

DIASTEREOSELECTIVE INDIUM-PROMOTED ADDITION OF FUNCTIONALIZED ALLYL BROMIDES TO *N*-BENZYL-2,3-AZETIDINEDIONE UNDER AQUEOUS CONDITIONS[‡]

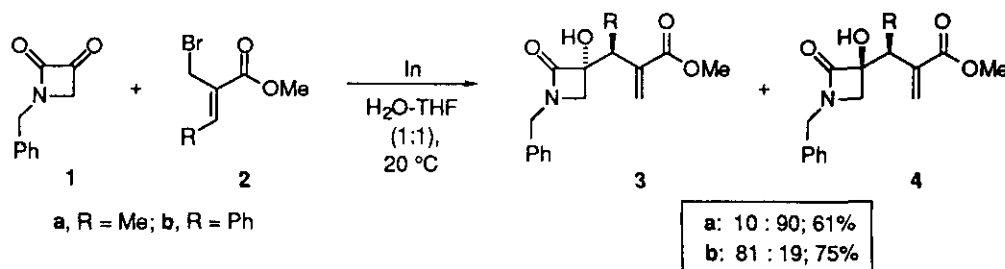
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Abstract - The stereodifferentiation attending the coupling of geometrically stable allylindium reagents to a 2,3-azetidinedione has been assessed and found to operate at a synthetically useful level in most cases.

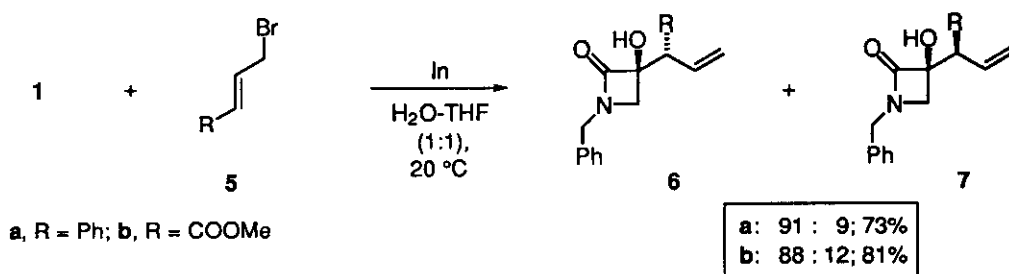
The synthetic potential of organoindium reagents, as generated in the presence of water, is now recognized to be highly utilitarian on several fronts.² Recent developments include an awareness that this class of organometallics is capable of engaging in chelation control,³ is amenable to stereodifferentiation in setting multiple contiguous stereogenic centers,⁴ and is entirely reliable in situations involving long-range asymmetric induction.⁵ The attractive safety and environmental benefits of these transformations have prompted a study in this laboratory of the diastereoselectivity with which the important heterocyclic building block *N*-benzyl-2,3-azetidinedione (**1**)⁶ reacts with variously substituted allylic bromides.⁷ At issue is whether the prochiral keto carbonyl group in **1** can respond stereochemically in a manner paralleling that exhibited by aldehydes.

Stirring a suspension of indium powder with **1** and methyl (*Z*)-2-bromomethyl-2-butenoate (**2a**)⁸ in THF and water (1:1) at 20 °C for 5 h resulted in complete consumption of the reactants and afforded **3a** and **4a** with a significant bias in the *syn* direction. When **2b**⁹ was brought



[‡]This paper is dedicated to Professor Koji Nakanishi as we celebrate his 75th birthday and his very substantive contributions to organic chemistry for half a century.

analogously into reaction, good π -facial discrimination in the opposite direction was observed. The stereochemical assignments in these examples rest on spectral correlations and X-Ray crystallographic analyses of **3b** (Figure 1) and analogues of **4a**. Indeed, the preferred sense of asymmetric induction does not compare directly with that exhibited by α -oxy aldehydes.⁴ Significantly, a change in the geometry of the allylic bromide as in **5a** and **5b** was not met with a corresponding crossover in stereoinduction. In both examples, formation of the *anti* diastereomer proved to be kinetically dominant at a level of approximately 9:1. As before, the relative stereochemistries resident in **6** and **7** were established by means of a crystal structure determination for **6a** (Figure 2). The preference for formation of **6** observed in these examples



cannot seemingly be attributed to significant levels of *E/Z* equilibration in **2** and **5** following indation.⁴ Crotyl bromide and 1,3-dibromopropene have earlier been shown not to be capable of maintaining comparable stereochemical integrity under these conditions.¹⁰ Where the oxygenated bromides (**8a**) and (**8b**)⁵ are concerned, diminished levels of stereoselectivity were seen. The near-equitable distribution of **9b** and **10b** suggests that

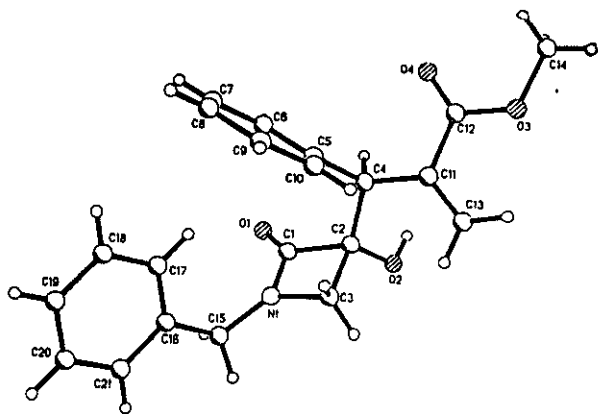


Figure 1. ORTEP diagram of **3b**.

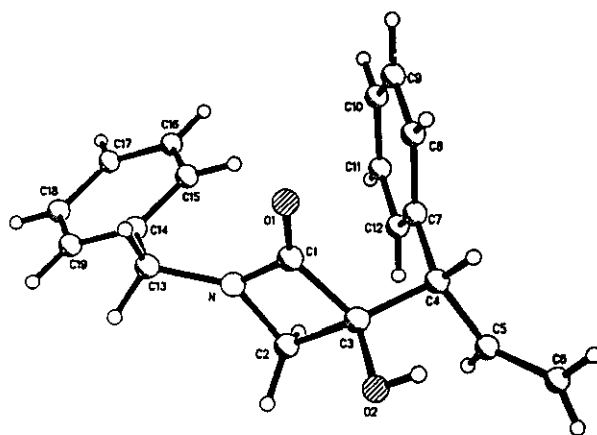
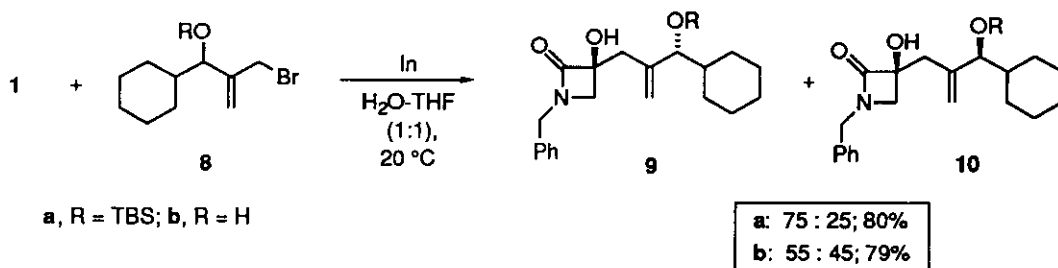
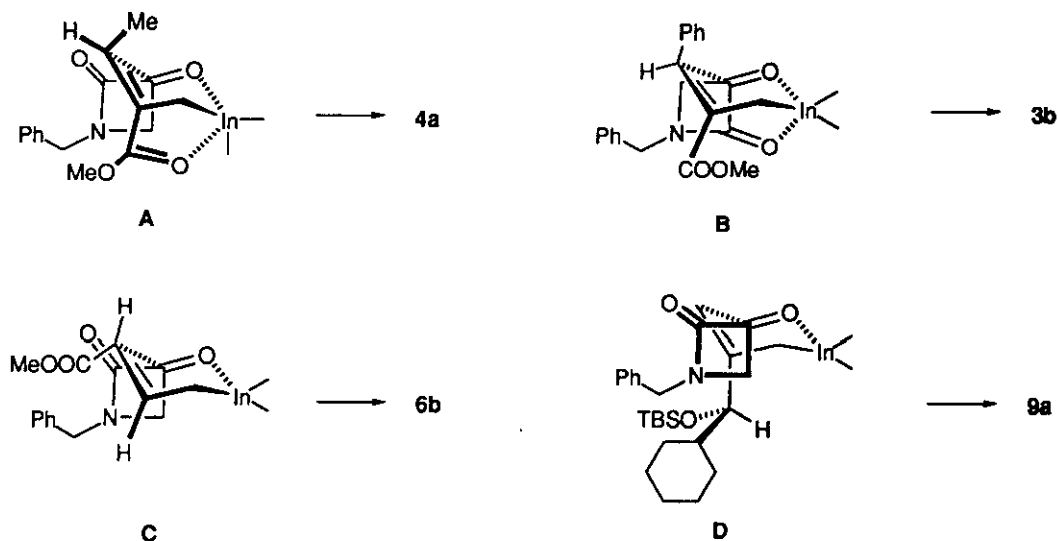


Figure 2. ORTEP diagram of **6a**.

internal chelation to the free hydroxyl group is mismatched with the steric demands that materialize within the normal indium coordination sphere. Diastereomers (**9**) and (**10**) were differentiated by the chemical shifts and coupling patterns of the allylic and vinylic protons as earlier established in related studies.⁵ The downfield position of the =CH₂ singlets in **9a** (δ 5.08 and 5.06 in CDCl₃) relative to those in **9b** (δ 5.02 and 5.00) is illustrative of the trend.



The diastereoselectivities observed in these reactions can be explained in terms of chelated transition states represented by **A-D**. Coordination of the indium atom to the ketonic carbonyl of the heterocycle provides a quite suitable platform for S_N' delivery of the allyl residue. Bromide (**2a**) has available the added option of internal chelation to the ester carbonyl (see **A**), but it is not known with any certainty whether this added binding operates. Certainly, this phenomenon is not a necessary condition for effective 1,2-addition, since **5a** and **5b**, like **2a**, add smoothly and efficiently to **1**. The contrasting *E*-double bond geometry of **5** is clearly conducive to the preferred formation of *anti* product via **C**. Where bromide (**2b**) is concerned, the stabilizing effect of the phenyl substituent enables enhanced electron density to build at the benzylic center, thereby increasing its nucleophilic capability for attacking the azetidinone. The associated heightened reactivity appears to be such that added internal chelation to the



β -lactam carbonyl as in **B** can now be tolerated, with resultant turnover in stereoselectivity as one progresses from **2a** to **2b**.

Finally, if the assumption is made for **8a** and **8b** that the location where chelation operates is sterically congested such that the tertiary hydrogen is projected in the direction shown in **D**, then π -facial discrimination is decided by the relative bulk of the cyclohexyl and OTBS substituents. When the hydroxyl group is unprotected, other sensitive dependencies likely grow in importance.

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REFERENCES AND NOTES

1. The Ohio State University Postdoctoral Fellow, 1996-1997.
2. Reviews: (a) C.-J. Li, *Chem. Rev.*, 1993, **93**, 2023. (b) A. Lubineau, J. Augé, and Y. Queneau, *Synthesis*, 1994, 741. (c) C.-J. Li, *Tetrahedron*, 1996, **52**, 5643. (d) L. A. Paquette In "Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing," ed. by P. Anastas and T. Williamson, Oxford University Press, 1997.
3. (a) L. A. Paquette and T. M. Mitzel, *J. Am. Chem. Soc.*, 1996, **118**, 1931. (b) L. A. Paquette and P. C. Lobben, *J. Am. Chem. Soc.*, 1996, **118**, 1917. (c) L. A. Paquette, T. M. Mitzel, M. B. Isaac, C. F. Crasto, and W. W. Schomer, *J. Org. Chem.*, 1997, **62**, in press.
4. M. B. Isaac and L. A. Paquette, *J. Org. Chem.*, 1997, **62**, in press.
5. (a) R. J. Maguire, J. Mulzer, and J. W. Bats, *J. Org. Chem.*, 1996, **61**, 6939. (b) L. A. Paquette, G. D. Bennett, A. Chhatiwalla, and M. B. Isaac, *J. Org. Chem.*, 1997, **62**, 3370.
6. (a) J. J. Tufariello, D. J. P. Pinto, A. S. Milowsky, and D. V. Reinhardt, *Tetrahedron Lett.*, 1987, **28**, 5481. (b) C. Behrens and L. A. Paquette, *Org. Synth.*, 1997, **75**, in press.
7. The indium-mediated coupling of allyl bromide to selected α -keto β -lactams has recently been reported: M. Jayaraman, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1997, **38**, 709.
8. (a) A. Goldberg and A. S. Dreiding, *Helv. Chim. Acta*, 1976, **59**, 1904. (b) H. M. R. Hoffmann and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 795.
9. (a) R. Buchholz and H. M. R. Hoffmann, *Helv. Chim. Acta*, 1991, **74**, 1213. (b) S. E. Drewes and R. F. A. Hoole, *Synth. Commun.*, 1985, **15**, 1067.
10. L. A. Paquette and T. M. Mitzel, *J. Org. Chem.*, 1996, **61**, 8799.

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