JOC Article

# Straightforward Asymmetric Entry to Highly Functionalized 3-Substituted 3-Hydroxy-β-lactams via Baylis−Hillman or Bromoallylation Reactions

Benito Alcaide,*,† Pedro Almendros,*,‡ Cristina Aragoncillo,† and Raquel Rodríguez-Acebes†

*Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain, and Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain*

*alcaideb@quim.ucm.es; iqoa392@iqog.csic.es*

*Received October 7, 2003*

The reaction of various activated vinyl systems, including 2-cyclopenten-1-one, with enantiopure azetidine-2,3-diones **1** was promoted by DABCO to afford the corresponding optically pure Baylis−Hillman adducts **2** without detectable epimerization. However, the reaction of α-keto lactams **1** with but-3-yn-2-one was not as successful, giving the corresponding β-halo Baylis−Hillman adduct in low yield. Metal-mediated bromoallylation reaction between 2,3-dibromopropene and azetidine-2,3-diones **1** was investigated in aqueous media. Surprisingly, indium was unable to promote the bromoallylation reaction of α-keto lactams **1**, but the Sn−$Hf_4Cl$-promoted bromoallylation of ketones **1** proceeded efficiently to achieve bromohomoallyl alcohols **5** as single diastereomers. On this basis, simple and fast protocols for the asymmetric synthesis of the potentially bioactive 3-substituted 3-hydroxy-β-lactam moiety were developed.

## Introduction

Since 3-substituted 3-hydroxy-β-lactams are important substrates both for studies of biological activity and as versatile building blocks for β-amino acid synthesis, development of practical methods for their stereocontrolled preparation is of interest. The 3-substituted 3-hydroxy-β-lactam moiety represents an efficient carboxylate mimic,[1] and it is present in several pharmacologically active monobactams such as sulfazecin and related products,[2] and in enzyme inhibitors such as tabtoxin and its analogues.[3] In addition, these compounds with correct absolute configurations serve as precursors to the corresponding α-hydroxy-β-amino acids (isoserines), which are key components of a large number of therapeutically important compounds. As an example, (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanoic acid (norstatine) and (3*R*,4*S*)-4-amino-3-hydroxy-5-methylheptanoic acid (statine) are residues for peptide inhibitors of enzymes, such as renin[4] and HIV-1 protease.[5] Moreover, phenylisoserine analogues are used to synthesize new taxoids.[6]

A stereoselective carbon−carbon bond formation is one of the most important reactions to construct a carbon skeleton in organic synthesis. The Baylis−Hillman reaction is an atom economical carbon−carbon bond-forming reaction leading to multifunctional derivatives.[7] These products have been utilized as building blocks for natural products and biologically active compounds. This reaction in general involves the coupling of the α-position of electron-deficient alkenes with aldehydes in the presence of a suitable catalyst (tertiary amine, tertiary phosphine, or Lewis acid). However, as the typical Baylis−Hillman reaction suffers from a slow reaction rate and limited scope of substrates, most of the recent publications have focused on these aspects.[8] On the other hand, propenylmetal compounds have been of increasing interest in organic synthesis. In particular, diastereoselective addi-

* Corresponding author.
† Universidad Complutense de Madrid.
‡ Instituto de Química Orgánica General.

(1) (a) Unkefer, C. J.; London, R. E.; Durbin, R. D.; Uchytil, T. F.; Langston-Unkefer, P. J. *J. Biol. Chem.* **1987**, *262*, 4993. (b) Meek, T. D.; Villafranca, J. V. *Biochemistry* **1980**, *19*, 5513. (c) Sinden, S. L.; Durbin, R. D. *Nature* **1968**, *219*, 379.

(2) Imada, A.; Kitano, K.; Kintana, K.; Muroi, M.; Asai, M. *Nature* **1981**, *289*, 590.

(3) (a) Dolle, R. E.; Hughes, M. J.; Li, C.-S.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1989**, 1448. (b) Greenlee, W. J.; Springer, J. P.; Patchett, A. A. *J. Med. Chem.* **1989**, *32*, 165. (c) Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Tetrahedron* **1986**, *42*, 3097. (d) Stewart, W. W. *Nature* **1971**, *229*, 174.

(4) Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976.

(5) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305.

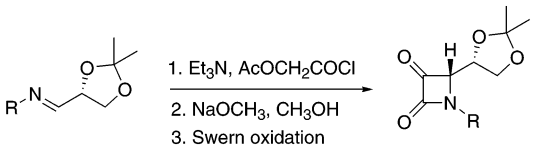
(6) (a) Lucatelli, C.; Viton, F.; Gimbert, Y.; Greene, A. E. *J. Org. Chem.* **2002**, *67*, 9468. (b) Ojima, I.; Wang, T.; Delaloge, F. *Tetrahedron Lett.* **1998**, *39*, 3663. (c) Ojima, I.; Kuduk, S. D.; Pera, P.; Veith, J. M.; Bernacki, R. J. *J. Med. Chem.* **1997**, *40*, 267.

(7) For reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Nyoung, K. J.; Young, L. K. *Curr. Org. Chem.* **2002**, *6*, 627. (c) Langer, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3049. (d) Ciganek, E. *Org. React.* **1997**, *51*, 201. (e) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.

(8) For selected recent references, see: (a) Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, *44*, 4365. (b) Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604. (c) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687. (d) Patra, A.; Batra, S.; Joshi, B. S.; Roy, R.; Kundu, B.; Bhaduri, A. P. *J. Org. Chem.* **2002**, *67*, 5783. (e) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 2412. (f) Rose, P. M.; Clifford, A. A.; Rayner, C. M. *Chem. Commun.* **2002**, 968. (g) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510. (h) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723. (i) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219.

10.1021/jo0354721 CCC: $27.50 
Published on Web 01/13/2004

**SCHEME 1**




**(+)-1a** R = 4-MeOC$_6$H$_4$ (58%)
**(–)-1b** R = 2-propenyl (46%)
**(–)-1c** R = 3-butenyl (88%)
**(+)-1d** R = 4-pentenyl (48%)
**(+)-1e** R = 2-propynyl (56%)
**(–)-1f** R = 3-butynyl (32%)
**(+)-1g** R = 4-pentynyl (47%)
**(–)-1h** R = benzyl (75%)

tion of allylmetallic reagents to chiral aldehydes plays an important role in stereoselective synthesis.[9] In contrast, the analogous reaction involving bromoallylmetals has been scarcely investigated,[10] despite being able to provide useful intermediates, the corresponding bromohomoallylic alcohols.[11] Continuing with our work on the asymmetric synthesis of nitrogenated compounds of biological interest,[12] we now report full details of the Baylis−Hillman reaction of enantiopure azetidine-2,3-diones,[13] which resulted in the corresponding 3-functionalized 3-hydroxy-*β*-lactams. In addition, a study on the metal-mediated bromoallylation of these α-keto lactams in aqueous media with use of 2,3-dibromopropene is also described.

## Results and Discussion

Starting materials, azetidine-2,3-diones **1a**−**h**, were efficiently prepared in optically pure form from aromatic or aliphatic (*R*)-2,3-*O*-isopropylideneglyceraldehyde-derived imines, via Staudinger reaction with acetoxyacetyl chloride in the presence of $Et_3N$, followed by sequential transesterification and Swern oxidation, as we previously reported (Scheme 1).[14]

Surprisingly, so far the synthesis of Baylis−Hillman adducts derived from chiral nonracemic α-amino carbonyl compounds has not been well documented. This situation is mainly due to the fact that under normal conditions, racemization of the carbonyl compound is observed after prolongate exposure times to catalyst,[15] or due to poor diastereoselection.[16] A model reaction of α-keto lactam (+)-**1a** was carried out by sequentially adding 1.5 equiv of methyl vinyl ketone and 1.0 equiv of azetidine-2,3-dione to a dichloromethane solution of $TiCl_4$ (2 equiv) at −78 °C to give the Baylis−Hillman adduct (+)-**2a** in 40% yield. Preliminary results encouraged us to screen other catalysis for the above reaction for better yield. We were pleased to find that use of DABCO under appropriate conditions also gave (+)-**2a** with improved yield. Thus, reaction of azetidine-2,3-dione (+)-**1a** (1 equiv) with methyl vinyl ketone (10 equiv) in the presence of DABCO (1 equiv) in acetonitrile at −20 °C for 1 h gave functionalized allylic alcohol (+)-**2a** in good yield (80%) and complete diastereoselectivity. However, when the reaction was carried out at ambient temperature maintaining the molar ratio of reagents (ketone/DABCO/alkene = 1:1:10), partial epimerization was observed. The volatility of the reactant alkene facilitates its convenient removal even when used in excess. Next, the effect of the amount of catalyst (tertiary amine) on the conversion rate was studied, finding that the process can be significantly accelerated on increasing the amount of DABCO, without detectable racemization. In terms of achieving good yields with a reasonable rate of reaction, 50 mol % of DABCO seemed to be the catalyst amount of choice for this reaction. The effect of altering the reaction solvent (acetonitrile, tetrahydrofuran, diethyl ether, or dichloromethane) was then explored. There is not a significant solvent effect in the observed yield, but enhancing solvent polarity slightly improved the yield. Besides, the reaction proceeded more quickly in polar solvents, with the best yield and reaction rate obtained in acetonitrile, which became the solvent of choice. Other alkenes and α-keto lactams were screened for the Baylis−Hillman reaction. Adducts **2a**−**k** can be prepared as single diastereomers by the DABCO-promoted reaction of various activated vinyl systems with the appropriate azetidine-2,3-dione **1**, and performing the experiment in acetonitrile at −20 °C (Table 1). The reaction with the cyclic ketone 2-cyclopenten-1-one took place after extended reaction time, because of the difficulty of performing the Baylis−Hillman reaction with *β*-substituted olefinic substrates due to steric reasons.

Next, we decided to explore the Lewis acid-mediated reaction of electron-deficient alkynes with azetidine-2,3-diones **1** as an entry to *β*-halo Baylis−Hillman adducts.[17] However, the reaction of α-keto lactam (+)-**1a** with but-3-yn-2-one under a variety of conditions was not very

(9) For recent reviews of allylmetal additions, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Roush, W. R.; Chemler, C. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 11. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10. (d) Thomas, E. J. *Chem. Commun.* **1997**, 411. (e) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(10) (a) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 6879. (b) Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172.

(11) See, for example: Trost, B. M.; Corte, J. R.; Gudiksen, M. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3662.

(12) See, for instance: (a) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Eur. J.* **2003**, *9*, 3415. (b) Alcaide, B.; Almendros, P.; Pardo, C.; Rodríguez-Ranera, C.; Rodríguez-Vicente, A. *J. Org. Chem.* **2003**, *68*, 3106. (c) Alcaide, B.; Almendros, P.; Alonso, J. M.; Redondo, M. C. *J. Org. Chem.* **2003**, *68*, 1426. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719. (e) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *Chem. Commun.* **2002**, 1472. (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 3646.

(13) For the preliminary communication of a part of this work, see: Alcaide, B.; Almendros, P.; Aragoncillo, C. *Tetrahedron Lett.* **1999**, *40*, 7537.

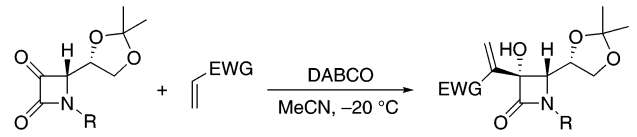
(14) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208. For a review on the chemistry of azetidine-2,3-diones, see: (b) Alcaide, B.; Almendros, P. *Org. Prepr. Proced. Int.* **2001**, *33*, 315.

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

(16) (a) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867. (b) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981. (c) Manickum, T.; Roos, G. *Synth. Commun.* **1991**, *21*, 2269.

(17) This coupling is called the chalcogeno-Baylis−Hillman reaction. For selected references, see: (a) Kinoshita, S.; Kinoshita, H.; Iwamura, T.; Watanabe, S.-i.; Kataoka, T. *Chem. Eur. J.* **2003**, *9*, 1496. (b) Wei, H.-X.; Chen, D.; Xu, X.; Li, G.; Paré, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971. (c) Wei, H.-X.; Gao, J. J.; Li, G.; Paré, P. W. *Tetrahedron Lett.* **2002**, *43*, 5677. (d) Li, G.; Wein, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823. (e) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S.-i. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358.

**TABLE 1. Baylis−Hillman Reaction of Enantiopure Azetidine-2,3-diones 1[a]**

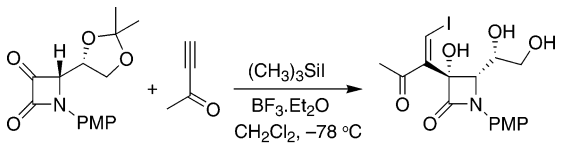



1 2

| substrate | R | EWG | catalyst (mol %) | *t* (h)[b] | product[c] | yield (%)[e] |
|---|---|---|---|---|---|---|
| (+)-**1a** | PMP | COMe | $TiCl_4$ (200)[f] | 21 | (+)-**2a** | 40 |
| (+)-**1a** | PMP | COMe | DABCO (10) | 72 | (+)-**2a** | 80 |
| (+)-**1a** | PMP | COMe | DABCO (20) | 16 | (+)-**2a** | 80 |
| (+)-**1a** | PMP | COMe | DABCO (50) | 2 | (+)-**2a** | 80 |
| (+)-**1a** | PMP | COMe | DABCO (100) | 1 | (+)-**2a** | 80 |
| (+)-**1a** | PMP | CN | DABCO (50) | 24 | (+)-**2b**[d] | 90 |
| (+)-**1a** | PMP | $CO_2Me$ | DABCO (50) | 3 | (−)-**2c** | 87 |
| (+)-**1a** | PMP | $SO_2Ph$ | DABCO (50) | 30 | (+)-**2d** | 69 |
| (−)-**1b** | 2-propenyl | COMe | DABCO (50) | 2 | (−)-**2e** | 69 |
| (−)-**1c** | 3-butenyl | COMe | DABCO (50) | 12 | (+)-**2f** | 47 |
| (+)-**1d** | 4-pentenyl | COMe | DABCO (50) | 12 | (+)-**2g** | 73 |
| (+)-**1e** | 2-propynyl | COMe | DABCO (50) | 5 | (+)-**2h** | 68 |
| (−)-**1f** | 3-butynyl | COMe | DABCO (50) | 2 | (+)-**2i** | 70 |
| (+)-**1g** | 4-pentynyl | COMe | DABCO (50) | 9 | (+)-**2j** | 54 |
| (+)-**1a** | PMP | *g* | DABCO (50) | 168 | (+)-**2k** | 40 |

[a] PMP = 4-$MeOC_6H_4$. [b] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate azetidine-2,3-dione. [c] Analysis of the $^1H$ NMR spectra (300 MHz) of the crude reaction mixtures revealed compounds **2** as the only detected isomer. [d] A 97:3 diastereomeric ratio was determined by integration of well-resolved signals in the $^1H$ NMR spectra (300 MHz) of the crude reaction mixture before purification. Thus, one of the vinylic hydrogens for the major isomer appeared as a singlet at $\delta$ 6.41 ppm, while the corresponding vinylic hydrogen for the minor isomer appeared as a singlet at $\delta$ 6.46 ppm. [e] Yield of pure, isolated product with correct analytical and spectral data. [f] This experiment was carried out in dichloromethane at −78 °C. [g] Compound (+)-**2k** was prepared with 2-cyclopenten-1-one.

**SCHEME 2**




(+)-**1a** (−)-**3** (33%)

successful. In the end, the coupling product (−)-**3** was achieved with concomitant acetonide cleavage as a single *E*-isomer in low yield, in the presence of trimethylsilyl iodide under $BF_3{\cdot}Et_2O$-induced catalysis (Scheme 2). The mechanism for the formation of the *E*-isomer is believed to involve an allenolate species, which is formed by the addition of an iodide ion to the ynone.

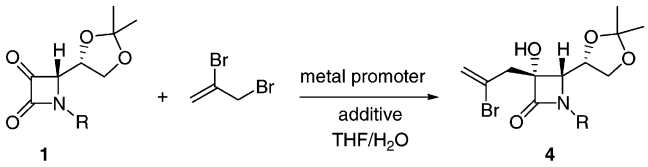
The appealing properties of organometallic reactions in aqueous media include their synthetic advantages (many reactive functional groups, such as hydroxy and carboxylic functions, do not require the protection−deprotection protocol in such reactions, and many water-soluble compounds do not need to be converted into their derivatives and can be reacted directly), its potential as an environmentally benign chemical process (the use of anhydrous flammable solvents can be avoided and the burden of solvent disposal may be reduced), as well as a unique reactivity and selectivity that are not often attained under dry conditions, making them profitable in many cases.[18] On the other hand, two general protocols are available for the carbonyl-allylation with use of organic halides: the stepwise Grignard procedure where the propenylmetal reagent is preformed and then added to the carbonyl compound, or the in situ Barbier procedure where the allylic organometallic species is formed in the presence of the carbonyl. Since indium-mediated allylation of aldehydes has attracted much interest among organic chemists due to its compatibility with many common organic functional groups and stability under aqueous conditions,[19] we decided to introduce the halovinyl moiety on the $\beta$-lactam ring via indium-promoted Barbier-type bromoallylation of azetidine-2,3-diones in an aqueous environment.

Unfortunately, when the reaction of azetidine-2,3-dione (+)-**1a** with 2,3-dibromopropene was conducted in the presence of indium in aqueous tetrahydrofuran, the corresponding bromoallylated product was not formed. Next, using a standard protocol we screened different metal mediators (zinc, tin, bismuth, and cadmium) but no coupling product was observed. Since the incorporation of water-stable additives could improve both yield and conversion rate, we explored further the metal-promoted bromoallylation of azetidine-2,3-dione (+)-**1a** in the presence of different Lewis or protic acids. Disappointingly, indium was again unable to promote the bromoallylation reaction of α-keto lactam (+)-**1a** even in the presence of several additives. However, the addition of ammonium chloride to the aqueous medium containing zinc, 2,3-dibromopropene, and ketone (+)-**1a** was effective, achieving the bromohomoallylic alcohol (+)-**4a** in a low 30% yield after several days of reaction. This encouraging observation prompted us to investigate tin, bismuth, and cadmium as promoters. When bismuth or cadmium were used the reaction did not proceed at all. To our delight, when the above reaction was mediated by tin and was conducted in a saturated aqueous solution of $NH_4Cl$ in THF at room temperature, it gave rise to the optically pure bromohomoallyl alcohol (+)-**4a** as a single diastereoisomer in a reasonable 73% yield after 26 h of reaction. The use of THF as cosolvent was necessary to increase the solubility of both starting material and product. The addition of indium(III) chloride, indium(III) triflate, hafnium(IV) chloride, hydrochloric acid, and hydrobromic acid to the aqueous media of the tin-promoted bromoallylation reaction shortened reaction times while retaining the same facial preference (Table 2). The tin-mediated carbonyl bromoallylation of azetidine-2,3-dione (+)-**1a** in water/tetrahydrofuran in the presence of hydrobromic acid proceeded with concomitant acetonide cleavage, requiring an extra protection step with 2,2-dimethoxypropane to afford the product (+)-**4a**. From these results, we chose the Sn−$Hf_4Cl$-promoted bromoallylation in our study with different substituted azetidine-2,3-diones **1**. Good or excellent yields (74−98%) were obtained in the metal-mediated

(18) For recents reviews on organic reactions in aqueous media, see: (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4095. (c) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299. (d) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (e) Lubineau, A.; Augé, J. *Top. Curr. Chem.* **1999**, *206*, 1. (f) Paquette, L. A. In *Green Chemistry*: *Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: New York, 1998.

(19) *Synthesis* **2003**, issue 5, Special Topic, Carreira, E. M., Ed.

**TABLE 2. Bromoallylation Reaction of Enantiopure Azetidine-2,3-diones 1[a]**




1 4

| substrate | R | metal | additive | *t* (h)[b] | product[c] | yield (%)[d] |
|---|---|---|---|---|---|---|
| (+)-**1a** | PMP | In | $NH_4Cl$ | 72 | | |
| (+)-**1a** | PMP | Zn | $NH_4Cl$ | 96 | (+)-**4a** | 30 |
| (+)-**1a** | PMP | Sn | $NH_4Cl$ | 26 | (+)-**4a** | 73 |
| (+)-**1a** | PMP | Sn | $InCl_3$ | 3 | (+)-**4a** | 64 |
| (+)-**1a** | PMP | Sn | $In(OTf)_3$ | 6 | (+)-**4a** | 75 |
| (+)-**1a** | PMP | Sn | $HfCl_4$ | 2 | (+)-**4a** | 85 |
| (+)-**1a** | PMP | Sn | HCl | 2 | (+)-**4a** | 48 |
| (+)-**1a** | PMP | Sn | HBr | 2 | (+)-**4a** | 50 |
| (−)-**1b** | 2-propenyl | Sn | $HfCl_4$ | 4 | (−)-**4b** | 80 |
| (−)-**1c** | 3-butenyl | Sn | $HfCl_4$ | 4 | (+)-**4c** | 74 |
| (+)-**1e** | 2-propynyl | Sn | $HfCl_4$ | 4 | (−)-**4d** | 92 |
| (−)-**1f** | 3-butynyl | Sn | $HfCl_4$ | 3 | (+)-**4e** | 98 |

[a] PMP = 4-$MeOC_6H_4$. [b] Reaction progress was followed by TLC but could also be noted by the disappearance of the yellow color of the appropriate azetidine-2,3-dione. [c] Analysis of the $^1H$ NMR spectra (300 MHz) of the crude reaction mixtures before purification revealed compounds **4** as the only detected isomer. [d] Yield of pure, isolated product with correct analytical and spectral data. The yield with hydrobromic acid as additive refers to the overall yield after the diol protection step with 2,2-dimethoxypropane.

bromoallylation reaction of different *N*-substituted α-keto-lactams **1** (Table 2). The formation of these bromo-homoallylic alcohols can be easily followed by the variation of coloration of the reaction. Usually, the color of the mixtures containing azetidine-2,3-diones is bright yellow. In the present bromoallylation reaction, the color became pale as the reaction proceeded, and finally turned colorless.

In the dilute acidic medium provided by the presence of hydrochloric or hydrobromic acids, protonation of the carbonyl occurs, facilitating the addition process by the nucleophile. It is presumed that the ionic strength enhancement of the reaction solvent provided by the ammonium chloride accelerated the process.[20] Although the role of the indium- and hafnium-derived additives is not completely understood, it may be explained in terms of Lewis acid, which activates both the carbonyl group as well as the softness of these reagents. A transmetalation of the initially formed allylmetal with indium(III) chloride, indium(III) triflate, or hafnium(IV) chloride as Lewis acids may be involved.[21]

The stereochemistry at the C3-heterosubstituted quaternary center for compounds **2**, **3**, and **4** was assigned by qualitative homonuclear NOE difference spectra. The stereoselective reaction of carbon nucleophiles with ketones instead of aldehydes has been less reported. This

(20) Modification in the diastereomeric ratio or acceleration of the process has been reported on changing the ionic strength of the solvent in the allylation of enantiopure 2-aminoaldehydes: (a) Chappell, M. D.; Halcomb, R. L. *Org. Lett* **2000**, *2*, 2003. In a recent paper on the allylation of mucohalic acids, it has been suggested that the role $NH_4Cl$ plays is perhaps 2-fold: (1) to activate the carbonyl group and (2) to polish the metal surface. See: Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett.* **2003**, *44*, 5579.

(21) For an allyltin−indium trichloride transmetalation, see: Li, X.-R.; Loh, T.-P. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1996.

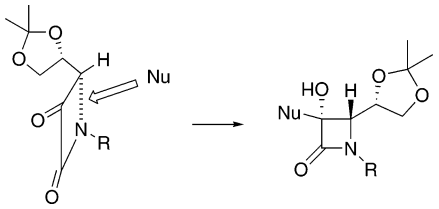



**FIGURE 1.** Model to explain the observed stereochemistry by delivery of the nucleophile to the less hindered face.

is probably due to the smaller difference in steric demand between the two substituents on the carbonyl carbon, which leads to the stereoselection, in ketones than in aldehydes. On azetidine-2,3-diones **1**, the full stereocontrol was achieved due to the presence of a bulky chiral group at C4, which was able to control the stereochemistry of the new C3-substituted C3-hydroxy quaternary center. One face of the carbonyl group is blocked preferentially, thus the nucleophile species is delivered to the less hindered face, and as a consequence the diastereoselectivity was complete in all cases (Figure 1).

## Conclusions

In conclusion, we have achieved an efficient DABCO-promoted Baylis−Hillman reaction of enantiopure azetidine-2,3-diones, which proceeded with full stereocontrol. In addition, a metal-mediated procedure for the bromoallylation reaction of optically pure α-keto lactams in aqueous media has been developed. The simple reaction protocols for achieving the functionalized adducts, in combination with the chemical and biological interest of the 3-substituted 3-hydroxy-*β*-lactam moiety, makes these processes very appealing.

## Experimental Section

**General.** General experimental data and procedures have been previously reported.[12] $^1H$ NMR and $^{13}C$ NMR spectra were recorded at 300 or 75 MHz, respectively. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS ($^1H$, 0.0 ppm), or $CDCl_3$ ($^{13}C$, 76.9 ppm). Specific rotation $[\alpha]_D$ is given in deg per dm at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

**General Procedure for the $TiCl_4$-Promoted Baylis−Hillman Reaction.** A solution of titanium(IV) chloride (2.0 mmol, 1.0 M solution in $CH_2Cl_2$) in dichloromethane (4.3 mL) was added dropwise to a stirred solution of the appropriate azetidine-2,3-dione **1** (1.5 mmol) in dichloromethane (5.0 mL) at −78 °C. After 5 min, a solution of the corresponding activated olefin (2.0 mmol) in dichloromethane (2 mL) was added dropwise, and the mixture was stirred at −78 °C until complete disappearance of the α-keto-*β*-lactam (TLC). Saturated aqueous sodium hydrogen carbonate (5 mL) was added, and the mixture was allowed to warm to room temperature before being partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexane mixtures gave analytically pure compounds **2**.

**General Procedure for the DABCO-Promoted Baylis−Hillman Reaction. Synthesis of Compounds 2a−k.** A solution of the appropriate azetidine-2,3-dione **1** (0.20 mmol) in acetonitrile (2 mL) was added dropwise to a stirred solution of DABCO (11.2 mg, 0.10 mmol) in acetonitrile (2 mL) at −20

°C. After 5 min, the corresponding activated olefin (2.00 mmol) was added at −20 °C and the reaction mixture was placed in a −20 °C freezer until complete disappearance of the ketone (TLC). The mixture was concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **2**. Spectroscopic and analytical data for some representative forms of **2** follow.[22]

**(3*R*,4*S*)-3-(1-Acetylvinyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-2a.** From 220 mg (0.75 mmol) of azetidine-2,3-dione (+)-**1a** and after 1 h at −20 °C was obtained 207 mg (80%) of compound (+)-**2a** as a pale yellow solid after purification by flash chromatography (hexanes/ethyl acetate, 1/1). Mp 155−157 °C (hexanes/ethyl acetate). $[\alpha]_D$ +120.1 (*c* 1.0, $CHCl_3$). $^1$H NMR: $\delta$ 1.34 and 1.43 (s, each 3H), 2.40 (s, 3H), 3.79 (s, 3H), 3.81 (dd, 1H, $J$ = 8.8, 6.6 Hz), 4.09 (d, 1H, $J$ = 7.1 Hz), 4.26 (dd, 1H, $J$ = 8.8, 6.6 Hz), 4.58 (q, 1H, $J$ = 6.6 Hz), 4.96 (br s, 1H), 5.96 (s, 1H), 6.30 (s, 1H), 6.87 and 7.58 (d, each 2H, $J$ = 9.0 Hz). $^{13}$C NMR: $\delta$ 199.3, 166.4, 156.8, 145.0, 130.9, 129.4, 120.4, 114.1, 109.7, 83.9, 76.3, 67.1, 66.4, 55.4, 26.6, 26.5, 25.1. IR (KBr, $cm^{-1}$): $\nu$ 3431, 1738, 1676. MS (CI), *m*/*z*: 362 ($M^+$ + 1, 100), 361 ($M^+$, 5). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.42; N, 3.88. Found: C, 63.01; H, 6.64; N, 4.11.

**Procedure for the Synthesis of the $\beta$-Halo Baylis−Hillman Adduct (−)-3.** Trimethylsilyl iodide (31 $\mu$L, 0.225 mmol) was added to a stirred solution of 4-butyn-2-one (12 $\mu$L, 0.243 mmol) in dichloromethane (1.0 mL) at −78 °C. After 1 h, boron trifluoride diethyl etherate (28 $\mu$L, 0.225 mmol) and a solution of the α-keto-$\beta$-lactam (+)-**1a** (50 mg, 0.172 mmol) in dichloromethane (1.5 mL) were sequentially added dropwise at −78 °C. Saturated aqueous sodium hydrogen carbonate (3 mL) was added, and the mixture was allowed to warm to room temperature, before being partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes (1:1 containing 1% of methanol) gave 28 mg (33%) of analytically pure compound (−)-**3** as a colorless oil.

**(3*R*,4*S*)-3-(1-Acetyliodovinyl)-4-[(*S*)-1,2-dihydroxyethyl]-3-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone, (−)-3.** $[\alpha]_D$ −29.4 (*c* 1.1, $CHCl_3$). $^1$H NMR: $\delta$ 2.05 (s, 3H), 3.78 (d, 1H, $J$ = 9.0 Hz), 3.84 (s, 3H), 4.30 (m, 4H), 4.71 (d, 1H, $J$ = 9.3 Hz), 4.98 (d, 1H, $J$ = 12.2 Hz), 6.95 and 7.29 (d, each 2H, $J$ = 9.0 Hz), 7.76 (d, 1H, $J$ = 12.7 Hz). $^{13}$C NMR: $\delta$ 198.0, 171.2, 159.8, 154.5, 129.6, 118.7, 115.3, 114.8, 100.9, 77.3, 70.1, 68.6, 55.6, 31.0. IR ($CHCl_3$, $cm^{-1}$): $\nu$ 3440, 1738, 1680. MS (CI), *m*/*z*: 447 ($M^+$, 100). Anal. Calcd for $C_{16}H_{18}INO_6$: C, 42.97; H, 4.06; N, 3.13. Found: C, 43.06; H, 4.03; N, 3.10.

**Tin-Promoted Reaction between 2,3-Dibromopropene and Azetidine-2,3-dione (+)-1a in an Aqueous Medium Containing HCl.** 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well-stirred suspension of the α-keto lactam (+)-**1a** (291 mg, 1.0 mmol), tin powder (178 mg, 1.5 mmol), and 35% HCl (0.2 mmol) in THF/$H_2O$ (1:1, 10 mL) at room temperature. After 1.5 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes (1:2) as an eluent gave 198 mg (48%) of compound (+)-**4a**. Anal. Calcd for $C_{18}H_{22}NO_5Br$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.55; H, 5.41; N, 3.38.

**Tin-Promoted Reaction between 2,3-Dibromopropene and Azetidine-2,3-dione (+)-1a in an Aqueous Medium Containing HBr.** 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well-stirred suspension of the α-keto lactam (+)-**1a** (291 mg, 1.0 mmol), tin powder (178 mg, 1.5 mmol), and 48% HBr (0.2 mmol) in THF/$H_2O$ (1:1, 10 mL) at room temperature. After 1.5 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (4 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude diol was dissolved in 2,2-dimethoxypropane (5 mL) and PPTS (25 mg, 0.1 mmol) was added. The reaction was stirred at room temperature for 16 h before being concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes (1:2) as an eluent gave 206 mg (50%) of compound (+)-**4a**. Anal. Calcd for $C_{18}H_{22}NO_5Br$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.56; H, 5.36; N, 3.41.

**Tin-Promoted Reaction between 2,3-Dibromopropene and Azetidine-2,3-dione (+)-1a in an Aqueous Medium Containing $NH_4Cl$.** 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well-stirred suspension of the α-keto lactam (+)-**1a** (291 mg, 1.0 mmol) and tin powder (178 mg, 1.5 mmol) in THF/$NH_4Cl$ (aq satd) (1:5, 10 mL) at room temperature. After 26 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes (1:2) as an eluent gave 301 mg (73%) of compound (+)-**4a**. Anal. Calcd for $C_{18}H_{22}NO_5Br$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.34; H, 5.41; N, 3.42.

**Tin-Promoted Reaction between 2,3-Dibromopropene and Azetidine-2,3-dione (+)-1a in an Aqueous Medium Containing $InCl_3$.** 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well-stirred suspension of the α-keto lactam (+)-**1a** (291 mg, 1.0 mmol), tin powder (178 mg, 1.5 mmol), and indium(III) chloride (44 mg, 0.2 mmol) in THF/$H_2O$ (1:1, 10 mL) at room temperature. After 3 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (4 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes (1:2) as an eluent gave 264 mg (64%) of compound (+)-**4a**. Anal. Calcd for $C_{18}H_{22}NO_5Br$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.34; H, 5.36; N, 3.42.

**Tin-Promoted Reaction between 2,3-Dibromopropene and Azetidine-2,3-dione (+)-1a in an Aqueous Medium Containing $In(OTf)_3$.** 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well-stirred suspension of the α-keto lactam (+)-**1a** (291 mg, 1.0 mmol), tin powder (178 mg, 1.5 mmol), and indium(III) triflate (112 mg, 0.2 mmol) in THF/$H_2O$ (1:1, 10 mL) at room temperature. After 6 h, saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (4 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue with ethyl acetate/hexanes (1:2) as an eluent gave 309 mg (75%) of compound (+)-**4a**. Anal. Calcd for $C_{18}H_{22}NO_5Br$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.35; H, 5.43; N, 3.38.

**Indium-Promoted Reaction between 2,3-Dibromopropene and Azetidine-2,3-diones 1 in an Aqueous Medium Containing $HfCl_4$. General Procedure for the Synthesis of Bromohomoallylic Alcohols 4.** 2,3-Dibromopropene (600 mg, 3 mmol) was added to a well-stirred suspension of the appropriate α-keto lactam **1** (1.0 mmol), tin powder (178 mg, 1.5 mmol), and hafnium(IV) chloride (64 mg, 0.2 mmol) in THF/$H_2O$ (1:1, 10 mL) at room temperature. After dissappearance of the starting material (TLC), saturated aqueous sodium hydrogen carbonate (10 mL) was added at 0 °C, and the mixture was allowed to warm to room temperature, before being extracted with ethyl acetate (3 × 10 mL). The organic

(22) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **4**. Spectroscopic and analytical data for some representative forms of **4** follow.

**(3*R*,4*S*)-3-(2-Bromo-allyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-1-(*p*-methoxyphenyl)-2-azetidinone, (+)-4a.** From 61 mg (0.21 mmol) of azetidine-2,3-dione (+)-**1a** was obtained 73 mg (85%) of compound (+)-**4a** as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ +92.4 (*c* 1.0, $CHCl_3$). $^1$H NMR: $\delta$ 1.37 and 1.44 (s, each 3H), 2.96 and 3.15 (d, each 1H, $J$ = 14.7 Hz), 3.80 (s, 3H), 3.93 (dd, 1H, $J$ = 8.9, 6.5 Hz), 4.26 (dd, 1H, $J$ = 9.0, 6.1 Hz), 4.52 (m, 2H), 5.69 (d, 1H, $J$ = 1.7 Hz), 5.87 (d, 1H, $J$ = 1.9 Hz), 6.87 and 7.53 (d, each 2H, $J$ = 9.0 Hz). $^{13}$C NMR: $\delta$ 167.6, 156.7, 130.3, 125.0, 122.6, 120.1, 114.0, 109.7, 82.8, 76.0, 66.4, 64.8, 55.3, 45.9, 26.2, 25.2. IR ($CHCl_3$, $cm^{-1}$): $\nu$ 3428, 1740. MS (EI), *m*/*z* 413 ($M^+$ + 2, 100), 411 ($M^+$, 98). Anal. Calcd for $C_{18}H_{22}NO_5Br$: C, 52.44; H, 5.38; N, 3.40. Found: C, 52.34; H, 5.34; N, 3.36.

**Acknowledgment.** We would like to thank the DGI-MCYT (Project BQU2003-07793-C02-01) for financial support. C.A. and R.R.-A. thank the CAM and MCYT, respectively, for predoctoral grants.

**Supporting Information Available:** Compound characterization data and experimental procedures for compounds **1a**−**h**, **2b**−**k**, and **4b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035472L