Asymmetric Catalysis

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Allylic Alcohols: Sustainable Sources for Catalytic Enantioselective Alkylation Reactions**

*Marco Bandini**

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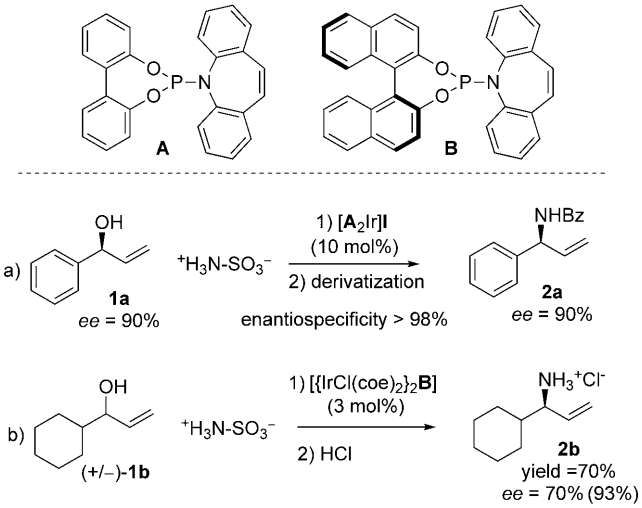
Catalytic asymmetric allylic alkylation (AAA) is a well-established synthetic protocol to realize complex molecular architectures in a stereochemically defined manner.[1] This method routinely requires preinstalled or in situ formed allylic leaving groups (i.e. acetates, carbonates, phosphates) to generate η^3-metal allyl complexes amenable to nucleophilic attack at the allylic termini.

A conceptually simple way for improving both the economic and the environmental impact of AAA reactions would be the direct employment of allylic alcohols as precursors of the η^3-allyl fragment. As a matter of fact, alcohols are largely available and eco-friendly because they give water as the only by-product. Last but not least, substantial shortening of the whole synthetic process would occur because most of the common AAA partners are obtained from the corresponding alcohols. On the other hand, the poor leaving group character of the hydroxy function, combined with the possible inhibiting effect exerted by the released water on the metal catalysts, have prevented allylic alcohols from emerging as reliable key players in this field.

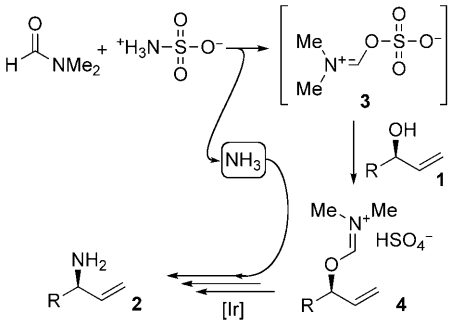
Currently, the scenario is changing rapidly and innovative metal-catalyzed AAA methods, which include the use of alcohols, have been proposed. Such synthetic strategies exploit late-transition-metal salts/complexes through isohypsic or redox ($M^{n+}/M^{(n+2)+}$) catalysis. Although the use of allylic alcohols in catalytic enantioselective alkylation processes (i.e. amination reaction and arene alkylation) has been efficiently addressed in the recent past, the use of external activating agents to enhance the reactivity of alcohols was required.[2] Very recently, a breakthrough in the field was provided by Roggen and Carreira, who documented the first stereoselective synthesis of primary amines from alcohols by means of sulfamic acid as an ammonia equivalent.[3] The efficiency of new phosphoramidite [(P,olefin)$_2$IrX] complexes was highlighted in the stereospecific displacement of enantiomerically enriched secondary alcohols by the amino group (Scheme 1 a).



Scheme 1. Stereospecific iridium(I)-catalyzed synthesis of primary amines from allylic alcohols. Bz = benzoyl, coe = cyclooctene.

A key aspect of this method relies on the use of *N*,*N*-dimethylformamide, which was proposed to assist the activation of the secondary allylic alcohols by forming the Vilsmeier-like-intermediate **3** with the sulfamic acid (Scheme 2).[4]

Although the method is far from synthetic utilization, preliminary results on the enantioselective conversion of



Scheme 2. The solvent makes the difference in the stereoselective amination of allylic alcohols catalyzed by $Ir^{I/III}$.

[*] Dr. M. Bandini
Dipartimento di Chimica "G. Ciamician"
Alma Mater Studiorum - Università di Bologna
via Selmi 2, Bologna 40126 (Italy)
Fax: (+39) 051-209-9456
E-mail: marco.bandini@unibo.it
Homepage: http://www.mbandini-group.com

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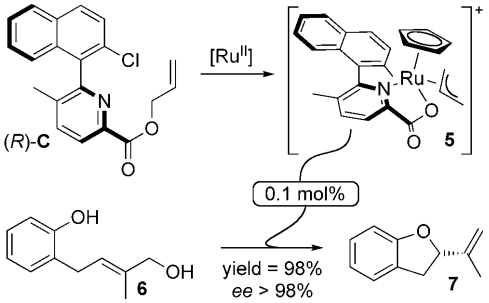
racemic alcohols into the corresponding optically active amines ($[\mathbf{B}_2Ir]Cl \rightarrow ee = 70\,\%$, $[\{IrCl(coe)_2\}_2\mathbf{B}] \rightarrow ee = 93\,\%$; Scheme 1b), lent credence to the direct activation of allylic alcohols toward further AAA reactions.

Expanding the substrate scope to primary allylic alcohols is a stringent requisite to ensure a synthetic competitiveness of the present method with respect to the well-established use of allylic acetates/carbonates.

In line with this demand, Kitamura and co-workers have recently scrutinized the competence of primary allylic alcohols in enantioselective dehydrative alkoxyalkylation of aliphatic alcohols as well as phenols.[5a] Previous findings from the same research group traced the guidelines for the catalyst design.[5b] An unprecedented $CpRu^{IV}$–π-allyl carboxylato complex **5** (S/C up to 10000), synthesized in situ from the chiral allylic pyridine-2-carboxylic ester (*R*)-**C** and $[CpRu(CH_3CN)_3]PF_6$ (Cp = cyclopentadienyl), provided cyclic ethers in a highly stereoselective manner ($ee > 98\,\%$; Scheme 3).

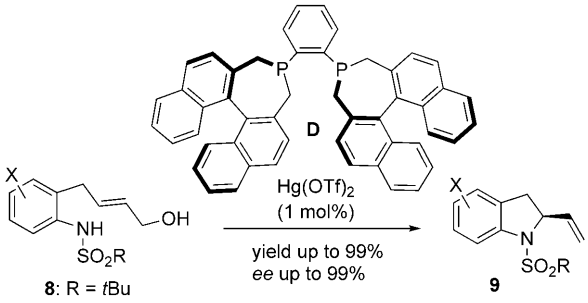


Scheme 3. Enantioselective ruthenium-catalyzed dehydrative alkoxyallylation of alcohols ($[Ru^{II}] = [CpRu(CH_3CN)_3]PF_6$).

A parallel strategy that involves the stereodiscriminating electrophilic activation of prochiral C–C double bonds by means of isohypsic chiral late-transition-metal catalysis, is receiving great attention by the chemical community. The combination of chiral, soft π-acids with allylic alcohols guarantees a highly chemoselective activation of the olefinic function and minimizes deactivation phenomena that result from the poor oxophilicity of these species.

Yamamoto et al. have addressed this challenge and have proposed an enantioselective intramolecular allylic amination of primary alcohols **8** mediated by a chiral binaphane **D**–$Hg(OTf)_2$ complex.[6] Despite the questionable environmental appeal deserved by mercury derivatives, the low loading of the catalyst (1 mol%), combined with mild reaction conditions (−30 °C, < 1 h reaction time) argues for the synthetic usefulness of the protocol in the synthesis of enantiomerically pure *N*-sulfonyl-2-vinyl indolines **9** (99% *ee*; Scheme 4).

The current boom of gold catalysis has positively affected the catalytic stereoselective manipulation of C–C multiple bonds. However, contrary to the more reactive allenes and



Scheme 4. Mercury-driven enantioselective synthesis of 2-vinyl indolines **9** through allylic amination with alcohols **8**. OTf = trifluoromethanesulfonate.

alkynes, the gold-mediated enantioselective functionalization of unactivated alkenes is still far from full development.

Interestingly, configurationally defined allylic alcohols proved to be competent substrates in stereoselective gold-catalyzed amination reactions and Friedel–Crafts-type alkylations, thus providing fascinating insights into the role of the configuration of the olefinic units over the whole chemical outcomes of the transformations.[7]

In summary, the studies presented in this Highlight drawn a clear picture on the current growing interest in catalytic AAA transformations with allylic alcohols. The combination of undoubted synthetic potential and still significant chemical limitations suggests that much more is still to come in this fascinating area, with particular emphasis on substrate scope, catalyst efficiency, and likely, organocatalysis.[8]

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