ENANTIOSELECTIVE α-FUNCTIONALIZATION OF ALDEHYDES VIA SOMO CATALYSIS

Reported by Seiko Fujii September 10th, 2009

INTRODUCTION

The field of asymmetric synthesis has rapidly advanced as a result of the increasing need for enantiopure compounds. In particular, organocatalysis is recognized as a complementary approach to well-established organometallic or biological methodologies in asymmetric synthesis. Traditional modes of activation in organocatalysis proceed via condensation of a chiral amine catalyst with a carbonyl compound to form an enamine or iminium ion intermediate. These two modes of activation are called enamine catalysis[1] and iminium ion catalysis,[2] respectively. Although the development of organocatalysis has made advancements in the α-functionalization of carbonyl compounds, there are transformations that have not been realized, such as catalytic, enantioselective, intermolecular α-alkylation of aldehydes.[3] To address this outstanding synthetic challenge, MacMillan and co-workers introduced a third mode activation in organocatalysis termed singly occupied molecular orbital (SOMO) catalysis, in which the substrate is activated as a cationic radical-enamine intermediate.[4] The introduction of this novel mode of activation has expanded the scope of organocatalysis to include highly enantioselective α-allylic alkylation, α-enolation, α-vinylation, α-arylation, α-trifluoromethylation, and α-homobenzylation of aldehydes. Furthermore, the application of SOMO catalysis has improved upon the current state-of-the-art methods, such as α-chlorination, and has even improved upon its own limitations by merging with photoredox catalysis.

THE ENGINEERING OF SOMO CATALYSIS

Enamine catalysis is activated by increasing the energy of the highest-occupied molecular orbital (HOMO).[5] On the other hand, iminium ion catalysis is activated by decreasing the energy of the lowest-unoccupied molecular orbital (LUMO). Both enamine and iminium catalysis involve activation of substrates based on the natural polarity of the reactants, which has limited organocatalysis to two-electron chemistry.[6] MacMillan and co-workers designed SOMO catalysis to solve current limitations in α-alkylation of aldehydes. Because enamines and the corresponding iminium ions rapidly interconvert, an interruption of this interconversion was proposed to lead to a mode of activation that bisects enamine and iminium catalyses. It was hypothesized that a selective one-electron oxidation of an electron-rich enamine would generate a reactive radical cation with three-π-electrons that can undergo subsequent

one-electron chemistry. Early examples had shown precedent for radical cations to participate in non-catalytic enantioselective C-C bond formations.[7]

Three key design elements were identified to substantiate this proposal. First, enamine intermediate **2** must undergo selective oxidation in the presence of imidazolidinone catalyst **1** and a simple aldehyde to form radical cation **3** that is more prone to subsequent reactions than the original aldehyde (Figure 1). Theoretical support for the chemoselectivity of oxidation between **2** and other substrates was derived from the ionization potentials (IPs) of similar substrates: 1-(but-1-enyl)pyrrolidine (IP=7.2 eV), pyrrolidine (IP=8.8 eV), and butanal (IP=9.8 eV).[4] The IP of **2** was lower than the aldehyde or **1**, suggesting that **2** is more susceptible to oxidation than the other reagents.

Identification of an amine catalyst that could be widely applicable in highly enantioselective transformations was also necessary. Calculations conducted with density functional theory (DFT) led to a prediction that catalyst **1** would selectively form a SOMO-activated cation that projects the three-π-electron system away from the bulky *t*-butyl and benzyl groups. In addition, it was shown that radical-centered enamine **3** selectively orients in an *E*-configuration to minimize nonbonding interactions with the imidazolidinone ring. DFT calculations also revealed that the benzyl group shields the *Re* face of the radical cation, exposing the *Si* face for the subsequent enantioselective reaction to take place.

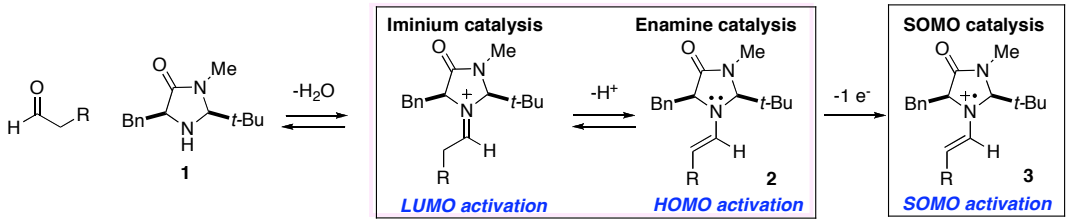


Figure 1. SOMO Catalysis via Single-Electron Oxidation of a Transiently Formed Enamine.

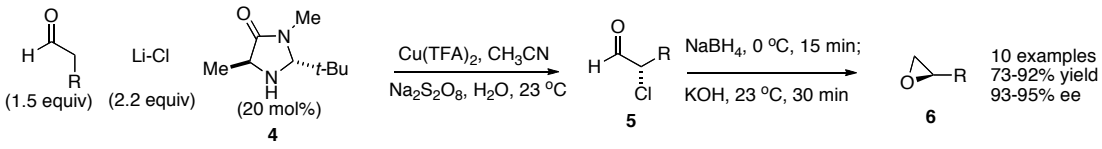
INCREASED REACTICITY VIA SOMO CATALYSIS

α–Chlorination of Aldehydes and *In Situ* Conversion to Terminal Epoxides

The development of SOMO catalysis improved upon the well-established enantioselective α-chlorination of aldehydes by taking advantage of the increased reactivity of the radical cation intermediate. α-Chloro aldehydes are valuable synthetic intermediates to important classes of building blocks for the synthesis of many active pharmaceuticals and agricultural products, such as terminal epoxides. Prior to SOMO catalysis, direct enantioselective α-chlorination of aldehydes was achieved by MacMillan[8] and Jørgensen,[9] employing enamine catalysis with perchlorinated quinone and *N*-chlorosuccinimide (NCS) as chlorinating sources, respectively. The introduction of SOMO catalysis has improved upon these methodologies by allowing low molecular weight, low-cost, and environmentally

friendly reagents such as LiCl and NaCl to act as suitable chloride sources (Scheme 1). A simple aldehyde, catalyst **4**, and an oxidant combination of sodium persulfate and catalytic copper (II) trifluoroacetate yielded aldehyde products in 75-95% yield and 91-96% ee. In addition, previous reports have shown that the α-chloro aldehydes could be converted into useful synthons, such as epoxides and amino acids, over several discrete steps. MacMillan and co-workers expanded this strategy, in which the key induction step does not lead to the final product, but instead, to an enantioenriched reactive intermediate that can be rapidly converted into a broad range of valuable synthons. The employment of this strategy eliminated the isolation and purification of the possibly unstable synthetic intermediates by an *in situ* conversion of aldehyde **5** to terminal epoxide **6** (Scheme 1).[10] Considerable variation in the steric demand of the aldehyde component was possible without decreasing the enantioselectivity or yield, and a wide range of functional groups including olefins, esters, amines, carbamates, and aryl rings were tolerated.

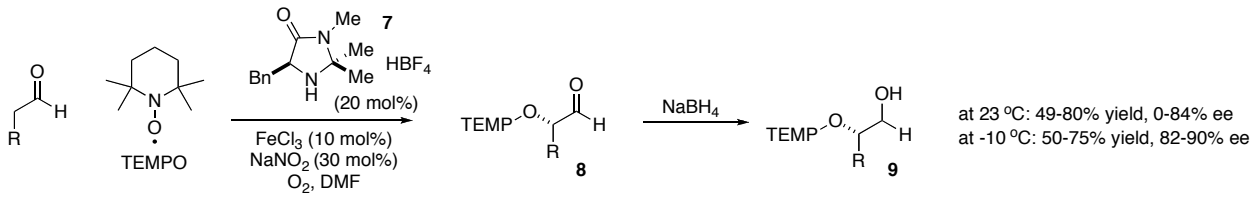
Scheme 1. Synthesis of α-Chloro Aldehydes and *In Situ* Conversion to Terminal Epoxides.



α–Oxyamination

Sibi and co-workers reported an enantioselective α-oxyamination of aldehydes via SOMO catalysis.[11] Unlike the SOMO catalysis reported by MacMillan, persistent radicals were allowed to react with enamine intermediates. Substoichiometric amounts of $FeCl_3$ as a single electron transfer (SET) reagent with $NaNO_2$ and O_2 repeatedly oxidized the enamine intermediate to the corresponding SOMO-activated enamine. α-Oxyaminated aldehyde **8** was synthesized from a simple aldehyde, MacMillan's catalyst **7**, and 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) (Scheme 2). Despite these reactions being sensitive to temperature and solvent, alcohol **9** was isolated in 50-75% yield and 82-90% ee. α-Oxyamination products were already accessible by other organocatalytic procedures.[12] Employment of a substoichiometric amount of the SET reagent and oxygen as a terminal oxidant was an attractive new development in the field of SOMO catalysis.

Scheme 2. α-Oxyamination of Aldehydes via SOMO Catalysis.

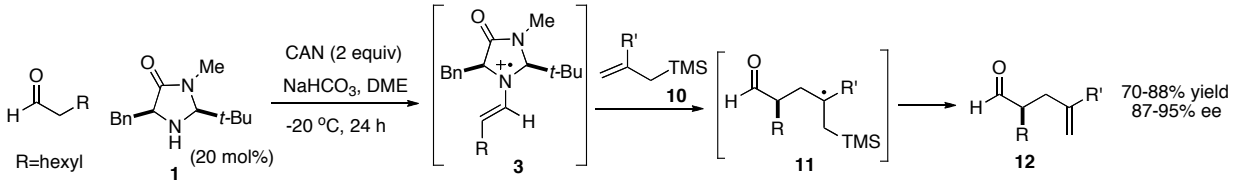


THE DEVELOPMENT OF NEW REACTION MANIFOLDS

α-Allylic Alkylation

Significant advances were made in the α-chlorination of aldehydes, yet an even more attractive feature of SOMO catalysis is its capacity to enable the development of new transformations that have not been accessible by current synthetic methods. Electron-deficient radicals have been shown to react with π-rich olefins to construct C-C bonds,[13] yet enantioselective α-allylic alkylation of aldehydes had only been reported in low yields and enantioselectivities prior to the introduction of SOMO catalysis.[14] As a representative transformation, octanal was allowed to react with imidazolidinone catalyst **1** in dimethoxy ethane (DME) (Scheme 3). Ceric ammonium nitrate (CAN)-mediated oxidation of the enamine produced intermediate **3**. Cationic radical enamine **3** and allyltrimethylsilane **10** formed radical intermediate **11**, and a second oxidation and removal of the silyl group afforded a range of γ-δ unsaturated α-functionalized aldehydes **12** in good yields and enantioselectivities.[7] A range of π-rich olefinic silanes, as well as electron-deficient olefinic silanes, reacted with **3**. Moreover, olefins, ketones, esters, and carbamate functionalities were inert under these mild oxidative conditions. MacMillan and co-workers employed simple olefins as compatible alkylating partners in the α-allylic alkylation of aldehydes, a reaction that was not possible via a two-electron pathway.

Scheme 3. Enantioselective α-Allylation of Aldehydes via SOMO-Catalysis.



α-Enolation

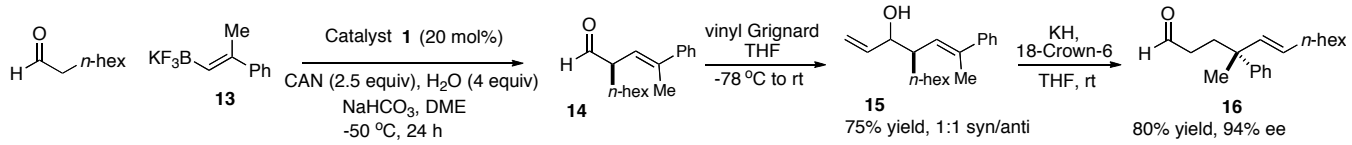
The generality of this new mode of activation was demonstrated by MacMillan and co-workers via a direct, catalytic, and enantioselective α-enolation of aldehydes with silyl enol ethers as alkylating partners to afford γ-ketoaldehydes.[15] Aldehydes with hexyl, cyclohexyl, or 4-piperidyl functional groups all consistently yielded the corresponding products in high yields and enantioselectivities. Electron-rich heteroaromatic silanes that are often unstable to mild oxidative conditions were compatible, affording the corresponding products in 70-77% yields and greater than 92% ee.

α-Vinylation

Enantioselective α-vinylation of enolates has been slow to develop and has been limited to the

construction of molecules containing stereogenic centers that cannot epimerize prior to the advancement of SOMO catalysis.[16] In this vein, MacMillan and co-workers successfully achieved the enantioselective α-vinylation of aldehydes by employing vinyl trifluoroborate salts.[17] Octanal and trisubstituted olefin **13** were allowed to react to form alkylated aldehyde **14** (Scheme 4). Various aldehydes and vinyl trifluoroborate salts were tolerated under mild reaction conditions. In addition, the applicability of this novel transformation was shown by the three-step conversion to enantioenriched oxy-Cope products. *In situ* addition of a Grignard reagent to **14** provided 1,5-dienyl alcohol **15** in 1:1 dr. Under Evans' anionic oxy-Cope conditions, rapid stereoconvergent rearrangement aldehyde **16** in 80% yield and 94% ee (Scheme 4).

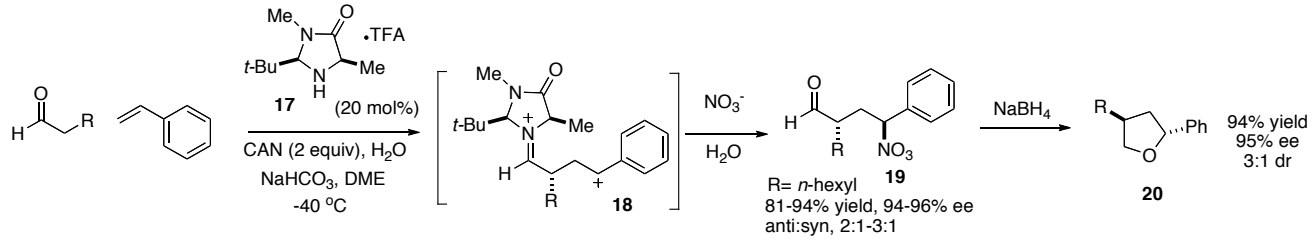
Scheme 4. α-Vinylations of Aldehydes with Vinyl Potassium Trifluoroborate Salt.



Carbo-oxidation of Styrenes

MacMillan and co-workers further advanced the novel SOMO activation concept by demonstrating the construction of γ-nitrate-α-alkyl aldehydes that are valuable synthons for the production of enantioenriched heterocycles.[18] The use of simple styrenes as enantioselective α-alkylation partners for aldehydes was not precedented, yet this transformation was made possible via SOMO catalysis (Scheme 5). Unlike α-vinylations, an intermolecular addition of an anionic or neutral heteroatom to the high-energy cationic intermediate **18** was demonstrated. Octanal and styrene were allowed to react with imidazolidinone catalyst **17** to yield product **19** in 91% yield and 96% ee. The diastereoselectivity was moderate (anti/syn 3:1) for the cation-trapping step, yet the nitrate ester products were utilized in the construction of enantioenriched heterocycles. For example, *in situ* treatment of **19** with $NaBH_4$ yielded substituted tetrahydrofuran **20**.

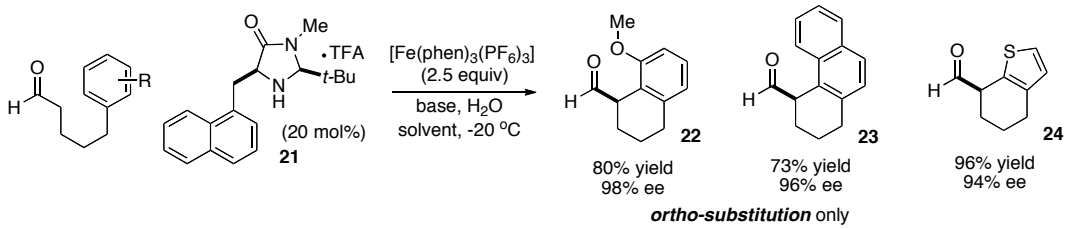
Scheme 5. Carbo-Oxidation of Styrenes via SOMO Catalysis.



α-Arylation

Significant advances in the area of α-arylation of aldehydes have been made using transition metal mediated methods, and most recently, an enantioselective, Pd-mediated intramolecular α-arylation of aldehydes was reported for the construction of quaternary carbon centers.[19] The introduction of SOMO catalysis offered an alternative method for the enantioselective intramolecular α-arylation of aldehydes to produce enolizable α-formyl-α-aryl products without epimerzation (Scheme 6).[20] Electron-rich heterocycles were tolerant of the mild oxidative conditions, as shown by product **24**. It was proposed that α-arylation occurs via an ortho-selective radical mechanism, unlike the Friedel-Crafts-type mechanism proposed by Nicolaou.[21] This proposal was based on mechanistic studies that employed a radical-clock probe, which showed evidence for a radical-mediated pathway. Furthermore, only ortho-substituted products **22** and **23** containing 1,3-disubstituted aryl rings were observed. In addition, an increase in enantioselectivity was shown when $[Fe(phen)_3]\bullet(PF_6)_3]$ was employed as an oxidant instead of CAN.

Scheme 6. Enantioselective Intramolecular α-Arylation of Aldehydes via SOMO catalysis.

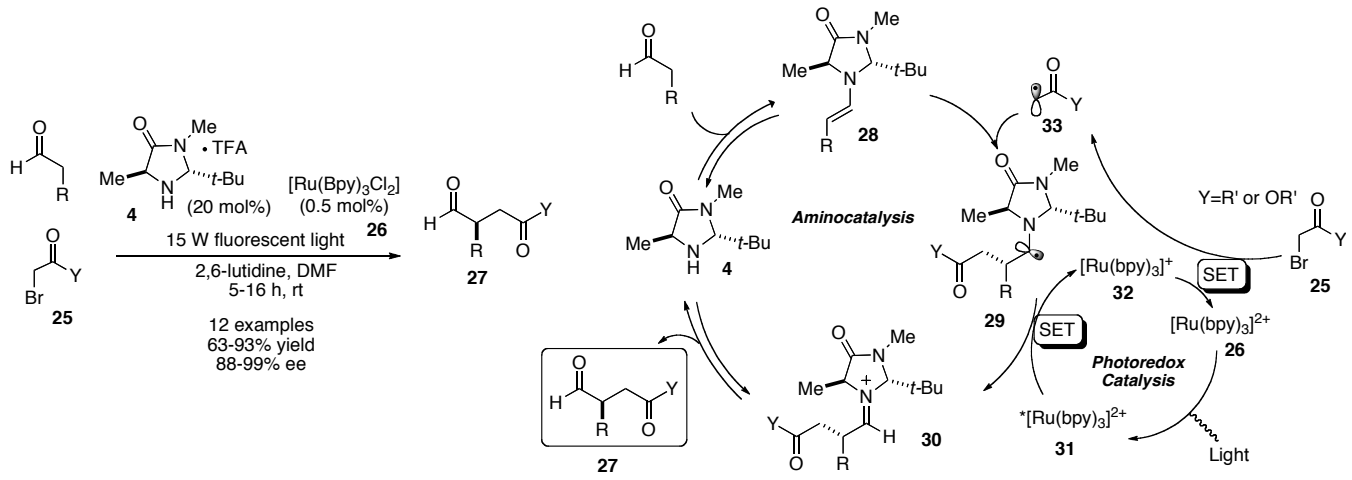


FURTHER IMPROVEMENT ON SOMO CATALYSIS: PHOTOREDOX ORGANOCATALYSIS

Traditionally, asymmetric α-alkylation of aldehydes relied heavily on methods that employ chiral auxillaries. Because chiral auxillaries require additional steps for their attachment and removal, catalytic methods are desirable. However, catalytic enantioselective α-alkylation of aldehydes has been a long-standing challenge. By merging photoredox catalysis with organocatalysis, MacMillan and Nicewicz addressed this unsolved problem in an even more efficient manner compared to the double oxidation procedure reported earlier.[22] Incorporation of a photoredox catalyst eliminated the need for a stoichiometric oxidant. Direct alkylation of simple aldehydes with α-bromo carbonyl compounds was accomplished via two independent catalytic cycles working in a synchronous fashion (Scheme 7). The generation of electron-rich enamine **28** from the classic enamine activation pathway and the production of electron-deficient α-alkyl radical **33** from α-bromo carbonyl **25** was accomplished with the use of ruthenium (II) tris-2,2'-bipyridine complex **26**, a well-established photoredox catalyst.[23] With irradiation by a household 15 W fluorescent light, **26** populates the $*[Ru(bpy)_3]^{2+}$ (**31**) metal-to-ligand charge-transfer (MLCT) excited state, which has enhanced oxidizing and reducing capabilities. Alkylation

occurs when an electron deficient alkyl radical **33** removes a single electron from enamine **28**. The reduced Ru complex **32** functions as a SET reagent and reduces **25**, regenerating **26** to complete the catalytic cycle. In the second photoredox cycle, **31** functions as a SET reagent to remove a single electron from **29** to yield iminium ion **30**. The practical advantages of this approach were mild reaction conditions, inexpensive and commercially available starting materials, and a simple light source. This versatile α-alkylation reaction expanded the scope of SOMO catalysis. Instead of a cationic radical enamine reacting with an olefinic partner as shown in previous examples, the enamine reacts with an electron-deficient radical in photoredox organocatalysis. Recently, enantioselective α-trifluoromethylation of aldehydes via photoredox organocatalysis was reported, further illustrating the applicability of the improved SOMO catalysis manifold.[24]

Scheme 7. Asymmetric Intermolecular α-Alkylation via Photoredox Organocatalysis.



CONCLUSION

In the development of SOMO catalysis, MacMillan and co-workers have shown that design and implementation of novel activation modes can not only complement established methods, but also overcome limitations and enable the development of unprecedented transformations. Catalytic, enantioselective, α-alkylation of aldehydes, a long-standing synthetic problem, has now been achieved via SOMO catalysis in high yields and enantioselectivities. Furthermore, through the development of photoredox organocatalysis, MacMillan and co-workers have demonstrated that the current progress of asymmetric organocatalysis relies on the capacity of merging concepts that come from different areas of chemistry. The emerging field of SOMO catalysis has potential to further expand the scope of asymmetric catalysis.

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