Highly Diastereoselective Diels–Alder Reactions of Baylis–Hillman Adducts

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ABSTRACT



Baylis-Hillman adducts were found to be excellent dienophiles in Diels-Alder reactions, providing essentially complete diastereocontrol (although mixtures of *endolexo* isomers) with all dienes.

The Baylis-Hillman reaction^{1,2} is a C-C bond-forming reaction between a Michael acceptor (e.g., an acrylate) and an electrophile (e.g., an aldehvde). Although the reaction traditionally suffered limited substrate scope, improved reaction conditions now allow a much broader range of Michael acceptors and electrophiles to be employed.³ The utility of the Baylis-Hillman reaction lies in the dense functionality that is generated, providing handles for further manipulation.⁴ Although a broad array of synthetic transformations have been carried out on Baylis-Hillman adducts, a surprising omission is that of Diels-Alder reactions. Such reactions, especially if they could be made diastereoselective, would enhance the synthetic utility of the Baylis-Hillman reaction still further. We believed that through hydrogen bonding or metal chelation between the two oxygens of the hydroxyl and the carbonyl group, the conformation of the dienophile (Baylis-Hillman adduct) could be controlled, thus promoting diastereocontrol (Scheme 1).

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Indeed, enones bearing α -hydroxyalkyl substituents have been employed in highly selective Diels—Alder reactions in the presence of Brønsted acids.⁵ In such a system, the diene, approaching in the *endo* mode, sits directly above the carbinol stereocenter, providing high levels of stereocontrol (Scheme 2).

It was not clear whether Baylis—Hillman adducts could offer similar levels of stereocontrol, as the carbinol stereocenter is positioned remotely from the diene (Scheme 1). On the basis of these uncertainties, we undertook a study of Diels—Alder reaction between a series of representative Baylis—Hillman adducts bearing groups of different steric hindrance (phenyl, cyclohexyl, and ethyl) and both cyclic and acyclic dienes.

The Baylis—Hillman adducts were prepared in good yield and short reaction time using our optimized conditions, which consist of quinuclidine (0.25 equiv) and methanol (0.75 equiv) (Scheme 3).³



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The Diels-Alder reaction of each of these adducts with cyclopentadiene under thermal conditions was initially investigated (Table 1).



Four Diels-Alder isomers can be formed in the reaction, a diastereomeric pair of exo isomers (2c/3c, illustrated with R = Ph) and a diastereomeric pair of *endo* isomers (2c'/3c'), but only two isomers were observed in all cases (Scheme 4).

Table 1. Results of Diels-Alder Reaction with

 Cyclopentadiene under Thermal Conditions

	°C, o/n		OOMe ₊	Сооме
1a-c		2a-c	2	a'-c'
product	time	yield (%)	exo/endo	d.r. ^a
2a, R = cyclohexyl	20 h	85	70/30	>98:2
$\mathbf{2b}, \mathbf{R} = \mathbf{ethyl}$	14 h	88	62/38	>98:2
2c, R = phenyl	8 h	89	60/40	>98:2

^a Diastereomeric ratio of *exo* $(2\mathbf{a}-\mathbf{c}:3\mathbf{a}-\mathbf{c})$ and *endo* $(2\mathbf{a}'-\mathbf{c}':3\mathbf{a}'-\mathbf{c}')$ isomers determined by ¹H NMR.

We proved that the mixture of isomers obtained were *exo/ endo* isomers 2c and 2c' rather than a pair of *exo* (or *endo*) isomers 2c/3c (or 2c'/3c') by oxidation of the alcohols obtained to the corresponding ketones (Scheme 4). If they had been a pair of *exo* (or *endo*) isomers 2c/3c (or 2c'/3c'), this would have furnished a single ketone 4 as a mixture of



enantiomers 4(R) + 4(S) (or 5(R) + 5(S)), whereas if they had been *exo/endo* isomers 2c/2c' (or 3c/3c'), this would have furnished a mixture of diastereomeric ketones 4(R) + 5(R)(or 4(S) + 5(S)). In the event, oxidation of the two separated compounds obtained after the DA reaction yielded two different ketones 4(R) + 5(R) (or 4(S) + 5(S)), establishing that either 2c/2c' or 3c/3c' had been formed. From X-ray analysis of related adducts (see later), we believe that the isomers obtained are 2c/2c' with the *exo* isomer being favored over the *endo* isomer, as proved by NOESY (see Supporting Information).

Attempts to improve the endo/exo ratio with Lewis or Brønsted acids were unsuccessful.⁶ In fact, using EtAlCl₂, a mixture of exo:endo adducts was obtained but now with the endo isomer predominating (28/72). Exo isomers are favored for the methacrylates 5 $(3:1)^7$ and actually dominate for α -exo-methylene cyclic enones/lactones/lactams 6 (95:5) (Scheme 5).⁸ The high *exo* selectivity is believed to result from the fixed cisoid conformation⁹ of the dienophile and subsequent minimization of the overall dipole moment of the transition state 7.8 Interestingly, the Baylis-Hillman dienophile is uniquely locked in a transoid conformation⁹ (especially in the presence of Lewis acids); thus, minimization of the dipole cannot be an issue in this case, as the dipoles of the diene and dienophile are perpendicular (8, Scheme 5). Instead, we believe that the exo/endo ratio is controlled by a balance of steric and electronic factors. The usual secondary orbital interaction favors the endo isomer,

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⁽⁶⁾ Lewis acid (2 equiv) was used at -78 C for 3 h, warming to room temperature for 1 h in each case: EtAlCl₂ (*exo/endo* 28/72); ZnBr₂ (*exo/endo* 30/70). Using SnCl₄, TiCl₄, Ti(O*i*Pr)₄, or TFA, no Diels–Alder adducts were obtained.

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⁽⁹⁾ Cisoid or transoid conformation refers to the conformation around the σ -bond linking the alkene and the carbonyl group in the Baylis—Hillman dienophile.



but this transition state is destabilized by steric interactions between the C7 syn hydrogen and the carbinol.¹⁰

We next investigated the Diels–Alder reaction with isoprene, a more demanding diene due to its lower reactivity and issues of regioselectivity. Although thermal reactions gave a mixture of stereo- and regioisomers, we found that use of $EtAlCl_2$ furnished essentially a single diastereoisomer and regioisomer in every case (Table 2).

$R + CO_2Me + 1 a-c$	EtAICl₂ (2 eq.) CH₂Cl₂, 0 °C→ rt, o/n	PHCO ₂ Me
product	yield (%)	dr
9a, R = cyclohexyl	90 (98 <i>^{<i>a</i>})</i>	98:2
9b , $R = ethyl$	$95 (96^a)$	96:4
9c, R = phenyl	$52~(98^a)$	97:3

 a Di-*tert*-butylpyridine (1 equiv) was added to the reaction before addition of EtAlCl₂.

Although good yields were obtained in cases where R = alkyl, low yields were observed in the case of R = Ph due to the sensitivity of the substrate toward acid-promoted carbocation formation. To suppress this pathway, we tested the use of hindered bases to buffer the reaction medium and found that di-*tert*-butylpyridine was highly effective. Adding this base to the reaction medium resulted in essentially quantitative yield for not only the alkyl but also the aryl carbinols. The base did not interfere with the progress of the reaction presumably because it was too hindered to complex with the Lewis acid. Thus, the base and Lewis acid were able to fulfill their respective roles without interference from each other.

The X-ray structure of the cyclohexyl adduct 9a proved the relative stereochemistry (Figure 1). With this information, we propose a simple rationale for the stereochemical outcome of the Diels-Alder reaction. In this model, a metal or



Figure 1. X-ray structure of 9a.

hydrogen-bonded chelate controls the conformation of the dieneophile to create two diastereotopic faces. The diene then approaches the face of the dienophile opposite the R substituent. If the diene approaches in the *endo* mode, it is surprising that very high diastereocontrol is achieved with the smallest of the Baylis–Hillman adducts (**1b**, R = Et), especially in the case of isoprene where steric interactions differentiating the two possible approaches must be minimal (Scheme 6).



In conclusion, we have found that Baylis—Hillman adducts are excellent dienophiles in Diels—Alder reactions, providing essentially complete diastereocontrol with all dienes. Although *exo/endo* stereoisomers were formed with cyclopentadiene, no regioisomers were obtained with isoprene. The emerging asymmetric Baylis—Hillman reaction coupled with these new Diels—Alder reactions rapidly builds up complex architectures in a stereocontrolled process from very simple and inexpensive starting materials, and this will no doubt find applications in synthesis. Efforts in this area are currently ongoing.

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Supporting Information Available: Experimental procedures and characterization data for new compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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