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## A Simple, Reliable, Catalytic Asymmetric Allylation of Ketones**

Karen M. Waltz, Jason Gavenonis, and Patrick J. Walsh*

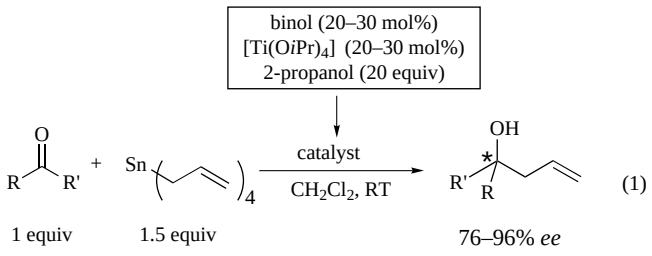
The asymmetric allylation of carbonyl groups to furnish homoallylic alcohols is a fundamental transformation in synthetic organic chemistry.[1–3] Several catalysts will promote the asymmetric allylation of aldehydes to give secondary homoallylic alcohols with excellent enantioselectivities.[4–15] The catalytic asymmetric allylation of ketones, however, has proven to be a more challenging transformation owing to the significant difference in reactivity between aldehydes and ketones. Thus, with one exception,[16] catalysts that promote the enantioselective allylation of aldehydes fail to catalyze the analogous reaction with ketones. In general, the enantioselective formation of quaternary stereocenters, as generated in the asymmetric allylation of ketones, is of considerable difficulty.[17,18]

To compensate for the reduced reactivity of ketones, a more reactive allylating agent was needed. Baba and co-workers found that tetraallylstannane added to ketones in the presence of methanol and 200 mol% binol to give the homoallylic alcohol in up to 60% *ee*.[19] An important discovery in the asymmetric allylation of ketones was recently reported by Casolari, D'Addario, and Tagliavini.[20] Their catalyst preparation involved the reaction of $[Cl_2Ti(OiPr)_2]$ and binol with allyltributylstannane. After mixing for one hour, tetraallylstannane and the substrate ketone were added. They observed the formation of the ketone allylation product with up to 65% *ee* at 20 mol% binol (80% *ee* with 40 mol% binol).

Based on the results of the Italian team,[20] Maruoka and co-workers[16] recently reported a system for the catalytic asymmetric allylation of aldehydes with a catalyst that is based on titanium, binol, and an achiral diamine spacer (2:2:1 ratio). This catalyst (60 mol% titanium and binol) was examined in the asymmetric allylation of only two ketones, acetophenone and methyl 2-naphthyl ketone, which underwent allylation with 90 and 92% *ee*, respectively.[16] More recently, Cunningham and Woodward[21] demonstrated that monothiobinaphthol will promote the allylation of acetophenone derivatives with a mixture of $[RSn(allyl)_3]/[Sn(allyl)_4]$ (R = Et, Bu) with *ee* values as high as 92% (51% yield).

The ketone allylation reaction of Casolari, D′Addario, and Tagliavini[20] attracted our attention because of our interest in the mechanisms of titanium-based asymmetric Lewis acid catalysts[22–24] and the need for a more versatile and enantioselective catalyst for this important process. While investigating the catalyst structure of the Tagliavini system, we made several key observations that allowed us to develop the most general and enantioselective catalyst for the asymmetric allylation of ketones to date.

We repeated the catalyst preparation of Tagliavini[20] described above in $CDCl_3$ to probe the nature of the (binolate)Ti species by NMR spectroscopy. Like Tagliavini and co-workers,[20] we observed the production of tributyltin chloride. However, we were surprised to find that the major titanium-containing product was $[(binolate)Ti(OiPr)_2]$, which is dimeric in solution and trimeric in the solid state.[25,26] We prepared this compound on a gram scale simply by mixing titanium tetraisopropoxide and binol followed by removal of the solvent and liberated 2-propanol.[26] Using the isolated $[(binolate)Ti(OiPr)_2]$, we found that the enantioselectivities in the allylation reaction were about the same as those reported by Tagliavini and co-workers.[20] An important breakthrough was made when the catalyst was prepared directly from titanium tetraisopropoxide and binol (1:1, 20 or 30 mol%) *without removal of the liberated 2-propanol*. When we employed this catalyst preparation, the *ee* of the product formed from 3-methylacetophenone rose from 51% to 73%. These results suggested that the liberated 2-propanol had a beneficial impact on the enantioselectivity of the catalyst. We therefore prepared the catalyst with additional 2-propanol and observed a significant increase in the catalyst enantioselectivity [Eq. (1)].



(1)

The advantageous effect of the 2-propanol on the enantioselectivity of the catalyst reached a maximum when 20 equiv

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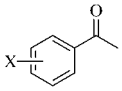
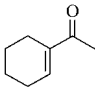
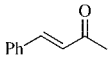
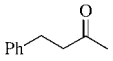
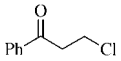
(relative to the ketone) of 2-propanol were added. A further increase in 2-propanol to 100 equiv resulted in a slight decrease in the enantioselectivity of the tertiary homoallylic alcohol. Using this combination of binol, titanium tetraisopropoxide, 2-propanol, and tetraallylstannane [Eq. (1)], the *ee* value of 3-methylacetophenone rose to 96%! The results of our catalytic asymmetric allylation of ketones are displayed in Table 1. Only a marginal electronic influence with substituted

Table 1. Asymmetric allylation of ketones [Eq. (1)].

| Entry | Ketone | [mol%] | Yield [%][b] | *ee* [%][a] |
|---|---|---|---|---|
| |  | | | |
| 1 | X = 3-Me | 20 | 82 | 96 |
| 2 | X = 4-OMe | 30 | 99 | 89 |
| 3 | X = 3-$CF_3$ | 30 | 93 | 92 |
| 4 | X = 2-Me | 30 | 77[c] | 84 |
| 5 |  | 30 | 96 | 95 |
| 6 |  | 30 | 88 | 90 |
| 7 |  | 30 | 99 | 90 |
| 8 |  | 30 | 96 | 80 |
| 9 |  | 30 | 99 | 76 |
| 10 |  | 30 | 67 | 84 |

[a] Enantiomeric excesses determined by GC or HPLC (see Supporting Information). [b] Yields of isolated products. [c] 7% recovered substrate after 4.5 d.

acetophenones was observed, as 4-methoxyacetophenone and 3-trifluoromethylacetophenone formed products with 89 and 92% *ee*, respectively (Table 1, entries 2 and 3). Substitution of the acetophenone with a 2-methyl group resulted in a lower *ee* value (84%) and turnover frequency, with the allylation product formed in 77% yield after 4.5 days (Table 1, entry 4).

The ketone $\alpha$-tetralone often forms products of aldol condensation/dehydration in the presence of basic reagents.[27] However, under the conditions of the allylation reaction [Eq. (1)], this substrate gave 95% *ee* with 96% yield (Table 1, entry 5).

Allylation of conjugated enones gave exclusive 1,2-allylation in high yield and with high enantioselectivity (Table 1, entries 6 and 7). Interestingly, while *trans*-4-phenyl-3-buten-2-one underwent allylation with 90% *ee*, the saturated derivative reacted to give the homoallylic alcohol with 80% *ee*. Nonetheless, 80% *ee* in entry 8 is impressive, given that the catalyst must differentiate between a methyl and an alkyl group.

The functionalized 3-chloropropiophenone exhibited moderate enantioselectivity (76%). The reaction of the heteroaromatic substrate acetylfuran under the conditions described in [Eq. (1)] furnished the homoallylic alcohol with 84% *ee*. As a cautionary note, care must be used during work-up and chromatography to avoid racemization of tertiary alcohols.

Although we have not yet studied the catalyst structure or the mechanism of the allylation reaction in detail, preliminary experiments do provide meaningful information about the catalyst. When reactions were performed with binol of varying enantiopurity, a strong positive nonlinear effect was observed (see Supporting Information). Several possible catalyst structures and mechanisms could explain the nonlinear effects, including the formation of hetero- and homochiral $(binolate)_2Ti$ species or $[\{(binolate)TiX_2\}_2]$ dimers (X = O*i*Pr or $X_2$ = O). In such cases, the dimers could dissociate to reactive monomers, or the dimers themselves could be the active catalysts.[28] Interestingly, reaction of 3-methylacetophenone under conditions in Eq. (1) with a 1:1 or 2:1 ratio of binol to $[Ti(O\mathit{i}Pr)_4]$ gave products with the same *ee* values.

Like other carbonyl allylations with tin reagents, we have found that our allylation procedure [Eq. (1)] exhibited an induction period. Reactions run with binol (20 mol%) and $[Ti(O\mathit{i}Pr)_4]$ (20 mol%), with no added 2-propanol, were complete after 2 h (73% *ee*). Our procedure with 2-propanol [Eq. (1)] resulted in increased initiation times (3% conversion at 2 h) with completion in under 6 h (96% *ee*). Premixing the binol (20 mol%), $[Ti(O\mathit{i}Pr)_4]$, tetraallylstannane, and 2-propanol for 22 h followed by addition of 3-methylacetophenone virtually eliminated the induction period (95% conversion in 1 h, 96% *ee*).

While the addition of alcohol is important in obtaining high enantioselectivity, the nature of the alcohol additive did not affect the *ee* value, as identical enantioselectivities were obtained from catalysts prepared from 2-propanol, cyclopentanol, cyclohexanol, and cycloheptanol. The use of as little as 0.25 equivalents of tetraallylstannane resulted in greater than 92% conversion and no decrease in enantioselectivity, indicating that each tetraallyltin complex can transfer at least three of its allyl groups to the substrate. These results suggest that the mechanism does not involve initial protonation of a tin allyl to generate a tin alkoxide that is the active allylating reagent. Furthermore, we have examined several sources of tetraallylstannane (homemade and from four vendors) and observed no differences in the *ee* values of the products.

In summary, we have developed a very practical enantioselective catalyst for the allylation of ketones that provides tertiary homoallylic alcohols. Homoallylic alcohols are versatile materials in organic synthesis and can be converted into $\beta$-hydroxy ketones, $\beta$-hydroxy aldehydes, $\gamma$-lactones (by hydroformylation), and can be epoxidized diastereoselectively.[29] Our catalyst is prepared by simply mixing commercially available reagents at room temperature under nitrogen. This ketone allylation procedure is more reliable and experimentally simpler than the allylation of aldehydes.[10,13,30] We are currently applying our catalyst system to other Lewis acid catalyzed processes.

### *Experimental Section*

General procedure: $[Ti(O\mathit{i}Pr)_4]$ (98 μL, 0.332 mmol, 20 mol% or 147 μL, 0.498 mmol, 30 mol%) was added to a solution of (*R*)- or (*S*)-binol (95 mg, 0.332 mmol, 20 mol% or 142.5 mg, 0.498 mmol, 30 mol%) in dichloro-

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methane (4.0 mL), and this orange solution was stirred for several minutes at room temperature. 2-Propanol (2.54 mL, 33.2 mmol) was added to this solution, followed by the ketone substrate (1.66 mmol) and tetraallylstannane (0.6 mL, 2.49 mmol). After an initial induction period, the color of the solution lightened from orange to yellow, indicating the commencement of the reaction. After stirring for 20 h, the reaction was quenched with saturated ammonium chloride and extracted with dichloromethane. After removal of the solvent under reduced pressure, the resulting oily orange residue was extracted with hexanes, dried over magnesium sulfate, filtered through celite, and purified by chromatography on silica, starting with hexanes to elute the majority of the tin species, and then with diethyl ether/hexanes (10–20 %) to obtain the alcohol product (see Table 1 for yields and *ee* values). It is important to use ammonium chloride to quench the reactions instead of dilute hydrochloric acid, which resulted in partial racemization of the product. It is also best to run the column quickly, as some of the alcohol products racemize slightly when in contact with the silica for extended periods of time.

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