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TETRAHEDRON: *ASYMMETRY*

Catalytic enantioselective 1,3-dipolar cycloaddition of nitrones to cyclopent-1-enecarbaldehyde

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Abstract—A variety of pyrrolidinium salts have been found to catalyse the reaction between nitrones and a cyclic α,β-unsaturated aldehyde furnishing bicyclic adducts with high diastereoselectivity and enantioselectivity.

The enantioselective 1,3-dipolar cycloaddition of nitrones to alkenes is one of the most efficient approaches for the preparation of chiral non-racemic isoxazolidines[1,2] and these reactions can serve as routes to building blocks for the construction of biologically important compounds.[3] Such 1,3-dipolar cycloaddition reactions catalysed by chiral imidazolidinone salts and involving acyclic α,β-unsaturated aldehydes furnish cycloadducts with excellent diastereoselectivity and enantioselectivity.[4] In this case, the organocatalyst works in the absence of metal salts because the catalytic effect is due to activation of the α,β-unsaturated aldehyde by iminium salt formation between the catalyst and the starting aldehyde, resulting in a decrease in the LUMO energy of the alkene moiety.[4]

Although, the imidazolidinone salts obviously serve as excellent catalysts in the reaction between nitrones and acyclic α,β-unsaturated aldehydes, enantioselective organocatalytic 1,3-dipolar cycloaddition of nitrones to cyclic α,β-unsaturated aldehydes have to our knowledge not been investigated.

We report herein our preliminary results from a study of additions of acyclic nitrones to cyclopent-1-enecarbaldehyde **10** (Scheme 1) catalysed by a variety of chiral pyrrolidinium salts, resulting in highly enantio- and diastereoselective formation of fused bicyclic isoxazolidines.

When aldehyde **10** and nitrone **11** were mixed in either CH_3NO_2 or DMF in the absence of a catalyst, no reaction occurred at ambient temperature. When the catalyst **1**[4] (Fig. 1, 13 mol%) was added, reaction took place and after reduction of the bicyclic aldehyde product to the corresponding alcohol, a low yield of cycloadduct **12** was obtained in low e.e. together with its diastereomer **13** (Table 1, entries 1 and 2).

These disappointing results prompted us to investigate the catalytic performance of the chiral ammonium salts

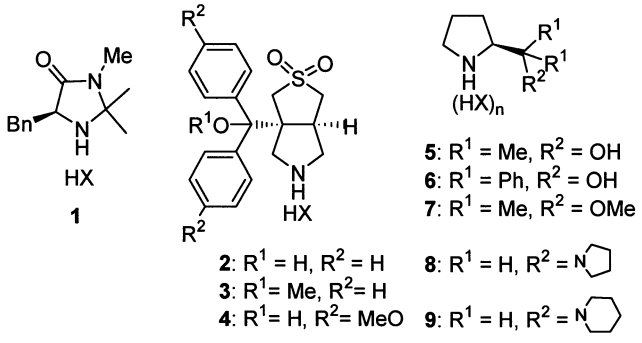
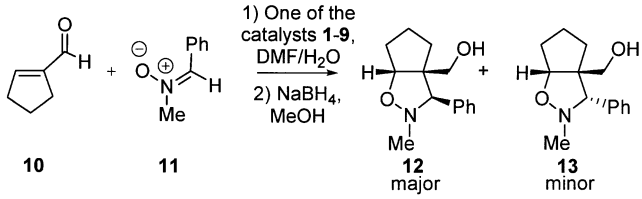


Figure 1. Catalysts for use in 1,3-dipolar cycloadditions of nitrones.



Scheme 1.

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Table 1. 1,3-Dipolar cycloaddition between aldehyde **10** and nitrone **11** in DMF catalysed by a variety of catalysts (13 mol%) at +10°C[a]

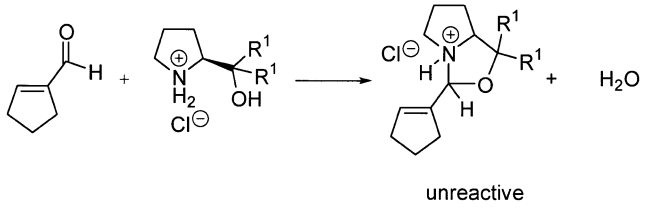
Entry	Catalyst	Salt (HX)	Time (h)	% Yield[b]	D.r.[c]	e.e.[d] (%)
1[e]	**1**	HCl	120	7	–	0
2[e,f]	**1**	HCl	144	19	86:14	–5
3	**2**	HCl	72	59	83:17	67
4	**3**	HCl	48	39	89:11	23
5	**4**	HCl	120	61	80:20	70
6[g]	**4**	HCl	96	45	72:28	76
7[e]	**5**	HCl	72	0	–	–
8[e]	**6**	HCl	48	0	–	–
9[e]	**7**	HCl	96	12	80:20	68
10	**8**	HCl	144	26	95:5	85
11	**8**	2HCl	72	50	93:7	89
12	**9**	HCl	144	44	95:5	91
13	**9**	2HCl	72	49	97:3	92
14	**9**	$2HClO_4$	120	44	80:20	78
15	**9**	2TFA	72	31	84:16	85
16[g]	**9**	2HCl	120	23	93:7	93
17[h]	**9**	2HCl	120	21	97:3	91
18[i]	**9**	2HCl	144	70	95:5	91

[a] The nitrone **11** (3.7 mmol) and a catalyst (0.48 mmol) were added to a solution of the aldehyde **10** (4.8 mmol) in DMF (15 mL) and H_2O (86 μL). After the specified time, water (50 mL) and EtOAc (50 mL) were added. Extraction with EtOAc (2×25 mL), drying (Na_2SO_4) filtration and concentration gave a residue, which was subjected to chromatography (silica gel, EtOAc/cyclohexane as eluent). All fractions containing the desired product were collected and subjected to $NaBH_4$ reduction. The resulting mixture of **12** and **13** was separated (silica gel, EtOAc/cyclohexane as eluent). No regioisomers could be detected in any instance.
[b] Combined overall isolated yield of **12** and **13**.
[c] Isolated diastereomeric ratio.
[d] Determined by GC-analysis on a chiral β-dex-325 column of the corresponding trifluoroacetate of **12**.
[e] Performed at room temperature.
[f] CH_3NO_2 as solvent.
[g] Performed at −10°C.
[h] 1 mol% catalyst, 1:1 ratio **10**:**11**.
[i] 1:2 ratio **10**:**11**.

of some azabicyclo[3.3.0]octanes in the cycloaddition reaction above (Scheme 1). Compounds **2**–**4** (Fig. 1) were prepared from the product of a 1,3-dipolar cycloaddition. Thus, a chiral azomethine ylide was added to a cyclic sulfur-containing dipolarophile.[5] Further transformations furnished compounds **2**–**4**. Fortunately, when these were used as catalysts in the reaction sequence above (Scheme 1), the reduced cycloadduct **12** was obtained in reasonable yields and up to 76% e.e. along with the separable diastereomer **13** (Table 1, entries 3–6).[6] When catalyst **2** was compared with its methyl ether **3**, it was evident (entry 3 versus 4) that the free hydroxyl group in **2** was important for achieving high enantioselectivity. When *p*-methoxy substituents were introduced onto the phenyl groups the electron density on the alcohol is increased, which resulted in a slight improvement in the enantioselectivity (entry 3 versus 5).[7]

For comparison, we also investigated some proline-based catalysts in the above reaction. Disappointingly, no conversion was obtained when the alcohols **5**[8] and **6**[9] were tried as catalysts (entries 7 and 8). However, albeit in low yield, the methyl ether **7**[10] (i.e. methylated **5**) yielded isoxazolidine **12** in high enantioselectivity (entry 9).

Formation of a protonated unreactive cyclic *N*–*O* acetal from the aldehyde **10** and either catalyst **5** or **6** was probably the reason why these catalysts were ineffective (Scheme 2).[11] On the other hand, when the proline based diamines **8**[12] and **9**[12] (Fig. 1) were used as catalysts in the reaction sequence above (Scheme 1), we were pleased to see that the isoxazolidine **12** was obtained with both very high diastereoselectivity and enantioselectivity (entries 10 and 12). Because catalyst **9** gave a slightly higher enantioselectivity than **8**, we continued our study using this. When the dihydrochloride salt of **9** was used, excellent diastereoselectivity and enantioselectivity were obtained although the yield was moderate (entry 13). When performing the reaction at a lower temperature, we observed no significant improvement in the enantioselectivity (entry 16). The nature of the counterion of the ammonium salt was important



Scheme 2.

(entries 14–15). Although the yield was low, when the reagent:substrate loading was decreased to 1:1 and the catalyst loading to 1 mol%, the enantioselectivity and diastereoselectivity remained almost unchanged (entry 17). A good yield could, however, be obtained when using an excess of the nitrone **11** (entry 18). Among all the catalysts studied so far, **8** and **9** seemed to give the highest enantioselectivity, while the fused bicyclic compounds, in particular **4**, gave the highest yields.

The relative configuration of the major diastereomer **12** was determined through 1D NOESY experiments (Fig. 2).

Thus, the minor diastereomer **13** displayed a 2% NOE between the two methine protons shown. This NOE was absent in the major diastereomer **12**.[13] However, a strong NOE effect was observed for this isomer between the phenyl protons and the $C\underline{H}_2$-OH protons. The assignment of relative configuration of the major and minor diastereomer is also supported by the strong shielding effect of the phenyl group resulting in a upfield shift of the $C\underline{H}_2$-OH signals (3.27–3.42 ppm) of the major diastereomer **12** relative to those of the minor diastereomer **13** (3.56–3.75 ppm). Compound **12** was transformed into one enantiomer of 2-benzyl-2-(hydroxymethyl)cyclopentanol and *tert*-butyl-(1*R*)-1-benzyl-2-oxocyclopentanecarboxylate of known absolute configuration[14] was converted to (1*S*,2*S*)-2-benzyl-2-(hydroxymethyl)cyclopentanol for comparison. These cyclopentanols displayed opposite signs of specific rotation. Thus, the absolute configuration of **12** was assigned as 3*R*,3a*R*,6a*R*. Complete details will be given in a full paper.

The low yields obtained under some conditions in the reactions studied (Scheme 1, Table 1) could be due partly to the fact that varying amounts of the diastereomeric by-products **15** and **16** were formed (Scheme 3).[15]

Thus, under the wet conditions (DMF/H_2O) applied in these reactions,[16] nitrone **11** underwent hydrolysis followed by condensation of the corresponding hydroxylamine with aldehyde **10**. The resulting nitrone **14** could now react with the aldehyde **10**, which was activated by the catalyst. Alternatively the nitrone **14** could react with the double bond of the cyclopentenyl moiety of a second molecule of this nitrone. The former pathway was found to be the predominant one because the reduced cycloadduct **15** was isolated as a by-product in 92% e.e. in one experiment (Table 1, entry 16). When

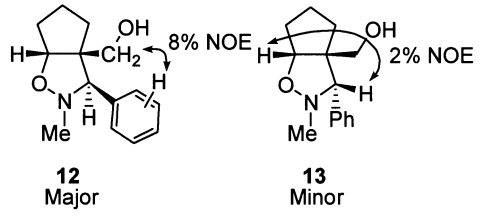
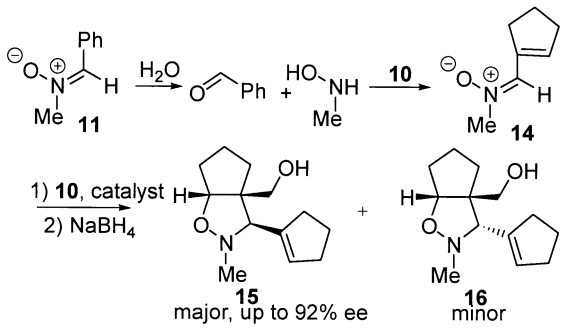


Figure 2.



Scheme 3.

using catalyst **1**, McMillan et al. obtained a high enantio- and diastereoselectivity in the reaction of crotonaldehyde with nitrone **11**.[4] Having demonstrated the utility of the catalysts **2**–**9** for a cyclic dipolarophile, we also studied the reaction of crotonaldehyde and nitrone **11** in the presence of some of the catalysts **2**–**9**. Interestingly, although in low enantioselectivity compared to catalyst **1**,[4] these catalysts showed reversed diastereoselectivity in the crotonaldehyde–nitrone reaction.

In summary, a variety of pyrrolidinium salts catalyse the reaction between nitrones and cyclopent-1-enecarbaldehyde furnishing fused bicyclic isoxazolidines in good yield and high diastereoselectivity and enantioselectivity. The low loading of catalyst and substrate necessary for achieving a reasonable yield of the cycloadducts should make this process useful in preparing isoxazolidines containing a fused bicyclic substructure. The application of this methodology towards the construction of a variety of heterocycles from other nitrones and other cyclic α,β-unsaturated aldehydes is currently being investigated.

Acknowledgements

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References

1. Karlsson, S.; Högberg, H.-E. *Org. Prep. Proc. Int.* **2001**, *33*, 103–172.
2. Gothelf, K. V.; Jensen, K. B.; Jörgensen, K. A. *Sci. Prog.* **1999**, *82*, 327–350.
3. Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
4. Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.
5. Karlsson, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1076–1082.
6. Some experiments revealed that DMF was the best solvent in terms of enantioselectivity.

7. It was obvious that a bulky tertiary alcohol and a sulfone functionality in the bicyclic catalysts were necessary for achieving high enantioselectivity, because related catalysts investigated, lacking those, gave much lower enantioselectivity.
8. Guoqiang, L.; Hjalmarsson, M.; Högberg, H.-E.; Jernstedt, K.; Norin, T. *Acta Chem. Scand. B* **1984**, *38*, 795–801.
9. Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863.
10. Bucher, C. B.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 935–946.
11. Due to the rigid structure of the fused bicyclic catalysts **2** and **4**, they are probably unable to form unreactive *N–O* acetals with aldehyde **10** (see Scheme 2).
12. Hendrie, S. K.; Leonard, J. *Tetrahedron* **1987**, *43*, 3289–3294.
13. **Data for compound 12**: e.e. = 93%, mp 68–70°C, $[\alpha]_D^{25} = -153.1$ (*c* 0.80, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 1.26–1.32 (m, 1H, -OH), 1.46–1.65 (m, 2H), 1.76–2.06 (m, 4H), 2.57 (s, 3H), 3.23 (s, 1H), 3.31 (dd, 1H, $J = 6.7$, 11.2 Hz), 3.39 (dd, 1H, $J = 4.9$, 11.2 Hz), 4.30 (d, 1H, $J = 5.1$ Hz), 7.28–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 24.0, 32.0, 33.6, 42.8, 64.0, 65.5, 81.2, 86.1, 127.3, 128.0, 128.8, 136.1. MS (EI): *m*/*z* (%) 233 (M^+, 57), 216 (2), 134 (100). Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.3; N, 6.0%.
Data for compound 13: mp 68–71°C, ^{1}H NMR ($CDCl_3$) δ 0.90–1.02 (m, 1H), 1.42–1.60 (m, 2H), 1.75–2.01 (m, 4H), 2.60 (s, 3H), 3.60 (dd, 1H, $J = 4.6$, 10.9 Hz), 3.63 (s, 1H), 3.71 (dd, 1H, $J = 5.6$, 10.9 Hz), 4.47–4.52 (m, 1H), 7.25–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 25.4, 30.6, 35.1, 43.8, 64.1, 66.2, 77.7, 85.1, 127.4, 128.1, 128.3, 137.5. MS (EI): *m*/*z* (%) 233 (M^+, 63), 216 (2), 134 (100). Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.3; H, 8.1; N, 5.9%.
14. Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807–5810.
15. **Data for compound 15**: e.e. = 92%, mp 121–123°C, $[\alpha]_D^{25} = -128.6$ (*c* 0.44, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 1.35–1.99 (m, 8H), 2.23–2.48 (m, 5H), 2.58 (s, 3H), 2.74 (s, 1H), 3.43 (dd, 1H, $J = 6.1$, 11.0 Hz), 3.60 (dd, 1H, $J = 3.5$, 11.0 Hz), 4.40 (d, 1H, $J = 5.4$ Hz), 5.66–5.70 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 23.0, 24.0, 31.8, 32.4, 33.6, 34.8, 43.3, 63.1, 65.7, 78.1, 85.3, 127.6, 139.1. MS (EI): *m*/*z* (%) 223 (M^+, 40), 125 (50), 68 (100). Anal. calcd for $C_{13}H_{21}NO_2$: C, 69.9; H, 9.5; N, 6.3. Found: C, 69.8; H, 9.6; N, 6.2%.
Data for compound 16: ^{1}H NMR ($CDCl_3$) δ 1.23–1.93 (m, 9H), 2.13–2.41 (m, 4H), 2.60 (s, 3H), 3.00 (s, 1H), 3.60 (d, 1H, $J = 10.8$ Hz), 3.69 (d, 1H, $J = 10.8$ Hz), 4.37 (t, 1H, $J = 4.6$ Hz), 5.60–5.66 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 23.3, 25.6, 30.7, 32.3, 34.7, 34.8, 44.3, 63.4, 67.0, 75.3, 85.2, 127.9, 139.7. MS (EI): *m*/*z* (%) 223 (M^+, 100), 125 (20), 68 (31).
16. In the absence of water the reactions were very sluggish and difficult to work-up.