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Diastereofacial Selectivity in Intermolecular Nitrone Cycloadditions to Chiral Allyl Ethers. Application to Chiral Synthesis of Coniine

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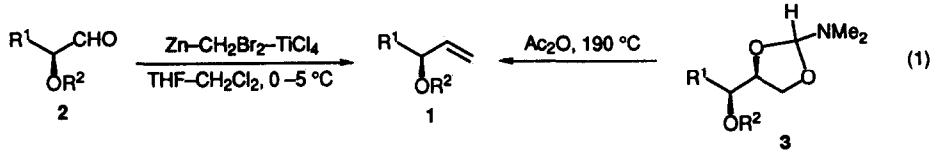
Abstract: The intermolecular cycloadditions of a cyclic nitrone to chiral allyl ethers take place with *erythro* selectivity, where the degree of selectivity achieved is dependent upon the size of the alkyl substituent attached to the allylic chiral center, and these reactions are applied to the synthesis of optically active alkaloid coniine.

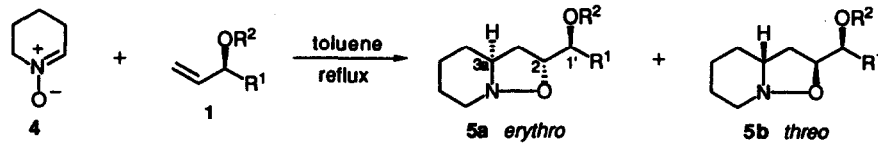
Asymmetric nitrone 1,3-dipolar cycloadditions involving the use of chiral nitrones bearing chiral substituents either at carbon or at nitrogen have been extensively explored.[1] In contrast, the use of chiral dipolarophiles, however, has received only limited study.[2] In this regard, we recently reported[3] the diastereofacial cycloaddition of a prochiral nitrone to a chiral allyl ether as a dipolarophile. Similar cycloaddition of a non-stereogenic nitrone to some terminal alkenes possessing a heterosubstituted allylic stereocenter has also been reported by Cinquini and Cozzi,[4] and Townsend.[5] The level of diastereoselectivity in these cases is, however, low to modest. The stereochemical outcome of these cycloadditions was rationalized by an "inside alkoxy" transition state model, which has been advanced by Houk through studies on nitrile oxide cycloadditions to allyl compounds.[6] On the basis of model calculations, this model is characterized by the alkoxy group preference for the inside conformation and the alkyl group preference for anti. In the latter case, the magnitude of facial selectivity is influenced by the size of the alkyl group. Here we disclose the results of our study on the steric influence of the alkyl group attached to the allylic chiral center on the π-facial selectivity in nitrone cycloaddition to chiral allyl ethers and application of this reaction to the synthesis of a naturally occurring alkaloid coniine.

Despite the synthetic and mechanistic importance of chiral allyl ethers, there are relatively few methods for their preparation. We thus initially elaborated a variety of the enantiomerically pure allyl ethers by utilizing ethyl L-lactate, L-valine, L-tartaric acid, and (*R*)-pantolactone as commercially available chiral precursors (see Table 1). Construction of the terminal π system (as in **1**) adjacent to the allylic chiral center was achieved under non-basic conditions without epimerization[7] by two different routes involving methylenation of the aldehyde **2** with the $Zn–CH_2Br_2–TiCl_4$ reagent[8] and elimination of the dimethylaminodioxolanes **3**[9] (eq 1).



(1)

A variety of allyl ethers so prepared underwent cycloadditions when heated with 2–5 equiv of 2,3,4,5-tetrahydropyridine 1-oxide (**4**)[10] in toluene for 12–24 h, affording chromatographically separable two C-2, C-3a-*trans*-cycloadducts (for rationale of the *trans* preference, see below), i.e., the *erythro*- and *threo*-isomers (with respect to C-2–O and C-1'–O) **5a** and **5b**. As can be seen from Table 1, *erythro* selectivities were observed in all of the examples. Evidently, the size of the alkyl group on the allylic stereocenter has a major effect on the level of diastereoselectivity: the *erythro* selectivities increased as the size of the alkyl group increased with the selectivity order Me < Bu < *i*-Pr < *t*-Bu, and the highest *erythro* selectivity 95 : 5 was obtained with the *tert*-butyl group (entry 9). However, the substituent bearing the allylic oxygen, i.e. benzyl or trialkylsilyl groups, had less influence on the selectivities.



4 + **1** → **5a** *erythro* + **5b** *threo*

Table 1. Nitrone Cycloaddition to Allyl Ethers

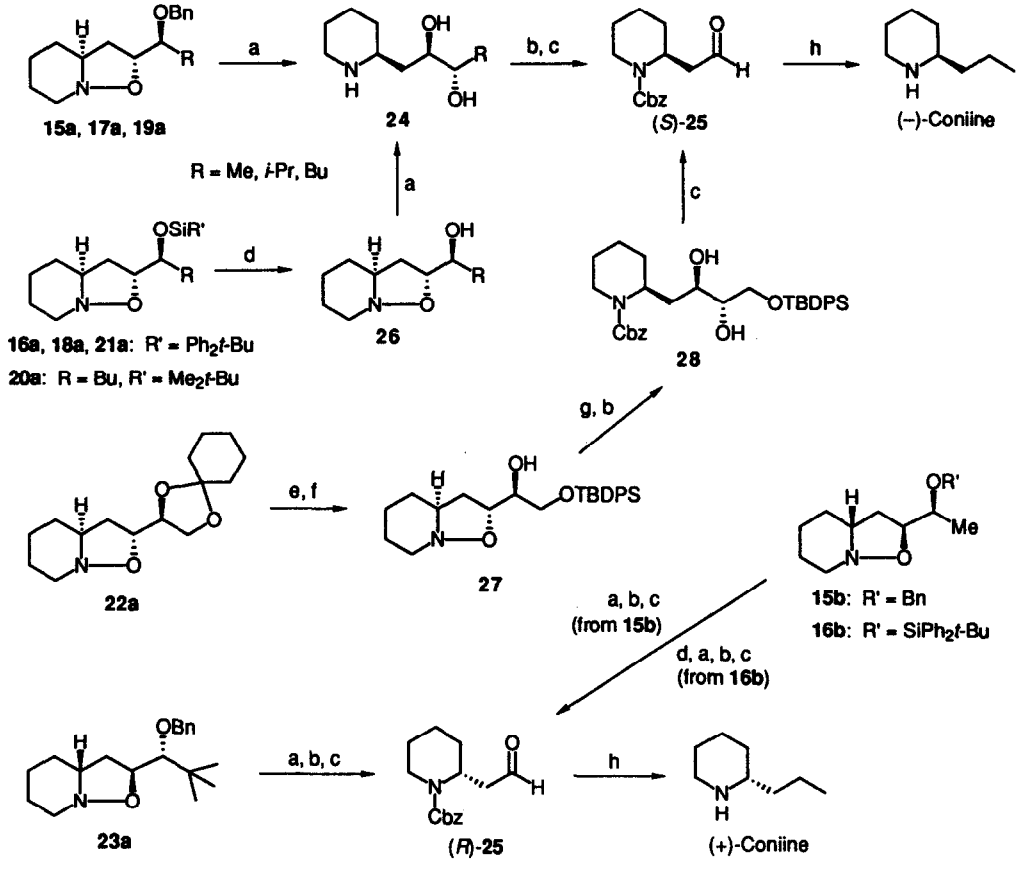
Entry	Allyl Ether			Product	*erythro* : *threo*	Yield,[a] %
		R[1]	R[2]			
1	**6**[b]	Me	Bn	**15a / 15b**	67 : 33[g]	68
2	**7**[b]	Me	$SiPh_2t$-Bu	**16a / 16b**	60 : 40[g]	86
3	**8**[c]	*i*-Pr	Bn	**17a / 17b**	91 : 9[h]	79
4	**9**[c]	*i*-Pr	$SiPh_2t$-Bu	**18a / 18b**	93 : 7[g]	85
5	**10**[d]	Bu	Bn	**19a / 19b**	79 : 21[h]	66
6	**11**[e]	Bu	$SiMe_2t$-Bu	**20a / 20b**	71 : 29[h]	67
7	**12**[e]	Bu	$SiPh_2t$-Bu	**21a / 21b**	75 : 25[g]	80
8	**13**[e]			**22a / 22b**	80 : 20[i]	74
9	**14**[f]			**23a / 23b**	95 : 5[h]	75

[a] Isolated yield. [b] Prepared from ethyl L-lactate. [c] Prepared from L-valine. [d] Ref. 3b. [e] Prepared from L-tartaric acid. [f] Prepared from (*R*)-pantolactone. [g] Determined by HPLC. [h] Determined by 400 MHz ^{1}H NMR. [i] Based on isolated yield.

The stereochemistry of all of the major *erythro*-cycloadducts **15a–23a** was confirmed by their ^{1}H NMR spectra and their transformation into the aldehydes **25** as outlined in Scheme 1. Thus, the series of cycloadducts **15a–22a** (entries 1–8) with the *S* configuration at C-3a were converted to the aldehyde (*S*)-**25**,

$[\alpha]^{20}_D$ –40.9° (*c* 0.59, $CHCl_3$) via a sequence involving reductive N–O bond cleavage followed by glycol cleavage. With this aldehyde (*S*)-**25** in hand, elaboration to (–)-coniine HCl salt, mp 217–220 °C (lit.[11] mp 220–221 °C); $[\alpha]^{29}_D$ –5.6° (*c* 0.88, EtOH) [lit.[12] $[\alpha]_D$ –5.80° (EtOH)], was achieved by a two-step procedure involving Wittig condensation and hydrogenation. Following the same sequence, **23a** (entry 9) was converted to (+)-coniine via (*R*)-**25**, $[\alpha]^{27}_D$ +39.6° (*c* 1.03, $CHCl_3$). These results established the C-2 absolute configuration of (*S*)-**25** and (*R*)-**25** and thus that for the corresponding cycloadducts as 2*R*,3a*S* for **15a**–**22a** and 2*S*,3a*R* for **23a**, respectively. Similarly, the transformation of the minor adducts **15b** and **16b** (entries 1 and 2) into the (*R*)-aldehyde (*R*)-**25** led to establishment of the absolute stereochemistry as 2*S*,3a*R* and thus the *threo* configuration of these adducts.

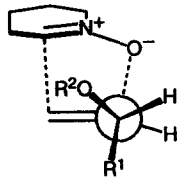
Scheme 1



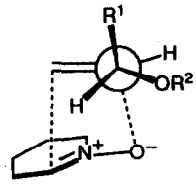
(a) H_2 (5 atm), $PdCl_2$, MeOH. (b) $PhCH_2OCOCl$, aq. Na_2CO_3, CH_2Cl_2. (c) HIO_4, THF–H_2O. (d) Bu_4NF, THF. (e) conc. HCl–MeOH. (f) *t*-$BuPh_2SiCl$, imidazole, DMF. (g) H_2, $Pd(OH)_2$ (5 atm), MeOH. (h) Ph_3PMeBr, BuLi, THF, then H_2, Pd–C, MeOH.

The cycloadditions involving the nitrone **4** with nonconjugated monosubstituted olefins have been shown[13] to proceed exclusively by way of *exo* oriented transition states, affording *trans*-adducts. In reactions

with cyclic nitrones, *endo* transition states are disfavored by steric interaction between the methylene group of the ring and substituent on the olefins.[1] Due to the *exo* preference and the Houk's steric and stereoelectronic rationale,[6] the overall *erythro* selection of the cycloaddition and enhancement of the selectivity with increase of the size of the alkyl substituent can be interpreted by considering a transition state model A. In electrophilic attack upon an allylic ether, the π bond becomes electron deficient. Electoron-donor substituents on the alkene stabilize the transition state, while electoron-withdrawing substituents destabilize the transition state. In the nitrone cycloaddition, the best σ-donor for stabilizing transition state would be the alkyl group (R^1) placed in the position anti to the approaching nitrone. The electronegative group, OR^2, prefers the inside to the outside position in order to minimize electron withdrawal from the π system via σ^*_{C-O} overlap and avoid the repulsive interaction between the allylic oxygen and the nitrone oxygen. When R^1 is large, the preference for A would increase over an outside alkoxy transition state B, which would lead to *threo* selectivity. In this case the dihedral angle between C–R^1 and C=C becomes large and, hence, B would suffer destabilization owing to increase of the unfavorable polar repulsion in the outside position. Further applications of these nitrone cycloadditions to enantioselective chiral synthesis of natural products are in progress.



A



B

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