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Enantioselective Synthesis of Allylic Alcohols via an Oxazaborolidinium Ion Catalyzed Diels−Alder/Retro-Diels−Alder Sequence

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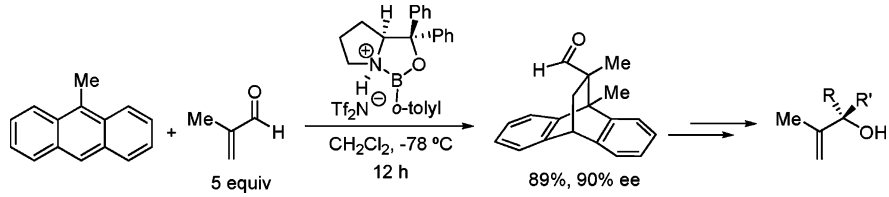
ABSTRACT



A triflimide-activated oxazaborolidine catalyst successfully promoted the asymmetric Diels−Alder reaction of 9-methylanthracene with methacrolein in high regio- and enantioselectivity. The cycloadduct obtained was subsequently used as a chiral template to access secondary and tertiary allylic alcohols in good to high enantiomeric excess via a cycloreversion by flash vacuum pyrolysis.

Chiral allylic alcohols are versatile synthetic intermediates and may be accessed by numerous routes, including selective 1,2-reduction of α,β-unsaturated carbonyl compounds,[1] kinetic resolution,[2] and enantioselective addition of vinyl groups to aldehydes.[3−5] Although the latter methodology allows the formation of a wide range of secondary alcohols, only a few asymmetric catalytic systems have been optimized to promote efficient vinyl addition to ketones.[6] In this paper, we report a new strategy to access secondary allylic alcohols in high enantioselectivity and quaternary centers in excellent yield.

Research from our group[7] and others[8] has previously demonstrated the efficiency of a Diels−Alder/retro-Diels−

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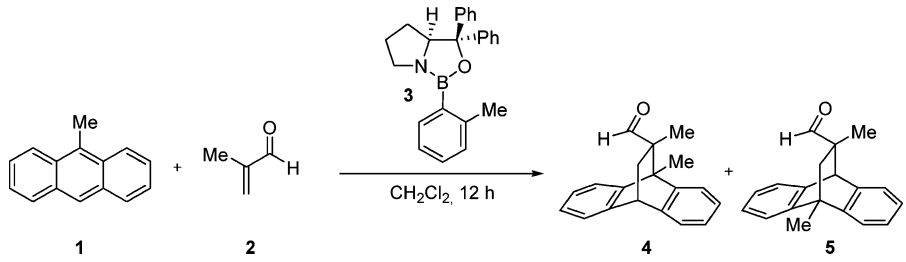
Table 1. Evaluation of a Suitable Catalytic System[a]



entry	concn of diene (M)	temp (°C)	catalyst loading (mol %)	activator	conv[b] (%)	**4**:**5**[b]	ee of **4** (%)	ee of **5**[c] (%)
1	0.25	−78	30		0			
2	0.5	−78	10	$AlBr_3$	8			
3	0.5	−78 to rt	10	$AlBr_3$	94	96:4	39[c]	64
4	0.5	rt	10	$AlBr_3$	100	97:3	19[c]	56
5	0.25	−78	30	Tf_2NH	100	92:8	90[c]	83
6	0.25	rt	30	Tf_2NH	100	92:8	84[c]	87
7	0.25	−78	30	TfOH	100	99:1	13[d]	
8	0.25	−78	30	$BF_3.Et_2O$	100	97:3	15[c]	
9	0.25	−78	30	$TiCl_4$	57	93:7	70[d]	

[a] Reactions performed in the presence of 5 equiv of dienophile under a nitrogen atmosphere. [b] Based on comparison of ratios of integrals of appropriate signals in the ^1H NMR spectrum of the crude reaction mixture. [c] Enantioselectivity was determined by reduction to the primary alcohol ($NaBH_4$) and chiral-phase HPLC analysis using a Daicel Chiralpak AD as a stationary phase. [d] Enantioselectivity was determined by reduction to the primary alcohol ($NaBH_4$) and chiral-phase HPLC analysis using a Phenomenex Lux column as a stationary phase.

Alder sequence based on a chiral-substituted anthracene template to generate small-molecule building blocks in high enantioselectivity. However, a drawback of this strategy remains the preparation of the parent chiral auxiliary via asymmetric synthesis. The use of substoichiomeric amounts of a chiral catalyst would make this chemistry significantly more appealing. Achiral anthracenes, such as anthrone, together with appropriate catalysts have been employed in the past,[9] including the use of a chiral oxazaborolidine catalyst, delivering the *N*-methylmaleimide cycloadduct in 60% ee.[10] Given the recent interest in the development of oxazaborolidium catalysts,[11,12] we became interested in developing this latter approach using 9-methylanthracene as a diene, since this is more reactive than the anthrone counterpart. Herein, we report the first catalytic Diels−Alder cycloaddition of 9-methylanthracene using Corey's cationic oxazaborolidine.

Our study commenced with the evaluation of a suitable activator for the oxazaborolidine precursor **3** in the Diels−Alder reaction of 9-methylanthracene with methacrolein (Table 1). Initial investigations were carried out with aluminum bromide as a Lewis acid activator. Using the procedure developed by Corey et al.,[13] the reaction proceeded with low conversion at −78 °C (entry 2). Pleasingly, we found that full conversion could be achieved when the reaction was warmed to room temperature (entries 3 and 4); however, the enantioselectivity dropped from 39 to 19% ee. Thus, we investigated the use of triflimide activation, previously reported to confer beneficial effects on the catalyst stability with no loss of potency.[14] Full conversion was observed irrespective of the reaction temperature in high enantioselectivity (entries 5 and 6).[15] A nonseparable mixture of regioisomers (ratio 92:8) was obtained in favor of cycloadduct **4** (determined by comparison of ^1H NMR data and independent synthesis). During our investigations, it emerged that any modification of reaction conditions as well as the catalyst loading resulted in a loss of both conversion and enantioselectivity. Among the other potential activators examined, TfOH, BF_3•Et_2O, and $TiCl_4$ gave less promising results (entries 7 to 9). The efficiency of the catalyst was also demonstrated compared to the racemic synthesis of the cycloadduct under thermal conditions which required about 5 days to complete in 78% yield.

With the major cycloadduct **4** in hand, addition of various Grignard reagents in toluene at room temperature was performed (Scheme 1). Alcohols **6** were obtained in moderate to good yields. However, the diastereoselectivity of the reaction was not fully controlled, presumably since free rotation of the carbon−carbon bond bearing the carbonyl group presented different prochiral faces amenable to nucleophilic addition.[16] Neither the use of a Lewis acid nor the use of lower reaction temperature improved the diastereoselectivity. Nevertheless, we found that the dr could be increased by further purification of the crude reaction mixture (up to 98:2, entry 1). It should be noted that attempts to functionalize cycloadduct **6** with *i*-propyl or *tert*-butyl groups resulted in the β-hydride elimination of the Grignard reagent and isolation of the reduced product.

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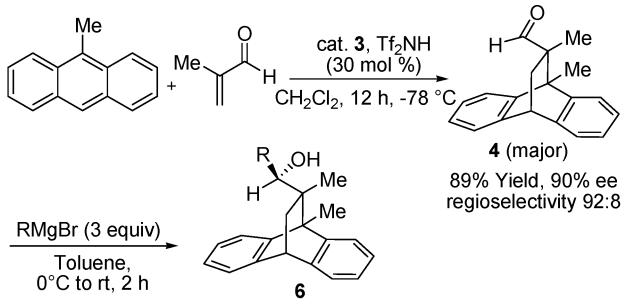
(11) For reviews, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2–20.

Scheme 1. Formation of Secondary Alcohols



entry	R	dr[a] (crude)	dr[a] (final)	yield (%) / **6**
1	Me	87:13	98:2[b]	68 / **6a**
2	Et	90:10	92:8[b]	42 / **6b**
3	Ph	73:27	95:5[c]	59 / **6c**
4	-CH=CH_2	83:17	84:16[b]	84/ **6d**
5	-CH_2-CH=CH_2	70:30	95:5[c]	82 / **6e**
6	-C≡CH	96:4	96:4[b]	87 / **6f**

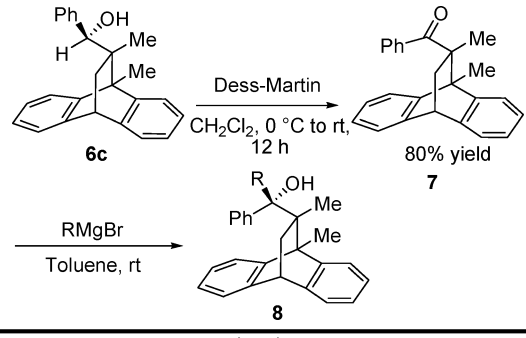
[a] Values for dr were based on comparison of ratios of integrals of appropriate signals of the major regioisomer in the ^{1}H NMR spectrum. [b] Purification by column chromatography. [c] Purification by recrystallization.

Attempts to add EtMgBr (entry 2) also led to reduction but in this case provided a 60:40 ratio in favor of cycloadduct **6b**, which was isolated in 42% yield by silica gel chromatography.

Considering the valuable interest in making quaternary stereogenic centers, we then focused on investigating the possibility of forming enantiomerically enriched tertiary allylic alcohols. Since cycloadduct **6c** was amenable to purification to remove the unwanted diastereoisomer, it was selected to carry out such transformations. Dess−Martin oxidation provided ketone **7** in 80% yield, and subsequent addition of Grignard reagents afforded cycloadducts **8** (Scheme 2). However, in contrast to the aldehyde, addition of Grignard reagents to the ketone resulted in a low diastereoselectivty; cycloadduct **8a** was obtained in a 78:22 dr within 2 h (entry 1), while addition of the ethynyl and vinyl groups required a longer reaction time to achieve completion with a poor dr (entries 2 and 3).

Cycloadducts **6** and **8** were then subjected to flash vacuum pyrolysis. Secondary allylic alcohols were isolated in excellent yields and high ee without any further purification (Table 2). Furthermore, the enantioselectivity of each product was

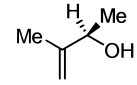
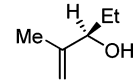
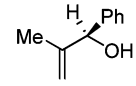
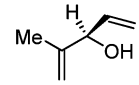
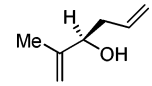
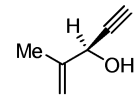
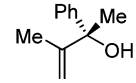
Scheme 2. Formation of Tertiary Alcohols



entry	R	reaction time (h)	dr[c]	yield (%) / **8**
1	Me[a]	2	78:22	91 / **8a**
2	-C≡CH[b]	48	53:47	66 / **8b**
3	-CH=CH_2[a]	12	60:40	91 / **8c**

[a] Reaction was performed using 3 equiv of Grignard reagent. [b] Reaction was performed using 11 equiv of Grignard reagent. [c] Values for dr were based on comparison of ratios of integrals of appropriate signals of the major regioisomer in the ^{1}H NMR spectrum.

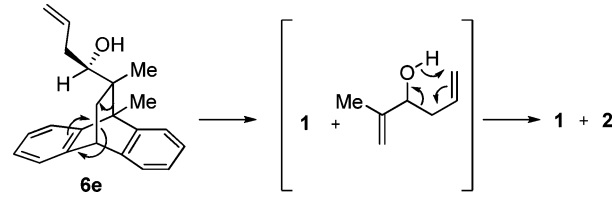
Table 2. Generation of Allylic Alcohols via Retro-Diels−Alder Reaction[a]

entry/substrate	alcohol	yield	ee[b]
1/**6a**		93	82
2/**6b**		94	76
3/**6c**		99	86[c]
4/**6d**		94	63
5/**6e**		-	-
6/**6f**		94	82
7/**8a**		87	52

[a] Cycloadducts were subjected to FVP (0.01 mmHg; see the Supporting Information for further details). [b] Values for ee determined by chiral-phase GC analysis using a Supelco fused silica capillary column as a stationary phase (see the Supporting Information for further details). [c] The ee was higher than expected due to several recrystallizations of the starting material.

in accordance with the dr of the cycloadducts before the retro-Diels−Alder process. Unfortunately, alcohol **6e** could not be isolated as it underwent a retro-ene reaction and methacrolein was isolated as a result (Scheme 3). The

Scheme 3



absolute stereochemistry of the allylic alcohol from the retro-Diels−Alder reaction of **6a** was established by comparison of its optical rotation with that reported in the literature and extended to the other secondary alcohols by analogy.[17]

The retro-Diels−Alder reaction of cycloadduct **8a** afforded a valuable tertiary alcohol in 52% ee (Table 2, entry 7).[18]

In summary, we have developed an asymmetric catalytic system for the Diels−Alder reaction of 9-methylanthracene with methacrolein. The utility of such a transformation was illustrated by the synthesis of secondary and tertiary allylic alcohols, both with good yield and enantioselectivity. Work is now underway to expand the range of substrates available.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We found that the enantioselectivity of the reaction was highly dependent on the quality of bis(trifluoromethanesulfonyl)imide. Ideally, a 0.2 M solution in CH_2Cl_2 was freshly prepared under an argon atmosphere in a glovebox (see the Supporting Information for further details).

(16) Due to this, the absolute configurations of cycloadducts **6** and **8** remain unknown.

(17) Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25–28.

(18) The absolute configuration of the tertiary alcohols remains unknown.