Organocatalysis

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Asymmetric α Alkylation of Aldehydes: Efficiency with Elegance

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Alkylations using the substitution reaction can be found in the first chapters of introductory level organic chemistry textbooks. Despite its apparent simplicity, the asymmetric α alkylation of aldehydes, even today, presents many unsolved practical problems.[1] Unlike aldol, Mannich, and 1,4-addition reactions, direct α alkylations of aldehydes are often characterized by narrow substrate scope or low stereoselectivity, or often both. As the majority of diastereoselective α alkylations of carbonyl compounds developed use preformed metal or metalloid enolates,[2] the replacement of these enolates by catalytically generated chiral enamines appears straightforward. Regardless of the daunting epimirization problem of the created asymmetric center, the challenge in developing an enantiocatalytic protocol for alkylation is to find reaction conditions for the synthesis of so-called unstabilized enolates in an environment where the nucleophilic catalyst may efficiently compete for the same substrate.

The α alkylation of aldehydes using simple alkyl halides as the electrophilic partner is problematic. Reaction conditions have been established for the intramolecular direct S_N2-type α alkylation of haloaldehydes using α-methyl proline as the catalyst.[3] Although this reaction offered a practical solution for the formation of cyclopropanes and five-membered cycles, and is still used in domino transformations,[4] the method performed poorly under intermolecular conditions owing to a number of competing side reactions, and in particular to the deactivation of the nucleophilic catalyst by alkylation. An elegant solution has been presented for the intermolecular asymmetric allylic alkylation (AAA) of α-branched aldehydes; in seminal work by List and Mukherjee the enantiodifferentiation was achieved by a chiral counteranion/anionic ligand rather than a more commonly used neutral ligand.[5] The reaction allows the creation of all-carbon quaternary stereogenic centers, but it is not suitable for the preparation of chiral tertiary centers. Reaction conditions are emerging for intermolecular alkylation by electron-transfer (ET) reactions.[6] The MacMillan group developed an impressive and complex array of highly enantioselective ET-mediated transformations including α allylation, enolation, vinylation, styrenation, polyene cyclization, benzylation, and alkylation of aldehydes.[6c] The inherent limitation of this elegant chemistry is in the substrate scope, as it cannot be used, for example, for the simple α methylation of enolisable aldehydes.

In parallel with the ET-mediated α alkylation reactions S_N1-type reactions between stabilized carbocations and enamines are gaining synthetic importance. Somewhat surprisingly S_N1-type transformations have been seldom considered in asymmetric organocatalysis until very recently. Pioneered by Petrini, Melchiorre, and co-workers,[7] and considerably extended by Cozzi et al.[8] the reaction of stabilized carbocations and π nucleophiles, such as enamines and enol ethers, led the way for a range of selective transformations. Under a variety of S_N1 conditions π nucleophiles such as enamines react fast with soft carbocations, while nucleophiles, including the amine catalyst and water, react slowly with these electrophiles. The reaction rate is not only dependent on the nature of the nucleophile and electrophile pair but also on the solvent. While the reactions of π nucleophiles are barely affected by the nature of the solvent and the reaction rate is almost independent of the solvent polarity as no charged species are involved in the rate-determining step, strongly solvent-dependent reaction rates are observed with *N*-nucleophiles in protic and aprotic solvents. Moreover, the nucleophilicity of the amines decreases also from aprotic to protic solvents owing to hydrogen-bond formation with the nitrogen atom. Thus, selective S_N1 reactions not only tolerate water, but often require the presence of water or protic additives for highly selective reactions.

A limited array of carbocations are commercially available, they can be also easily generated in situ from activated alcohols, acetates, halides, sulfonates, and sulfonamides in the presence of suitable Lewis or Brønsted acids or by oxidative C–H functionalization using oxidants, such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), or electrochemical methods.

In the Petrini–Melchiorre approach the stabilized carbocation was generated from bisaryl sulfonates on heterogenous KF/alumina, and the formed carbocation was intercepted by the proline enamine nucleophile (Scheme 1).[7] The stereoselectivity of the transformation is governed by the steric interplay between the generated chiral enamine and the indole C2 substituent.

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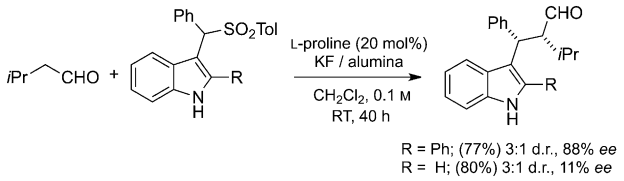
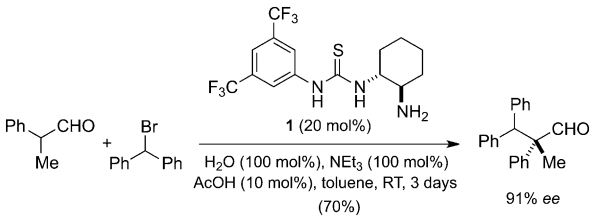


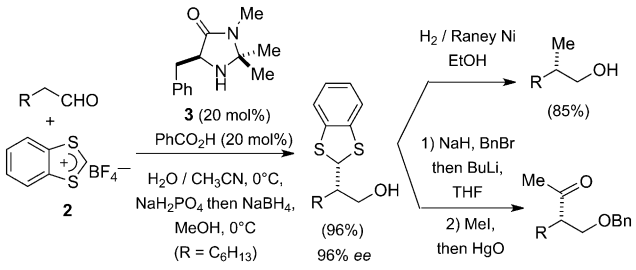
Scheme 1. The L-proline-catalyzed intermolecular α alkylation of aldehydes by arylsulfonyl indoles.[7]

Activated allylic alcohols can be used also as potential electrophiles in conjunction with a catalytic amount of Lewis acid, such as $InBr_3$.[8d] Under homogeneous conditions usually MacMillan-type catalysts were more stable and performed better than chiral diphenylprolinol TBS ether catalysts in terms of selectivity. Also, primary aminothiourea derivatives, such as **1**, which was also efficient in promoting additions of aldehydes and ketones to nitroalkenes, provided good yields and enantioselectivity in the alkylation of aldehydes by benzhydryliums, generated from the corresponding bromide (Scheme 2).[9] As well as the thiourea motif, which plays an essential role in promoting reactivity and stereocontrol, the presence of a primary amino group was necessary for catalysis.



Scheme 2. Chiral primary aminothiourea catalyzed alkylation of aldehydes.[9]

Recently, Cozzi et al. reported a remarkably simple and practical asymmetric α alkylation using a heteroatom-stabilized carbenium ion, such as the commercially available benzothiolium cation **2** (Scheme 3).[8f] Compound **2** was used almost exclusively in the past for the preparation of tetrathiofulvalenes, it also turned out to be a valuable formyl equivalent. The direct α alkylation of enolizable aldehydes by the benzothiolium cation was carried out in the presence of enamine catalysts, such as **3** (20 mol%), with benzoic acid as the co-catalyst (20 mol%). The reaction required the presence of a stoichiometric amount of base, which captured the HBF_4 liberated by the formation of the carbenium; organic



Scheme 3. Asymmetric formylation of aldehydes by benzothiolium and subsequent transformations of the 1,3-benzodithiol synthon by reduction, and by alkylation and oxidative thioketal cleavage.[8f]

bases such as 1,6-dimethylpyridine, 1,4-diazabicyclo-[2.2.2]octane (DABCO), and Et_3N afforded poor yields while inorganic bases were more suitable for the transformations. The reaction can be carried out in an open flask in solvents, containing traces of water, in fact, the presence of water is required for the highly selective reactions. This high-yielding, selective, and robust transformation is compatible with a variety of functional groups, such as chloro, cyano, amide, and acetal groups. Notably, the 1,3-benzodithiol group opens up the opportunity for further transformations; the adduct can be alkylated either under anionic conditions and the thioacetal can be removed under oxidative or reductive conditions, thus providing convenient procedures for the formal organocatalytic α acylation and methylation of aldehydes, respectively (Scheme 3).

The α alkylation of aldehydes was not considered as a reaction of central importance in the past. It is interesting to contemplate how this transformation has recently inspired novel reactions, thus allying efficiency, robustness, and elegance. Even though the S_N1 strategy is a new addition in asymmetric organocatalysis the principle is quickly gaining popularity in the development of novel methods.[10]

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