Asymmetric Organocatalysis

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Light in Aminocatalysis: The Asymmetric Intermolecular α-Alkylation of Aldehydes**

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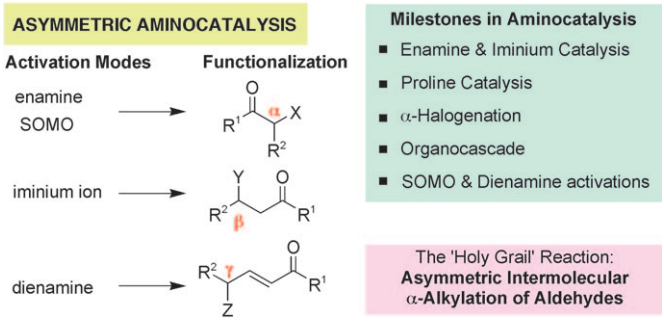
Catalysis using chiral secondary amines (asymmetric aminocatalysis) has become a fundamental tool within the domain of enantioselective synthesis.[1] By exploiting the formation of catalytically generated covalent intermediates, it can deliver unique and divergent carbonyl activation pathways. The different aminocatalytic activation modes provide chemists with novel means to solve challenging synthetic problems, complementing classic asymmetric methodologies and often overcoming their inherent restrictions. Even reactions that had been considered impossible have become a reality through aminocatalysis (Scheme 1).



Scheme 1. State of the art and milestone concepts of asymmetric aminocatalysis.

Despite this, an enormously important and sought after carbon–carbon bond forming reaction, the catalytic enantioselective intermolecular α-alkylation of carbonyl derivatives, has remained until very recently an unsolved problem for organocatalysis and organic synthesis in general. For many years, despite massive interest in what was considered the "holy grail" reaction for asymmetric aminocatalysis, no advances were made. Recently, however, by merging photoredox catalysis with organocatalysis, Nicewicz and MacMillan were able to address this longstanding issue.[2] In addition to the synthetic value of the discovery, which may pave the way for exciting developments in the future, this method nicely illustrates how the potential of aminocatalysis can be expanded by merging concepts that arise from different areas of chemistry.

The α-alkylation of carbonyl compounds is one of the fundamental C–C bond forming transformations in synthetic organic chemistry.[3] Conventional α-alkylation of carbonyl compounds is based on an S_N2-type addition to alkyl halides, which generally uses stoichiometric amounts of metal enolates. Extension of this strategy to an asymmetric version was accomplished with the use of stoichiometric amounts of chiral auxiliaries.[3c,d] Clearly for practical reasons, extensive efforts have been devoted to the development of general catalytic enantioselective α-alkylations of carbonyl compounds. However, this approach has proven extremely challenging, with the few reported methodologies being limited in scope.[4] For example, despite the utility of aldehydes as versatile building blocks in organic synthesis, the catalytic asymmetric α-alkylation reactions of aldehydes have remained elusive until recently. Even α-alkylations using stoichiometric amounts of preformed aldehyde enolate equivalents are very difficult to control: this is because several side reactions generally occur.[5] It was thought that aminocatalysis, which exploits the transient formation of catalytically in situ generated enamines, might in principle overcome some of the potential drawbacks. Eventually, it did indeed prove to be a suitable platform for developing general asymmetric strategies for the alkylation of aldehydes.

In 2004, Vignola and List presented the first catalytic asymmetric intramolecular α-alkylation of haloaldehydes to proceed through enamine catalysis—an unprecedented and highly useful transformation.[6] In the presence of one equivalent of triethylamine, proline (**1**) and its derivative α-methyl proline (**2**) can effectively cyclize haloaldehydes to give chiral substituted cyclopentane-, cyclopropane-, and pyrrolidinecarbaldehydes in high yield and enantioselectivity (Scheme 2).

This study represented a fundamental breakthrough in the field of asymmetric aminocatalysis. Conceptually, it constituted the first nucleophilic substitution reaction to proceed through enamine activation: this notion opened up unexplored routes, thus demonstrating that enamine catalysis was not limited to nucleophilic additions. Synthetically, this

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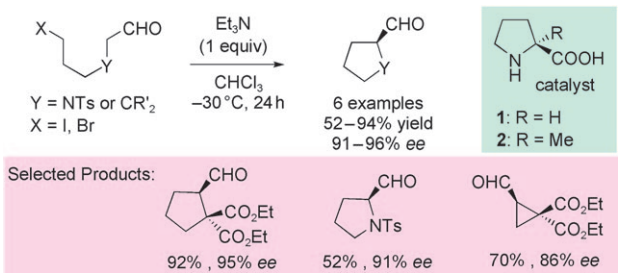


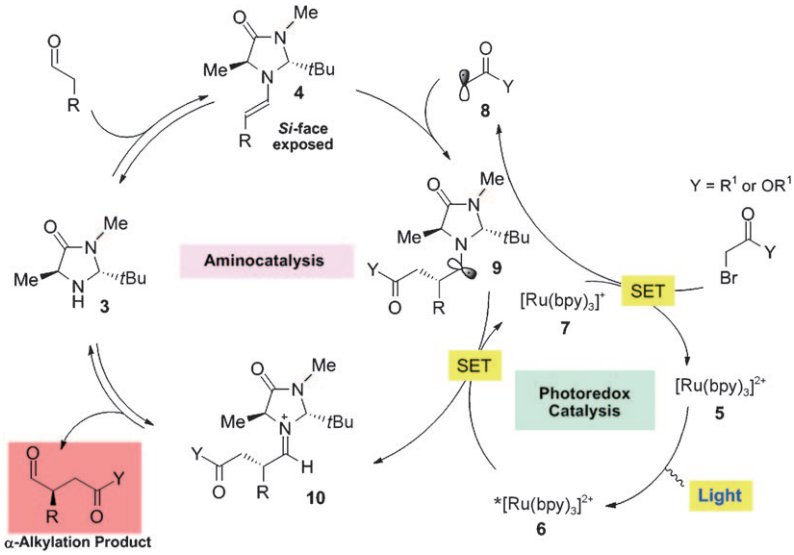
Scheme 2. Asymmetric enamine-catalyzed intramolecular α-alkylation of aldehydes. Ts = tosyl.

catalytic system solves the challenging problems associated with alkylation chemistry,[5,7] which includes possible product racemization.

Nevertheless, extension of the aminocatalytic alkylation strategy to an intermolecular version failed, mainly because of the deactivation of the amine catalyst by N-alkylation with the alkyl halides.[6a] Owing to its inherent problems, this process was touted as an inaccessible target—the "Holy Grail" reaction for asymmetric aminocatalysis. Thus, chemists moved toward aminocatalytic strategies based on the use of alternative alkylating agents to accomplish the challenging goal of a formal intermolecular α-alkylation of aldehydes. In 2006, a non-asymmetric catalytic intermolecular α-allylation of aldehydes by the combination of transition metal and enamine catalysis was reported.[8] More recently, MacMillan and co-workers[9] have exploited a new aminocatalytic activation concept—termed singly occupied molecular orbital (SOMO) catalysis—which is based on radical intermediates, to solve the synthetic problem of the catalytic asymmetric α-allylation,[9a] arylation,[9a] enolation,[9b] and vinylation[9c] of unmodified aldehydes. These studies, in particular the introduction of SOMO catalysis,[9] were essential background for the development of the actual catalytic asymmetric intermolecular α-alkylation of aldehydes with alkyl halides.

The inherent drawbacks associated with the intermolecular α-alkylations of aldehydes arise from the modest reactivity of alkyl halides, which complicates the ionic alkylation step while favoring side processes. Nicewicz and MacMillan found a solution to this challenging problem[2] by exploiting the knowledge accumulated in organo-SOMO catalysis—a one-electron mode of activation that introduced a totally different synthetic paradigm that goes beyond the established reactivity.[9] By considering that electron-deficient radicals are known to rapidly react with π-rich olefins to form even the most elusive C–C bonds,[10] they decided to pursue this idea to accomplish the direct asymmetric coupling of aldehydes with α-bromo carbonyl compounds, which is the actual intermolecular aldehyde alkylation.[2,11]

This ambitious plan was carried out by engineering a careful combination of two independent catalytic cycles that come from different areas of catalysis, namely photoredox catalysis and organocatalysis (Scheme 3). On one hand, the generation of an electron-rich enamine (**4**) is accomplished through the classic enamine activation path, by exploiting the condensation of the novel chiral imidazolidinone catalyst **3** with an aldehyde. On the other hand, the use of the ruthenium(II) complex of 2,2′-bipyridine ($[Ru(bpy)_3]^{2+}$, **5**), a well-established photoredox catalyst,[12] allows the generation of an electron-deficient alkyl radical from the starting halide by a reductive process. Under irradiation with a household 15 W fluorescent light, **5** populates the $*[Ru(bpy)_3]^{2+}$ (**6**) metal-to-ligand charge-transfer (MLCT) exited state, which



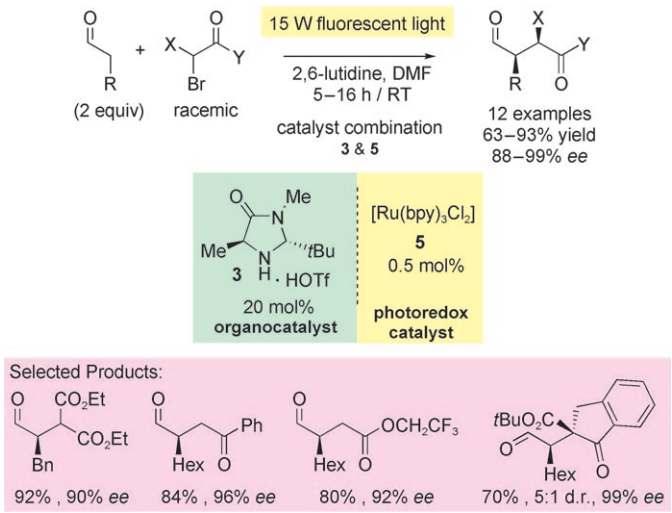
Scheme 3. The combination of photoredox catalysis and aminocatalysis. SET = single electron transfer.

has enhanced oxidizing and reducing power.[12] In the first photoredox cycle **6** acts as an oxidant by removing a single electron from a sacrificial quantity of the catalytically generated enamine.[13] This process leads to the generation of a Ru^{I} species ($[Ru(bpy)_3]^{+}$, **7**), which is a powerful reductant that, by SET to the α-bromo carbonyl compound, furnishes the desired electron-deficient radical **8** while closing the photoredox catalytic cycle. The subsequent coupling between the electrophilic radical **8** and the chiral enamine **4**[14] forms the electron-rich α-amino radical **9** that can be easily oxidized by the excited species **6** to give the corresponding iminium ion **10**,[15] which after hydrolysis regenerates the chiral amine **3** and releases the α-alkylation product. The oxidation step also regenerates $[Ru(bpy)_3]^{+}$ (**7**), thus continuing the photoredox cycle. The outstanding combination of the two catalytic cycles, which perfectly support each other, allows the asymmetric α-alkylation to take place following a well-established and correct sequence.

The usefulness of the dual catalytic cycle is, of course, dependent on the possibility of inducing high stereoselectivity during the alkylation step, which occurs between the π-rich enamine and the electron-deficient radical. The novel chiral secondary amine **3** provides excellent enantiocontrol through

a classic "steric-control approach". Interestingly, the pseudo-C_2 symmetry of imidazolidinone **3**—having the two chiral fragments in a *trans* relationship—ensures the efficient shielding of the *Re* face of the enamine intermediate **4** independently from the olefin geometry (double bond positioned toward the methyl group, as in intermediate **4**, or the *tert*-butyl group, not shown), thus enforcing a high level of enantiofacial discrimination. Moreover, catalyst **3** works well even in reactions carried out at ambient temperature, thus avoiding the potential erosion of product enantiopurity through a **3**-induced epimerization pathway.

In addition to the advantage of carrying out reactions at room temperature, this novel strategy is technically simple and uses commercially available starting materials and a simple light source, and it leads to the formation of a broad range of α-alkylation products in a relatively short period of time (5 to 16 h reaction time), with excellent yields (ranging from 63 to 93%) and outstanding enantioselectivity (up to 99% *ee*; Scheme 4). The α-alkylation of different aliphatic



Scheme 4. The asymmetric intermolecular α-alkylation of aldehydes. Bn = benzyl, DMF = dimethylformamide, Hex = hexyl, HOTf = triflic acid.

aldehydes has been carried out stereoselectively using a broad array of electron-deficient α-bromo carbonyl compounds, such as bromo acetophenone derivatives, bromo malonates and α-bromoesters. Notably, the use of a racemic bromo β-ketoester as the radical precursor resulted in the generation of two contiguous stereocenters (one of which is quaternary) with high diastereo- and enantioselectivity.

The results disclosed by Nicewicz and MacMillan on the cooperation between photoredox catalysis and aminocatalysis should have a profound impact on asymmetric synthesis. The synthetic problems associated with the valuable yet elusive asymmetric intermolecular α-alkylations of aldehydes have finally been addressed. Now, this direct methodology can be used by chemists to forge novel carbon–carbon bonds with high levels of stereocontrol by following a very simple procedure. Although the class of alkylating agents employed is still limited to α-bromo carbonyl compounds, the method has the potential to be extended to other activated bromo derivatives.[16] A more challenging advance would be the use of non-activated alkylating agents such as simple alkyl halides.

In addition to the synthetic value of the alkylation strategy described herein, other matters should be highlighted. The impressive results in terms of the stereocontrol achieved in this one-electron-mediated transformation dispel the common notion that the high reactivity of radicals precludes their use in asymmetric catalysis,[17] and reinforce the idea that the potential of organo-SOMO catalysis is far from being fully disclosed. Moreover, this study further illustrates how the current progress of asymmetric aminocatalysis relies on the capacity of merging concepts that come from different areas of chemistry—a strategy that may allow us to implement transformations otherwise impossible to realize.

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[3] a) *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-WCH, Weinheim, **2000**; b) D. Caine in *Comprehensive Organic Synthesis*, *Vol. 2* (Ed.: B. M. Trost), Pergamon Press, New York, **1991**, Chapter 1.1, and references therein; c) D. A. Evans in *Asymmetric Synthesis*, *Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1983**, Chapter 1; d) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253.

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[7] As validation of its reliability and effectiveness, the enamine-catalyzed asymmetric intramolecular α-alkylation of aldehydes has recently been integrated into domino sequences, thus leading to the synthesis of complex cyclic molecules with high optical purity: a) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886; b) R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziedzic, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*,

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[11] For a perspective on this discovery, see: P. Renaud, P. Leong, *Science* **2008**, *322*, 55.
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[13] In the course of luminescence-quenching studies, it was observed that preformed chiral enamines decreased the emission intensity of **6**, while the presence of α-bromo carbonyl compounds did not. This result supports the mechanistic proposal that **6** is acting as an oxidant in the photoredox cycle.
[14] Circumstantial evidence for the direct involvement of the enamine intermediate in the key bond-forming step has been collected. The coupling of an electron-rich enamine with electron-deficient radicals has the converse mechanism to that of the previously described SOMO-catalyzed reactions, where the susceptibility of the transient enamine for undergoing selective oxidation generates a reactive 3π-electron radical cation, see Ref. [9]. This complementary reactivity further expands the synthetic potential of SOMO catalysis.
[15] As a propagation step, the direct SET from the electron-rich α-amino radical **9** to the α-bromo carbonyl compound cannot be excluded. As a matter of fact, good results are obtained in the absence of any photoredox catalyst while irradiating the reaction mixture with a high-energy UV lamp. For an example of a catalytic enantioselective reaction driven by photo-induced electron transfer, see: A. Bauer, F. Westkaemper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139.
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