

Catalytic Asymmetric Methallylation of Ketones with an (H₈-BINOLate)Ti-Based Catalyst

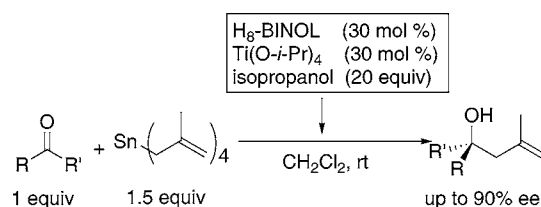
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Received June 9, 2006

ABSTRACT



The first catalytic asymmetric methallylation of ketones is reported. The catalyst, which is generated from titanium tetraisopropoxide, H₈-BINOL, 2-propanol, and tetramethylstannane, reacts with ketones in acetonitrile to afford tertiary homoallylic alcohols in fair to excellent yields (55–99%) and fair to high enantioselectivities (46–90%). Ozonolysis of the resulting products provides access to chiral β -hydroxy ketones, which are not readily prepared from direct asymmetric aldol reaction of acetone with ketones.

Catalytic asymmetric additions of carbon-based nucleophiles to carbonyl groups constitute an important class of C–C bond-forming reactions that are of great value in synthetic organic chemistry.^{1–5} In comparison to aldehydes, additions to ketones have proven to be more challenging due to their reduced reactivity and lower binding affinity to metals.^{1–5} Furthermore, the catalyst must differentiate between the lone pairs of the carbonyl oxygen to achieve high enantioselectivity. This task becomes very difficult when the groups R' and R of the ketone R'RCO are similar in size. Nonetheless, successful catalysts for additions to ketones are beginning to emerge, providing access to tertiary alcohols with high enantioselectivities.^{6–24}

We have been involved in the development of catalytic asymmetric additions of carbon-based nucleophiles to

ketones,^{6–11} including the allylation of ketones. We,^{12,13} among other groups,^{14–20} have recently reported catalytic asymmetric allylation of ketones with high enantioselectivity.

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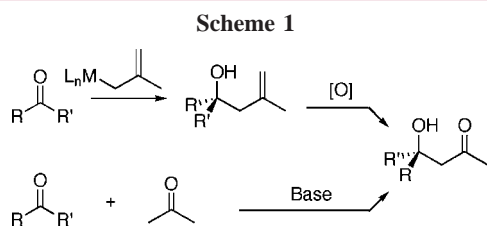
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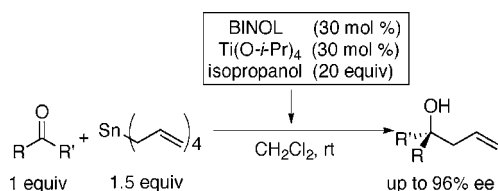
Despite the level of attention focused on the asymmetric allylation of ketones, related methallylation of these substrates remains unexplored. The paucity of methods for the asymmetric methallylation of ketones is surprising given the utility and versatility of the resulting homoallylic alcohols. For example, subsequent oxidative cleavage of the double bond of the methallylation products generates β -hydroxy ketones equivalent to those of the asymmetric cross aldol reaction between ketones and acetone. The direct aldol approach to enantioenriched tertiary aldol products remains challenging (Scheme 1).²⁵



Our success in the catalytic asymmetric allylation of ketones led us to examine additions of related allyl groups. We were surprised to find, however, that our catalyst for the allylation of ketones gave low enantioselectivities in the methallylation reaction. It was thus necessary to develop a new protocol for this important addition reaction. Herein, we report the first catalytic asymmetric methallylation of ketones.

During mechanistic studies of allylation of ketones with the titanium BINOL-based catalyst developed by Tagliavini,²⁶ we developed an improved catalyst for this reaction.¹³ Our catalyst for the asymmetric allylation of ketones employs titanium tetraisopropoxide, BINOL, a 2-propanol additive, and tetraallylstannane as the allyl source (Scheme 2).^{12,13} The

Scheme 2. Catalytic Asymmetric Allylation of Ketones



key to high selectivity in this process is the 2-propanol, although the role it plays in this reaction remains elusive.

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The methallylation of ketones was initially examined with the same catalyst and procedure as those employed in the asymmetric allylation reaction. Thus, titanium tetraisopropoxide, BINOL, 2-propanol, and tetramethylstannane were combined and 2-acetonaphthone was added. Unfortunately, the (BINOLate)/Ti-based catalyst gave only 53% enantioselectivity in the methallylation reaction. This result can be contrasted to the allylation of the same substrate, which provided the product with 96% enantioselectivity. Similar erosion in enantioselectivity was observed when the aldehyde allylation conditions were applied to the methallylation of aldehydes.²⁷

In an effort to improve enantioselectivity of the methallylation, several BINOL derivatives were examined with 2-acetonaphthone (Figure 1, Table 1). The impact of electron-

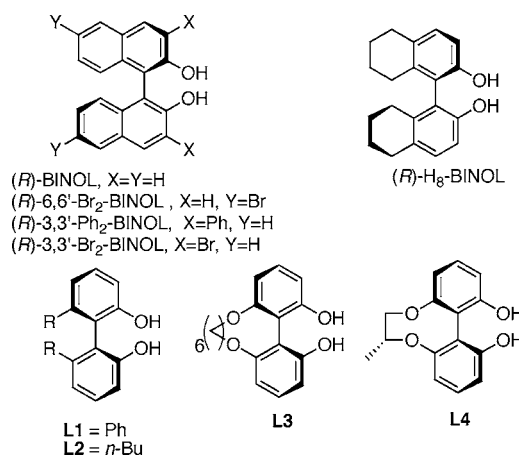
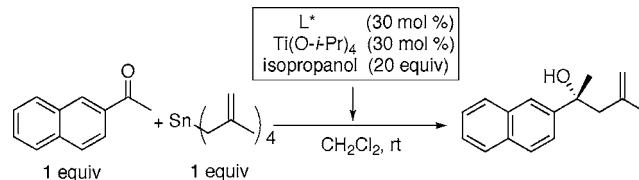


Figure 1. Additional axially chiral ligands tested.

withdrawing bromo groups at the 6,6'-positions of the BINOL ligand was found to be very small. Substitution at

Table 1. Asymmetric Methallylation of 2-Acetonaphthone with Various BINOL Derivatives



entry	L*	ee (%)
1	(R)-BINOL	53
2	(R)-6,6'-Br ₂ -BINOL	55
3	(R)-3,3'-Ph ₂ -BINOL	11
4	(R)-3,3'-Br ₂ -BINOL	4
5	(R)-H ₈ -BINOL	78
6	L1	71
7	L2	74
8	L3	57
9	L4	47

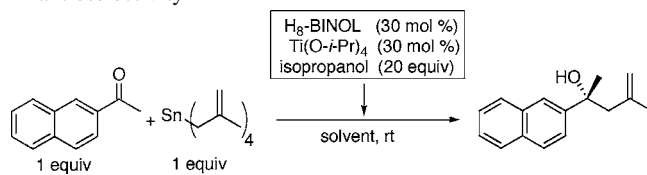
the 3,3'-positions is known to dramatically alter the chiral environment of the substrate binding site. Unfortunately, use of 3,3'-diphenyl-BINOL (3,3'-Ph₂-BINOL) and 3,3'-dibromo-BINOL (3,3'-Br₂-BINOL) led to significant decreases in enantioselectivity (entries 3 and 4).

We next desired to explore the effect of the dihedral angle of BINOL-based ligands on the enantioselectivity of the methallylation reaction. In some cases, hydrogenated derivatives of BINOL, such as H₈-BINOL (5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol, Figure 1) and H₄-BINOL (5,6,7,8-tetrahydro-1,1'-bi-2-naphthol), have been shown to promote asymmetric reactions with better efficiency and enantioselectivity than reactions utilizing BINOL as a chiral ligand. The solid-state structure and solution behavior of (BINOLate)Ti- and (H₈-BINOLate)Ti-based complexes have been studied.^{28–30} Crystallographically characterized (BINOLate)Ti- and (H₈-BINOLate)Ti-based complexes show a difference of about 7° in the dihedral angles between their naphthyl rings. The larger torsional angle of the H₈-BINOLate ligand results in an increase in the O–Ti–O bite angle of just over 2°. The difference in the dihedral angle may account for the enhanced performance of H₈-BINOL over BINOL as a chiral ligand for certain reactions.

Substituting H₈-BINOL for BINOL in our methallylation reaction gave a 25% increase in enantioselectivity (Table 1). In view of these favorable results with H₈-BINOL, we sought to test other axially chiral ligands having varied dihedral angles. In 1996, Harada used ligands **L1–L3** (Figure 1) in an asymmetric Diels–Alder reaction.³¹ Harada speculated that the dihedral angle of **L3** should be similar to that of BINOL, whereas those of **L1** and **L2** would be larger than BINOL. In 2000, Harada reported a streamlined synthesis of this set of ligands in which **L4** was an intermediate.³² Upon testing **L1–L4** in our methallylation reaction, we found that only ligands **L1** and **L2** gave enantioselectivities rivaling that of H₈-BINOL (Table 1).

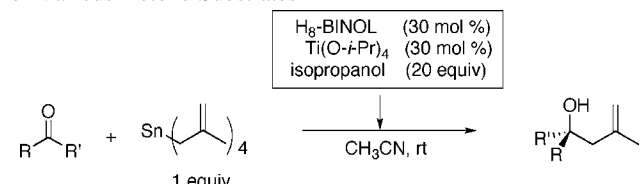
To maximize enantioselectivity, a variety of solvents were examined in the methallylation reactions with H₈-BINOL (Table 2). Unlike the allylation of ketones with our BINOL-based catalyst (Scheme 2), which exhibited virtually no

Table 2. Examination of the Effect of Solvents on Enantioselectivity



entry	solvent	ee (%)
1	CH ₂ Cl ₂	78
2	THF	73
3	Et ₂ O	79
4	1,4-dioxane	67
5	2-propanol	81
6	MeCN	87
7	EtCN	87

Table 3. Yields and Enantioselectivities for the Methallylation of Various Ketone Substrates



entry	substrate	temp	ee (%)	yield (%)
1	R = H	rt 0 °C	75 63	78 83
2	R = OMe	rt	72	99
3	R = CF ₃	rt	67	95
4		rt 0 °C	90 63	95 87
5		rt 0 °C	72 76	93 87
6		rt	84	85
7		rt	46	81
8		rt	80	90
9		rt	77	99
10		rt	49	55
11		rt	46	91

solvent effect, a significant solvent effect was observed in the methallylation reaction. Reactions conducted in acetonitrile and propionitrile resulted in the highest enantioselectivities (entries 6 and 7), and acetonitrile was chosen for further optimization. Titanium(IV) alkoxide complexes with ligands closely related to BINOL have been shown to coordinate acetonitrile in the solid state.³³

While concurrently testing a variety of solvents, the effect of differing amounts of 2-propanol on the enantioselectivity

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was examined. Consistent with our earlier investigations with the asymmetric allylation of ketones (Scheme 2),¹³ 2-propanol proved necessary for high enantioselectivity. Methallylation reactions conducted in the absence of 2-propanol led to racemic product. Enantioselectivities increased upon addition of 2-propanol and reached a plateau at about 20 equiv of 2-propanol (75% ee at 10 equiv of 2-propanol, 78% ee at 20 equiv of 2-propanol, and 79% ee at 30 equiv of 2-propanol in CH₂Cl₂ as solvent). However, there was a slight loss of ee with 2-propanol as solvent (81% ee, Table 2, entry 5).

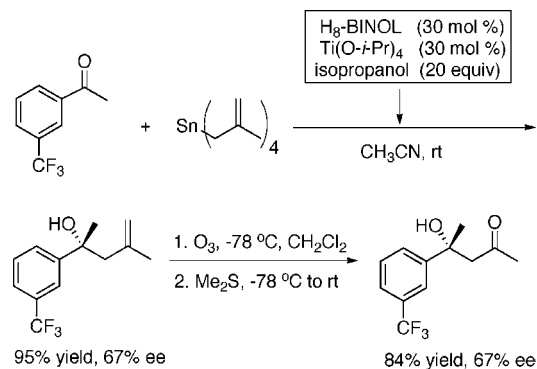
The results of our catalytic asymmetric methallylation of a range of ketones are presented in Table 3. Aryl methyl ketones were generally good substrates for our system with enantioselectivities reaching 90% (entries 1–4). Only marginal electronic influence was observed with substituted acetophenones (entries 1–3). Attempts to improve the enantioselectivity by decreasing the temperature gave mixed results. Acetophenone derivatives showed lower enantioselectivities at 0 °C than at room temperature (entries 1 and 4), although 4-phenyl-but-3-en-2-one gave higher enantioselectivity at 0 °C (entry 5). α,β -Unsaturated ketones gave mixed results under our methallylation conditions (compare entries 5, 8, and 9 vs 10 and 11).

The homoallylic alcohol products that result from the methallylation of ketones can be converted into chiral tertiary β -hydroxy ketones via ozonolysis. These β -hydroxy ketones are known precursors to several natural products and are currently only accessible through kinetic resolution of racemic products.²⁵ Subjecting 3'-(trifluoromethyl) acetophenone to methallylation conditions resulted in the formation of the product with 67% ee and 95% yield (Scheme 3).

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Scheme 3



Subsequent ozonolysis generated the tertiary β -hydroxy ketone with no loss of enantioselectivity.

In conclusion, we have developed an (H₈-BINOLate)Ti-based catalyst for the asymmetric methallylation of ketones. Good to high levels of enantioselectivity were observed across a range of substrates. These enantioenriched tertiary homoallylic alcohols can be converted to a variety of structures such as β -hydroxy ketones. We are currently examining the possibility of significantly reducing the catalyst loading below the 30 mol % currently required to obtain maximum levels of enantioselectivity. Furthermore, we are examining other allyl transfer reagents to circumvent the known toxicity of tin.

Acknowledgment. This work was supported by the NIH (National Institute of General Medical Sciences, GM58101).

Supporting Information Available: Procedures and full characterization of new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL061417Y