The diastereoselective cycloaddition of vinyl ethers with isomünchnones

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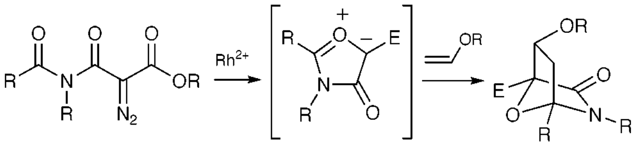
Complete diastereoselective product formation in the intermolecular 1,3-dipolar cycloaddition of isomünchnones with alkyl vinyl ethers is reported.

The 1,3-dipolar cycloaddition reaction is a powerful pericyclic process, leading to the concomitant formation of two carbon–carbon bonds in a single transformation.[1] While intramolecular cycloaddition reactions have been vigorously applied to natural product synthesis,[2] the intermolecular cycloaddition reaction suffers from a lack of diastereoselectivity,[3–5] resulting in diminished synthetic utility. During our efforts to utilize this reaction in the synthesis of biomimetic probes,[6,7] we discovered that the intermolecular cycloaddition of vinyl ethers with isomünchnones proceeds with complete diastereoselectivity (Scheme 1). Here we describe this unprecedented selectivity and explore the potential of vinyl ethers as dipolarophiles.



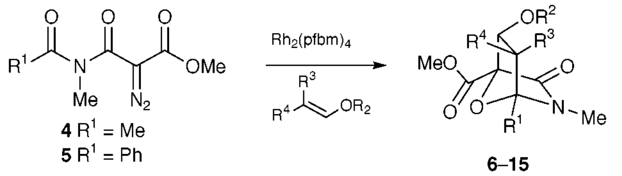
Scheme 1

We sought to investigate the 1,3-dipolar cycloaddition reaction as the principal component of our synthetic approach in the construction of a rigid bicyclic framework for molecular recognition. Mesoionic species such as isomünchnones (**2**) have been reported to undergo highly selective and mild pericyclic chemistry.[8,9] When formed from α-diazo imide precursors (**1**), with rhodium(II) mediated catalysis,[10,11] these 1,3-dipoles provide the possibility of a rapid and convergent construction of a heterocyclic system (**3**, E = CO_2Me) that would be well suited for the presentation of a wide variety of functional groups, in a highly dense array.

Although the isomünchnones are a well-studied class of 1,3-dipoles,[5] the selectivity of the intermolecular isomünchnone cycloaddition has primarily been explored with symmetric, electron-deficient dipolarophiles such as *N*-phenylmaleimide, tetracyanoethylene, fumarates, maleates and dimethyl acetylenedicarboxylate.[5,9] Only one example of an intermolecular isomünchnone cycloaddition with a monoactivated, electron-deficient olefin has been reported.[12] We therefore sought to explore the reactivity of various unsymmetric, monoactivated alkenes. The vinyl ethers, being a diverse and readily available set of substrates,[13] represented a good candidate functionality for this study. Treatment of α-diazo imides **4** or **5** with a catalytic amount of rhodium(II) perfluorobutyramidate [$Rh_2(pfbm)_4$], in the presence of various dipolarophiles (Table 1), led to the isolation of a single diastereomer in each case (**6**–**15**). The relative stereochemistry of compound **7** was verified by X-ray crystallographic structure analysis.[14]

For every dipolarophile evaluated, *endo* orientation of the alkoxy functionality was maintained. [15,16] Moreover, the steric properties of this substituent do not appear to influence either product yield or reaction rate. Even sterically demanding groups, such as *tert*-butyl (entry 6) and trimethylsilyl (entry 7), were accommodated with little variation in yield or rate. In order to evaluate the relative rates for β-substituted vinyl ethers, 1-methoxyoct-1-ene was tested (entries 8 and 9). When the starting *E*:*Z* ratio of the dipolarophile was 1:9, the *anti*:*syn* product distribution was 24:72 (entry 8). A starting *E*:*Z* ratio of 3:2 provided an 80:20 *anti*:*syn* product distribution (entry 9). When the *anti*:*syn* distribution of products is normalized according to the original *E*:*Z* ratio (74:26 and 72:28, in entries 8 and 9, respectively), the cycloaddition preference for the *E* isomer becomes apparent. β-Disubstituted vinyl ether (entry 10) provides the same extent of diastereoselectivity as the less sterically congested dipolarophiles. This result is remarkable, considering the high functional density of the cycloadduct (**15**) obtained *via* this cycloaddition.

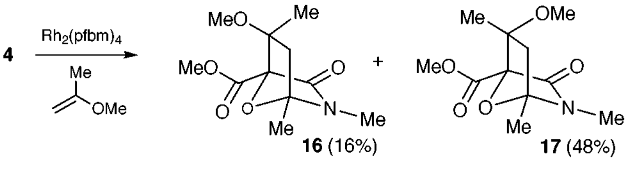
Table 1 Reaction of isomünchnones with electron-donating dipolarophiles



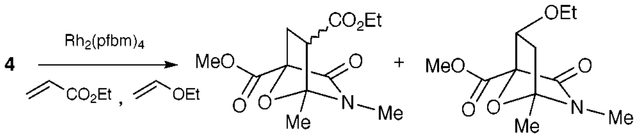
Entry	R¹	R²	R³	R⁴	Product	Yield (%)
1[a]	Me	Et	H	H	**6**	> 98
2[a]	Ph	Et	H	H	**7**	> 98
3[a]	Me	Bn	H	H	**8**	> 98
4[a]	Me	Cy	H	H	**9**	> 98
5[a]	Me	Ph	H	H	**10**	> 98
6[a]	Me	Bu^t	H	H	**11**	> 98
7[a]	Me	$SiMe_3$	H	H	**12**	> 98
8[b,d]	Me	Me	*n*-hexyl	H	**13**	95[f]
	Me	Me	H	*n*-hexyl	**14**	
9[b,e]	Me	Me	*n*-hexyl	H	**13**	97[f]
	Me	Me	H	*n*-hexyl	**14**	
10[c]	Me	Isopentyl	Me	Me	**15**	82

[a] 80 °C, benzene, 20 min. [b] 100 °C, benzene, 30 min. [c] 130 °C, chlorobenzene, 1 h. [d] 5 equiv. of dipolarophile with an *E*:Z ratio of 1:9 was used in this experiment. [e] 5 equiv. of dipolarophile with an E:Z ratio of 3:2 was used in this experiment. [f] Overall yield.

In order to evaluate whether our observed selectivity is steric or electronic in nature, we investigated the intermolecular cycloaddition of dipole precursor **4** with 2-methoxypropene, an *ipso*-substituted vinyl ether (Scheme 2). Interestingly, the reaction proceeded only at relatively high temperature (130 °C) and after prolonged exposure (8 h), to yield a 1:3 *exo*:*endo* ratio of the diastereomers **16** and **17**.[17] A similar reduction in rate has been reported with ketene acetals, which topologically resemble the *ipso*-substituted 2-methoxypropene.[12] Their low



Scheme 2



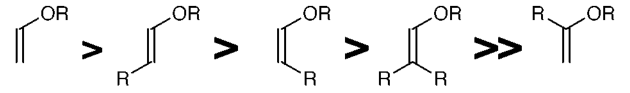
18,**19** (76%) **6** (19%)

Scheme 3

reactivity was attributed to the existence of a large HOMO–LUMO gap between the dipole and dipolarophile.[12,18] The dramatic decrease in reaction rate for these disubstituted dipolarophiles, compared to the vinyl ethers described in Table 1, supports a steric involvement in diastereoselectivity. Whether this effect is purely steric or stereoelectronic in nature is ambiguous, since there still appears to be a preference for the *endo*-product (**17**).

Frontier Molecular Orbital theory has successfully rationalized both the rates and regioselectivity of most 1,3-dipolar cycloaddition reactions.[19] The fact that isomünchnones can undergo cycloaddition with both electron-rich and electron-deficient dipolarophiles is a defining feature of dipoles which readily proceed through a type II process.[1] This remarkable and useful behavior may be understood in terms of a small HOMO–LUMO energy gap.[1,5,20] We sought to further evaluate the electronic preference of isomünchnones while minimizing the steric bias on the dipolarophile. For this reason, α-diazo imide **4** was treated with $Rh_2(pfbm)_4$ in the presence of an equimolar amount of ethyl acrylate and ethyl vinyl ether at 60 °C, which resulted in a 4 : 1 mixture of cycloaddition products (Scheme 3). This comparable reactivity indicates similar FMO energetics for both electron-rich and electron-deficient dipolarophiles in the isomünchnone cycloaddition.

A pattern of diastereoselectivity for the cycloaddition of isomünchnones with vinyl ethers is apparent and appears to be controlled by the electron-donating ether functionality. Relative cycloaddition rates for these dipolarophiles are summarized in Scheme 4. Dipolarophile reactivity does not seem to be directly correlated with the extent of substitution on the alkene, but rather the placement of substitution on the alkene.



Scheme 4

In summary, we have demonstrated the diastereoselectivity of the intermolecular 1,3-dipolar cycloaddition of isomünchnones with vinyl ethers. The general nature of this diastereoselectivity is unprecedented for this class of dipoles.[5,15,20] In addition, dipolarophiles of diverse topologies have been shown to provide a synthetically feasible entry into [2.2.1] bicyclic heterocycles, in a controlled manner. Future effort in this area will include the investigation of potential stereoelectronic factors for this selective cycloaddition and expansion of the scope of vinyl ethers as dipolarophiles in the 1,3-dipolar cycloaddition reaction.

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14 *Crystal data* for **7**: $C_{16}H_{19}NO_5$, M = 305.33, orthorhombic, a = 9.066(2), b = 9.841(4), c = 17.138(3) Å, U = 1529(1) Å^3, T = 273 K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo-Kα) = 1.9 mm^{-1}, 1811 reflections measured, 1116 unique [$I > 3.00\sigma(I)$] which were used in all calculations. The final $wR(F^2)$ was 0.057 (all data). A single pale yellow prism crystal of **7**, having approximate dimensions 0.29 × 0.43 × 0.48 mm, was mounted on a glass fiber and collected on an Enraf-Nonius CAD-4 diffractometer using the ω–2θ scan technique. The structure was solved using direct methods, and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2. CCDC 182/1341.
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16 In each case, only a single diastereomer could be detected by ^{1}NMR spectroscopy, suggesting a >96:4 diastereoselectivity. The structural analysis for cycloadducts **6** and **8**–**15** was extrapolated by correlating corresponding ^{1}H NMR chemical shift data with compound **7**, whose structure was determined crystallographically.
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