The Asymmetric Baylis−Hillman Reaction

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The controlled construction of carbon−carbon bonds is of fundamental importance in organic chemistry. Unfortunately, there are relatively few methods for performing this task with absolute stereocontrol. We wish to report here an asymmetric variation of the Baylis−Hillman reaction as a novel method to realize this objective.

The tertiary amine catalyzed addition of an acrylate to an aldehyde is widely referred to as the Baylis−Hillman reaction (Figure 1).[1] This reaction activates an acrylate group to form a carbon−carbon bond via nucleophilic attack of an aldehyde, thereby creating a new stereocenter. Selective formation of this stereocenter would provide a route to optically enriched α-methylene-β-hydroxy esters, useful building blocks in organic synthesis.[1] These compounds have previously been converted to a variety of other products with high stereospecificity, including aziridines,[2] epoxides,[3] triols,[4] and anti aldol adducts.[5] Numerous attempts have been made to introduce stereoselectivity into the Baylis−Hillman reaction using optically pure amine catalysts,[6] aldehydes,[7] and acrylates.[8] However, no reliable, highly enantioselective process has emerged to date. We have found a system that routinely provides Baylis−Hillman products in greater than 99% enantiomeric excess in moderate to excellent yields with a variety of achiral aldehydes. Chiral auxiliaries have been proven to be a highly effective method of introducing stereochemistry into a molecule in a recoverable fashion.[9] Particularly useful in this regard has been the camphor-derived Oppolzer's sultam.[10] It is readily available as either antipode and typically leads to excellent transfer of chirality.[11]

In practice, Oppolzer's sultam was found to be an ideal auxiliary in the Baylis−Hillman reaction (Table 1). The reaction proceeded smoothly with a variety of aldehydes to yield products

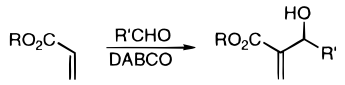
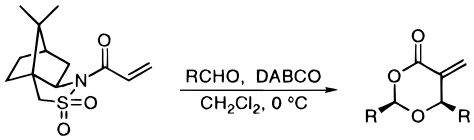


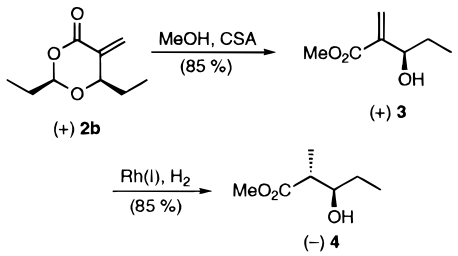
Figure 1.

Table 1



	R	yield (%)	ee (%)	$[\alpha]_D$
a	CH_3	85	>99	+ 73.4°
b	CH_3CH_2	98	>99	+ 70.2°
c	$CH_3CH_2CH_2$	70	>99	+87.2°
d	$(CH_3)_2CH$	33	>99	+42.7°
e	$PhCH_2CH_2$	68	>99	+ 47.2°
f	$AcOCH_2$	68	>99	+ 80.0°
g	$(CH_3)_2CHCH_2$	67	>99	+ 59.8°
h	Ph	0		

Scheme 1



that were essentially optically pure.[12] The reaction works best when the aldehyde substrates are unbranched at the α-position, as evidenced by the results with isobutyraldehyde (**2d**) and benzaldehyde (**2h**). Furthermore, the auxiliary was fortuitously cleaved under the reaction conditions by incorporation of a second equivalent of the aldehyde, thereby rendering **1** as a renewable source of chirality in this case.[13]

The 1,3-dioxan-4-ones produced in this manner were easily converted into α-methylene-β-hydroxy esters (Scheme 1). As mentioned above, this is a versatile template for further manipulation. For example, products such as **3** were directly converted into the corresponding anti aldol adducts (**4**) via directed reduction of the olefin.[5,14] Given the difficulty typically associated with direct generation of this stereochemical array,[15]

(1) For recent reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(2) Atkinson, R. S.; Fawcett, J.; Russel, D. R.; Williams, P. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2031. For an excellent review on directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(3) Bailey, M.; Markó, I. E.; Ollis, W. D. *Tetrahedron Lett.* **1991**, *32*, 2687.

(4) Markó, I. E.; Giles, P. R.; Janousek, Z.; Hindley, N. J.; Declercq, J.-P.; Tinant, B.; Feneau-Dupont, J.; Svendsen, J. S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 239.

(5) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

(6) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.

(7) Drewes, S. E.; Khan, A. A.: Rowland, K. *Synth. Commun.* **1993**, *23*, 183.

(8) (a) Drewes, S. E.; Emslie, N. D.; Khan, A. A. *Synth. Commun.* **1993**, *23*, 1215. (b) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S.; Rao, P. D. *Tetrahedron Lett.* **1990**, *31*, 1621. (c) Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969. (d) Khan, A. A.; Emslie, N. D.; Drewes, S. E.; Field, J. S.; Ramesar, N. *Chem. Ber.* **1993**, *126*, 1477. (e) Drewes, S. E.; Emslie, N. D.; Karodia, N.; Khan, A. A. *Chem. Ber.* **1990**, *123*, 1447. (f) Jensen, K. N.; Roos, G. H. P. *S. Afr. J. Chem.* **1992**, *45*, 112.

(9) See: Ager D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835 and references cited within.

(10) Several reviews have appeared, including the following: (a) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241. (b) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293. (c) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (d) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39.

(11) (a) Weismiller, M. C.; Towson, J. C.; Davis, F. A. *Org. Synth.* **1990**, *69*, 154. (b) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158. (c) Ho, G. J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

(12) A representative procedure for this transformation is as follows: A solution of acrylate **1**[11] (500 mg, 1.85 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C, and propionaldehyde (2.0 mL, 27 mmol) was added followed by DABCO (20.7 mg, 0.19 mmol). The solution was stirred at 0 °C for 12 h and then concentrated under reduced pressure without heat. The residue was purified by flash column chromatography to provide **2b** (310.3 mg, 98%) as a clear oil.

(13) While all auxiliaries can theoretically be reused/regenerated, they are often carried through several synthetic steps, thereby reducing the overall efficiency of this asymmetric induction. In this case, however, the auxiliary is automatically removed under the reaction conditions, regenerating the sultam for subsequent use without additional work. Typically, 90% of the theoretical amount of the sultam can be recovered from the reaction by further elution of the flash column.

(14) Generation of the anti aldol adducts via a directed reduction served the additional purpose of allowing us to confirm the stereochemical outcome of the Baylis−Hillman reactions by comparison with known scalemic products. These compounds (such as **4**) have been previously reported in enantiomerically pure fashion (Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4278).

(15) For useful reviews of the aldol reaction, see: (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 112−212. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133−238.

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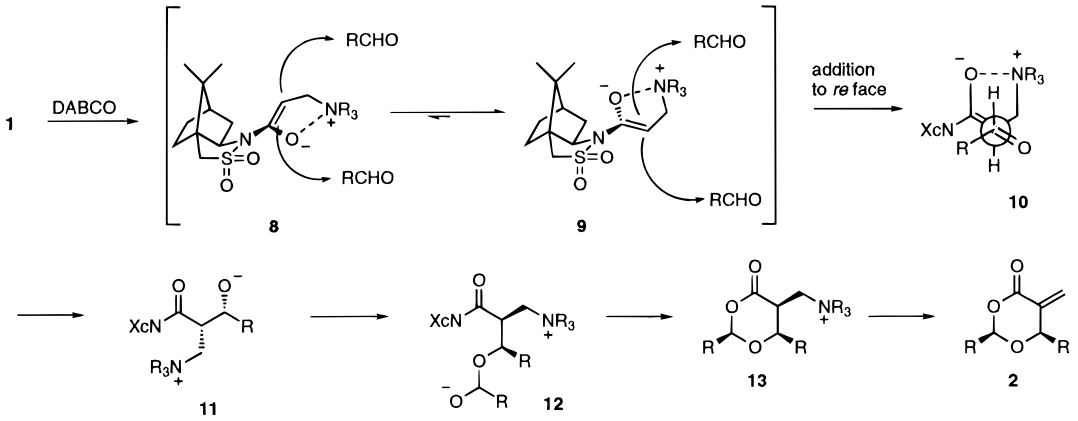
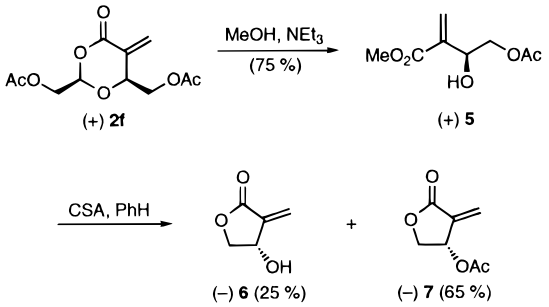


Figure 2.

Scheme 2



this serves as a practical alternative, affording the adducts in optically pure fashion in short order. These reductions also helped to confirm the absolute stereochemical outcome of the initial Baylis−Hillman reactions.[16]

A demonstration of the utility of this reaction is manifested in the total synthesis of tulipalin B (**6**, Scheme 2), the contact dermatitic agent in tulip bulbs.[17] The product could be obtained in essentially two steps from **2f**.[18]

Two factors are instrumental in controlling the absolute stereochemistry of the products: the demonstrated preference of acrylate **1** for addition to its C(α) *re* face[10] and the requirement of an open transition state. The addition of catalyst to **1** results in formation of the *Z* enolate,[19] which could lie in either of the two rotamers **8** or **9** (Figure 2). Rotamer **8**, with the carbonyl syn to the sulfonyl group, has been shown to be favored in reactions where a Lewis acid is present to chelate the carbonyl group and the sulfonyl group.[10a] Conversely, in **9** the carbonyl is preferentially oriented anti to the sulfonyl group in nonchelated reactions in order to minimize dipole interactions between these groups.[10b] This anti configuration should therefore be favored in the Baylis−Hillman reaction. In all reactions with acrylate **1**, addition to the *re* face of the acrylate is favored,[10] presumably due in this case to steric interactions with the axial oxygen of the sulfonyl group, which effectively prevents addition to the bottom (*si*) face.[10]

Reaction of the aldehyde at the *re* face of the enolate is represented by **10**, with the proton favorably approaching over the bulky quaternary ammonium group. Such a reaction would generate **11**, a product similar to that obtained via a syn aldol addition.[15] The α-stereocenter is subsequently lost upon elimination of the tertiary amine.

In summary, we have demonstrated that Oppolzer's sultam can be used in the Baylis−Hillman reaction to obtain products of very high enantiomeric purity. These cyclic products can easily be opened to give optically pure α-methylene-*β*-hydroxy esters, which are useful building blocks in organic synthesis and precursors to anti aldol adducts. The absolute stereochemistry of these compounds has been assigned through conversion to known products and by the total synthesis of tulipalin B. Coupled with the pronounced acceleration of this reaction at low temperature,[20] this should prove to be a generally useful and practical synthetic transformation, and work is underway to further expand the utility of these products.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**−**7** (7 pages). See any current masthead page for ordering and Internet access instructions.

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(16) The absolute stereochemistry of products such as **2** had never been rigorously proven (see Khan, A. A.; Emslie, N. D.; Drewes, S. E.; Field, J. S.; Ramesar, N. *Chem. Ber.* **1993**, *126*, 1477). Conversion of these products into known anti aldol adducts such as **4** unequivocally established the absolute sense of asymmetric induction in the initial Baylis−Hillman reactions.[14] As an additional test, the anti aldol adducts were also subjected to Mosher's ester analysis, and the data were in complete agreement with the structures assigned (see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092).

(17) Slob, A. *Phytochemistry* **1972**, *12*, 811.

(18) The synthetic material prepared in this fashion was virtually identical with natural tulipalin B. The (*S*) stereochemistry of tulipalin B has previously been confirmed by synthesis from malic acid (see: Papageorgiou, C.; Benezra, C. *J. Org. Chem.* **1985**, *50*, 1145 and references cited within).

(19) While either enolate geometry could be generated via the Michael addition of the catalyst to the acrylate in a reversible fashion, Drewes has proposed the *Z*-enolate as an explanation of the rate enhancement observed with 3-quinuclidinol.[1b]

(20) Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521.