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2,2-Dimethyl-4-phenyloxazolidine and 2,2-Dimethyl-4,5-diphenylimidazolidine as New Chiral Auxiliaries. Applications to Asymmetric Nitrile Oxide Cycloadditions

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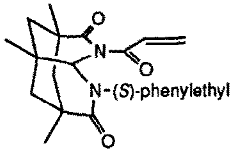
Abstract: Asymmetric dipolar cycloadditions of a nitrile oxide to the acrylamide derivatives of two new chiral auxiliaries, (*R*)-2,2-dimethyl-4-phenyloxazolidines and (*S*,*S*)-2,2-dimethyl-4,5-diphenylimidazolidine, show satisfactorily high diastereoselectivities (up to 91%).

In contrast with the well developed works on asymmetric Diels-Alder cycloadditions,[1] asymmetric versions of dipolar cycloadditions are limited. Diels-Alder cycloadditions are effectively catalyzed by a Lewis acid so that the catalyst may also work to stabilize a particular conformation in the transition state.[2,3] On the other hand, fixation of the diastereotopic faces of dipoles or dipolarophiles to the asymmetric field produced by a chirality-controlling auxiliary is rather difficult in dipolar cycloadditions because the use of Lewis acid catalysis has not been extensively investigated.[4]

1,3-Dipolar cycloadditions of nitrile oxides to terminal dipolarophiles are exclusively regioselctive to give the isoxazolines or isoxazoles bearing a substituent at the 5-position;[5] subsequent reductive cleavage of the resulting heterocycles offers high synthetic utility.[6] Accordingly, nitrile oxides behave as sterically rather small dipoles to terminal dipolarophiles so that highly diastereoselective cycloadditions of nitrile oxides are a challenging theme.[7] Although the acrylamide **1**[8] derived from the Kemp's triacid and the α,β-unsaturated ester **2**[9] bearing a C_2 symmetric imidazolidine chiral controller at the β-position show exclusively high



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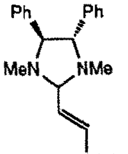

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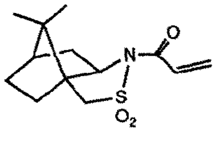

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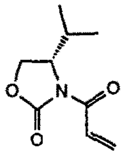

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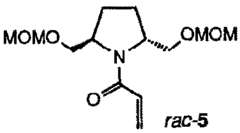
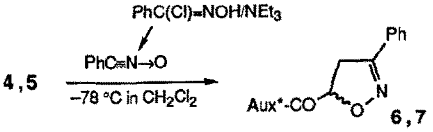


rac-**5**



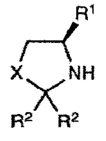
6: Aux* = 4-Isopropyl-2-oxooxazolidin-3-yl
7: Aux* = 2,5-Bis(methoxymethyloxymethyl)pyrrolidine

diastereoselectivities in nitrile oxide cycloadditions, the poor availability of **1** and the lack of regioselectivity in reactions of **2** discourage their use in organic synthesis. The acrylamide **3** derived from the Oppolzer's sultam is one of the most effective dipolarophiles to date, whose reactions with nitrile oxides are highly diastereoselective (up to 95%).[10]

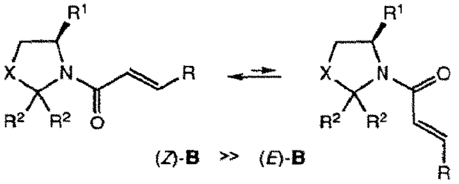
We introduce here two new chiral α,β-unsaturated amides whose asymmetric cycloadditions to nitrile oxide 1,3-dipoles show satisfactory diastereoselectivities.

Although the Evans' chiral 2-oxazolidinones[11] are readily available and widely applied chiral auxiliaries, metal chelation is necessary to attain a high diastereoselectivity (ds). Without Lewis acid catalysis, the olefin moiety is distant from the chiral center in the more favoured E-configuration. Therefore, acrylamide **4** is not useful in dipolar cycloadditions; reaction of **4** with benzonitrile oxide[12] led to a 70:30 mixture of diasteromers of **6** (–78 °C, 78%). The presence of a Lewis acid catalyst did not improve diastereoselectivity.[13]

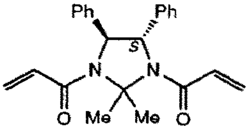
The acrylamide **5**[14] derived from the Katsuki's C_2-symmetric pyrrolidine seemed to be promising in dipolar cycloadditions since one diastereotopic face of **5** is always structurally hindered without the aid of a metallic additive. However, the diastereoselectivity actually observed in the reaction with benzonitrile oxide at –30 °C was only moderate (94%, ds = 73:27).



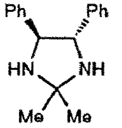
A



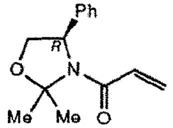
(*Z*)-**B** >> (*E*)-**B**



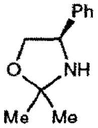
(*S*,*S*)-**8**



(*S*,*S*)-**9**



(*R*)-**10**



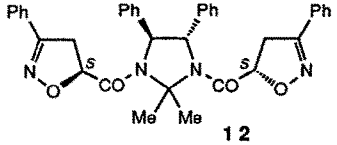
(*R*)-**11**

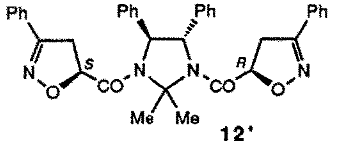
In saturated chiral nitrogen heterocycles **A**, the carbon atom adjacent to the nitrogen is highly substituted so that the acrylamide derivatives may occupy the more stable Z-configuration (*Z*)-**B**. Accordingly, one side of the diastereotopic olefin faces can be effectively hindered from the attack by a nucleophile. Their synthetic use as chiral auxiliaries should be promising since a variety of derivatives can be readily accessible in optically pure forms when X is a heteroatom.

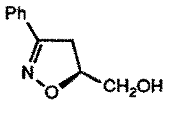
Imidazolidine bisacrylamide (*S*,*S*)-**8** and oxazolidine acrylamide (*R*)-**10** were readily prepared from C_2-symmetric 2,2-dimethyl-4,5-diphenylimidazolidine (*S*,*S*)-**9** and 2,2-dimethyl-4-phenyloxazolidine (*R*)-**11**, respectively.[15] These amides could be safely purified by column chromatography on silica gel. According to the ^{1}H NMR spectra recorded in $CDCl_3$ at rt, they exist as single Z,Z- and Z-configurations.[16]

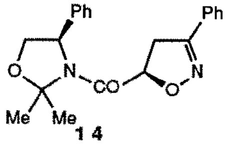
Reaction of optically pure (*S*,*S*)-**8** with benzonitrile oxide (3 equiv)[12] at –78 °C produced a mixture of diastereomeric cycloadducts **12** and **12'** (97%, 83:17) which were easily separated from each other by column chromatography on silica gel (**12**: mp 309-310 °C; **12'**: mp 220-221 °C). The reaction temperature is not important since essentially the same selectivities (ds = 80:20) resulted in both reactions at 0 °C and at rt. Based on the fact that the major diastereomer **12** is symmetric and the minor one **12'** is unsymmetric (^{1}H NMR),[17] the total diastereoselectivity in this reaction was 91:9. Reductive removal of the chiral auxiliary from **12** was performed by treatment with lithium triethylborohydride (reflux in dioxane, 0.5 h) to give (*S*)-**13** (42%) whose optical purity was 98:2 (HPLC on Daicel Chiralcel OB with hexane/2-propanol 3:1 v/v).[18]

Similar reaction of benzonitrile oxide with optically pure (*R*)-**10** at –50 °C gave a mixture of **14** and **14'** together with a side product **15** (95%, 82:5:13 by ^{1}H NMR). Hydrolysis of **14'** and **15** was catalyzed with trifluoroacetic acid (TFA in CH_2Cl_2, rt, 0.5 h) to produce the same compound **16'** in quantitative yields, but the major isomer **14** was stable under these conditions. Refluxing **14** in methanol in the presence of conc HCl gave **16** (81%, 4 h). When the crude reaction mixture was treated with TFA, a 80:20 mixture of **14** and **16'** was obtained. After separation of **14** by column chromatography on silica gel, it was reduced with lithium triethylborohydride (rt in THF, 5 min) to give optically pure (*R*)-**13** as confirmed by a chiral HPLC.[18] Thus, the diastereoselectivity in this reaction was 82:18.


12


12'


(*S*)-**13**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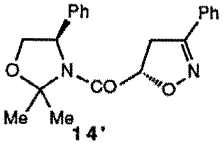
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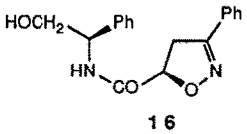
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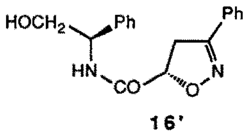
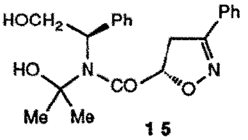

16'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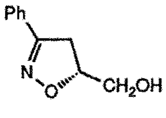
(*R*)-**13**

After all, acrylamides (*S*,*S*)-**8** and (*R*)-**10** predominantly occupy Z,Z- and Z-configurations and s-cis conformation in the transition state. Benzonitrile oxide attacks the olefin face from a side opposite to the phenyl substituent, si- and re-faces for (*S*,*S*)-**8** and (*R*)-**10**, respectively, to give **12** and **14** as major diastereomers. Although diastereoselectivities were not exclusively high, the major diastereomers can be readily separated to give optically pure isoxazolines after reductive removal of the chiral auxiliary. Structural modification of such chiral auxiliaries is now under progress in our laboratory to establish higher diastereoselectivity in nitrile oxide cycloadditions.

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12. Throughout this work, PhCNO was generated from PhC(Cl)=NOH and Et_3N in CH_2Cl_2.

13. Cycloadditions of benzonitrile oxide to **4** in the presence of Lewis acid result in poor diastereoselectivities (71:29 to 62:38): Kanemasa, S.; Nishiuchi, M.; Wada, E. Unpublished results.

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15. Condensation of (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine and (*R*)-2-phenyl-2-aminoethanol with acetone gave (*S*,*S*)-**9** and (*R*)-**11**, respectively, which were then used without further purification in the following transformation. Their treatment with acryloyl chloride and Et_3N (each 1 equiv) in THF produced (*S*,*S*)-**8** (74%, –78 °C, 0.5 h) and (*R*)-**10** (85%, 0 °C, 1 h).

16. Notable NOE (20%) was observed for H-4 by irradiation at the CH= proton in the case of (*S*,*S*)-**8**.

17. **12**: $[\alpha]_D^{25}$= 405.5 (*c* 1.08, $CHCl_3$); IR (KBr) 2900, 1625, 1350, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (6H, s, Me), 3.01 (2H, dd, J_{gem} = 16.9 and J_{trans} = 11.7 Hz, H-4'), 4.01 (2H, dd, J_{gem} = 16.9 and J_{cis} = 7.3 Hz, H-4'), 4.79 (2H, dd, J_{trans} = 11.7 and J_{cis} = 7.3 Hz, H-5'), 5.69 (2H, s, H-4 and H-5); ^{13}C NMR ($CDCl_3$) δ 24.23 (Me), 36.23 (C-4'), 68.64 (C-4 and C-5), 79.13 (C-5'), 84.88 (C-2), 157.14 (C-3'), 165.88 (CO); MS *m/z* 598 (M^+). **12'**: $[\alpha]_D^{25}$= 118.8 (*c* 0.73, $CHCl_3$); IR (KBr) 2900, 1630, 1350, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12, 2.26 (each 3H, s, Me), 3.06 (1H, dd, J_{gem} = 16.9 and J_{trans} = 11.0 Hz, H-4'), 3.28-3.47 (2H, br, H-4'), 4.03 (1H, dd, J_{gem} = 16.9 and J_{cis} = 7.7 Hz, H-4'), 4.82 (1H, dd, J_{trans} = 11.0 and J_{cis} = 7.7 Hz, H-5'), 5.02 (1H, br, H-5'), 5.41 (1H, br, H-4 or H-5), 5.94 (1H, d, $J_{4\text{-}5}$ = 2.2 Hz, H-4 or H-5); ^{13}C NMR ($CDCl_3$) δ 24.55, 29.70 (each Me), 36.28, 39.35 (each C-4'), 67.44, 69.03 (C-4 and C-5), 78.03, 79.26 (each C-5'), 84.33 (C-2), 155.47, 157.19 (each C-3'), 165.19, 167.69 (each CO); MS *m/z* 598 (M^+).

18. Optical rotations of (*S*)-**13** (96% ee): $[\alpha]_D^{25}$= 169.1 (*c* 0.41, $CHCl_3$); (*R*)-**13**: $[\alpha]_D^{25}$= –172.8 (*c* 0.63, $CHCl_3$). The reported value for a 95:5 diastereomer mixture of (*R*)-**13**:[10] $[\alpha]_D^{25}$= –161 (*c* 1.0, $CHCl_3$).