

A Chiral Acrylate Equivalent for Metal-Free Diels–Alder Reactions: *endo*-2-Acryloylisoborneol

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Methods based exclusively on organic catalysts have become of major significance in synthetic chemistry, especially when they involve diastereo- or enantioselective processes.¹ The Diels–Alder reaction is a challenging benchmark for such a development,² due to its inherent potential as both a C–C bond forming and a stereodiversity creating reaction (in a single synthetic operation up to four new stereocenters may be generated). Most of the methods described to date, however, are based on the use of a (metal-containing) Lewis acid³ to activate the dienophile component toward the diene counterpart. In the case where the dienophile is an enoyl derivative, this is most often realized on substrates such as **I**, Figure 1, which possess an oxazolidinone or similar tether^{3,4} that will be detached in the final step of the reaction. The role of the metal center is apparently dual: on one hand it activates the dienophile by lowering the LUMO energy content, and on the other hand, it provides a center for intramolecular chelation which rigidifies substrate conformation, thereby allowing an effective asymmetric induction. Any new design should, in principle, meet these two requirements which concern reactivity and stereoselectivity, respectively.

α -Hydroxyenones **II**⁵ are potentially good dienophile candidates as they are amenable to a simultaneous activation/rigidifying process through an intermolecular hydrogen-bond motif,⁶ as shown in either structure depicted as **III**, which would not necessarily involve a metal-containing catalyst (Figure 2).

Observations made in our laboratories on ketols derived from (1*R*)-(+)-camphor⁷ have led us to formulate the above hypothesis. The crystalline **3** is easily prepared by addition of 1-lithio-1-methoxyallene⁸ to the commercially available (1*R*)-(+)-camphor, followed by a mild acid hydrolysis of the resulting intermediate **2**. For comparative purposes dienes **4** and **5** were also prepared.

The validity of the above hypothesis soon became clear. Neither **4** nor **5** reacted with isoprene **11a** (8 equiv), even in the presence of the most active Brønsted acids, trifluoroacetic acid (TFA) or trifluoromethanesulfonic acid (TfOH), *vide infra*, regardless of the solvent used. In contrast, Table 1, α -hydroxyenone **3** and isoprene **11a** had reacted completely after 2 days in CH₂Cl₂ at room temperature, to give **12a** (70:30 ratio of regioisomeric products). Moreover, this result could be improved considerably when the reaction was carried out in the presence of a 30 mol % of TFA to give **12a** in 91% yield and a 94:6 ratio of regioisomers.

A survey of Brønsted acids⁹ identified TfOH as the most efficient in terms of both activity and stereoselectivity. For example, a TfOH

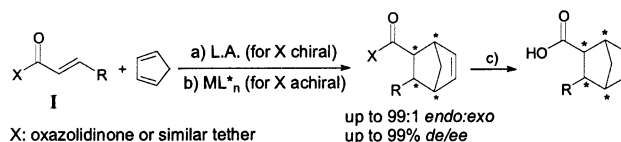


Figure 1. Metal-catalyzed Diels–Alder reactions: (a) Diastereoselective approach. (b) Enantioselective approach. (c) Detachment step.

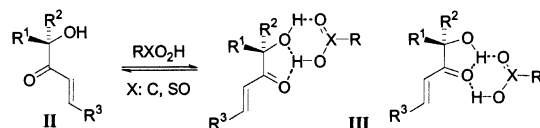
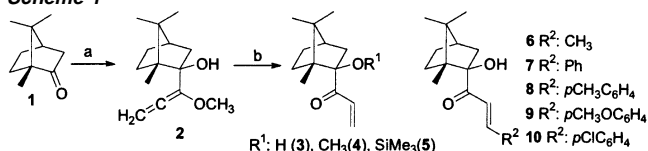


Figure 2. Working hypothesis that may account for the electrophilic activation of α -hydroxyenones by Brønsted acids.

Scheme 1^a



^a Conditions: (a) Methoxyallene, ⁿBuLi, TMDA, THF, –30 °C, 2 h. (b) For **3**: 1 M HCl, 75% overall yield. For preparation of derivatives **4**–**10**, see Supporting Information.

Table 1. Representative Diels–Alder Reactions with Enone **3**

com	diene 11	major diastereomer 12	<i>endo:exo</i> ^a	d.r. ^b	yield ^c %
a			--- ^d	>98:2	91
b			--- ^d	>98:2	75
c			16:1 ^f 49:1 ^e	98:2 ^a ≥98:2 ^a	95 98
d			>150:1 ^e	>98:2 ^a	85

^a Determined by HPLC. ^b Diastereomeric ratio of the *endo* or major regioisomer (as applicable) determined by ¹³C NMR. ^c Yield of isolated pure major diastereomer after column chromatography. ^d Reactions conducted on a 1 mmol scale in CH₂Cl₂ at –25 °C overnight; ratio diene:**3**: TFA, 5:1:0.3. ^e Reactions promoted either as in footnote *d* or by TfOH (10%) at –78 °C for 2–3 h. ^f Reaction conducted in the absence of TFA; ratio diene:**3**, 3:1.

loading of as low as 10 mol % promoted the reaction of **3** with **11b** to give **12b** as the exclusive product in just 3 h at –78 °C. Once again, in the absence of any catalyst, the reaction was comparatively slow (50% conversion after 24 h at ambient

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Table 2. Diels-Alder Reaction of Representative β -alkyl and β -aryl Enones with Dienes Catalyzed by TfOH^a

dieno phile	diene 11	t, h	major diastereomer	<i>endo:exo</i> ^b	d.r. ^c	yield, %
6		0.5		--	≥98:2	93
		1		--	≥98:2	95
6		1		>150:1	≥98:2	95
		72		5:1 ^d	96:4	-- ^e
6		1.5		>150:1	≥98:2	90
7		2 ^{f,g}		--	≥98:2	85
		3 ^f		>150:1	≥98:2	87
8		1.5 ^f		--	≥98:2	90
		1 ^f		>150:1	≥98:2	84
10		1		--	≥98:2	95

^a Reactions conducted on a 1 mmol scale in CH₂Cl₂ at -78 °C; ratio diene:enone:TfOH 5:1:0.1, unless otherwise stated. ^b Determined by HPLC or by ¹³C NMR. ^c Diastereomeric ratio of the *endo* or major regioisomer (as applicable) determined by ¹³C NMR. ^d Reaction conducted in the absence of catalyst. ^e Yield not determined. ^f Reaction performed with 30% of TfOH. ^g A byproduct is formed when a longer reaction time was applied. Not characterized.

temperature). Enone **3** reacted in a similar manner when cyclic dienes were employed. Even in the absence of any promoter, the highly reactive cyclopentadiene reacted with **3** to give **12c** with a 16:1 ratio of isomers. Notably, when the reaction was carried out with either TFA (30 mol %) or TfOH (10 mol %) catalysis, the *endo:exo* ratio of the produced isomers improved to 49:1. On the other hand, the reaction with cyclohexadiene once again required the presence of either TFA (30 mol %) or TfOH (10 mol %), which lead to **12d**, essentially as the only isomer.

On the basis of these results, which demonstrate the crucial effect that the Brønsted acid has, not only on the reactivity but also on the stereoselectivity,¹⁰ TfOH was selected as the optimal catalyst for further experiments. To this end, enones **6–10** were prepared easily from **2** and **3**,¹¹ and their reactions with representative dienes were examined (Table 2). In the presence of TfOH (10 mol %), enone **6** reacted with both acyclic and cyclic dienes **11a–d** at -78 °C in CH₂Cl₂ to give the respective cycloadducts within a short

time and with excellent yield and diastereoselectivity. Once again, although the reaction with cyclopentadiene to give **15** proceeded without the need for any catalyst, it gave a low *endo:exo* selectivity ratio, which could be improved when TfOH was used. The β -aryl-substituted enones **7–10**, in turn, also proved to be good substrates for the present Diels–Alder reaction, regardless of the electron-neutral, electron-rich, or electron-poor nature of the aryl substituent. The stereochemical assignment for the adducts was made by optical rotation measurements of the products obtained after detachment of the auxiliary, and by X-ray analyses.¹¹

In conclusion, we have documented a highly diastereoselective strategy for metal-free, Brønsted acid-activated Diels–Alder reactions and have set up the minimum structural requirements of the substrate dienophile.

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Supporting Information Available: Complete experimental procedures, determination of stereoisomeric mixtures, and spectroscopic data (PDF); crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) CH₃CO₂H, BrCH₂CO₂H, Cl₂CHCO₂H, HCO₂H led to inferior results compared to those with TFA in terms of reaction efficiency and stereoselectivity.
- (10) While essentially the same effect was observed when toluene was employed, the unchanged starting materials were recovered when Et₂O or THF were the solvents used. The ability of ethereal solvents to interfere during the hydrogen-bonding activation process might account for the differential behavior.
- (11) See Supporting Information for details.

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