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Mechanistic Evidence for Intermolecular Radical Carbonyl Additions Promoted by Samarium Diiodide

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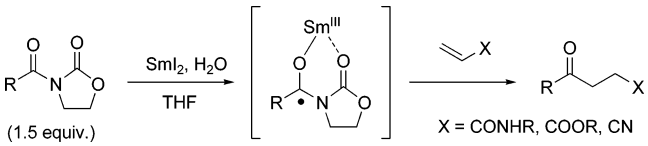
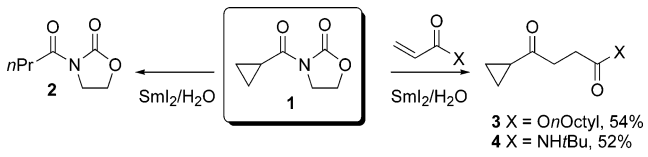
Since the introduction of SmI_2 by Kagan and co-workers in the late 1970's, this single-electron transferring agent has steadily developed into a successful reagent for promoting a multitude of synthetic organic transformations.[1] Intermolecular alkyl addition reactions to carbonyl substrates represents a principal category of such useful transformations (e.g., Barbier reaction). Kagan proposed a number of possible mechanistic scenarios for this reaction, including the addition of an alkyl radical to a carbonyl compound as the crucial C−C bond-forming step resulting in an alkoxy radical intermediate.[2] This mechanism was dispensed for several reasons including the low rate constants for bimolecular additions of radicals to ketones.[3b] Through elegant mechanistic studies by the Curran, Molander, Kagan, and Flowers groups,[3−6] it is now widely accepted that such reactions proceed through an ionic pathway, where alkyl radical intermediates, generated via the reduction of corresponding halides, are reduced to an organosamarium species prior to carbonyl addition. In this communication, we report experimental evidence that for certain SmI_2-promoted C−C bond-forming reactions intermolecular radical addition to carbonyl compounds can proceed with high efficiency without the intervention of an organosamarium intermediate.[7]

Scheme 1



We recently reported the aptitude of *N*-acyl oxazolidinones to couple with acrylates/acrylamides in the presence of SmI_2/H_2O, providing a general route to γ-carbonyl esters/amides (Scheme 1).[8,9] Although we originally proposed a mechanism proceeding via a metalated ketyl radical anion intermediate, after continual probing of the substitution pattern of both coupling partners, several observations suggested that an alternative mechanism was operating involving possibly initial reduction of the acrylate/acrylamide to a dianion, followed by subsequent nucleophilic acyl substitution of the *N*-acyl oxazolidinone.[10,11]

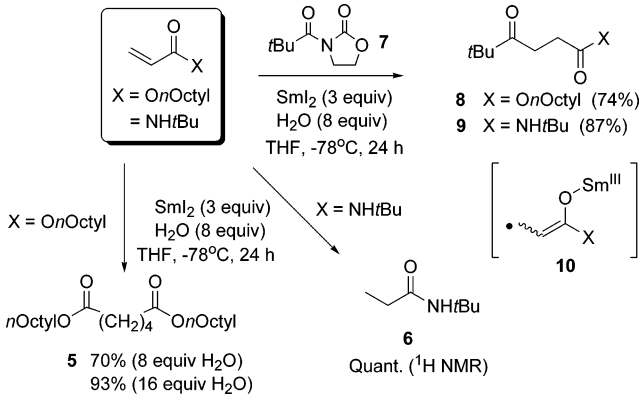
Scheme 2



To shed light onto this mechanistic enigma, the coupling potential of the cyclopropyl derivative **1** with the electron-deficient alkenes was examined (Scheme 2). Participation of a ketyl radical anion intermediate was predicted to lead to rapid ring opening of the cyclopropane substituent.[12] Conversely, normal coupling products with an intact cyclopropane ring would support a mechanism involving nucleophilic acyl substitution. Treatment of **1** with SmI_2/H_2O for 24 h at −78 °C led to the ring-opened product **2** along with substantial amounts of unreacted **1**. While this experiment demonstrates the feasibility of electron transfer to the carbonyl of **1**, the reaction is slow.[10] Yet, when either *n*-octyl acrylate or *tert*-butyl acrylamide was added to identical reaction conditions, only the products **3** and **4** could be isolated in yields of 54 and 52%, consistent with a mechanism invoking nucleophilic acyl substitution.

Additional experiments were performed to examine the validity of this proposal (Scheme 3). Subjecting *n*-octyl acrylate and *tert*-butyl acrylamide to the same reduction conditions without the *N*-acyl oxazolidinone produced the dimer **5** in 70% yield (93% yield with 16 equiv of H_2O) and a quantitative yield of *tert*-butyl propionamide **6**, respectively. However, in the presence of the *N*-acyl oxazolidinone **7**, the γ-keto ester **8** and amide **9**[8] were obtained in good yields with only traces of **5** and **6**, respectively.

Scheme 3



These experiments are inconsistent with a nucleophilic acyl substitution mechanism. There is no literature precedence for organosamarium species undergoing conjugate additions,[13] indicating that **5** arises from either the dimerization of **10** or the initial radical addition of **10** to the acrylate. The formation of **8** suggests that *this C−C bond-forming reaction is faster than the radical dimerization/addition step involving the acrylate*. We conclude, therefore, that the coupling reactions with acrylates proceed through a radical mechanism. The experiments with the *tert*-butyl acrylamide are less-conclusive, as only the reduced product **6** was obtained. Further evidence suggests that nucleophilic acyl substitution is not

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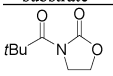
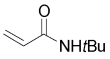
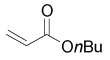
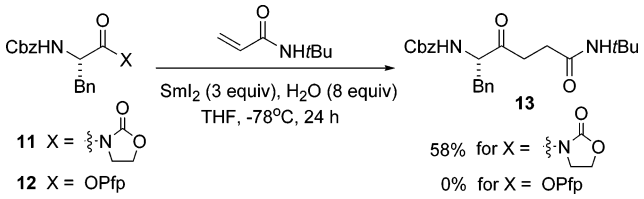
Table 1. Observed Rate Constants for the Reduction of the Substrates by SmI_2/H_2O in THF[a]

substrate	rate constant, s^{-1}
	1.90×10^{-3} [b]
	$3.80 \pm 0.03 \times 10^{-3}$
	$8.10 \pm 0.09 \times 10^{-3}$

[a] $[SmI_2] = 10$ mM, $[H_2O] = 40$ mM, [substrate] = 0.10 M. [b] Upper limit value.

the mechanistic pathway for this reaction (Scheme 4). The Pfp-ester **12** should provide a superior substrate for this coupling reaction due to its significantly enhanced leaving group ability compared to that of an oxazolidinone. Attempted coupling of **12** with *tert*-butyl acrylamide led to recovered **12** and *tert*-butyl propionamide **6**, according to the ^{1}H NMR spectrum of the crude reaction mixture. On the other hand, coupling of the phenylalanine derivative **11** to the acrylamide leads to ketone **13** in 58% yield.

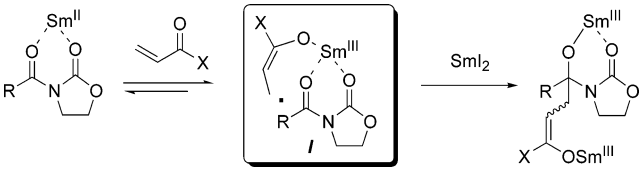
Scheme 4



Finally, it was also expected that an anionic mechanism would be sensitive to the number of equivalents of water in the reaction mixture, where competing protonation of the dianion species would reduce coupling yields. However, coupling reactions of **7** and the same acrylamide proceeded in over 50% yields, even with up to 40 equiv of water.

As a final point, rate measurements for the reduction of an acrylate, acrylamide, and a *N*-acyl oxazolidinone were carried out, the results of which support the favored reduction of the α,β-unsaturated ester or amide by SmI_2/H_2O in the presence of the derivatized oxazolidinone. Measurements were performed using stopped-flow spectrophotometry under pseudo first-order conditions, and the data are shown in Table 1. Although the rate constant for the oxazolidinone is only half that of the acrylamide, the value is an upper limit estimated from the rate data.[14]

Scheme 5



Scheme 5 depicts a possible mechanistic scenario consistent with the results described in the preceding discussion. The oxazolidinone likely has a high affinity for Sm(II) coordinating to SmI_2 and acting as a ligand such as HMPA.[15,16] This complex then reduces the acrylate/acrylamide to a radical anion, providing a chelated intermediate **I**. The effect of the lanthanide center is 2-fold for overcoming the otherwise slow rate constants for intermolecular radical additions to carbonyl groups.[3b] First, its hard Lewis acid character lowers the $\pi^*_{C=O}$ orbital to such an extent that radical addition to this C═O bond becomes favorable. Second, the metal center acts as a tether, thereby appropriately positioning the radical for a pseudo-intramolecular addition. The alkoxy radical formed is then reduced by a second SmI_2.

In conclusion, we have provided evidence lending support to a mechanism involving intermolecular alkyl radical addition to carbonyl compounds for the SmI_2-promoted coupling of α,β-unsaturated esters/amides to *N*-acyl oxazolidinones. Further work is underway to provide additional kinetic data for these reactions, as well as to examine the generality of this mechanism for other SmI_2-promoted C−C bond-forming reactions.

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Supporting Information Available: General experimental methods for the radical addition reactions and spectroscopic data for the coupling products, including copies of ^{1}H and ^{13}C NMR spectra, and Note added in Proof. This material is available free of charge via the Internet at http://pubs.acs.org.

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