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# Importance of C−N Bond Rotation in *N*-Acyl Oxazolidinones in their $SmI_2$-Promoted Coupling to Acrylamides

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***Abstract:*** A detailed mechanistic investigation was undertaken to determine the dominating factors of the postelectron transfer steps in the $SmI_2$-promoted carbon−carbon bond forming reaction between *N*-acyl oxazolidinones and acrylamides. Competition experiments were performed by reacting two *N*-acyl oxazolidinones with a limiting amount of *N*-*t*-butyl acrylamide, and from the product distribution, the relative reactivity values (*RV*) for a series of *N*-acyl oxazolidinones were then calculated against *N*-pivaloyl oxazolidinone as the reference. An almost linear correlation was obtained for the simple alkyl *N*-acyl oxazolidinones when ln *RV* was plotted against the activation barriers for C−N bond rotation (*s-trans* to *s-cis*) obtained by DFT calculations, implying that C−N bond rotation from the *s-trans* to *s-cis* conformation is one of the essential parameters controlling the reactivity. These results were substantiated by other competition experiments carried out for the corresponding imide derivatives, where rotation is not necessary for obtaining bidentate coordination and where no such correlation as described above was observable. The finding that the reactivity of the simple *N*-acyl oxazolidinones for these $SmI_2$-mediated transformations correlates with the activation barriers for C−N bond rotation may have implications for other useful synthetic organic reactions involving similar substrates. Finally, these studies were extrapolated to understanding the poor reactivity of *N*-acyl oxazolidinones, as those derived from Evans chiral auxiliaries, with *N*-*tert*-butyl acrylamide. These couplings appear to be dominated by the activation energy for addition because of arising *syn*-pentane interactions in the transition-state for C−C bond formation. We demonstrate that the addition of Lewis acids can have a beneficial effect on the coupling yields.

## Introduction

$SmI_2$-mediated reactions have gained substantial prominence by offering mild and selective alternatives for the creation of carbon−carbon bonds. This reagent is highly suitable for promoting a multitude of transformations including ketyl-olefin radical addition reactions, inter- and intramolecular pinacol couplings, Reformatsky and Barbier type reactions, as well as cascade reactions involving a variety of combinations of these transformations.[1] A particular fascinating feature about this reagent is the ability to fine-tune its electron-donating abilities and functional group selectivity through the addition of cosolvents and additives. Substantial efforts have been made by the groups of Flowers[2] and Hoz,[3] and by others including ourselves,[4] to understand the nature of this reagent in THF, as well as other solvents, the structure of the metal complexes formed upon addition of cosolvents/additives, the interaction of such complexes with the substrates, and the mechanistic intricacies of the electron transfer step.

Although this reagent has been at the hands of synthetic chemists for nearly 30 years, relatively little mechanistic information is available concerning the post electron transfer

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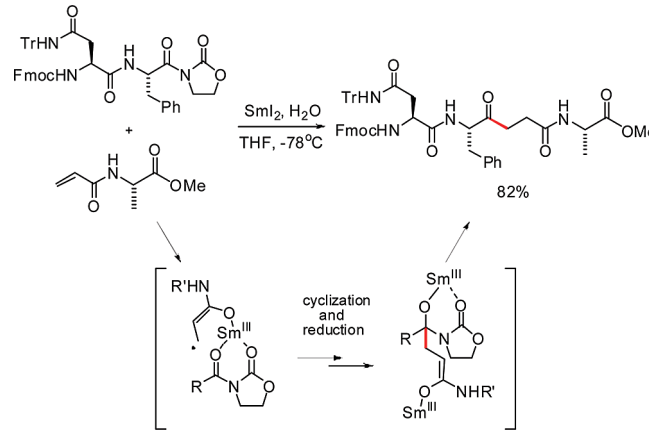
steps for the $SmI_2$-promoted reactions. Such knowledge would be essential for understanding the reactivity of $SmI_2$ and the nature of reactive intermediates generated after the electron transfer step. Furthermore, this information could be exploited for work directed at increasing selectivity of a given reaction promoted by this lanthanide reagent or even for the design of new reactions. The seminal work of Curran[5] and Molander[6] on the $SmI_2$-mediated reductive coupling of alkyl iodides with ketones in the presence of a cosolvent such as HMPA provided experimental evidence for the intermediacy of organosamarium reagents. Subsequently, the groups of Kagan[7] and Flowers[8] came to similar conclusions on the importance of organosamarium species.

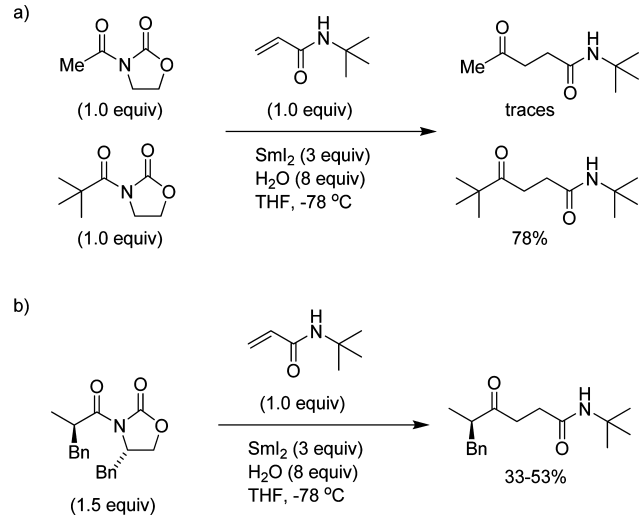
More recently, the laboratories of Hoz[9] and Flowers[10] have reported elegant studies in attempts to understand in more detail the structures of the intermediates involved in ketone reduction with and without additives present. In studies on the intramolecular carbonyl-olefin addition, Flowers and Prasad[10] were able to demonstrate, by using stopped-flow spectrophotometry, that HMPA not only increases the reduction potential of $SmI_2$ but also enhances the reactivity of the radical anion intermediate formed after the first electron transfer to the ketone functionality by promoting the formation of a solvent-separated ion pair. In continued studies on the reduction of diaryl ketones, Hoz and Farran[9] reported that HMPA also plays an important role after reduction to the ketyl radical anion. In this case, HMPA slowed the rate of the bimolecular pinacol coupling through complexation of the trivalent lanthanide ion necessary for bridging the two ketyl radical anions. Considerable efforts have also been undertaken by the groups of Hoz, Flowers, and Hilmersson to understand the role of proton donors in the protonation of ketyl and ketyl-like intermediates.[2a,f,3b−d,4b,9]

In collaboration with the Flowers group, we recently reported mechanistic information about the C−C bond forming step in an alternative reaction involving the reductive coupling of *N*-acyl oxazoldinones with electron deficient alkenes, such as acrylates, acrylamides, and acrylonitrile.[11] This reaction represents a general method for the preparation of $\gamma$-keto esters and amides in a rapid and convergent manner. In addition, the process tolerates a wide range of substituents on both the alkene and the *N*-acyl moiety of the oxazolidinone, facilitating access to products of biological relevance such as ketomethylene isosteres

***Scheme 1.*** Preparation of Ketomethylene Isosteres of Peptides in a Convergent Manner




***Scheme 2.*** Coupling Reactions that Inspired to Further Mechanistic Studies




of peptides (Scheme 1).[12] Through a combination of cyclic voltammetry measurments, stopped-flow spectrophotometry, and examination of substrate reactivity, we were led to conclude that these reactions proceed by initial electron transfer and reduction of the olefin to a radical anion species followed by radical addition to the exocyclic carbonyl group of the *N*-acyl oxazolidinone for C−C bond formation.[11]

Yet, there are still some features of this reaction that need further attention. For example, we have performed a competition experiment with a 1:1:1 ratio of *N*-acetyl oxazolidinone, the corresponding *N*-pivaloyl derivative, and *t*-butyl acrylamide.[11] In this case, the *tert*-butyl ketone was produced in a 78% yield with only traces of the corresponding methyl ketone, and the *N*-acetyl oxazolidinone was almost completely recovered (Scheme 2a). This result is counterintuitive when considering the relative bulk of the acyl moieties and their possible influence on the

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addition step to the carbonyl moiety. Although *N*-acetyl oxazolidinone can couple to the acrylamide, dimerization of reduced acrylamide or a second reduction step followed by protonation to the corresponding proprionamide is more prominent for this coupling reaction than for the pivaloyl analog, again supporting a slow cross-coupling for the *N*-acetyl derivative.

Furthermore, recent experiments in our laboratory have shown that chiral oxazolidinones can be exploited for these tranformations as well, allowing products from an Evans asymmetric alkylation to undergo C−C bond formation directly after the alkylation step (Scheme 2b).[13] Nevertheless, yields of these systems proved to be lower than those of the simple unsubstituted oxazolidinone, and again, substantial amounts of the reduced acrylamide were recovered, witnessing to a slow coupling reaction.

To gain further mechanistic insight into this $SmI_2$-mediated coupling of *N*-acyl oxazolidinones and acrylamides, and to understand the above-described productivity difference between the different *N*-acyl oxazolidinones, we embarked on an elaborate study to provide more specific knowledge on the determining factors for reactivity. We chose to expand on the competition experiments between two structurally related substrates competing for a common $SmI_2$-reduced reagent, exploiting the fact that the product distribution will reflect the relative rates of the reaction, thereby disclosing potentially useful information about relative activation energies. Combining these experiments with DFT calculations, we report the unexpected finding that the relative rate constants of product formation correlate with the barriers for C−N bond rotation of the simple alkyl *N*-acyl oxazolidinones. These findings are supported by additional coupling reactions with analogous carbonyl substrates that do not display a difference in reactivity depending on rotational barriers. Furthermore, we demonstrate a means of exploiting these results for increasing the reactivity of poorly reactive *N*-acyl oxazolidinones such as those derived from Evans chiral auxiliaries.

## Results and Discussion

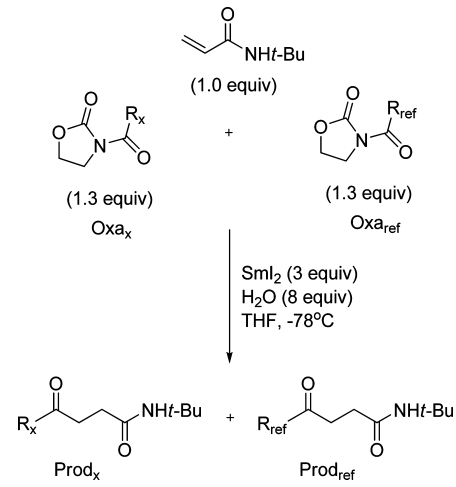
**Competition Studies.** To understand the productivity difference previously observed for the $SmI_2$-promoted reductive coupling of *N*-acyl oxazolidinones with acrylamide, competition experiments were carried out between several *N*-acyl oxazolidinones with variations in the *N*-acyl side-chain. In a typical experiment, the two *N*-acyl oxazolidinones were led to react with limiting amounts of *N-tert*-butyl acrylamide in the presence of $H_2O$. A 0.1 M solution of $SmI_2$ in THF was added dropwise over 10 min to produce the reactive intermediate *in situ*, whereby the relative reactivity of the two *N*-acyl oxazolidinones determines the product distribution (Scheme 3).

The fact that the two oxazolidinones compete in the addition step for the same reactant, being a reduced acrylamide species, leads to the following simple kinetic expression (eq 1) as outlined elsewhere:[14]

$$\frac{k_x}{k_{\mathrm{ref}}} = \frac{\ln(([\mathrm{Oxa}_{x,\mathrm{start}}] - [\mathrm{Prod}_{x,\mathrm{end}}])/[\mathrm{Oxa}_{x,\mathrm{start}}])}{\ln(([\mathrm{Oxa}_{\mathrm{ref,start}}] - [\mathrm{Prod}_{\mathrm{ref,end}}])/[\mathrm{Oxa}_{\mathrm{ref,start}}])} \quad (1)$$

The relative reactivity values ($RV = k_x/k_{\mathrm{ref}}$) can then be calculated knowing the initial concentration of the oxazolidinones and determining the product distribution by analysis of the $^1$H NMR spectrum of the crude product mixture (eq 1), under the assumption that the *N*-acyl oxazolidinones have no alternative reaction pathways. With the tools available to us, it was not possible to measure the absolute rates of product formation as the reaction was observed to take place nearly instantaneously upon addition of $SmI_2$. For a number of selected experiments, we were able to recover quantitatively all materials, and importantly, nearly identical *RV*'s could be measured as a function of recovered *N*-acyl oxazolidinones or as a function of isolated yields of the corresponding $\gamma$-ketoamide products. Equally important for the validity of the found *RV*'s is that in all of the experimental reactions carried out, a large excess of the *N*-acyl oxazolidinones was added, thereby minimizing nonproductive reaction pathways, that is, C=C double reduction and dimerization of the acrylamide.[15]

***Scheme 3.*** Setup of Competition Experiments




The *RV*'s for the *N*-acyl oxazolidinones tested were calculated against *N*-pivaloyl oxazolidinone **5** as an arbitrary standard ($R_{\mathrm{ref}}$ = *tert*-butyl) and the results of these competition experiments are collected in Table 1. It was interesting to observe, that the *N*-acyl oxazolidinones with the more bulky acyl moieties outcompeted the less bulky equivalents by as much as 10 to 30 times (i.e., entries 1−4). Moreover, it is evident that a heteroatom in the $\alpha$- or $\beta$-position has a beneficial effect on the rate of reaction. As can be seen from the *RV*'s measured (entries 8 and 9), **8** and **9** were more reactive than the *N*-butanoyl oxazolidinone **3** exhibiting similar bulk properties.

We anticipate that the mechanism for the C−C bond formation involves a Lewis acid coordinated *N*-acyl oxazolidinone with either a divalent or trivalent samarium metal cation. One explanation for the higher reactivity of the *N*-pivaloyl derivative **5** compared to the corresponding *N*-acetyl compound **1** might be the difference in Lewis basicity of the two *N*-acyl carbonyl groups. Hence, the greater inductive effect of the *tert*-butyl group compared to the methyl group would allow a stronger complexation of **5** with a Lewis acid, that is, Sm(II) or Sm(III).[16] However, such an explanation does not account for the high reactivity of the *N*-methoxyacetyl **9**, which in principle should

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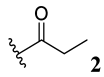
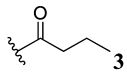
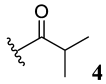
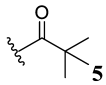
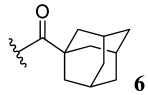
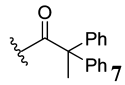
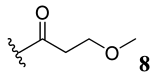
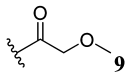
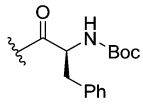
(15) Reductive coupling between two alkenes is possible, as reported by Inanaga: Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1999**, *40*, 7497.

(16) For a comprehensive review of Lewis acids in free radical reactions and the use of oxazolidinone based auxiliaries: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

***Table 1.*** Competition Experiments between "Simple" *N*-Acyl Oxazolidinones (**1**−**4** and **6**−**10**) and *N*-Pivaloyl Oxazolidinone **5** as the Reference[a]

| entry | | *RV*[b] |
|---|---|---|
| 1 |  **1** | 0.088 [c] |
| 2 |  **2** | 0.094 [c] |
| 3 |  **3** | 0.080 [c] |
| 4 |  **4** | 0.11 |
| 5 |  **5** | 1.0 |
| 6 |  **6** | 1.22 |
| 7 |  **7** | 3.16 |
| 8 |  **8** | 0.27 |
| 9 |  **9** | 0.84 |
| 10 |  **10** | 0.79[d] |

[a] *N*-acyl oxazolidinone (1.3 equiv), **5** (1.3 equiv), *N*-*tert*-butyl acrylamide (1.0 equiv), $SmI_2$ (0.1 M in THF, 3 equiv), $H_2O$ (8 equiv), THF, −78 °C, 1 h. [b] RV's were calculated from the product distribution observed in the $^1H$ NMR spectrum of the crude product mixture using eq 1. [c] Value obtained from an average of two experiments. [d] Product distribution was obtained from isolated yields of the resulting γ-ketoamides.

experience an opposite inductive effect resulting in a lower reactivity relative to the *N*-butanoyl oxazolidinone **3**.

Alternatively, the increased reactivity of **9** compared to **3** by way of the electron-withdrawing effect on the acyl carbonyl, thereby resulting in a reactivity enhancement toward nucleophilic addition, could account for this reactivity difference. This is not a convincing explanation for the difference in reactivity observed between the *N*-acetyl **1** and the *N*-pivaloyl **5**, as the electron donating ability (inductive effect) of the *tert*-butyl group is greater than that of the methyl group, and this should then reduce the reactivity of the carbonyl group in **5**. In addition, **5** would be expected to be less prone to nucleophilic attack because of increased steric hindrance around the carbonyl group.

Given the experimental trend observed for the reactivity of the nonheteroatom substituted acyl moieties, we therefore sought an alternative mechanistic explanation, which was not linked to the carbonyl reactivity but rather to the bulk and conformational properties of the *N*-acyl oxazolidinones under investigation. In particular, we wished to address the possibility of the rotational barrier for the C−N bond being the controlling parameter for the reactivity of "simple" *N*-acyl oxazolidinones.

**Rotational Barriers.** Imides have been shown to be most stable in their *s-trans* conformation.[17] *N*-acyl oxazolidinones, in general, are more stable in their *s-trans* conformation, and for *N*-acyl oxazolidinones lacking substitution on the ring, the calculated difference in zero-point energy between the *s-cis* and the *s-trans* conformation is approximately 8 kcal $mol^{-1}$.[18] However, in the case of a Lewis acid mediated radical addition, the energy difference would be smaller, and one might envision that the reactivity of the "simple" *N*-acyl oxazolidinones (based on 2-oxazolidinone) could be governed by the barrier for rotation around the C−N bond. Sibi et al. reported on diastereoselective radical allylations with *N*-α-bromoacyl oxazolidinones and found an interesting improvement of stereoselectivity at higher temperatures.[19] These observations were explained in part by the rotamer population around the C−N bond of the *N*-acyl oxazolidinone favoring the *s-trans*-rotamer and the hindered rotation to the *s-cis*-rotamer for achieving bidentate Lewis acid coordination of the two carbonyl groups.

To investigate this possibility in our reactions, we conducted a theoretical study to obtain activation energies ($E_a$) for the restricted rotation around the C−N bond. The two conformations in question were optimized employing DFT at the B3LYP/6-31+G(d) level of theory.[20] Subsequently, the transition states (TS's) for the rotations were identified using the *Synchronous Transit-Guided Quasi-Newton* method as implemented in Gaussian03.[21] The structure obtained at the energy maximum from a flexible dihedral scan of the C−N bond was used as starting structure for the TS search. All minima and TS's were validated by frequency analysis at the same level of theory showing only positive second derivatives for the minimum structures while TS's gave exactly one imaginary frequency. Finally, the natural logarithm of the relative reactivity values (ln *RV*) was plotted against the calculated activation energies ($E_a = E_{TS} - E_{s\text{-}trans}$) as depicted in Figure 1.

Interestingly, a reasonable correlation could be established between the reactivity of the *N*-acyl oxazolidinone and the barrier for rotation around the C−N bond. The linear correlation included in Figure 1 for the nonheteroatom substituted *N*-acyl oxazolidinones only serves as a guide to the eye as there undoubtedly will be other factors contributing to the actual $E_a$, such as Lewis acid coordination and solvation. These contributions were assumed to have an approximately equal effect on the rate of rotation for the various substances. Nevertheless,

(17) (a) Noe, E.; Raban, M. *J. Am. Chem. Soc.* **1975**, *97*, 5811. (b) Steinmetz, W. E. *J. Am. Chem. Soc.* **1973**, *95*, 2777. (c) Noe, E.; Raban, M. *J. Am. Chem. Soc.* **1973**, *95*, 6118.
(18) See Supporting Information.
(19) Sibi, M. P.; Rheault, T. R. *J. Am. Chem. Soc.* **2000**, *122*, 8873.
(20) For theoretical studies on the barriers for rotation around the C-N bond of similar compounds such as amides, carbamates and carbamoyl chlorides, where B3LYP calculations have been employed recently: (a) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261. (b) Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426. (c) Rablen, P. R. *J. Org. Chem.* **2000**, *65*, 7930. (d) Deetz, M. J.; Forbes, C. C.; Jonas, M.; Malerich, J. P.; Smith, B. D.; Wiest, O. *J. Org. Chem.* **2002**, *67*, 3949. (e) Horwath, M.; Benin, V. *J. Mol. Struct. (Theochem)* **2008**, *850*, 105.
(21) (a) Peng, C.; Schlegel, H. B. *Israel J. of Chem.* **1993**, *33*, 449. (b) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49.

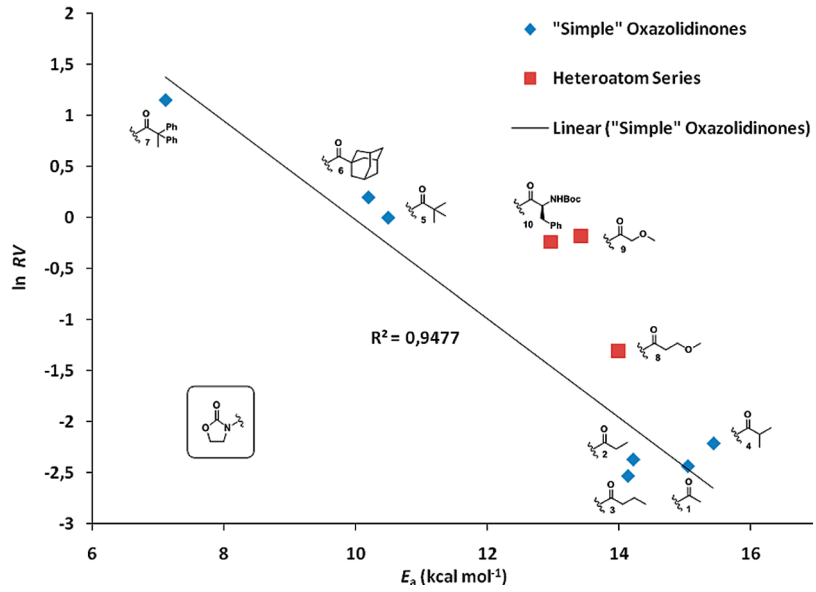
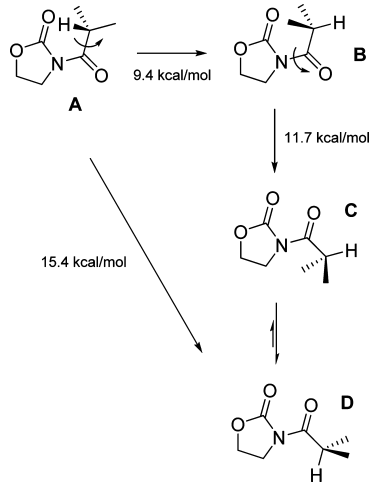
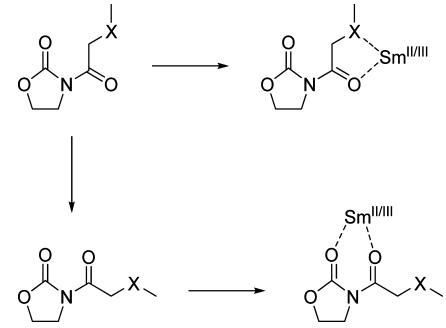



***Figure 1.*** Natural logarithm of the relative reactivity values (ln *RV*) plotted against the activation energy ($E_a$) for rotation around the C−N bond of the *N*-acyl oxazolidinone.

***Scheme 4.*** Modes of C−N Bond Rotation for *iso*-Butanoyl Oxazolidinone **4**




***Scheme 5.*** Alternative Lewis Acid Activation of the α- and β-Heteroatom Substituted Equivalents




there were some discrepancies. The *iso*-butanoyl oxazolidinone **4** gave a rotational barrier that is higher than what would be expected considering the relative bulk, despite that the observed reactivity agreed well with formerly obtained rotational barriers for *N*,*N*-disubstituted amides.[22] The activation energy for rotation from the global minimum **A** in Scheme 4 to the *s-cis* conformation was found to be 15.4 kcal mol$^{-1}$. Yet rotation could also be divided into two sequential conformational changes from the ground state, i.e. for the *iso*-butanoyl oxazolidinone **4** and other nonspherical acyl moieties, one could envisage that the conformational change is broken into a rotation around the C(=O)−$C_\alpha$ bond (**A**−**B** in Scheme 4) followed by the actual C−N bond rotation (**B**−**C** in Scheme 4). These were found to be 9.4 and 11.7 kcal mol$^{-1}$, respectively,[18] whereby **A** to **B** to **C** constitutes a faster pathway for C−N bond rotation than the direct **A** to **D**. The conformational change **A** to **B** to **C** is most likely concerted, and therefore, the true $E_a$ for *iso*-butanoyl oxazolidinone **4** C−N bond rotation is presumed to be between 11.7 and 15.4 kcal mol$^{-1}$.

Another obvious deviation from linearity is the higher than expected relative reactivity of the α- and β-heteroatom substituted equivalents **8**−**10**. We propose that these *N*-acyl oxazolidinones react through an alternative Lewis acid activation, namely through coordination of the acyl carbonyl and the heteroatom in the acyl moiety,[23] thereby bypassing rotation around the C−N bond (Scheme 5).

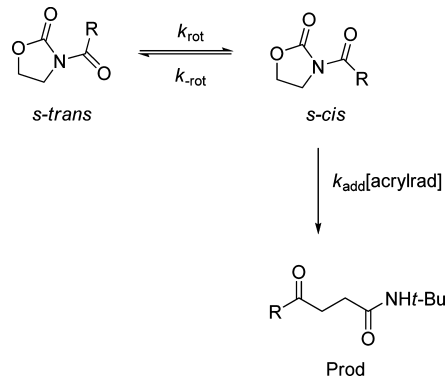
**Kinetic Interpretation and Experimental Validation of the Relative Reactivity Values (*RV*).** A suggested mechanistic scheme containing the essential kinetic steps is shown in Scheme 6, where "acrylrad" denotes the samarium diiodide reduced acrylamide, and "Prod" the product.

As hypothesized in the above section, the first step in the kinetic scheme is the *s-trans* to *s-cis* rotation of the *N*-acyl oxazolidinone, which is characterized by the equilibrium

(22) (a) Yoder, C. H.; Meyer, K. D.; Sandberg, J. A.; Leung, L. K.; Wunderlich, M. D. *J. Am. Chem. Soc.* **1978**, *100*, 1500. (b) Martins, M. A. P.; Zanatta, N.; Caro, M. S. B.; Bonacorso, H. G. *Magn. Reson. Chem.* **1993**, *31*, 451. (c) Neuman, R. C., Jr.; Jonas, V. *J. Org. Chem.* **1974**, *39*, 925.

(23) For examples of β-substituent effects on rate and mechanism of ketone reduction, see: (a) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (b) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2002**, *124*, 6357.

***Scheme 6.*** Essential Kinetic Steps for the C−C Bond Formation in the $SmI_2$-Mediated Reductive Coupling of *N*-Acyl Oxazolidinones and Acrylamides




constant $K_{rot} = k_{rot}/k_{-rot}$ with $k_{rot}$ denoting the rate constant for the *s-trans* to *s-cis* rotation and $k_{-rot}$ the rate constant for the reverse rotation. In the samarium diiodide containing solutions, the driving force for the *s-trans* to *s-cis* rotation is expected to be enhanced because of the ability of the metal center to coordinate with the two C═O groups of the *N*-acyl oxazolidinone, resulting in a bidentate coordination of samarium. We assume that this coordination occurs concertedly with the rotation process, but even if it should take place in a follow-up step the kinetic expression will be the same as long as this step is fast. The final essential reaction is the addition reaction between the *s-cis* conformation of the *N*-acyl oxazolidinone (coordinated with the samarium center) and a $SmI_2$-reduced form of *N-t*-butyl acrylamide. Using the steady-state assumption on the *s-cis* conformation the following kinetic expression ensues:[24]

$$\frac{\delta[\text{Prod}]}{\delta t} = \frac{-\delta[s\text{-}trans]}{\delta t} = k[s\text{-}trans], \text{ where}$$

$$k = \frac{k_{rot}k_{add}[\text{acrylrad}]}{(k_{-rot} + k_{add}[\text{acrylrad}])} \quad (2)$$

Two limiting situations then arise according to the relative size of $k_{-rot}$ and $k_{add}$[acrylrad]:

$$\text{For } k_{-rot} \gg k_{add}[\text{acrylrad}]\text{: } k = \frac{k_{rot}k_{add}}{k_{-rot}}[\text{acrylrad}] = K_{rot}k_{add}[\text{acrylrad}] \quad (3)$$

$$\text{For } k_{-rot} \ll k_{add}[\text{acrylrad}]\text{: } k = k_{rot} \quad (4)$$

Applying the two limiting situations to the expression for *RV* (eq 1) gives:

$$\text{For } k_{-rot} \gg k_{add}[\text{acrylrad}]\text{: } \frac{k_x}{k_{ref}} = \frac{K_{rot,x}k_{add,x}}{K_{rot,ref}k_{add,ref}} \quad (5)$$

$$\text{For } k_{-rot} \ll k_{add}[\text{acrylrad}]\text{: } \frac{k_x}{k_{ref}} = \frac{k_{rot,x}}{k_{rot,ref}} \quad (6)$$

If the second limiting case (eqs 4 and 6) applies, the expectation is thus, that the relative reactivity values exhibit a correlation with the activation barrier for the *s-trans* to *s-cis* rotation as is most likely the case for the "simple" *N*-acyl oxazolidinones, as shown in Figure 1. On the other hand, for the limiting first case (eqs 3 and 5) the kinetics becomes more complex in the sense that the addition step is rate-controlling with a pre-equilibrium process (*s-trans* to *s-cis* rotation) established first.

(24) Espenson, J. H. in *Chemical Kinetics and Reaction Mechanism*, 2nd ed.; McGraw-Hill: New York, 1995; Chapter 4.

***Table 2.*** Competition Reaction between the *N*-Pivaloyl Oxazolidinone **5** and the *N*-Acetyl Oxazolidinone **1** under Varying Reaction Conditions[a]

| entry | [*N-tert*-butyl acrylamide]$_{t=0}$ | equiv $SmI_2$ added (*n*) | addition time | RV |
|---|---|---|---|---|
| 1 | 0.10 M | 0.33 | ∼2 min[b] | 0.16 |
| 2 | 0.10 M | 0.66 | ∼2 min[b] | 0.12 |
| 3 | 0.10 M | 1 | ∼2 min[b] | 0.13 |
| 4 | 0.10 M | 2 | ∼2 min[b] | 0.16 |
| 5 | 0.10 M | 4 | ∼2 min[b] | 0.14 |
| 6 | 0.10 M | 3 | 1 min[c] | 0.17 |
| 7 | 0.10 M | 3 | 10 min[c] | 0.087 |
| 8 | 0.10 M | 3 | 30 min[c] | 0.087 |
| 9 | 0.02 M | 3 | 10 min[c] | 0.12 |
| 10 | 0.50 M | 3 | 10 min[c] | 0.091 |
| 11 | 0.10 M | 3 | 10 min[c] | 0.072[d] |
| 12 | 0.10 M | 3 | 10 min[c] | 0.12[e] |

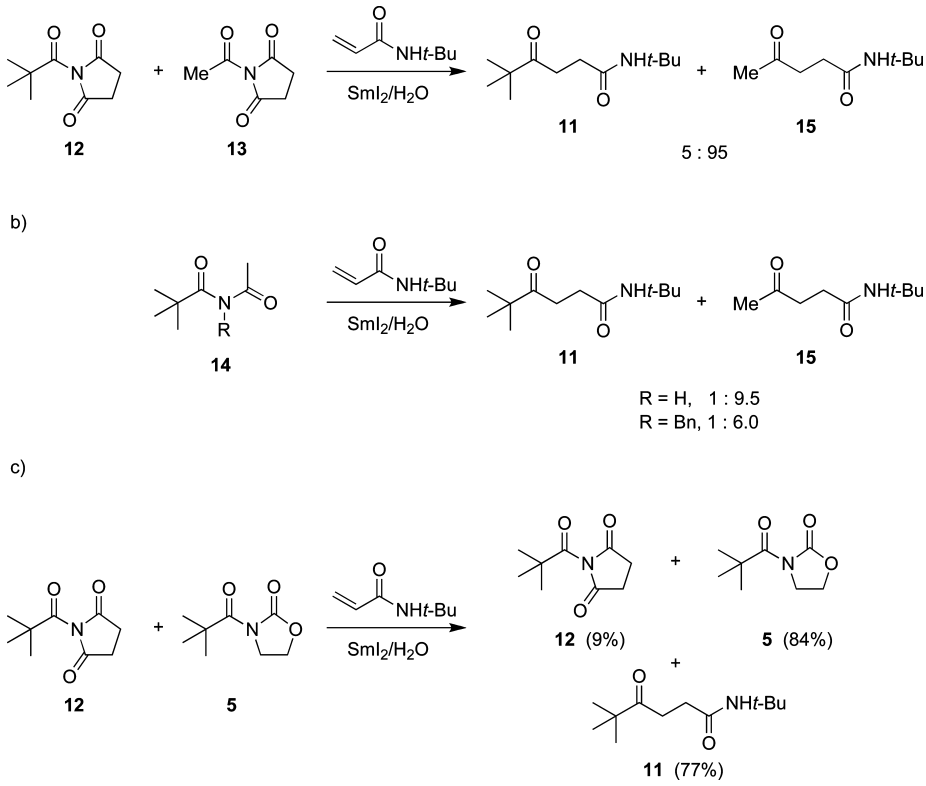
[a] **1** (1.3 equiv), **5** (1.3 equiv), *N-tert*-butyl acrylamide (1.0 equiv), $SmI_2$ (0.1 M in THF, *n* equiv), $H_2O$ (8 equiv), THF, −78 °C, 1 h. [b] Manual addition. [c] Addition using a syringe pump. [d] Ratio of the concentrations of **1** and **5** was 4:1. [e] $Sm(OTf)_3$ (1.5 equiv) was added to the reaction mixture.

To ascertain that the reaction mechanism did not change as the reaction proceeded, we stopped the reaction prematurely by the addition of a limited amount of samarium diiodide (Table 2, entries 1−5). Since the product distributions in all cases led to nearly identical RV's, the mechanism most likely does not change during the progress of the reaction. Furthermore, the observation that the variation in the concentration from 0.02 to 0.5 M of *N-tert*-butyl acrylamide (Table 2, entries 7 and 9−10) and a variation in the ratio of the concentration of **1** and **5** (1:1 and 4:1, Table 2, entries 7 and 11, respectively) produced no significant change in RV's. We can therefore conclude that the reaction is first order with respect to the *N*-acyl oxazolidinone as assumed for eq 1.

While the technique of addition, that is, manual or a syringe pump, exerted no influence on the results (Table 2, entries 5 and 6) a decrease in *RV* was observed if the addition time was increased (Table 2, entries 6−8). We have no certain explanation for this phenomenon but temperature increases during rapid additions of $SmI_2$, which involve a relatively large volume of an ethereal samarium diiodide solution at room temperature compared to the solution in the flask at −78 °C. For addition times equal to or longer than 10 min consistent results were obtained. Noteworthy, the addition of 1.5 equivalents of $Sm(OTf)_3$ produced no significant change in *RV* (Table 2, entry 12), indicating that even in the presence of high concentrations of a Lewis acid, the *s-trans*/*s-cis* equilibrium is shifted toward the left.

**Additional Experimental Evidence Supporting the Importance of C−N Bond Rotation.** In Figure 1, we observed an approximately linear relationship between the reactivity of the simple alkyl *N*-acyl oxazolidinones toward radical addition and the barrier for rotation around the C−N bond involving the exocyclic C═O group. Also from this graph, it can be deduced that the reactivity of this class of substrates augments with increasing bulk of the acyl moiety. Nevertheless, these two observations alone do not exclude the possibility that the driving force for the reactivity of the acyl carbonyl group could instead be pyramidalization in the C−C bond forming step. The release of allylic strain by pyrimidalization at the C═O group upon

***Scheme 7.*** Competition Studies Involving Carbonyl Compounds in which the Effect of C−N Bond Rotation is Excluded




addition of the nucleophilic carbon-centered radical would be expected to be greater with increasing bulk of the acyl moiety. To investigate whether the observed relative reactivities are governed by the C−N bond rotation or pyramidalization, we conducted further competition experiments on analogous carbonyl substrates, which inherently would exclude a possible dependence on the C−N bond rotation (Scheme 7).

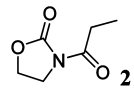
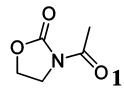
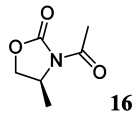
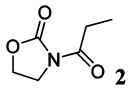
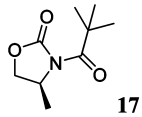
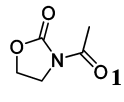
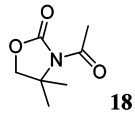
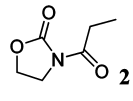
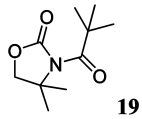
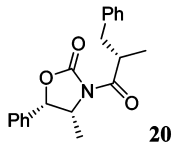
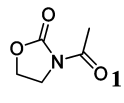
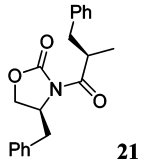
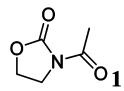
Two types of imide substrates were chosen, which in both cases allow bidentate coordination with a Lewis acid. In the first set of experiments, the *N*-*tert*-butyl acrylamide was reacted in the presence of $SmI_2$ with an excess of the *N*-pivaloyl succinimide **12** and *N*-acetyl succinimide **13**[25,26] in a 1:1 ratio under identical reaction conditions as described for the competition experiments with the *N*-acyl oxazolidinones. This resulted in the exclusive formation of the methyl ketone **15** in a 75% isolated yield (Scheme 7a). It was verified in separate experiments that the major product from the coupling reaction with the individual succinimides was indeed the *tert*-butyl ketone **11** obtained in a 60% isolated yield, and the methyl ketone **15** in a 75% yield. In a second set of experiments, the mixed imides **14** were reacted with the *N*-*tert*-butyl acrylamide and $SmI_2$ to produce preferentially the methyl ketone **15** (Scheme 7b). In both these sets of experiments steric encumbrance around the reacting carbonyl group appears to be the dominant factor for the product distribution rather than release of strain through pyramidalization of the C═O carbon in the addition step. Since this must also be valid for the *N*-acyl oxazolidinones, it leads us to conclude, that the relative reactivities observed in Table 1 does not originate from discrimination between two activated *N*-acyl oxazolidinones, but rather from the kinetically selective formation of one activated *N*-acyl oxazolidinone over the other determined by the barrier for rotation around the C−N bond.

Finally, because substrates such as *N*-acyl succinimide **12** do not require C−N bond rotation for the C−C bond forming step with the $SmI_2$-reduced acrylamide as for the corresponding *N*-acyl oxazolidinones **5**, it would be expected that **12** should display higher reactivity in a competition experiment between these two substrates for *N*-*tert*-butyl acrylamide. As illustrated in Scheme 7c, this turned out to be the case, where 1.3 equivalents of **5** and **12** were reacted with 1 equivalent of the acrylamide leading to a 77% isolated yield of the coupling product and with an 84 and 7% recovery of **5** and **12**, respectively. This corresponds to an RV of 14.4 for the *N*-pivaloyl succinimide.

**Investigation of Chiral *N*-Acyl Oxazolidinones with Ring Substitution at the 4-Position.** As previously stated in the introductory section, one of our incentives for conducting this mechanistic study was to understand why the productivity of the coupling reaction drops for substrates possessing a "simple" oxazolidin-2-one auxiliary to those with chiral 4-substituted oxazolidin-2-one auxiliaries. A small set of competition experiments with 4-substituted-*N*-acyl oxazolidinones was therefore carried out, as illustrated in Table 3. It was necessary to use a less reactive reference compound than the *N*-pivaloyl oxazolidinone **5**, as the more substituted oxazolidinone derivatives proved much less reactive than the previous cases tested. Instead, the compounds were competed against either the *N*-acetyl oxazolidinone **1** or the *N*-propanoyl oxazolidinone **2** to facilitate the $^1$H NMR analysis of the crude product mixture. To validate that the *RV*'s were comparable, we conducted a competition study between **2** and **1** giving $k_2/k_1 = 1.21$ (Table 3; entry 1) which by multiplying with 0.088 for $k_1/k_5$ (Table 1; entry 1) can be converted to a *RV* of 0.11 for **2**. This value is close to

(25) Heller, G.; Jacobsohn, P. *Ber.* **1921**, *54*, 1107. McAlees, A. J.; McCrindle, R. *J. Chem. Soc. (C)* **1969**, 2425.
(26) For the synthesis of these imides, see Supporting Information.

***Table 3.*** Competition Studies with the 4-Substituted Oxazolidinones[a]

| entry | compound (x) | reference (ref) | $k_x/k_{ref}$ | $RV^b$ |
|---|---|---|---|---|
| 1 |  **2** |  **1** | 1.21 | 0.11 |
| 2 |  **16** |  **2** | 0.54 | 0.050 |
| 3 |  **17** |  **1** | 0.57 | 0.050 |
| 4 |  **18** |  **2** | 0.027 | 0.0025 |
| 5[c] |  **19** | - | - | - |
| 6 |  **20** |  **1** | 0.65 | 0.057 |
| 7 |  **21** |  **1** | 0.16 | 0.014 |

[a] *N*-acyl-4-substituted oxazolidinone (1.3 equiv), **1** or **2** (1.3 equiv), *N*-*tert*-butyl acrylamide (1.0 equiv), $SmI_2$ (0.1 M in THF, 3 equiv), $H_2O$ (8 equiv), THF, −78 °C, 1 h. [b] The RV's are the relative reactivities of product formation using *N*-pivaloyl oxazolidinone **5** as reference compound, calculated from the two relevant sets of $k_x/k_{ref}$ values given in Table 3 and 1 (i.e., 0.088 for *N*-acetyl oxazolidinone **1** and 0.094 for *N*-propanoyl oxazolidinone **2**). [c] The designated compound does not react under the specified conditions.

that of 0.094 obtained in the direct competition experiment with the *N*-pivaloyl oxazolidinone **5**.

In Figure 2, the relative reactivity values (ln *RV*) are plotted against the activation energy ($E_a$) for C−N bond rotation to illustrate trends in reactivity for the 4-substituted oxazolidinones. As we have previously stated, $A_{1,3}$ strain does not contribute to a significant extent to the reactivity of the "simple" *N*-acyl oxazolidinones. The low reactivity observed for the (*S*)-4-methyl-*N*-pivaloyl oxazolidinone (**17**), (*S*)-4-methyl-*N*-acetyl (**16**), and the 4,4-dimethyl-*N*-acetyl oxazolidinones (**18**) (Table 3; entries 2−4) compared to the 4-nonsubstitued reference compounds **1** and **2** leads us to conclude that addition of the reduced acrylamide species must occur from the *s-cis* conformation, as it would otherwise be difficult to explain the profound effect of the 4-methyl substituent.

For the 4-substituted cases, pyramidilization of the acyl carbonyl group will result in a *syn*-pentane interaction between

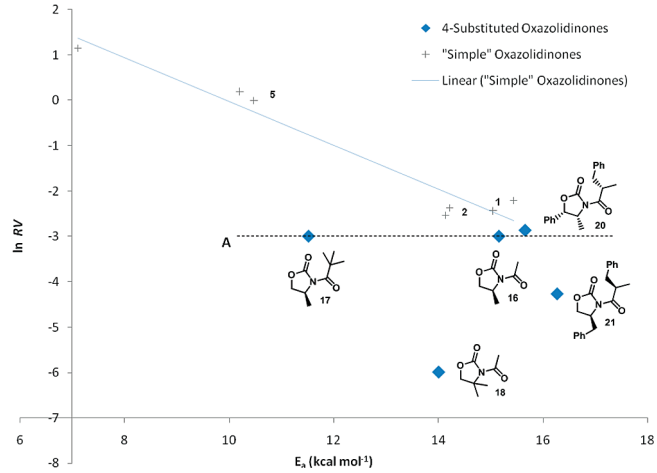



***Figure 2.*** Natural logarithm to the relative reactivity values (ln RV) plotted against the activation energy ($E_a$) for C−N bond rotation.

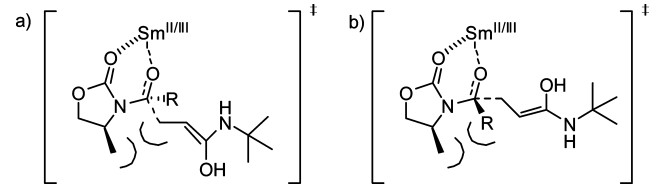
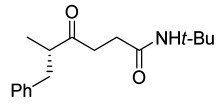
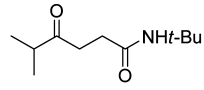
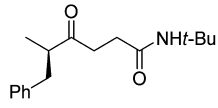



***Figure 3.*** Proposed transition-state for addition to *N*-acyl oxazolidinones possessing substitution at the 4-position and illustrating the arising *syn*-pentane interaction.

a substituent in the 4-position of the oxazolidinone ring and the α-carbon of the incoming nucleophilic radical in the transition-state for addition, as depicted in Figure 3. The horizontal punctured line inserted in Figure 2 illustrates the seemingly equal reactivity of the 4-methyl substituted compounds indicating that substitution in the 4-position of the 2-oxazolidinone ring dictates the reactivity. The reactivity is neither affected by the barrier of rotation around the C−N bond nor by the bulk properties presented by the R group of the *N*-acyl moiety. This is difficult to explain were the nucleophilic radical to attack the *N*-acyl carbonyl on the opposite side of the 4-methyl substituent (Figure 3b), as the rate of addition in that case must be expected to be influenced by the size of R. Therefore, we suggest that the radical addition possibly occurs from the same side of the *N*-acyl carbonyl as the 4-methyl substituent for (*S*)-4-methyl-*N*-pivaloyl oxazolidinone **17** and possibly also for **20** (Figure 3a). In conclusion, while the determining factor for product distribution was shown to be the rate of rotation around the C−N bond for the "simple" *N*-acyl oxazolidinones, the reactivities of the 4-substituted oxazolidinones are clearly dominated by the activation energy for addition due to the arising *syn*-pentane interactions in the transition-state for addition. Kinetically this would then correspond better to the limiting first case presented (eqs 3 and 5).

**Effect of Lewis Acids on the Reactivity of the 4-Substituted Oxazolidinone Derived Substrates.** In an attempt to increase the reactivity of the 4-substituted-*N*-acyl oxazolidinones toward radical addition, we conducted a small screening on the effect of added Lewis acids, which have previously been used with success in the stereoselective radical allylations with chiral oxazolidinone auxiliaries.[27] We hypothesized that the addition of an appropriate Lewis acid could facilitate the rotation around the C−N bond, as well as increase the reactivity of the C═O

***Table 4.*** Lewis Acids Promoting the Reductive Coupling of Less Reactive *N*-Acyl Oxazolidinones[a]

| entry | substrate | Lewis acid | product | yield [b,c] | yield γ-hydroxyamide [b] |
|---|---|---|---|---|---|
| 1 | **20** | - |  **22** | 45 % | 16 % |
| 2 | **20** | $MgBr_2$ | **22** | 57 % | 12 % |
| 3 | **20** | $MgI_2$ | **22** | (57 %) | - |
| 4 | **20** | $Mg(OTf)_2$ | **22** | 60 % | 15 % |
| 5 | **20** | $Cu(OTf)_2$ | **22** | (55 %) | - |
| 6 | **20** | $Zn(OTf)_2$ | **22** | (87 %) 76 % | 11 % |
| 7 | **20** | $Sm(OTf)_3$ | **22** | (83 %) | - |
| 8 | **4** | - |  **23** | 61 % | - |
| 9 | **4** | $Mg(OTf)_2$ | **23** | 73 % | - |
| 10 | **21** | - |  **24** | 33 % | - [d] |
| 11 | **21** | $Zn(OTf)_2$ | **24** | 59 % | - [e] |

[a] *N*-acyl oxazolidinone (1.5 equiv), *N-tert*-butyl acrylamide (1.0 equiv), $SmI_2$ (0.1 M in THF, 2.5 equiv), $H_2O$ (8 equiv), THF, −78 °C, 1 h. [b] Isolated yields after column chromatography. [c] Yields in parentheses are conversions of acrylamide based on the ratio of substrate to product obtained from analysis of the $^1H$ NMR spectrum of the crude product and encompasses both the ketone and the γ-hydroxy product. [d] The major byproduct was propionamide. [e] The major byproduct could not be identified, but neither the reduced acrylamide nor the γ-hydroxy product was observed.

carbon, thereby increasing the rate of the addition step over reduction/dimerization of the acrylamide.

$SmI_2$-mediated reductive coupling of *N-tert*-butyl acrylamide with **20** results in the formation of two major products (Table 4, entry 1). One is the desired γ-keto amide **22**, and the other is the corresponding γ-hydroxy amide, presumably originating from the premature collapse of the resulting hemiketal intermediate after the addition step and subsequent reduction of the exposed ketone.

Addition of $MgBr_2$, $MgI_2$ and $Mg(OTf)_2$ resulted in a modest increase of overall yields (γ-keto- and γ-hydroxy amide) and no significant effect of the counterion was observed (Table 4, entries 2−4). $Mg(OTf)_2$ also has a beneficial effect on the yield for the "simple" *N*-acyl oxazolidinone substrate **4**. Adding $Zn(OTf)_2$, however, resulted in a considerable overall yield increase from 61% without additive to a satisfying 87% for **20** and from 33 to 59% for **21** with this Lewis acid (Table 4, entries 1, 6, 10, and 11). No reduced acrylamide (propionamide) was detected with the use of $Zn(OTf)_2$ despite that this is a major byproduct for substrates **20** and **21** without the Lewis acid being present. On the other hand Lewis acids have no effect on the propensity of the hemiketal to collapse, as is evident from the near equal amount of γ-hydroxy amide produced when changing Lewis acid (Table 4, entries 1, 2, 4, and 6). Although $Sm(OTf)_3$ was shown to have no effect on the relative rate of reaction (Table 2, entry 12), it has a significant effect on yields producing a conversion of 83% (Table 4, entry 7).

## Conclusions

In summary, an elaborate study was undertaken to examine some of the post electron transfer steps in the $SmI_2$-mediated coupling of *N*-acyl oxazolidinones with acrylamides, representing a novel C−C bond forming reaction for accessing γ-ketoamides. For the simple alkyl *N*-acyl oxazolidinones, our results suggest that the efficiency of the coupling depends on the propensity for C−N bond rotation from the *s-trans* to *s-cis* conformation. This was illustrated by an almost linear relationship when ln *RV* was plotted against the activation barriers for C−N bond rotation (*s-trans* to *s-cis*) obtained by DFT calculations. In contrast, substrates bearing chiral

(27) For some pertinent references, see: (a) Hein, J. E.; Zimmerman, J.; Sibi, M. P.; Hultin, P. G. *Org. Lett.* **2005**, *7*, 2755. (b) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J. *J. Org. Chem.* **2002**, *67*, 1738. (c) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517. (d) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (e) Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (f) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (g) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (h) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (i) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

4-substituted oxazolidinones appear to be dominated by the activation energy for addition because of arising *syn*-pentane interactions in the transition-state for C−C bond formation. What implications such results will have for other synthetic transformations which exploit this important auxiliary will be the topic of future investigations.

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**Supporting Information Available:** Experimental details and copies of $^{1}$H NMR and $^{13}$C NMR spectra for all the coupling products and crude $^{1}$H NMR spectra of competition experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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