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The osmium-catalyzed aminohydroxylation of Baylis–Hillman olefins

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Abstract

The Baylis–Hillman class of olefins undergoes a facile osmium-catalyzed aminohydroxylation reaction. The diastereoselectivity for the aminohydroxylation is influenced by the aldehyde-derived substituent, while the acrylate-derived substituent has a minimal effect. A variety of derivatives and close analogs of the Baylis–Hillman product-core failed to aminohydroxylate, emphasizing the unique reactivity of this class of olefins. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Baylis–Hillman reactions; catalysis; amino alcohols; osmylations.

The osmium-catalyzed aminohydroxylation reaction is a powerful synthetic transformation capable of converting a lipophilic carbon–carbon double bond into a hydrophilic *syn*-hydroxyamide.[1] The profound effect this reaction has upon the molecular properties of its substrates has fueled the search for classes of olefins with exceptional reactivity. A majority of olefin substrates studied in the asymmetric aminohydroxylation (AA) require a high catalyst loading (4 mol%) as well as a large excess of oxidant (3 equiv.) in order to obtain a good yield of product. One class of olefins, α,β-unsaturated amides, have been shown to possess exceptional reactivity in the racemic, sulfonamide-based version of this reaction, proceeding in high yields with low catalyst loading while requiring little or no excess oxidant.[2] This communication reports similar reactivity for the Baylis–Hillman class of olefins.

The Baylis–Hillman reaction, the condensation of an acrylate or otherwise activated terminal olefin with an aldehyde, provides a simple and convenient route to a very useful class of functionalized olefins.[3,4] The majority of the Baylis–Hillman olefins utilized in this study contain an asymmetric center and will potentially exhibit diastereoselectivity in their aminohydroxylation. Thus, in addition to the yield of the aminohydroxylated product, the diastereomeric ratios of the products have also been determined.

In a typical procedure the Baylis–Hillman olefin is dissolved to 0.2 M in MeCN:H_2O (1:1 v/v)[5] and 1 mol% $K_2OsO_2(OH)_4$ is added along with 1.2 equiv. of chloramine-T trihydrate. The reaction is stirred

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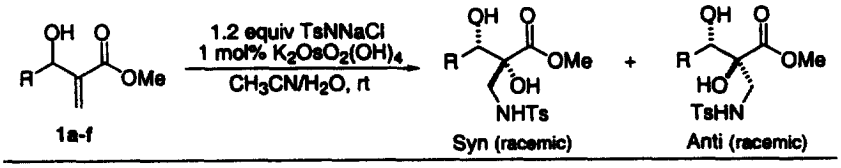
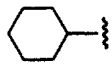
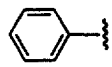
Table 1
Aminohydroxylation results with various aldehyde-derived substituents



Entry	R	Olefin	Diastereoselectivity (Syn:Anti)	Yield (%)[a]
1	H	1a	N.A.	73
2	Me	1b	88 : 12	88
3		1c	90 : 10	78
4		1d	98 : 2	71
5		1e	98 : 2	76
6		1f	>99 : 1	23[b]

[a]Yields for the mixture of diastereomers. [b]Obtained with 5 mol% catalyst.

at room temperature until TLC indicates complete consumption of the olefin (8–24 h). Sodium sulfite is then added, and after stirring for 4 h the reaction is extracted thrice with ethyl acetate and the organic extracts are combined, washed with brine, then dried over sodium sulfate. The resulting solution is filtered and concentrated under reduced pressure. The crude reaction product is then purified by either recrystallization or flash chromatography on silica gel.

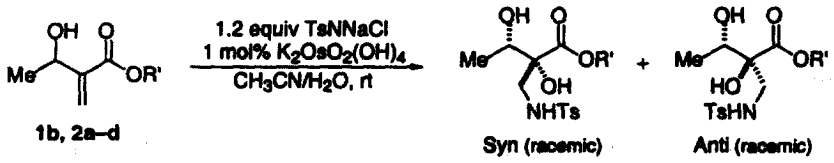
Examination of the results presented in Tables 1 and 2 reveal that the aminohydroxylation of Baylis–Hillman olefins can be highly diastereoselective. It is apparent that as the steric bulk of the aldehyde-derived substituent (R, Table 1) increases, so does the *syn/anti* ratio in the product. Similarly, but to a lesser degree, as the size of the acrylate-derived substituent (R′, Table 2) increases, so does the diastereoselectivity of the reaction. The X-ray crystal structure of the major diastereomer from entry 4, Table 1, establishes the *syn* relationship between the two hydroxy groups.[6] As was observed in the earlier studies of 2,3-unsaturated amides, neither the rate, the selectivity, nor the yield are noticeably affected when the AA ligand [e.g., $(DHQ)_2PHAL$] is added.

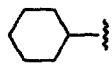
Of the initial olefins tried (Table 1), only **1f** gave a poor result (23% yield even at a catalyst loading of 5 mol%). This result led us to examine the structural features in these Baylis–Hillman olefins which most affect the desired aminohydroxylation process. The deoxy and homo-allylic[7] analogs (**3a** and **3b**, Fig. 1) were tested and produced only trace amounts of aminohydroxylated product. The methylated and benzylated derivatives (**3c** and **3d**, Fig. 1) also exhibited limited reactivity. Interestingly, the acetylated derivative **3e** reacted readily leading to a high yield of product, albeit with low diastereoselectivity (Scheme 1).

An alternate oxidant/nitrogen source, $MeSO_2NNaCl$,[8] was also successfully used in this aminohydroxylation process (Scheme 2), giving a higher yield than the analogous reaction using chloramine-T, but with a lower diastereoselectivity (cf. Table 2, entry 4).

In summary, a new class of excellent substrates for the ligand-independent, osmium-catalyzed ami-

Table 2
Aminohydroxylation results with various acrylate-derived substituents



Entry	R'	Olefin	Diastereoselectivity (Syn:Anti)	Yield (%)[a]
1	Me	1b	88 : 12	88
2		2a	86 : 14	70
3		2b	89 : 11	65
4		2c	91 : 9	68
5		2d	92 : 8	71

[a]Yields for the mixture of diastereomers.

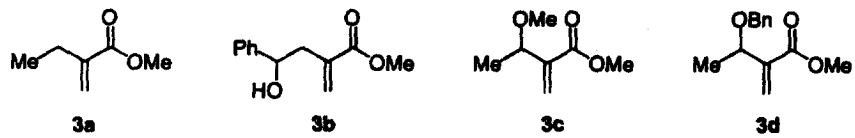
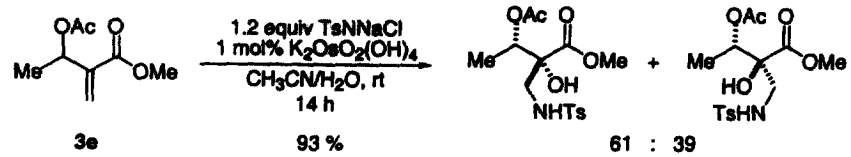
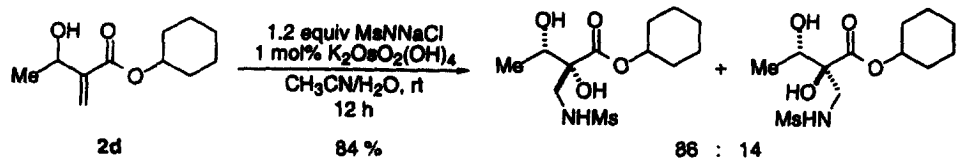


Figure 1. Baylis–Hillman analogs of limited reactivity



Scheme 1. The aminohydroxylation of an acetylated Baylis–Hillman olefin



Scheme 2. Aminohydroxylation with chloramine-M

nohydroxylation process (i.e., 'A' reaction) has been discovered. In contrast to the wide array of olefin classes already successfully utilized in the AA reaction (i.e., ligand dependent), neither the yield, rate or selectivity of this reaction with Baylis–Hillman olefins are appreciably affected by the addition of cinchona alkaloid ligands. The stereogenic center, present in almost all members of this class, does influence the outcome and high diastereoselectivities are regularly observed. The easy accessibility of many Baylis–Hillman olefins,[3,4] and the rich array of functionality which arises in their genesis, makes this synthetic manifold very useful. With the present addition of such a powerful transformation as

aminohydroxylation, the Baylis–Hillman approach to the rapid assembly of drug-like compounds should continue to grow in popularity.

Acknowledgements

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References

1. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. (b) Kolb, H. C.; Sharpless, K. B. Asymmetric Aminohydroxylation; in *Transition Metals for Fine Chemicals and Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: New York; in press. (c) Schlingloff, G.; Sharpless, K. B. Asymmetric Aminohydroxylation; in *Asymmetric Oxidation Reactions: A Practical Approach*; Katsuki, T., Ed.; Oxford University Press: Oxford; in press.
2. Rubin A. E.; Sharpless K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637.
3. For reviews on the Baylis–Hillman reaction 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.
4. For recent advances of the Baylis–Hillman reaction see: (a) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539. (b) Kataoka, T.; Iwama, T.; Kinoshita, H.; Tsujiyama, S.; Tsurukami, Y.; Iwamure, T.; Watanabe, S. *Synlett* **1999**, 197. (c) Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun.* **1998**, 197. (d) Aggarwal, V. K.; Tarver, G. J.; McCague, R. *Chem. Commun.* **1996**, 2713.
5. *t*-BuOH:H_2O (1:1 v/v) is also a suitable solvent system for this reaction.
6. This *syn* selectivity is consistent with that observed in the osmium-catalyzed dihydroxylation of this class of olefins see: Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 491.
7. Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.
8. Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810.