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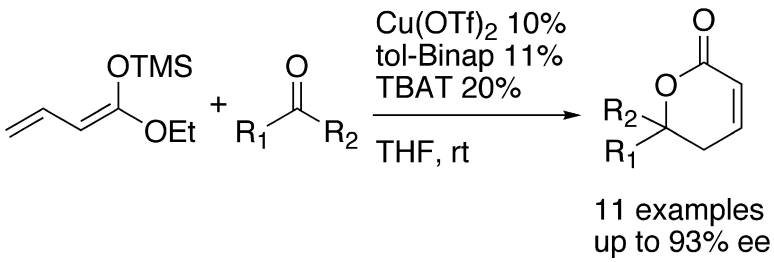

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Catalytic and Asymmetric Vinylogous Mukaiyama Reactions on Aliphatic Ketones: Formal Asymmetric Synthesis of Taurospongin A

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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] tin[8] and boron[9] allylations[10]) 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 Denmark[11] and copper−bisoxazoline 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*)-tolBinap[15] 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 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.

Scheme 1

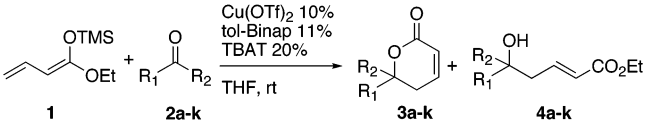


Chart 1

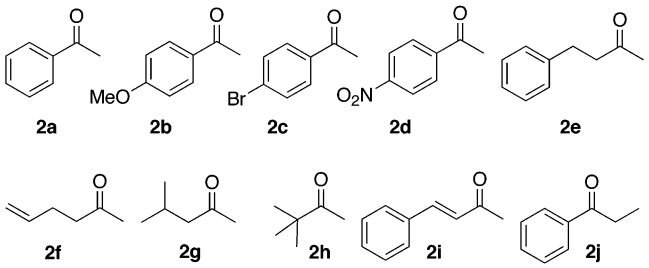
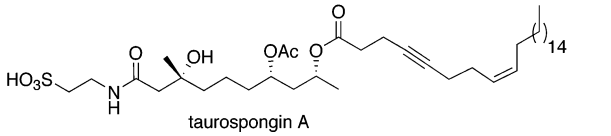


Table 1. Catalyzed Additions of **1** to Ketones **2**

entry	ketone	lactone	isolated yield (%)[a]	ee[b]
1	**2a**	**3a**	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



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 Jacobsen[19] and Ley[20] as well as a formal synthesis by Ghosh[21] and a synthesis of the central fragment by Lu.[22] In our retrosynthetic

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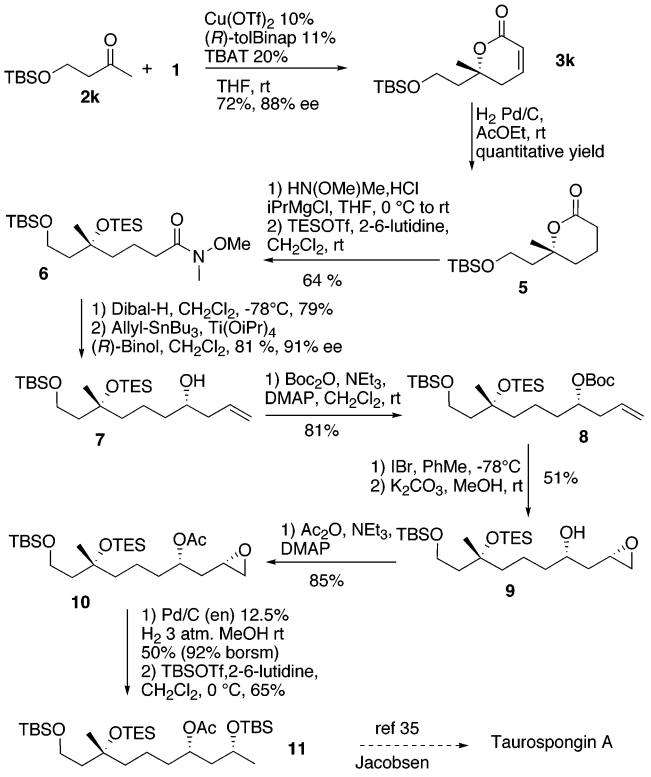
Scheme 2. Formal Enantioselective Synthesis of Taurospongin A



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 allylation[23] 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 K_2CO_3/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 hydrogenated[25] 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 silyl 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.

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