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Catalytic and Asymmetric Vinylogous Mukaiyama Reactions on Aliphatic Ketones: Formal Asymmetric Synthesis of Taurospongin A

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The asymmetric construction of tertiary alcohols is a continuing stimulating task.¹ In particular, catalytic and asymmetric C-C bond reactions on ketones are difficult due to their lower reactivity and lesser steric dissimilarity compared to that of aldehydes.^{2,3} Unbranched aliphatic ketones are particularly challenging substrates where the catalyst needs to discriminate between a methyl and a methylene group. Recently, efficient enantioselective addition of organometallics (mainly zinc alkylation,⁴ zinc arylation,⁵ zinc vinylation,⁶ zinc alkynylation,⁷ tin⁸ and boron⁹ allylations¹⁰) to ketones to form tertiary alcohols has been described. However, catalytic and asymmetric aldol reactions on ketones are rather rare, to the notable exception of the enantioselective chiral Lewis base promoted aldol reactions developed by Denmark11 and copperbisoxazoline catalyzed aldol reactions on α -diketones and pyruvate esters developed by Evans.¹² Shibasaki has also reported one example of an asymmetric aldol reaction to a ketone using a CuF catalyst.13 We previously reported catalytic and asymmetric vinylogous Mukaiyama reactions with aldehydes leading to the formation α,β -unsaturated lactones in good enantioselectivities.¹⁴ These results prompt us to investigate this reaction with ketones (Scheme 1).

Initial studies carried out in the presence of silyl dienolate **1** and acetophenone **2a** in the presence of CuF–(*S*)-tolBinap¹⁵ were quite encouraging, leading to the isolation of lactone **3a** in 71% yield and 80% ee.¹⁶ The "linear" product **4a** could also be detected in the crude mixture, albeit in a relatively small amount (<10% yield and <10% ee). The scope of the reaction has then been surveyed using various aromatic, olefinic, and aliphatic (branched and linear) ketones (Chart 1). Results obtained in these reactions are summarized in Table 1.

Reactions on aromatic ketones (entries 1–4) gave the corresponding lactones 2a-2d in 19–71% yield and 59–81% ee. These reactions are sensitive to electronic effects with lower selectivities/ yields for electron-poor and electron-rich ketones (entries 2–4). In the presence of the *p*-nitroacetophenone 2d, the major product is the linear product 4d, isolated in 39% yield with a very low enantioselectivity (<10% ee). The more impressive results have been obtained with aliphatic ketones (entries 5–8), leading to the lactones in high enantioselectivities (87–93%). In the presence of branched aliphatic ketones, such as isobutylmethyl ketone 2g and tertbutylmethyl ketone 2h (entries 7 and 8), yields are somewhat lower due to steric hindrance, with however no marked difference in enantioselectivity.

As previously observed (in a lesser extent) for α,β -unsaturated aldehydes,¹⁷ limits of this methodology have been found in the presence of α,β -unsaturated ketone **2i** (entry 9), where the lactone has been isolated in a modest 17% yield and 24% ee. In the presence of propiophenone **2j** (entry 10), enantioselectivity was disappointingly low (39% ee). Nevertheless, the enantioselectivity could be increased up to 60% by simply changing tolBinap to Binap. A

Scheme 1





Table 1. Catalyzed Additions of 1 to Ketones 2

		isolated		
entry	ketone	lactone	yield (%) ^a	ee ^b
1	2a	3 a	71	80
2	2b	3b	39	59
3	2c	3c	58	81
4	2d	3d	19	75
5	2e	3e	70	87
6	2f	3f	81	90
7	2g	3g	40	93
8	2h	3h	39	92
9	2i	3i	17	24
10	2j	3j	73	39 (60%) ^c
11	2k	3k	72	88

 a Yields of analytically pure materials. b Determined by chiral HPLC. c In the presence of Binap.

Chart 2



deeper understanding of the reaction mechanism and ligand effects will now be necessary to further improve the scope and results in this methodology. Mechanistic investigation and ligand screening are in progress.

The strategic potential offered by these reactions led us to target taurospongin A (Chart 2), a natural product isolated from the marine sponge *Hippospongia* sp. in 1997, which is a potent inhibitor of DNA polymerase and HIV reverse transcriptase.¹⁸

Two total syntheses of taurospongin A have been reported by Jacobsen¹⁹ and Ley²⁰ as well as a formal synthesis by Ghosh²¹ and a synthesis of the central fragment by Lu.²² In our retrosynthetic



analysis, we anticipated that the tertiary alcohol could be created using a catalytic and asymmetric vinylogous Mukaiyama reaction on ketone 2k (Scheme 2 and Table 1, entry 11).

Indeed, in the presence of (R)-tolBinap, the corresponding lactone 3k was obtained in 72% yield and 88% ee. After hydrogenation of the double bond, the lactone 5 was opened-up in the presence of the Weinreb amine, and the tertiary alcohol was protected as a TES silyl ether in 64% yield (two steps). After reduction to the corresponding aldehyde using Dibal-H, an asymmetric Keck allylation²³ afforded the corresponding homoallylic alcohol 7 in 81% yield (and 91% ee, determined using the Mosher ester method). Compound 7 was then transformed into the corresponding epoxide 9 using a diastereoselective three-step Smith's methodology.²⁴ After Boc protection (81% yield) followed by treatment with IBr and K₂CO₃/MeOH, epoxide 9 was thus obtained in 51% yield in a 9:1 diastereoselectivity. After acetylation, diastereomerically pure epoxide 10 was obtained (after flash chromatography) and selectively hydrogenated²⁵ in the presence of palladium ethylenediamine (Pd/C(en)) to the expected secondary alcohol in 50% yield (92% based on recovered starting material). As previously observed by Jacobsen,¹⁹ this compound is quite unstable, and to prevent acetyl migration, the secondary alcohol was rapidly protected as a TBS silvl ether using TBSOTf (65% yield). The conversion of 11 to taurospongin A (Chart 2) has been demonstrated by Jacobsen. In conclusion, we have completed a formal synthesis of taurospongin

in 12 steps from ketone 2k and with 6% overall yield. This work illustrates for the first time the use of catalytic and asymmetric vinylogous Mukaiyama reactions on aliphatic ketones to create enantiomerically enriched lactones with tertiary alcohols. Further developments and optimization of this methodology will be published in due course.

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

References

- (a) Denissova, I.; Barriault, L. Tetrahedron 2003, 59, 10105. (b) (1)Christoffers, J.; Baro, A. Angew. Chem., Int. Ed. 2003, 42, 1688. (c) Corey, E. J.; Guzman-Perez, A. Angew. Chem., Int. Ed. 1998, 37, 388
- (2) For an excellent highlight on this topic, see: Ramon, D. J.; Yus, M. Angew. Chem., Int. Ed. 2004, 43, 284
- (4) (a) Reamon, D. J.; Yus, M. Tetrahedron 1998, 54, 5651. (b) Ramon, D. J.;
- (4)Yus, M. Tetrahedron Lett. 1998, 39, 1239. (c) Yus, M.; Ramon, D. J.; Prieto, O. Tetrahedron: Asymmetry 2002, 13, 2291. (d) Yus, M.; Ramon, D. J.; Prieto, O. Tetrahedron: Asymmetry 2003, 14, 1103. (e) Garcia, C. LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (f) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544.
- (a) Dosa, P. I.; Fu, G. C. J. Am. Chem. Soc. 1998, 120, 445. (b) Garcia, C.; Walsh, P. J. Org. Lett. 2003, 5, 3641. (c) Prieto, O.; Ramon, D. J.; Yus, M. Tetrahedron: Asymmetry 2003, 14, 1955
- (6) Li, H.; Walsh, P. J. J. Am. Chem. Soc. 2004, 126, 6538
- (a) Cozzi, P. G. Angew. Chem., Int. Ed. **2003**, 42, 2895. (b) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. Angew. Chem., Int. Ed. **2003**, 42, 5057.
- (8) (a) Casolari, S.; D'Addario, D.; Tagliavini, E. Org. Lett. 1999, 1, 1061. (b) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. Angew. Chem., Int. Ed. 2002, 41, 3697. (c) Kim, J. G.; Waltz, K. M.; Garcia, I. F.; Kwiatkowski, D.; Walsh, P. J. J. Am. Chem. Soc. 2004, 126, 12580. (d) Kii, S.; Maruoka, K. Chirality 2003, 15, 68. (e) Cunningham, A.; Woodward, S. Synlett 2002, 43. (f) Cunningham, A.; Mokal-Parekh, V.; Wilson, C.; Woodward, S. Org. Biomol. Chem 2004, 2, 741.
- Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2004, 126, 8910.
- (10) Denmark, S. E.; Fu, J. *Chem. Rev.* 2003, *103*, 2763.
 (11) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* 2002, *124*, 4233.
 (12) Evans, D. A.; Johnson, J. *Acc. Chem. Res.* 2000, *33*, 325.
- (13) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2003, 125, 5644
- (14) (a) Bluet, G.; Campagne, J.-M. Tetrahedron Lett. 1999, 40, 5507. (b) Bluet, G.; Campagne, J.-M. J. Org. Chem. 2001, 66, 4293. (c) Bluet, G.; Bazán-Tejeda, B.; Campagne, J.-M. Org. Lett. 2001, 3, 3807.
 (15) (a) Pagenkopf, B. L.; Kruger, J.; Stojanovic, A.; Carreira, E. M. Angew.
- Chem., Int. Ed. 1998, 37, 3124. (b) Kruger, J.; Carreira, E. M. J. Am. Chem. Soc. 1998, 120, 837.
- (16) Absolute configurations have been attributed by correlation after hydrogenation of lactone **3a** to the known reduced (*R*)-lactone. Date, M.; Tamai, Y.; Hattori, T.; Takayama, H.; Kamikubo, Y.; Miyano, S. J. Chem. Soc., Perkin Trans. 1 **2001**, 645 (see Supporting Information). (17) Unpublished work from this laboratory
- (18) Ishiyama, H.; Ishibashi, M.; Ogawa, A.; Yoshida, S.; Kobayashi, J.-i. J. Org. Chem. 1997, 62, 3831.
- (19) Lebel, H.; Jacobsen, E. N. J. Org. Chem. 1998, 63, 9624.
 (20) (a) Hollowood, C. J.; Ley, S. V.; Yamanoi, S. Chem. Commun. 2002, 1624. (b) Hollowood, C. J.; Yamanoi, S.; Ley, S. V. Org. Biomol. Chem. 2003, 1, 1664.
- (21) Ghosh, A. K.; Lei, H. Tetrahedron: Asymmetry 2003, 14, 629.
- (22) Zheng, G. R.; Lu, W.; Cai, J. C. Chin. Chem. Lett. 2001, 12, 961.
- (23) Keck, G. E.; Krishnamurthy, D. Org. Synth. 1998, 75, 12.
- (24) Duan, J. J. W.; Smith, A. B., III. J. Org. Chem. 1993, 58, 3703.
 (25) Sajiki, H.; Hattori, K.; Hirota, K. Chem. Commun. 1999, 1041.

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