Asymmetric Catalysis

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Radicals in Asymmetric Organocatalysis**

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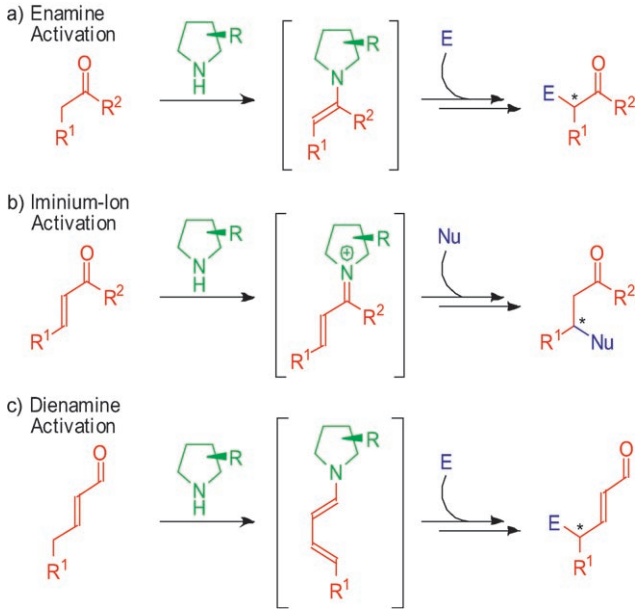
Introduction

Since the turn of the millennium, the field of organic chemistry has witnessed a tremendous rise in the number of synthetic applications of organocatalysis.[1] In this upcoming area of chemistry, the use of chiral secondary amines as catalysts has already played a pivotal role in many important nonradical transformations.[2] Catalysis using chiral secondary amines allows a number of highly chemo- and stereoselective functionalizations of carbonyl compounds, and many of these procedures give access to molecules of high interest to synthetic chemists. The protocols are often complementary to the established metal-catalyzed procedures. Until recently, three different methods of activation have been known using aminocatalysis: enamine, iminium ion, and dienamine activation. More recently, a new activation methodology using radical intermediates was introduced by the research groups of Sibi[3] and MacMillan.[4,5] This new radical activation is being introduced as SOMO (singly occupied molecular orbital)-enamine activation.[4a]



Scheme 1. Aminocatalytic α-, β-, and γ-functionalizations of carbonyl compounds. E = electrophile, Nu = nucleophile.

Aminocatalytic Functionalizations

Few early examples of organocatalytic aldol reactions had been reported[6] when List, Lerner, and Barbas presented the highly stereoselective proline-catalyzed aldol reaction in 2000.[7] Since then, enamine activation has become a standard tool used in a vast number of functionalizations of the α position of aldehydes and ketones with both carbon- and heteroatom based electrophilic reagents.[8] The general mechanism for the aminocatalytic α-functionalization of carbonyl compounds is an initial condensation of the secondary amine catalyst and a carbonyl functionality that leads to a nucleophilic enamine intermediate, which reacts with an electrophilic reagent (Scheme 1a). Stereoselective formation of either enantiomer of a product may be achieved through selection of the catalyst—of which both enantiomers are often readily available.[8a]

A complementary approach to the aminocatalytic functionalization of aldehydes and ketones was presented by MacMillan and co-workers in which iminium-ion activation allowed for selective functionalizations of the β position (Scheme 1b).[9] This type of catalysis exploits a lowering of the LUMO energy of the iminium-ion intermediate as compared to that of the α,β-unsaturated carbonyl compound. A range of nucleophiles have been shown to attack the β position to give rise to numerous important products.[10]

Recently, a third method for the functionalization of carbonyl compounds, in which an α,β-unsaturated aldehyde was transformed into an electron-rich dienamine, was presented (Scheme 1c). The dienamine intermediate was shown to react with electrophilic dienophiles to give rise to γ-functionalized enals.[11]

The new aminocatalytic activation method presented by the research groups of Sibi and MacMillan gives synthetic chemists a fourth tool for the organocatalytic asymmetric functionalization of carbonyl compounds.[3,4] In contrast to

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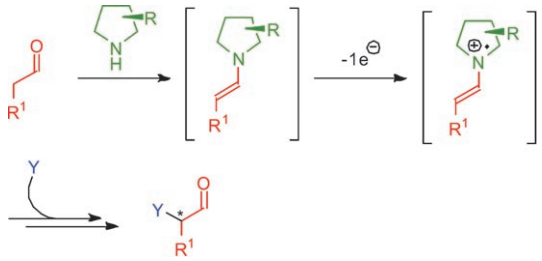
the three previous activation methods, this approach uses a single unpaired electron in the activated enamine intermediate, thereby allowing for the use of a group of reagents that has not previously been applicable to aminocatalysis (Scheme 2). The prerequisite for such a reaction to proceed



Scheme 2. Aminocatalytic α-functionalization through SOMO-enamine activation. Y = functional group.

in a catalytic stereoselective manner is that the enamine should be more easily oxidized than the corresponding enol, and this has indeed been shown to be the case.[4a]

Radicals in Organic Chemistry

Since the first identification of a free radical by Gomberg in 1900,[12] radicals have become an increasingly important class of reagents in organic synthesis.[13] For many years, radicals were considered too reactive to allow chemo- or stereoselective reactions using them. Yet, the existence of persistent radicals in nature bear witness that radicals can be stable,[14] and several enzymatic pathways have been proved to proceed via radical intermediates.[15]

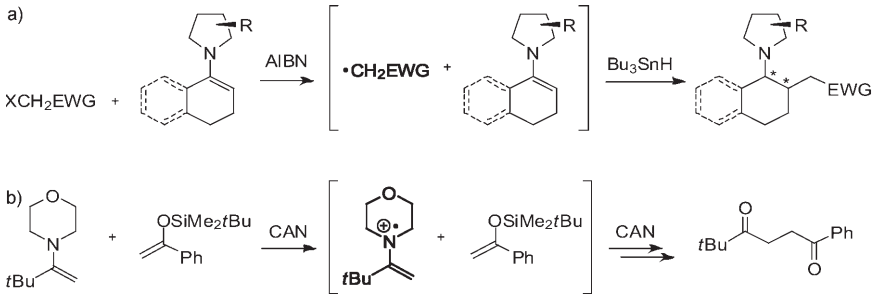
Within the last 20 years, the number of reactions of radicals and enamine substrates has increased. An early example of stereoselective additions of carbon-centered radicals to preformed cyclic enamines was reported by Renaud and Schubert (Scheme 3a).[16] Yields between 40 and 88% were reported and *Re*/*Si* selectivities of up to 95:5 were achieved for the highly favored *cis* diastereomer.

The oxidation of an enamine to a cationic radical and subsequent reaction with nonradical enolsilanes was reported by Narasaka et al., and exemplifies a case in which the radical intermediate originates from the enamine (Scheme 3b).[17] The approach used by Narasaka et al. involves an S_H2'-type reaction in which two distinct oxidative steps are necessary. CAN was found to be a successful oxidant giving 63% yield of the product.

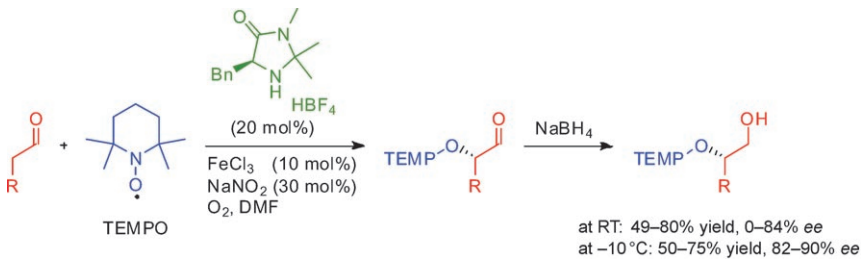
The use of radical intermediates in organocatalysis has received only sparse attention,[18] and the new aminocatalytic approaches by the research groups of Sibi and MacMillan enhance the synthetic applicability of radical reactions. The former group used radicals that were formed from enamine intermediates to react with preformed persistent radicals.[3] In contrast, MacMillan et al.[4] utilized a double oxidation procedure akin to the work of Narasaka et al.[17] albeit in a catalytic enantioselective manner.

Enantioselective α-Oxyamination of Aldehydes

Sibi et al. presented a stereoselective α-oxyamination of aldehydes using SOMO activation of the enamine and TEMPO as the oxygen source and applying the MacMillan catalyst (Scheme 4).[3,19] Similar products have previously been shown to be available through aminocatalytic α-oxy-



Scheme 3. Radical reactions involving enamines: a) the radical reagent is the activated methylene group, b) the enamine represents the radical intermediate. AIBN = azobisisobutyronitrile, CAN = ceric ammonium nitrate, EWG = electron-withdrawing group, X = leaving group.



Scheme 4. SOMO-enamine activation and α-oxyamination of aldehydes. Bn = benzyl, DMF = *N*,*N*-dimethylformamide.

amination using nitrosobenzene as the oxygen source and proline as the catalyst.[20]

A screening of various oxidative conditions revealed that the use of a substoichiometric amount of $FeCl_3$ as single-electron transfer (SET) reagent coupled with a $NaNO_2/O_2$ system was sufficient to repeatably oxidize the enamine intermediate to the corresponding SOMO-activated enamine. Various aldehydes were shown to undergo oxidation to form cationic radical intermediates, which were trapped with TEMPO to form the corresponding α-oxyaminated aldehydes. These were isolated as the corresponding alcohols in good yields and enantioselectivities.

The reaction was shown to be very dependent on the solvent and temperature, and performing the reaction in DMF at −10 °C led to the highest enantioselectivities. An extension of the scope of the reaction to involve ketones was attempted, and cyclohexanone gave the α-oxyamination product in 86 % yield, but as a racemate. Cleavage of the O–N bond in the alcohol product (using Zn/AcOH) led to the free diol from which the absolute stereochemistry was determined to be *S*.

Enantioselective α-C–C Bond Formation

The SOMO-activated enamine was introduced and employed by MacMillan and co-workers for an organocatalytic double oxidative C–C bond formation.[4,5] The cationic radical intermediate was obtained through a CAN-mediated oxidation of the enamine intermediate. After reaction with a nonradical silylated reagent, a second oxidation and removal of the silyl group led to a range of γ,δ-unsaturated α-functionalized aldehydes (Scheme 5).

It was demonstrated that various aldehydes and different allylsilanes (Scheme 5, $Z = CH_2$) reacted to afford α-allylated products in high yields and enantioselectivities.[4a] This constitutes an organocatalytic example of a C–C bond formation between a nucleophilic carbon center and the α-position of an aldehyde. A proof for the presence of a radical cationic enamine intermediate was established using a radical clock, as described by Newcomb and co-workers.[21]

Simultaneously, a methodology for the reaction of aldehydes and enolsilanes (Scheme 5, Z = O) was developed.[4b] A range of α-alkyl γ-ketoaldehydes were obtained with generally high yields and enantioselectivities. A strong dependency on the base additive was observed and 2,6 di-*tert*-butyl pyridine was shown to be necessary to achieve high yields. Again, two distinct oxidative steps were necessary to obtain the products.

The high chemoselectivity of the reaction was illustrated by an experiment in which the radical cyclization of *cis*-7-decenal could be fully depressed by the addition of an enolsilane.[4b] Alternatively, a chlorinated cyclization product could be isolated in high yield and excellent enantiomeric excess as a result of the reaction of *cis*-6-nonenal and LiCl.[4a] Furthermore, it was demonstrated that an *N*-Boc-protected pyrrole reacted with octanal under similar conditions to give an α-arylated aldehyde in 85 % yield and 84 % *ee*.[4a]

Outlook

Two different methodologies for aminocatalytic SOMO-enamine activation have been presented. The α-oxyamino-type products that were obtained through the protocol reported by Sibi and Hasegawa[3] are already accessible by other organocatalytic procedures. Additionally, the use of a single oxidative step in the mechanism limits the scope of the reaction to persistent radical reagents. Yet, the reaction shows promising features as it only employs a substoichiometric amount of a metallic SET reagent and O_2 as the terminal oxidant. The identification of other persistent radical reagents for this reaction will undoubtedly be pursued in the future. Alternatively, a double oxidation procedure using the $FeCl_3/NaNO_2/O_2$ oxidation system would be an interesting extension to the methodology, thus increasing the scope of the reaction.

Such a double oxidation was achieved by MacMillan and co-workers,[4] although they used two equivalents of the metallic SET-reagent CAN. The metal-mediated SOMO-enamine activated reaction resulted in the synthesis of a number of novel α-functionalized aldehydes. The stereoselective formation of a C–C bond is an important transformation and the procedure of MacMillan and co-workers will constitute a useful tool for the synthetic chemists if the conditions prove to be applicable to a larger range of reactants.

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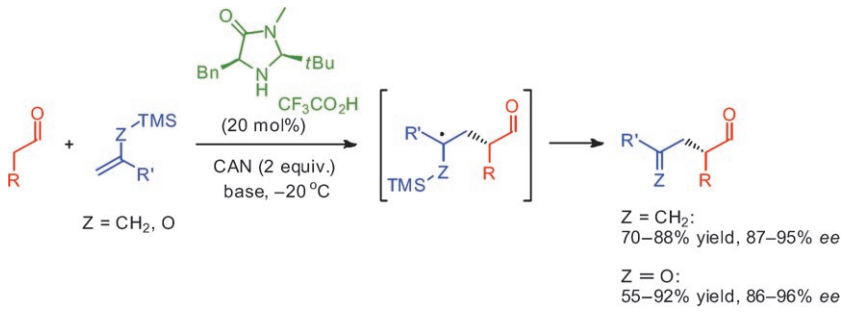

Scheme 5. SOMO-enamine ctivation and double oxidative C–C bond formation at the α-position of aldehydes. TMS = trimethylsilyl.

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