utilization of the enantiomerically pure nitro compounds **3** as chiral building blocks for the synthesis of functionalized carbocyclic and heterocyclic compounds is in progress.

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8. General procedure for the additions of alcohols to chiral nitroalkene: A solution of alcohols (1.0 mmol) in 20 mL of THF was placed in a flame dried flask at room temperature under argon and cooled to -98℃. Potassium tert-butoxide (2.0 mmol), catalysts (1.2 mmol) were added. After stirring for 10 min, chiral nitroalkene **1** (1.0 mmol) in 20 mL of THF was injected slowly and stirring was continued for 1 h, then the glacial acetic acid (1 mL) was added. The mixture was filtered, the inorganic salts were washed with ether and the combined filtrate were dried with $MgSO_4$ and concentrated. The residue was chromatographied on silica gel which gave the products 74-87% yields. The detailed data are shown in **Table 1**. All products were determined by ^{1}H-NMR, ^{13}C-NMR, MS and HRMS. Selected samples are follows:
   anti-isomer 3a: colorless oil, $[\alpha]_D^{25}$=-41.7 (c, 0.62, $CHCl_3$). ^{1}H-NMR (500MHz, $CDCl_3$) δ ppm: 1.34 and 1.43 (2xd, J=0.5Hz, 6H), 3.92 (dd, J=8.5Hz, 4.0Hz, 1H), 4.05 (ddd, J=10.5, 3.0Hz, 1H), 4.07-4.11 (m, 2H), 4.12 (dd, J=8.5, 6.0Hz, 1H), 4.13 (dt, J=10.5, 4.0Hz, 1H), 4.54 (dd, J=13.0, 7.5Hz, 1H), 4.67 (dd, J=13.0, 3.0Hz, 1H), 5.21 (dq, J=10.5, 1.5Hz, 1H), 5.27 (dq, J=17.0, 1.5Hz, 1H), 5.84 (m, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ ppm: 24.95 (q), 26.23 (q), 66.85 (t), 72.45 (t), 75.10 (d), 76.63 (t), 77.51 (d), 110.11 (s), 118.36 (t), 133.57 (d). MS (CI+NH_3, M/z): 249 ($MNH4^+$, 61), 232 (MH^+, 56), 209 (100). HRMS (CI+CH_4) calcd. For $C_{10}H_{18}NO_5$ (MH^+): 232.1185, Found: 232.1160.
   syn-isomer 4a in mixture: ^{1}H-NMR (500MHz, $CDCl_3$) δ ppm: 1.34 and 1.43 (2xd, J=0.5Hz, 6H), 3.74 (dd, J=11.0Hz, 4.0Hz, 1H), 3.80 (dt, J=4.0, 3.5Hz, 1H), 3.83 (dd, J=11.0, 4.0Hz, 1H), 3.90 (ddd, J=7.5, 3.5Hz, 1H), 4.08-4.13 (m, 2H), 4.62 (dd, J=13.0, 7.5Hz, 1H), 4.75 (dd, J=13.0, 3.5Hz, 1H), 5.21 (dq, J=10.5, 1.5Hz, 1H), 5.28 (dq, J=17.5, 1.5Hz, 1H), 5.85 (m, 1H).
   antiisomer 3b: colorless oil, $[\alpha]_D^{25}$=-39.5 (c, 0.3, $CHCl_3$). ^{1}H-NMR (500MHz, $CDCl_3$) δ ppm: 1.33and 1.41 (2xd, J=0.5Hz, 6H), 3.21 (m, 1H), 3.22 (m, 1H), 3.28 (ddd, J=10.0, 8.0, 5.5Hz,

1H), 3.93 (dd, J=9.0, 5.5Hz, 1H), 4.08 (ddd, J=10.0, 6.0, 5.5Hz, 1H), 4.19 (dd, J=9.0, 6.0Hz, 1H), 4.55 (dd, J=13.0, 8.0Hz, 1H), 4.79 (dd, J=13.0, 5.5Hz, 1H), 5.20 (m, 1H), 5.21 (m, 1H), 5.78 (m, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ ppm: 25.26 (q), 26.57 (q), 35.08 (d), 45.03 (t), 68.34 (t), 76.21 (t), 77.58 (d), 110.62 (s), 118.75 (t), 133.56 (d).

syn-isomer 4b in mixture: ^{1}H-NMR (500MHz, $CDCl_3$) δ ppm: 1.32 and 1.43 (2xd, J=0.5Hz, 6H), 3.21 (m, 1H), 3.23 (m, 1H), 3.42 (ddd, J=6.0, 3.0Hz, 1H), 3.79 (dt, J=6.0, 3.0Hz, 1H),3.82 (dd, J=11.0, 6.0Hz, 1H), 3.89 (dd, J=11.0, 3.0Hz, 1H), 4.61 (dd, J=13.0, 7.5Hz, 1H), 4.84 (dd, J=13.0, 6.0Hz, 1H), 5.20 (m, 1H), 5.21 (m, 1H), 5.80 (m, 1H).

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10. Calculation from measured dihedral angles by using SpecTool software.

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