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Highly Enantioselective Vinyl Additions of Vinylaluminum to Ketones Catalyzed by a Titanium(IV) Catalyst of (*S*)-BINOL

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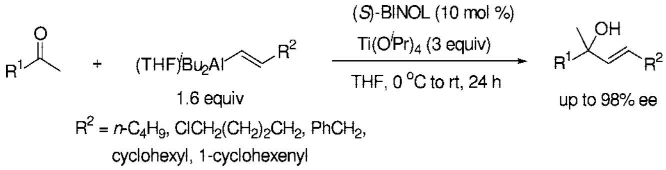
ABSTRACT



We report a novel asymmetric addition of vinyl group to ketones using vinylaluminum reagents catalyzed by in situ prepared Ti(O^{i}Pr)$_4$ complexes of (*S*)-BINOL to afford diversified tertiary allylic alochols. Varieties of aromatic ketones bearing either an electron-donating or an electron-withdrawing substituent on the aromatic ring were examined to afford products in excellent enantioselectivities of up to 98% ee with high yields. A 10-fold scale-up reaction afforded the product in a similar yield with a comparable enantioselectivity. More importantly, additions of a variety of vinyl reagents including functionalized vinyls were demonstrated, affording tertiary allylic alcohols with good to excellent enantioselectivities of up to 96% ee.

One of the major challanges in organic methodology focuses on the enantioselective construction of quaternary carbon centers and especially the synthesis of enantiomerically pure tertiary alcohols due to their importance in the construction of bioactive molecules. The enantioselective addition of organometallic reagents to ketones is one of the most popular and powerful methods to generate such chiral alcohols. Numerous chiral auxiliaries or stiochiometric reagents have been reported regarding their selective addition to aldehydes,[1] resulting in the formation of secondary alcohols, while only a few catalysts promote the addition of organometallic reagents to ketones. Organozinc compounds have been used for asymmetric additions of alkyl compounds to ketones[2] or α-ketoesters[3] and for additions of vinyl,[4] alkynyl,[5] or aryl compounds[6] to ketones. For allyl addition reactions, allyltin compounds have been the commonly used reagents,[7] and in fewer cases, allyl silicon[8] or allyl boron compounds[9] have been used. In addition to the above reagents, organoalumi-

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num compounds had been extensively used as nucleophiles for organic reactions.[10] However, organoaluminum reagents were used in limited cases of asymmetric catalytic alkylation,[11] allylation,[12] allylic alkylation,[13] and alkynylation[14] reactions, achieving products in good to excellent enantioselectivies. Recently, our group demonstrated that the [$AlAr_3$(THF)] reagents are efficient aryl nucleophiles for the additions to aldehydes[15] and ketones[16] catalyzed by titanium catalyst of (*R*)-H_8-BINOL, (*S*)-BINOL (BINOL = 2,2′-dihydroxy-1,1′-binaphthyl), or sulfonamide alcohols. Furthermore, [$AlAr_3$(THF)] is an effective coupling reagent with aryl halides.[17] In a recent paper by us, the asymmetric addition of (2-furyl)aluminum to a variety of ketones was established to furnish tertiary furyl alcohols in excellent enantioselectivities.[18]

The catalytic asymmetric vinylation of ketone has attracted considerable attention among many research groups due to its more challanging transformation, owing to the significant difference in reactivity between aldehydes and ketones. Highly enantioselective catalysts for the vinylation of aldehydes have been developed by Oppolzer,[19] Wipf,[20] and others.[21] Despite the success of asymmetric vinylation of aldehydes, vinyl additions to the inert ketones remain challenging for chemists. To counterbalance the reduced reactivity of ketones, a more reactive vinylating agent is needed. An important discovery in the asymmetric vinylation of ketones was recently reported by Walsh using a protocol in which the reaction couples hydrozirconation/transmetalation to zinc with the catalyst to furnish the chiral tertiary alcohols (Scheme 1).[4]

Given the knowledge about the inertness of ketones that need a reactive vinylating reagent to counterbalance their reduced reactivity, we decided to prepare the organoaluminum compound for the asymmetric addition to ketones because of their high reactivity and the greater lewis acidity of the aluminum center. In a pioneering study, Wilke and Müller[22] demonstrated that dialkylaluminum hydrides add to alkynes via hydroalumination to form vinylaluminum reagents which had been used recently by Hoveyda et al. in asymmetric allylic vinylation reactions.[13] By using the same protocol, we prepared the vinylaluminum reagents and successfully applied asymmetric vinyl addition to ketones catalyzed by in situ prepared Ti(O^iPr)$_4$ complexes of (*S*)-BINOL to afford diversified tertiary allylic alcohols in excellent enantioselectivities of up to 98% ee.

Scheme 1

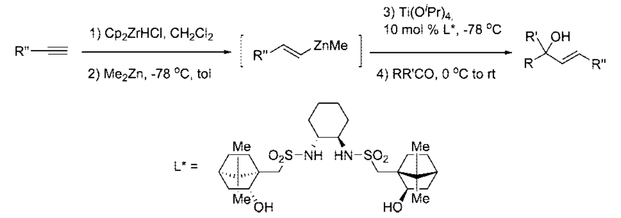
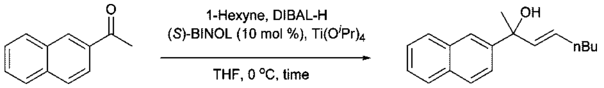


Table 1. Optimizations of Vinyl Additions to 2′-Acetonaphthone Catalyzed by the in Situ Formed (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ Systems[a,b]



entry	Al reagent (equiv)	Ti(O^iPr)$_4$ (equiv)	time (h)	yield[c] (%)	ee[d] (%)
1	1.5	1.5	16	71	79
2	1.5	2.25	16	75	87
3	1.5	3	16	80	89
4	1.5	3.75	16	72	88
5[e]	1.5	3	24	90	89
6[e]	1.6	3	24	94	92
7[e]	1.7	3	24	89	91
8[e]	1.8	3	24	88	91
9[e,f]	1.6	3	24	85	86
10[e,g]	1.6	3	24	80	79
11[e,h]	1.6	3	24	90	87

[a] 2′-Acetonaphthone/(*S*)-BINOL = 0.5/0.05 mmol; THF, 3 mL. [b] Equivalents of Al reagent and Ti(O^iPr)$_4$ were relative to 2′-acetonaphthone. [c] Yields are based on ^1H NMR spectra. [d] ee values were determined by HPLC analysis. [e] Reaction run at 0 °C to rt. [f] 5 mol % of (*S*)-BINOL. [g] 2 mol % of (*S*)-BINOL. [h] 15 mol % of (*S*)-BINOL.

We initiated our investigation into the vinylation of ketones using 2′-acetonaphthone and 1-hexyne for optimization of reaction conditions with the catalytic system of (*S*)-BINOL and Ti(O^iPr)$_4$; the results are summarized in Table 1. In the

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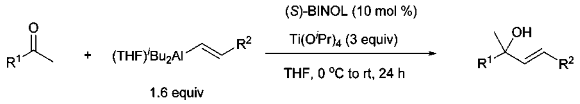
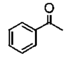
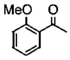
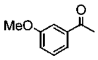
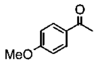
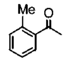
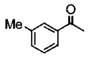
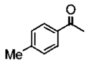
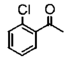
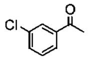
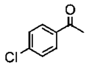
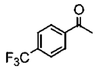
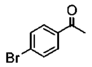
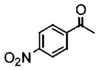
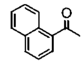
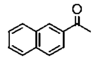
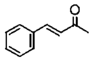
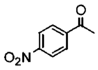
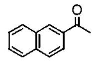
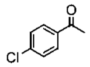
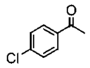
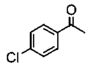
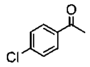
presence of 10 mol % of BINOL and 1.5 molar equiv of both Ti(O^{i}Pr)$_4$ and the aluminum reagent in THF, the reaction was carried out at 0 °C for 16 h and furnished the tertiary alcohol in a 71% yield with a 79% ee (entry 1). Increasing Ti(O^{i}Pr)$_4$ to 2.25 and 3 equiv, enantioselectivities increased to 87% and 89% ee (entries 2 and 3), respectively. A further increase in Ti(O^{i}Pr)$_4$ to 3.75 equiv gave the product in a decreasing yield of 72% with the enantioselectivity decreased to 88% ee (entry 4). When the reaction was conducted at 0 °C to room temperature for 24 h with 3.0 equiv of Ti(O^{i}Pr)$_4$, the highest 90% yield was obtained with a 89% ee (entry 5). From entries 6−11, reactions were conducted at optimized temperatures from 0 °C to room temperature. Increasing the aluminum reagent to 1.6 equiv increased the yield to 94% and the enantioselectivity to 92% ee (entry 6). Further increases in the aluminum reagent to 1.7 and 1.8 equiv gave the product in decreasing yields of 89% and 88% with comparable enantioselectivities of 91% ee (entries 7 and 8). Reducing (*S*)-BINOL to 5 and 2 mol % afforded the product in 85 and 80% yields with enantioselectivities of 86 and 79% ee (entries 9 and 10), respectively. Increasing (*S*)-BINOL to 15 mol % reduced the enantioselectivity to 87% ee with a 90% yield (entry 11). This study shows that the optimized catalytic conditions required an excess of 3 equiv Ti(O^{i}Pr)$_4$ relative to 0.1 equiv (*S*)-BINOL ligand. The requirement of higher equivalents of Ti(O^{i}Pr)$_4$ is a general feature for titanium-catalyzed asymmetric additions to organic carbonyls. It had been demonstrated that higher equivalents of Ti(O^{i}Pr)$_4$ would increase the amount of active catalytic species to ensure better enantioselectivities of products.[23]

Generalities of the catalytic system were examined with various aromatic ketones, and results are summarized in Table 2. Vinyl additions to aromatic ketones bearing electron-withdrawing or electron-donating substituents afforded tertiary allylic alcohols in good to excellent enantioselectivities from 86% to 98% ee (entries 1−15) except 3′-methoxyacetophenone in 81% ee (entry 3), suggesting the excellence of the catalytic system. Differences in enantioselectivities in terms of substituent types on the aromatic group were observed to be around 10% ee. For example, additions to ortho-substituted acetophenones such as 2′-methoxyacetophenone (entry 2), 2′-methylacetophenone (entry 5), or 2′-chloroacetophenone (entry 8) afforded corresponding allylic alcohols with enantioselectivities of 86, 98, and 90%, respectively. Additions to meta-substituted acetophenones gave tertiary allylic alcohols with enantioselectivities ranging from 81 to 93% ee (entries 3, 6, and 9), and additions to para-substituted acetophenones furnished products with enantioselectivities from 87 to 97% ee (entries 4, 7, and 10−13). Effects of substituent positions were also studied, and it was found that differences in enantioselectivities are 6% from 81 to 87% ee for additions to methoxyacetophenones (entries 2−4), 6% ee for additions to methylacetophenones (98, 93, and 92% ee, entries 5−7), and 7% ee for additions to chloroacetophenones (90, 91, and 97% ee, entries 8−10). For acetonaphthones, the addition to 1′-acetonaph-

Table 2. Asymmetric Vinyl Addition to Ketones Catalyzed by 10 mol % of (*S*)-BINOL/3.0 equiv of Ti(O^{i}Pr)$_4$ Catalytic System[a]



entry	substrate	R^2	yield[b] (%)	ee[c] (%)
1		*n*-C$_4$H$_9$	91	92
2		*n*-C$_4$H$_9$	87	86
3		*n*-C$_4$H$_9$	80	81
4		*n*-C$_4$H$_9$	93	87
5		*n*-C$_4$H$_9$	87	98
6		*n*-C$_4$H$_9$	87	93
7		*n*-C$_4$H$_9$	92	92
8		*n*-C$_4$H$_9$	85	90
9		*n*-C$_4$H$_9$	88	91
10		*n*-C$_4$H$_9$	90	97
11		*n*-C$_4$H$_9$	94	96
12		*n*-C$_4$H$_9$	89	91
13		*n*-C$_4$H$_9$	92	95
14		*n*-C$_4$H$_9$	82	87
15		*n*-C$_4$H$_9$	92	92
16		*n*-C$_4$H$_9$	92	82
17		ClCH$_2$(CH$_2$)$_2$CH$_2$	93	96
18		ClCH$_2$(CH$_2$)$_2$CH$_2$	90	86
19		ClCH$_2$(CH$_2$)$_2$CH$_2$	91	86
20		PhCH$_2$	94	95
21		cyclohexyl	90	85
22		1-cyclohexenyl	89	88

[a] 2′-Acetonaphthone/(*S*)-BINOL = 0.5/0.05 mmol; THF, 3 mL. [b] Isolated yields of products. [c] ee values were determined by HPLC analysis using chiral columns from Daicel.

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thone gave the corresponding product in a lower 82% yield with a lower enantioselectivity of 87% ee (entry 14) compared to a 92% yield with a 92% ee for the product obtained from the addition to 2′-acetonaphthone (entry 15). We also demonstrated an example of 1-hexenyl addition to an α,*β*-unsaturated ketone, affording the product in an excellent 92% yield but with a lower 82% ee (entry 16).

Further comparability of the catalytic system was examined with a functionalized hexyne, i.e., 6-chloro-1-hexyne, and the resulting tertiary alcohols were produced in excellent yields with good to excellent enantioselectivities from 86 to 96% ee (entries 17−19). Additions of vinylaluminum reagents derived from 3-phenyl-1-propyne, cyclohexylacetylene, or 1-ethynylcyclohexene were also conducted. The 3-phenyl-1-propenyl addition to 4′-chloroacetophenone furnished the allylic alcohol in an excellent 94% yield with an excellent 95% ee (entry 20). Though the addition of cyclohexylvinyl or cyclohexenylvinyl to 4′-chloroacetophenone produced corresponding allylic alcohols in excellent 90 and 89% yields, products of somewhat lower enantioselectivities of 85 and 88% ee were observed (entries 21 and 22).

In this study, an asymmetric addition reaction employing 5 mmol of substrate of 4′-chloroacetophenone, which is a 10-fold scale relative to the reactions presented in Table 2, was carried out. The scale-up reaction produced the desired product in a comparable 91% yield with a 95% ee relative to the 90% yield and the 97% ee obtained from the reaction of 0.5 mmol substrate (Table 2, entry 10).

In summary, asymmetric additions of the vinyl to ketones catalyzed by the titanium catalyst of (*S*)-BINOL using a strategy of the in situ formed vinylaluminum reagents from the reaction of DIBAL-H and alkynes are reported. Varieties of aromatic ketones and an α,*β*-unsaturated ketone were examined to afford products in excellent enantioselectivities of up to 98% ee with high yields. More importantly, additions of vinylaluminum reagents derived from a variety of alkynes also produced allylic alcohols in excellent enatioselectivities of up to 96% ee. The scale-up reactions was demonstrated to produce the product in the similar yield and enantioselectivity.

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Supporting Information Available: Full experimental and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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