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Tricarbonyl(benzaldehyde)chromium(0) Complexes in Organic Synthesis: A Highly Stereoselective 1,3-Dipolar Cycloaddition of Chromium(0)-Complexed Nitrones

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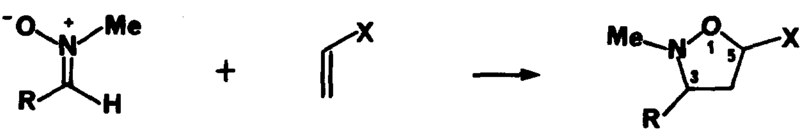
Summary: The 1,3-dipolar cycloaddition of chromium(0)-complexed nitrones (**10**, **11**) with electron-rich olefins (**2**) provided, after decomplexation with CAN, cis-3,5-disubstituted isoxazolidines (cis-**14**, **15**) in a highly stereoselective as well as regioselective manner.

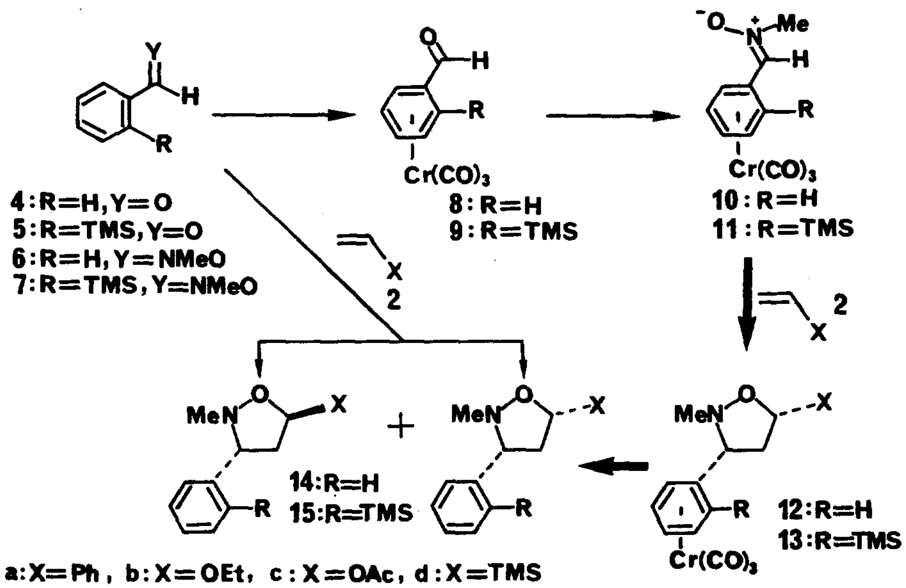
The 1,3-dipolar cycloaddition of nitrones[1)] has been extensively investigated and shown to be a useful tool in the synthesis of natural products, especially alkaloids.[1,2)] The nitrone cycloaddition with various dipolarophiles occurs regioselectively or nonselectively depending on the electronic property[1)] of the dipolarophile. With electron-rich olefins (**2**),[1a)] the 1,3-dipolar cycloaddition of the nitrone (**1**) proceeded in a highly regioselective manner to produce the 3,5-disubstituted isoxazolidines (**3**), although the poor stereoselectivity[1)] was often encountered.

In connection with the program[3)] aiming at the development of a highly stereoselective reaction mediated by (arene)chromium(0) complexes, we introduced the tricarbonyl(benzaldehyde)chromium(0) complexes into the nitrone chemistry to overcome the lack of diastereoselectivity between the C_3 and C_5 positions of isoxazolidines (**3**). We wish to describe our preliminary results on a highly stereoselective 1,3-dipolar cycloaddition of the nitrones (**10**, **11**) with electron-rich olefins where the chromium complexation would play an significant role to control the selectivity.



1 **2** **3**

The chromium(0)-complexed nitrone (**10**, 95%) was prepared by treatment of the tricarbonylchromium(0)-complexed benzaldehyde (**8**) with N-



methylhydroxylamine[4] in refluxing methylene chloride in the presence of sodium bicarbonate. The o-trimethylsilyl (TMS) derivative (**11**) was also obtained from the corresponding aldehyde (**9**)[3,5] in 98% yield. The geometries of the novel nitrones (**7**,**10**,**11**) were unambiguously established as (Z) by NOE experiment and comparison with **6**.[1a] The nitrone (**10**) was heated in styrene[6] at 90°C under nitrogen atmosphere for 6 h to give the adduct (**12a**), which was subsequently decomplexed with cerium ammonium nitrate (CAN)[7] in methanol at 0°C to yield cis-**14a**[6] in 80% yield. No trans-isomer (trans-**14a**) could be virtually detected in the reaction mixture. Similar treatment of the TMS derivative (**11**) with styrene furnished cis-**15a** (69% yield) exclusively. The structure of cis-**15a** was unambiguously determined by conversion of **13a** into cis-**14a**[(i) TBAF/THF, (ii) CAN/MeOH); 78%]. Several representative results obtained under the standard condition[8] were summarized along with those of the control experiments in Table 1.

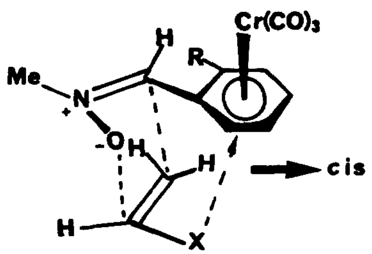
The chromium(0)-complexed isoxazolidines (**12**, **13**) could be isolated before decomplexation as a single isomer and characterized by their spectral evidence. For instance, **13a** showed a diagnostic C_3-H signal at 4.10 ppm (dd, J=8.7 and 5.8 Hz),[9] while the C_3-H and C_5-H of **12c** appeared at 3.38 ppm (t, J=8.5 Hz) and 6.33 ppm (dd, J=6.4 and 1.8 Hz), respectively in their ^{1}H NMR spectra. These observation strongly suggests that this 1,3-dipolar cycloaddition must occur π-facial selectively with respect to the benzene ring in the nitrones (**10**, **11**)[10]. The mechanism[12]

Table 1. 1,3-Dipolar Cycloaddition of Chromium(0)-Complexed and Uncomplexed Nitrones with Electron Rich Olefins

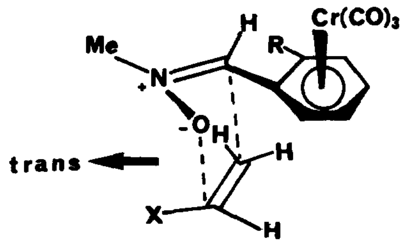
entry	nitrone	olefin	adduct	yield,[a]	(cis : trans)[b]
1	**10**	**2a**	**14a**	80	(>98[c] : 0)
2	**11**	**2a**	**15a**	69	(>98[c] : 0)
3	**6**	**2a**	**14a**	95	(67 : 33)[d]
				64	(69 : 31)[e]
4	**7**	**2a**	**15a**	96	(18 : 82)
5	**10**	**2b**	**14b**	63	(>98[c] : 0)
6	**11**	**2b**	**15b**	70	(>98[c] : 0)
7	**6**	**2b**	**14b**	78	(50 : 50)[f]
				70	(46 : 54)[e]
8	**10**	**2c**	**14c**	85	(>98[c] : 0)
9	**6**	**2c**	**14c**	71	(67 : 33)[e]
10	**10**	**2d**	**14d**	42	(80 : 20)
11	**6**	**2d**	**14d**	54	(40 : 60)[e]

[a] Yields of products isolated, after decomplexation with CAN, by chromatography. [b] Ratio of each isomer isolated by chromatography. [c] No <u>trans</u> isomer could be virtually detected by ^{1}H NMR spectrum. [d] The ratio taken from the literature.[6)] [e] The result obtained by us. [f] The ratio taken from the literature.[14)]

for this high stereoselectivity has been not yet fully clarified. However, it would be tentatively rationalized in terms of the intermediacy of the <u>exo</u>-transition state (A) rather than the <u>endo</u>-transition state (B).[1)] The electron-releasing substituent[13)] on the dipolarophile might anchimerically stabilize the electron-deficient aromatic ring of the nitrones in the <u>exo</u>-transition state (A). On the other hand, a similar stabilizing effect would not be expected in the <u>endo</u>-transition state (B).



exo—(A)



endo—(B)

We are currently undertaking more detailed work on the present stereoselective cycloaddition from the mechanistic point of view and its application (including the chiral one) to a synthesis of natural products.

References and Notes

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8) The nitrones (**6,7,10,11**) were heated with dipolarophiles under reflux or in a sealed tube.
9) The C_5-H signal was completely obscured by high field-shifted signals of aromatic protons.
10) We took advantage of this π-facial selectivity. For example, optically pure (-)-**11** [$[\alpha]_D^{25}$ -1527°(c, 0.44, $CHCl_3$)], prepared from (-)-**9**,[5,11] underwent cycloaddition with ethyl vinyl ether, followed by decomplexation to produce the optically active (+)-*cis*-**15b** [$[\alpha]_D^{27}$, +206°(c, 0.17, $CHCl_3$)] *via* (+)-**13b** [$[\alpha]_D^{28}$ +79.6° (c, 0.38, $CHCl_3$)]. Optical purity and absolute configuration of (+)-**13b** ,(+)-*cis*-**15b**, and their related compounds will be reported in somewhere else.
11) C. Mukai, W.-J. Cho, I.-J. Kim, and M. Hanaoka, in preparation.
12) Regioselectivity could be interpreted on the basis of the frontier orbital theory by analogy with the case of the nitrone (**6**).[1)]
13) When acrylonitrile, an electron-deficient dipolarophile, was submitted to the cycloaddition with **10**, no characteristic improvement in the diastereoselectivity was recognized. This observation might well support our explanation for the high *cis*-selectivity in the reaction between **10,11** and electron-rich dipolarophiles.
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