Published in final edited form as:

Angew Chem Int Ed Engl. 2016 August 8; 55(33): 9610–9614. doi:10.1002/anie.201603894.

Practical and Broadly Applicable Catalytic Enantioselective Additions of Allyl–B(pin) Compounds to Ketones and α -Ketoesters

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Abstract

Broadly applicable methods for efficient and catalytic additions of easy-to-handle allyl–B(pin) (pin = pinacolato) compounds to ketones and acyclic α -ketoesters have been developed. Accordingly, a large array of tertiary alcohols can be obtained in up to >98% yield and 99:1 enantiomeric ratio. At the heart of this development is rational alteration of the structures of small-molecule aminophenol-based catalysts. Notably, with ketones, increasing the size of a catalyst moiety (tBu to SiPh₃) results in much higher enantioselectivity. With α -ketoesters, on the other hand, not only does the opposite hold true, as Me-substitution leads to substantially higher enantioselectivity, the sense of induction is reversed as well.

Keywords

α -ketoesters; catalysis; enantioselective synthesis; homoallylic alcohols; ketones

Tertiary homoallylic alcohols of high enantiomeric purity hold considerable value in chemical synthesis.^[1] As expertly demonstrated by Shibasaki and Kanai,^[2] Yamamoto,^[3] Sigman^[4] and Schaus,^[5] a direct way to access these entities is by catalytic allyl addition to

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Dedicated to Professor Stuart L. Schreiber for his 60th Birthday

ketones; enantioselectivities are exceptional in these and several subsequent disclosures.^[6] Despite such groundbreaking advances, an approach that offers the following key attributes simultaneously remains lacking: a catalyst that does not contain a toxic metal and can be prepared inexpensively and easily, a readily available set of reagents that are air and moisture stable, and broad substrate scope.

Our interest in this problem originated from an earlier discovery that easily modifiable aminophenol compounds (e.g., **1a**, Scheme 1a) may be used to catalyze efficient enantioselective addition of allyl–B(pin) (pin = pinacolato) to isatins.^[7] High selectivity was found to arise from structural organization caused by H-bonding between the amide carbonyl and the catalyst's ammonium group;^[8] this is despite the electronic repulsion between the non-bonding aryloxy and carbonyl electrons (**I**; Scheme 1a). Additions to acetophenone (Scheme 1b) are therefore substantially less selective [**2a** in 68:32 enantiomeric ratio (e.r.)] because there is little energy difference between **II** and the alternative complex with a pseudoaxial phenyl group. The enhanced selectivity with the naphthyl ketone (**2b**, 93.5:6.5 e.r.) suggests that in modified aminophenol-based catalysts, as illustrated by **III** and **IV** (Scheme 1b), steric factors may be manipulated for achieving high enantioselectivity.

Related additions to acyclic α -ketoesters afford valuable products and are also of interest. We know of only one report that is dedicated to this class of catalytic enantioselective transformations where an (expensive) indium-based complex and (toxic) tetraallyltin is required.^[9] Another disclosure, involving a Zn-based catalyst and an allylboronate compound, contains just a single example.^[10] We were interested in developing a more general and practical protocol for allyl additions to α -ketoesters, aiming to investigate whether various electronic (e.g., dipolar interactions and electron–electron repulsive forces) and steric features illustrated for complexes **V** and **VI** may be manipulated such that the desired products can be obtained in appreciable enantiomeric purity.

We started by examining the reactions of acetophenone and allyl–B(pin) with aminophenols **1b–f** to generate tertiary alcohol **2a** (Scheme 3). Phenyl-substituted **1b** was selected based on the reasoning that an aryl unit extends farther (vs. a *t*-Bu group), thus expanding the catalyst's reach in the desired direction (cf. **1c–d**). There was however no more than an incremental increase in e.r. with **1b–d** (up to 81:19), leading us to envision that incorporating longer C–Si bonds at the same site could prove to be more effective. In the event, although selectivity with triisopropylsilyl-substituted **1e** took was somewhat disappointing (77:23 e.r.), with triphenylsilyl variant **1f**, **2a** was formed in 90:10 e.r. Subsequent optimization revealed that with 3.0 mol % **1g** at –30 °C for eight hours, **2a** may be isolated in 89% yield and 98:2 e.r. (Scheme 4).^[11]

The catalytic protocol is broadly applicable, and the requisite aminophenol **1g**, which is indefinitely air stable, can be prepared in ~40% overall yield from readily available starting materials.^[12] Aryl-substituted ketones, including those with an electron donating (e.g., **2c**; Scheme 4) or withdrawing substituent (e.g., **2e–2f**) undergo efficient and highly enantioselective addition. Notably, unprotected aniline- and phenol-containing tertiary homoallylic alcohols **2i** and **2j** were obtained in 82% and 91% yield and 91.5:8.5 and

96.5:3.5 e.r., respectively. As represented by **2n-p** (Scheme 4), ketones with an N-, O- and/or S-containing heterocyclic moiety are suitable. Products from aryl ketones that contain a larger alkyl unit (e.g., **3-4**), an alkenyl group (e.g., **5**) or a comparatively diminutive alkynyl moiety (e.g., **6**) were accessed efficiently and in high enantiomeric purity. While reasonably efficient, enantioselectivities were lower with ketones containing two alkyl substituents (cf. **7-8**). With only electronic factors distinguishing the ketone substituents, measurable enantiofacial differentiation was still observed (**9** in 73:27 e.r.). Synthesis of **10-12** (Scheme 4) demonstrates that 2-substituted allylboron reagents may be used.

Reactions of cyclic ketones afforded products in high yield and up to 99:1 e.r., as represented by **13-15** (Scheme 5). The case of alkenyl iodide **15** is particularly notable as it has been utilized in an approach toward enantioselective synthesis of the *veratrum* family of alkaloid natural products (anti-cancer activity).^[13]

Allyl additions to α -ketoesters were next (cf. Scheme 2). It did not take long before we faced a surprise: Whereas addition of allyl-B(pin) to **17a** with the *t*Bu-substituted aminophenol (**1a**) afforded α -hydroxy ester **18a** in 82:18 e.r. (Scheme 6a), with triphenylsilyl-substituted **1f**, unlike the transformations with ketones, selectivity was lower (75:25 e.r.). Moreover, the major enantiomer is derived from the opposite sense of enantioselectivity compared to the ketone additions (cf. X-ray structure in Scheme 6a), indicating that reaction may occur via **VII** (Scheme 6b). The competing mode of addition is probably best represented by **VIII**, wherein although the net dipole-dipole repulsion is minimized there is electron-electron repulsion between the non-bonding electrons of the aryloxy and ester groups. We suspected that steric strain between the axially oriented ketone substituent and the catalyst's protruding aryloxide moiety (**VII**, R = *t*Bu or SiPh₃ in **1a** and **1f**, respectively) might be less costly than the indicated electron-electron repulsion in **VIII** (cf. **VI**, Scheme 2). Hence, an H-bonded complex such as **V** in Scheme 2 might not play a major role because of the dipole-dipole repulsion associated with the bound α -ketoester (unlike with structurally rigid isatins).^[7a]

An implication of the above hypothesis is that enantioselectivity could improve with an aminophenol that contains a smaller substituent (vs. a *t*-Bu or SiPh₃). Indeed, when methyl-substituted ligand **1h** was used, under otherwise identical conditions, **17a** was generated in 92:8 e.r.^[14] Reaction with the unsubstituted aminophenol did not cause further improvement;^[15] this might be because the energy gained by lowering of strain in **VII** is not large enough to compensate for the residual steric repulsion between the methyl ester and the catalyst substituent in **VIII** that is no longer present either.^[16]

Additions to α -ketoesters have notable scope (Scheme 7). Transformations are exceptionally efficient (often >98% yield after purification) regardless of the electronic attributes of the aryl unit (e.g., **18b** vs. **18f**) or whether an alkyl-substituted ketoester is involved (cf. **18h**). The somewhat less enantioselective additions compared to those with linear ketones (cf. Scheme 4) imply that there is greater competition between the two modes of reaction (**VII** vs. **VIII**, Scheme 6b). Utility is highlighted by concise synthesis of lactone **19** in 60% overall yield (94:6 e.r.), a compound that has been converted to antiviral nucleoside analogues.^[17] Two other points are noteworthy: a) Aminophenol **1h** was prepared in 76%

overall yield from an inexpensive aldehyde and Boc-valine.^[12] b) Reactions can be easily carried out without the need for rigorous exclusion of air and moisture in a fume hood (e.g., **18f** in 94% yield, 91:9 e.r.).

To conclude, two catalytic enantioselective methods involving acyclic and cyclic ketones and acyclic α -ketoesters are presented. The transformations offer broader substrate scope (including unprotected phenols and anilines) than the previously reported approaches, and involve the use of inexpensive catalysts along with easy-to-handle and reagents that are mostly commercially available. A key aspect of the present studies is the possibility of maximizing enantioselectivity by means of rational alteration of the size of an aminophenol's aryloxy substituent based on the available stereochemical models. We show that with ketones, exchanging the *tert*-butyl unit with a triphenylsilyl group is needed whereas with acyclic α -ketoesters, the catalyst bearing a smaller methyl unit is superior. The advances described here offer additional evidence regarding considerable potential of the aminophenol-derived catalysts for future developments in enantioselective synthesis. Studies along these lines including reactions with more functionalized allyl-B(pin) compounds are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Financial support was provided by the NIH (GM-57212). A. V. acknowledges an Olle Engkvist Byggmästare scholarship.

References & Footnotes

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a. Previous work: Two-point catalyst substrate contact ensures high enantioselectivity:

b. Can high enantioselectivity be achieved with ketones containing one contact point?

Scheme 1.

Is high enantioselectivity feasible without a second catalyst-substrate contact point?

Scheme 2.

Another key question: which pathway, if any, would be preferred for allyl-B(pin) addition to α -ketoesters?

Scheme 3.

Screening of ligands for enantioselective allyl addition to acetophenone as the model.

Scheme 4.

Tertiary homoallylic alcohols obtained from catalytic enantioselective additions of allyl-B(pin) compounds to acyclic ketones. The absolute stereochemistry of the major isomer of **9** has not been determined. [a] At -15 °C, 8 h. [b] At -15 °C, 12 h.

Scheme 5.

Catalytic enantioselective additions to cyclic ketones.

a. Initial examination of different amino alcohols:

b. Stereochemical model: The smaller, the more selective:

Scheme 6.

Unexpected sense of selectivity in reactions of α -ketoesters and identification of an optimal aminophenol.

a. Scope of the method: **b. Representative application:** **Scheme 7.**

Catalytic enantioselective allyl-B(pin) addition to α -ketoesters and a representative application.