Enantioselective Synthesis

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

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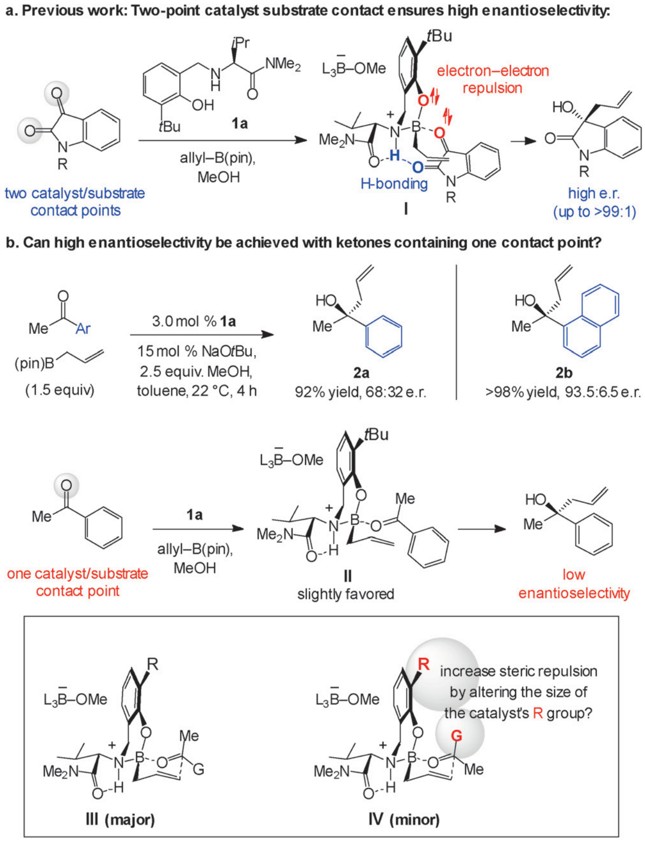
Dedicated to Professor Stuart L. Schreiber on the occasion of his 60th Birthday

Abstract: *A set of broadly applicable methods for efficient catalytic additions of easy-to-handle allyl-B(pin) (pin = pinacolato) compounds to ketones and acyclic α-ketoesters was developed. Accordingly, a large array of tertiary alcohols can be obtained in 60 to > 98 % yield and up to 99:1 enantiomeric ratio. At the heart of this development is rational alteration of the structures of the small-molecule aminophenol-based catalysts. Notably, with ketones, increasing the size of a catalyst moiety (tBu to $SiPh_3$) results in much higher enantioselectivity. With α-ketoesters, on the other hand, not only does the opposite hold true, since Me substitution leads to substantially higher enantioselectivity, but the sense of the selectivity is reversed as well.*

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

Our interest in this problem originated from an earlier discovery that easily modifiable aminophenol compounds (e.g., **1a**, Scheme 1 a) 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 ammonium group;[8] this is despite electronic repulsion between the non-bonding aryloxide and carbonyl electrons (**I**; Scheme 1 a). Additions to acetophenone (Scheme 1 b) are therefore substantially less selective (**2a**, 68:32 e.r.) because there is little energy difference



Scheme 1. Is high enantioselectivity feasible without a second catalyst–substrate contact point?

between **II** and the alternative complex with a pseudo-axial 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 1 b), 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, and in this case, an (expensive) indium-based complex and (toxic) tetraallyltin are required.[9] Another report, 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

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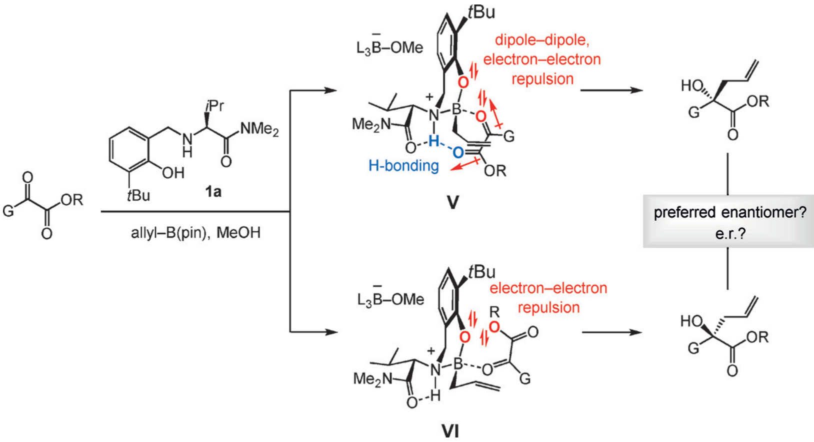
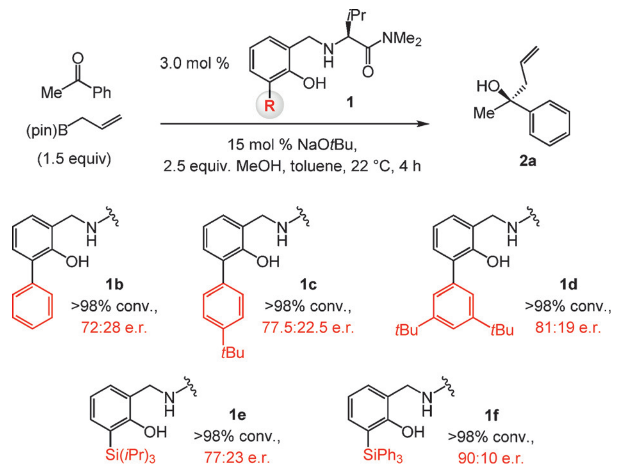
method for allyl additions to α-ketoesters, aiming to investigate whether various electronic (e.g., dipolar interactions and electron–electron repulsive forces) and steric features illustrated for complexes **V** and **VI** (Scheme 2) may be manipulated such that the desired products can be obtained in appreciable enantiomeric purity.



Scheme 2. Another key question: which pathway, if any, would be preferred for allyl-B(pin) addition to α-ketoesters?

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 further (vs. a *t*Bu group), thus expanding the reach of the catalyst in the desired direction (cf. **1c**,**d**). There was no more than an incremental increase in e.r. (up to 81:19) with **1b–d**, however, thus leading us to envision that incorporating longer C–Si bonds at the same site could prove to be more effective. In the event, although the selectivity with triisopropylsilyl-substituted **1e** 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]



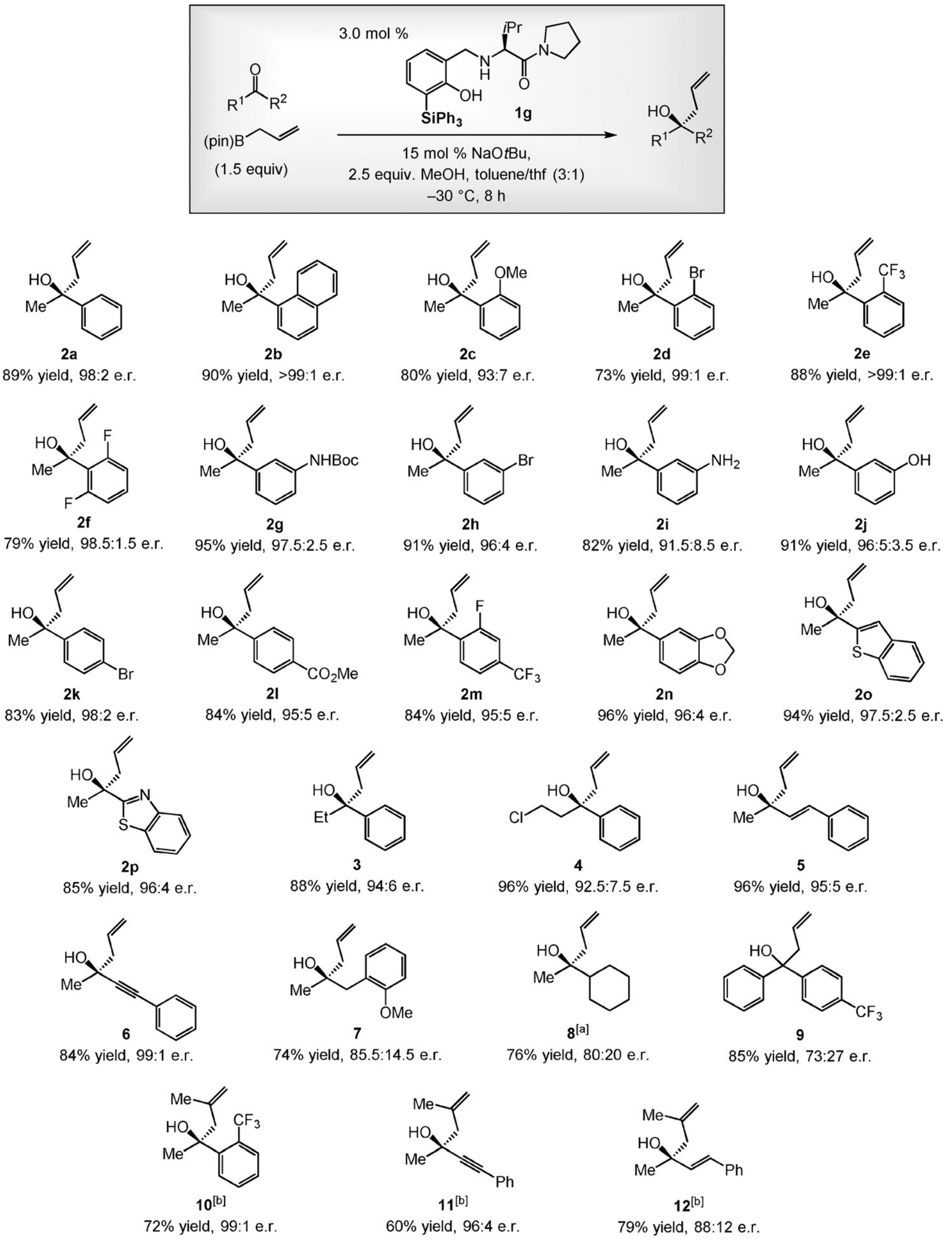
Scheme 3. Screening of ligands for enantioselective allyl addition to acetophenone as the model.

The catalytic method is broadly applicable, and the requisite aminophenol **1g**, which is indefinitely air stable, can be prepared in approximately 40 % overall yield from readily available starting materials.[12] Aryl-substituted ketones, including those with an electron-donating (**2c**; Scheme 4) or electron-withdrawing substituent (**2e**,**f**) undergo efficient and highly enantioselective addition. Notably, the 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 (**3–4**), an alkenyl group (**5**) or a comparatively diminutive alkynyl moiety (**6**) were accessed efficiently and in high enantiomeric purity. While the reactions were reasonably efficient, the enantioselectivity was 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.). The synthesis of **10–12** (Scheme 4) demonstrates that 2-substituted allylboron reagents may be used.

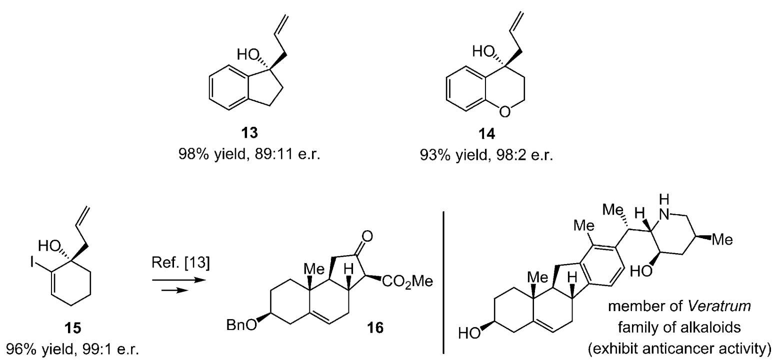
Reactions of cyclic ketones afforded products in high yield and up to 99:1 e.r., as demonstrated by **13–15** (Scheme 5). The case of alkenyl iodide **15** is particularly notable since it has been utilized in an approach toward enantioselective synthesis of the *veratrum* family of alkaloid natural products (anticancer 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, the 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), thus indicating that the 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 repulsion between the nonbonding electrons of the aryloxy and ester groups. We suspected that steric strain between the axially oriented ketone substituent and the protruding aryloxide moiety of the catalyst (**VII**, R = *t*Bu or $SiPh_3$ 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 be improved with an aminophenol that



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.

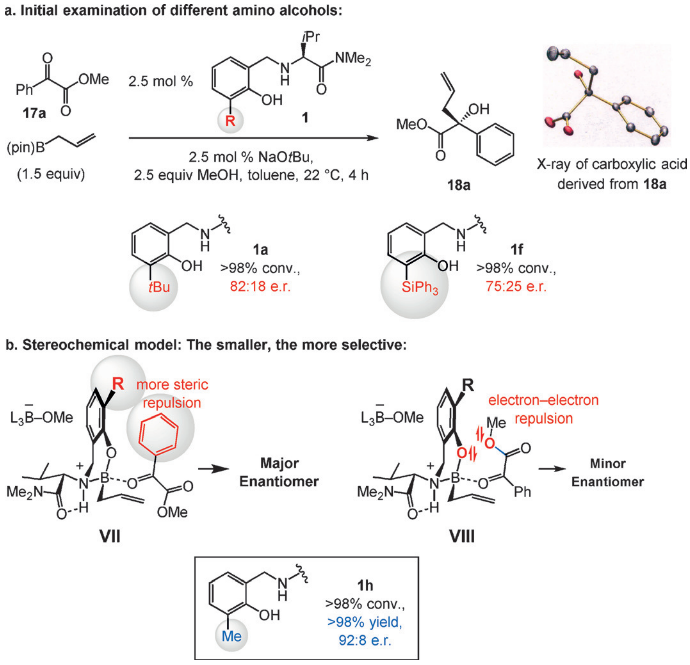


Scheme 5. Catalytic enantioselective additions to cyclic ketones.

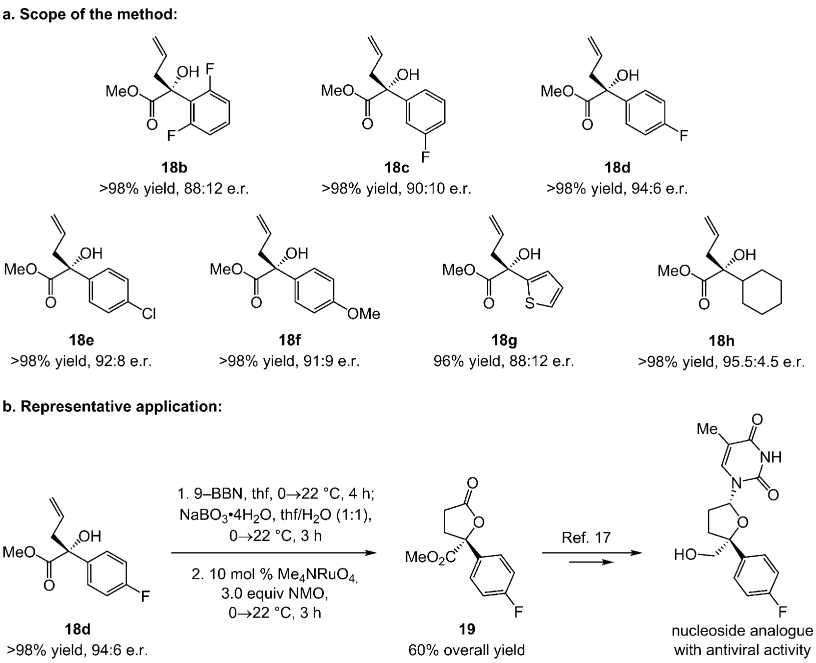
contains a smaller substituent (vs. *t*Bu or $SiPh_3$). Indeed, when methyl-substituted ligand **1h** was used, under otherwise identical conditions, **17a** was generated in 92:8 e.r.[14] Reaction with the unsubstituted aminophenol did not cause further improvement;[15] this might be because the energy gained by lowering the 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.[16]

The additions to α-ketoesters show notable scope (Scheme 7). The 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). The utility of the method is highlighted by the concise synthesis of lactone **19**, a compound that has been converted to antiviral nucleoside analogues,[17] in 60% overall yield (94:6 e.r.). Two other points are worthy of note: 1) Aminophenol **1h** was prepared in 76% overall yield from an inexpensive aldehyde and Boc-valine.[12] 2) The 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 reactions 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 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



Scheme 6. An unexpected reversal of selectivity in reactions of α-ketoesters and identification of an optimal aminophenol.



Scheme 7. Catalytic enantioselective allyl-B(pin) addition to α-ketoesters and a representative application.

aryloxy substituent on the aminophenol 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, a catalyst bearing a smaller methyl unit is superior. The advances described herein offer additional evidence regarding the considerable potential of aminophenol-derived catalysts for future developments in enantioselective synthesis. Studies along these lines, including reactions with more functionalized allyl-B(pin) compounds, are underway.

Acknowledgements

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