Lewis Acid-Promoted Atom-Transfer Free Radical Additions

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Abstract: The reactions of α-bromo oxazolidinone imides of acetic and propionic acid and terminal and internal alkenes were investigated in the presence of Lewis acids. Thus, the primary bromide, bromoacetyl-2-oxazolidinone amide (**1**), undegoes clean atom-transfer addition to 1-hexene as well as *cis*- or *trans*-3-hexene at room temperature or below. The best Lewis acids for this conversion are Sc(Otf)$_3$ and Yb(Otf)$_3$. Quantitative yields are obtained with Yb(Otf)$_3$ for addtion of the bromide to both 1-hexene and *cis*-3-hexene, while the yield with *trans*-3-hexene is 63%. Yields obtained with Sc(Otf)$_3$ are somewhat lower. The effects of solvent, temperature, and Lewis acid loading have been investigated. The secondary bromide, α-bromoproprionyl-2-oxazolidinone amide (**7**), was also investigated in atom-transfer addition to 1-hexene. Yields are comparable to those in the reaction of **1** with 1-hexene, but internal alkenes fail to react with this substrate. Tertiary bromides do not react with any of the alkenes studied. Control of stereochemistry in the atom-transfer addition is possible by the use of chiral auxiliary oxazolidinones. Thus, the benzyl oxazolidinone and isopropyl analogue give excellent control of configuration in the new stereogenic center generated in the addition of the propionate to 1-hexene. Attempts to achieve enantioselective atom-transfer addition fail to give product in high yield or stereoselectivity.

Atom-transfer addition, sometimes called the Kharasch reaction, has been the focus of extensive investigation in recent years. This transformation, shown in eqs 1 and 2, results in the addition of R−X to a carbon−carbon double bond.[1−5] Although respectable yields are possible with certain R−X/alkene combinations, recent studies have provided insight into some of the limitations of intermolecular atom-transfer reactions and how these limitations might be overcome.
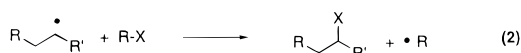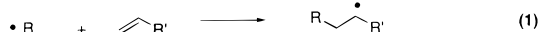
The classical Kharasch reaction, where R−X is a polyhalomethane such as carbon tetrachloride,[5] typically requires high reaction temperatures, long reaction times, and large excesses of the halogenated starting material to ensure efficient propagation and good yields. On the other hand, choosing R−X starting materials which are both electrophilic and with X = I leads to an improvement in yield and a moderation of reaction conditions required for the conversion. These features presumably enhance the rate of both propagation steps, addition and atom transfer. Atom-transfer additions are generally favored as I > Br > Cl = X in R−X since this is the order of reactivity in eq 2.[2] Indeed, atom-transfer additions occur readily for α-iodo esters and malonates, while large excesses of α-bromo compounds are

required in order to obtain moderate yields in analogous transformations. Often the halogenated compound is the more expensive or difficult to obtain of the starting materials.

There are additional limitations in the existing atom-transfer methodology. The higher reactivity of iodides can be a drawback as the products are more liable to decompose and are sometimes difficult to isolate. Only terminal alkenes give good yields, even in reactions with iodo ester derivatives. This limits the scope of intermolecular atom-transfer reactions in synthesis. Finally, halo precursors are preferred that have two electron-withdrawing groups on the carbon bearing halide. Thus, bromo and iodo malonates and malononitriles are much better substrates than simple α-halo esters or nitriles, and this may limit the scope of applications.

The use of Lewis acids in free radical reactions[6−13] offers the possibility to improve the reactivity of sluggish atom-transfer reactions of α-halo esters, nitriles, or amides. This can be

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(13) For an excellent recent review of Lewis acid-promoted free radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem.* **1998**, *38*, 2661.

Scheme 1. Atom-Transfer Reactions with Primary Bromide
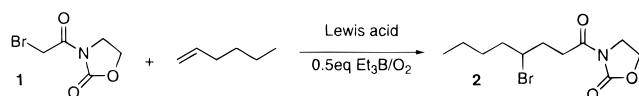
Table 1. Products from Atom-Transfer Reactions with **1**

alkene	bromide products	reduced products

Table 2. Effect of Lewis Acid on Conversion with Primary Bromide[a]

Lewis acid	conversion with	conversion with	conversion with
none	25%	<10%	<10%
MgBr$_2$	34%	<10%	<10%
Mg(OTf)$_2$	37%	16%	<10%
Zn(OTf)$_2$	37%	<10%	<10%
La(OTf)$_3$	46%	20%	<10%
Eu(OTf)$_3$	54%	19%	11%
Sc(OTf)$_3$	86%	47%	23%
Yb(OTf)$_3$	100%	100%	63%

[a] All reactions were carried out with 5 equiv of alkene, 1 equiv of Lewis acid, 25 °C, 1,2-dichloroethane solvent, 0.5 equiv of Et$_3$B. Conversion was determined by NMR of crude product with 1 equiv of CH$_2$Cl$_2$ standard added.

Scheme 2. Competition between Terminal and Cis Alkenes

With Yb(OTf)$_3$		
alkene	Direct[a]	Reduced[b]
	79%	81%
	21%	19%

Reaction went to completion.

With Sc(OTf)$_3$		
alkene	Direct[a]	Reduced[b]
	73%	75%
	27%	25%

Reaction consumed 64% of starting material. The remainder was unreacted.

[a] Percent conversion determined by NMR analysis of bromide products. [b] Percent conversion determined by GC analysis of reduced products.

achieved by increasing the electron-withdrawing nature of the group attached to the carbon bearing halogen via complexation with a Lewis acid. This should increase both the rate of the addition of the α-carbonyl radical to the alkene and perhaps also the halogen abstraction by the resulting nucleophilic carbon radical. Indeed, Guindon and collaborators have shown that allyl-transfer reactions from allyltrimethylsilane to radicals α to carbonyls proceed through an atom-transfer addition promoted by Lewis acids.[7] We report here experiments that explore a set of Lewis acid-promoted atom-transfer reactions. These experiments lead to the conclusion that Lewis acids provide an opportunity to expand the scope of atom-transfer addition reactions.
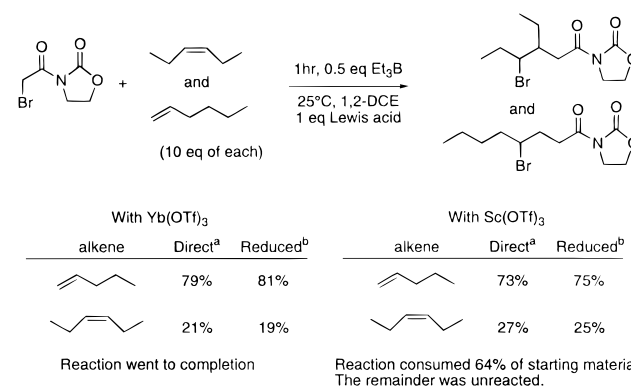
Results and Discussion

The first system chosen for study was the reaction of the primary bromide, bromoacetyl 2-oxazolidinone amide (**1**),[14] with a range of simple alkenes (Scheme 1 and Table 1). The reactions generally proceed cleanly, giving only the desired product and unreacted starting material. The product bromides are stable enough to be chromatographed on silica, to be isolated, and to be stored. All of the bromide products could be reduced quantitatively by treatment with (TMS)$_3$SiH at 75 °C in benzene with AIBN initiation to give products **2−6 (H)** that could be analyzed by gas chromatography.

In reactions with 2-ethyl-1-butene, two addition products, **5** and **6**, were observed. Compound **6** results from the atom-transfer reaction of **1** with 3-methyl-2-pentene, formed by Lewis acid-catalyzed rearrangement of the starting alkene. This rearrangement is favored thermodynamically and does not require the presence of initiator or bromide to occur; simply stirring

the starting alkene with 1 equiv of Sc(OTf)$_3$ for 40 min at room temperature is sufficient to convert over 80% of 2-ethyl-1-butene into 3-methyl-2-pentene.
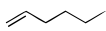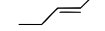
A series of Lewis acids was surveyed with three of the alkenes to determine which were most effective at promoting atom-transfer reactions (Table 2). In the absence of a Lewis acid, poor conversion was seen. Several common Lewis acids (e.g., MgBr$_2$, Zn(OTf)$_2$, and La(OTf)$_3$), which are effective promoters of free radical allyl-transfer reaction,[8−10] failed to improve conversion significantly. Sc(OTf)$_3$ performed moderately well with the primary bromide, while Yb(OTf)$_3$ gave the best results for the systems studied. The reactions utilizing Yb(OTf)$_3$ were, in general, rapid and efficient; complete conversion was seen within 15 min at room temperature.

Conversion also varied depending on the degree of substitution on the alkene. To provide direct comparisons of reactivity, competition experiments were performed. In the first example, a terminal alkene, 1-hexene, and a *cis*-disubstituted alkene, *cis*-3-hexene, were compared by reacting 10 equiv of each in the same pot with **1** (Scheme 2). Analysis of the product mixtures was determined both by integration of NMR signals unique to each product and by gas chromatography analysis of the reduced products. Agreement between the two methods was good. In reactions with Yb(OTf)$_3$ and Sc(OTf)$_3$, there is a strong preference for reaction with 1-hexene over *cis*-3-hexene. This is not surprising, given the usual preference for radical addition to the less substituted end of an olefin for steric reasons.[15]

(14) Bromide **1** was synthesized via a procedure given in the following: Narasaka, K.; Shimada, S.; Yamada, J. *Isr. J. Chem.* **1991**, *31*, 261.

(15) (a) Tedder, J. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 401. For a discussion of acyclic diastereoselection in radical reactions, see: (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995. (c) Porter, N. A.; Giese, B.; Curran, D. P *Acc. Chem. Res.* **1991**, *24*, 296. (d) Smadja, W. *Synlett* **1994**, 1.

Table 3. Alkene and Lewis Acid Concentration Effects with Primary Bromide[a]

entry	Sc(OTf)$_3$	alkene	conversion with ⌒⌒⌒	conversion with ⌒⌒	conversion with ⌒⌒
1	1.0 eq.	1 eq.	76%	41%	18%
2	1.0 eq.	2 eq.	74%	45%	22%
3	1.0 eq.	5 eq.	86%	47%	23%
4	0.50 eq.	5 eq.	71%	46%	21%
5	0.25 eq.	5 eq.	53%	26%	17%
6	0.10 eq.	5 eq.	43%	<10%	<10%
7	none	5 eq.	25%	<10%	<10%

[a] All reactions were carried out at 25 °C, 1 h, 0.5 equiv of Et$_3$B/O$_2$ initiation, 1,2-dichloroethane solvent.

To compare the reactivities of cis vs trans alkenes, a competition experiment with *cis*-3-hexene and *trans*-4-octene was performed. Direct NMR analysis of the bromide products proved impossible as the signals for both products overlapped. Gas chromatography analysis of the reduced products, however, shows a 2:1 preference for reaction with the cis alkene as opposed to the trans alkene. It is possible that this difference in reactivity could lie in part with the relative stabilities of cis vs trans alkenes. In both cases, an identical σ bond is formed, but with the cis alkene, a weaker π bond is being broken in the process. The difference in reactivity could also be explained by the ease with which each alkene can approach the radical center. The cis alkene may provide a less sterically demanding transition state.

In addition to studying the effects of different Lewis acids on conversion, both alkene and Lewis acid concentrations were varied to determine the effects on the yields (Table 3). Varying the amount of alkene from 5 to 1 equiv (entries 1−3) only slightly decreased the yields. Lowering the amount of Lewis acid present to substoichiometric amounts (entries 3−7) did have a negative effect on conversion. Both starting material and product are capable of complexing the Lewis acid, and the product would be expected to be a slightly better substrate, as the electronegative bromine is now remote from the oxazolidinone auxiliary.

The effect of temperature on the transformation was also studied. Not surprisingly, lowering the temperature lowered the yields. At lower temperatures, the radical chains become more difficult to sustain, and conversions drop accordingly. At −40 °C, conversion of 1-hexene promoted by scandium triflate drops to 55% from 86% at 25 °C under conditions that are otherwise the same. Finally, the reaction was surveyed in a series of solvents. The best solvent studied was 1,2-dichloroethane, with ether being a close second. Dichloromethane gave generally poorer conversion than dichloroethane and ether, while THF, ethyl acetate, benzene, and acetonitrile gave little or no conversion.

The solubility of the starting bromide and Lewis acid appeared to have a significant effect on conversion. Solvents which completely solubilized both the starting material and Sc(OTf)$_3$ (tetrahydrofuran, ethyl acetate, acetonitrile) gave poor results. Presumably, the scandium complexes with the solvent rather than the starting bromide, **1**, and no rate enhancement is possible. Benzene solubilized neither starting bromide nor Sc(OTf)$_3$. Again, with little complexation between the starting material and scandium, poor conversion was seen. Although Sc(OTf)$_3$ was not soluble by itself in 1,2-dichloroethane or ether, addition of the bromide starting material did partially solubilize some (but not all) of the Lewis acid. Similar solubility characteristics were seen in reactions with Yb(OTf)$_3$.

Lewis Acid-Promoted Atom-Transfer Reactions of Secondary and Tertiary Bromides. The secondary bromide **7** and the tertiary bromide **8** were studied under the conditions

Scheme 3. Atom-Transfer Reactions of Secondary and Tertiary Bromides
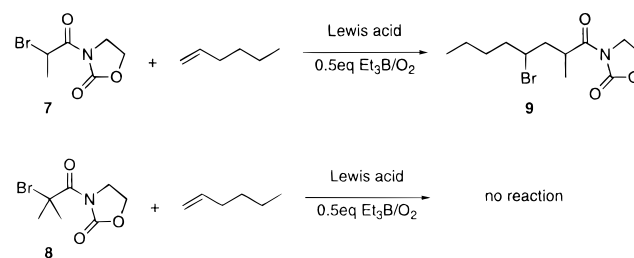
Table 4. Alkene and Lewis Acid Concentration and Temperature Effects with Secondary Bromide **7**

entry	Sc(OTf)$_3$ (equiv)	T (°C)	1-hexene (equiv)	conversion (%)
1	1.0	25	1	74
2	1.0	25	2	100
3	1.0	25	5	100
4	0.50	25	5	95
5	0.25	25	5	90
6	0.10	25	5	73
7	none	25	5	32
8	1.0	0	5	100
9	1.0	−40	5	60

[a] All reactions were carried out with 0.5 equiv of Et$_3$B/O$_2$ initiation, 1,2-dichloroethane solvent.

described for the reactions of the primary bromide **1** (Scheme 3). The secondary bromide reacts with 1-hexene to give product **9** in good to excellent yields if scandium or ytterbium Lewis acids are used to promote the reaction.

While **7** reacts efficiently with terminal alkenes in the presence of a Lewis acid, reaction of this bromide with any internal alkene (cis or trans) gives very little conversion. Instead, **7** is recovered almost quantitatively. The tertiary bromide **8** does not react with either terminal or internal alkenes under any of the conditions studied.

A series of Lewis acids was surveyed to determine their effect on the reactivity of the secondary bromide with 1-hexene. Again, both Yb(OTf)$_3$ and Sc(OTf)$_3$ proved to be effective promoters of the atom-transfer reaction. Complete conversion is possible with **7** in the presence of Sc(OTf)$_3$, in contrast to the reaction with primary bromide **1**. Varying the alkene concentration, Sc-(OTf)$_3$ concentration, and temperature had much the same effects as in the experiments with **1** (Table 4). The reaction was tolerant of lowering alkene concentration (entries 1−3). Lowering the amount of Sc(OTf)$_3$ present (entries 3−7) does not have as great an impact as in the reaction of **1**. Conversions as high as 90% are possible with as little as 0.25 equiv of Lewis acid. Lowering the temperature also has less of an impact (entries 3, 8, and 9), although the yields still suffer at −40 °C. Sc(OTf)$_3$ appears to be an ideal choice of Lewis acid for this particular substrate. The effects of different solvents on conversion mirrored those found with reactions of the primary bromide (data not shown).

The reduction in reactivity of both **7** and **8** compared to **1** in the reaction with internal alkenes is likely a result of both electronic effects and steric effects. The attached methyl groups should both render the α-carbonyl radical more electron rich than is the case for primary radicals and make the approach to the transition state more sterically crowded. The electronic effect is significant enough that Curran has shown, in the atom-transfer reaction of tertiary iodoesters with alkynes, that the radical behaves in a nucleophilic rather than an electrophilic fashion, adding cleanly to ester-substituted alkynes but poorly with alkyl-substituted alkynes.[4,16,17]

Table 5. Diastereoselectivities in Atom-Transfer Reaction

entry	bromide	solvent	T (°C)	conversion (%)	*R:S*
1	**12b**	1,2-DCE	25	100	82:18
2	**12b**	1,2-DCE	25	na	84:16
3	**12b**	ether	25	85	92:8
4	**11b**	1,2-DCE	25	85	93:7
5	**11b**	ether	25	>90	95:5
6	**11a**	ether	25	>90	96:4
7	**11b**	ether	0	44	96:4

[a] All reactions were carried out with 1 equiv of Sc(OTf)$_3$, 5 equiv of 1-hexene, 0.5 equiv of Et$_3$B/O$_2$.
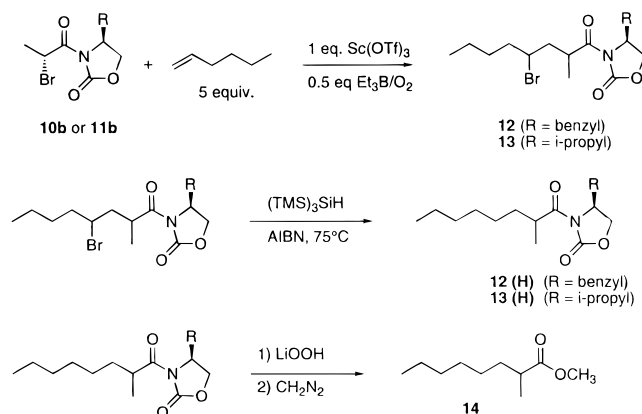
Diastereoselective and Enantioselective Atom-Transfer Reactions. Diastereoselectivity was studied by employing chiral oxazolidinone auxiliaries in atom-transfer reactions with 1-hexene. Bromides **10a,b** and **11a,b** were synthesized and reacted with 1-hexene.[8] In both cases, the diastereomers of **10** and **11**

10a (1st eluting)   **10b** (2nd eluting)   **11a** (1st eluting)   **11b** (2nd eluting)
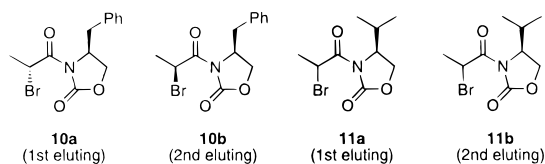
could be separated by column chromatography, and the absolute stereochemistry of **10a** and **10b** has been established by X-ray crystallography.[18]

To determine diastereoselectivity in the atom-transfer reactions, the products were reduced, hydrolyzed, and converted to the methyl esters (Scheme 4). Analysis was performed by chiral

Scheme 4. Diastereoselective Atom-Transfer Reaction

gas chromatography. The absolute stereochemistry of the methyl esters was assigned by co-injection with methyl esters prepared using Evans's enolate chemistry.[19] The results of the diastereoselective atom-transfer reactions are summarized in Table 5. Conversions were determined by NMR analysis of the crude bromide products. In all cases, the expected *R* configuration was observed as the major product formed. This expected configuration is based upon the chelation model of Lewis acid and oxazolidinone in which the carbonyl-imide C−N bond is fixed in the *Z* orientation by the Lewis acid. The 4*R* substituent of the oxazolidinone then shields one face of the radical, and this leads to a selective result.

Diastereoselectivities were excellent in all cases, although the benzyl-substituted oxazolidinone appears to be a better auxiliary than the isopropyl compound. Ether as solvent gave slightly higher diastereoselectivities (entries 1 and 2 vs 3 and entry 4 vs 5−7) than 1,2-dichloroethane. Lowering the temperature to 0 °C did not enhance the selectivity greatly (entry 6 vs 7), while the yield dropped dramatically. Also, as expected, using the first-eluting diastereomer as opposed to the second-eluting one did not affect either the conversion or selectivity.

Enantioselective atom-transfer reactions were attempted by reacting **15** with 1-octene in the presence of either Zn(OTf)$_2$ or Sc(OTf)$_3$ and ligand **16** under conditions that proved successful in the diastereoselective atom-transfer reactions. In each case,


1.1 equiv of Lewis acid and 1.0 equiv of **16** were used. Unfortunately, with Zn(OTf)$_2$/**16**, conversion was very poor (<15%), and no attempt was made to determine stereoselectivity.

With Sc(OTf)$_3$, conversion was better (64%), but chiral GC analysis of the methyl ester derivative showed no enantioselectivity. This result is not entirely surprising, given Sc(OTf)$_3$'s poor performance in enantioselective allyl-transfer reactions (10% ee).[8,9] Sc(OTf)$_3$ has an appreciable affinity for **16**, as shown by the fact that addition of **16** to a suspension of Sc(OTf)$_3$, Sc(OTf)$_3$ quickly solubilizes all of the scandium. Once complexed to **16**, the scandium may no longer be electrophilic enough to bind strongly to the carbonyl oxygens of the oxazolidinone auxiliary. Any scandium that remains unbound to **16**, though, is capable of promoting atom-transfer reactions as usual, leading to racemic products.

The zinc triflate/**16** combination was explored further given its success in allyl-transfer reactions and in enantioselective copolymerizations.[21] To improve yields, **15** was converted to the corresponding iodide **17**, and the iodide was reacted with 1-octene in the presence of Zn(OTf)$_2$ and **16**. The iodide product **18** was reduced in situ with Zn dust/acetic acid, and isolated yields of the reduced products were determined after column chromatography (Scheme 5). The two enantiomers of **19** are

Scheme 5. Enantioselective Atom-Transfer Reaction
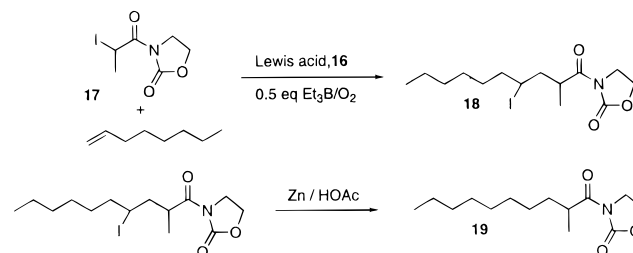
separable by chiral gas chromatography, so no derivatization was required. Again, absolute stereochemistry was assigned by comparison to materials synthesized by Evans's enolate chemistry.

The results of the atom-transfer reactions of **17** in the presence of Zn(OTf)$_2$ and **16** are disappointing. Despite the use of iodide precursors, yields of the reduced products were still quite low, 5−15%. The expected *S* enantiomer was formed preferentially, but selectivities were unimpressive, the best enantiomer ratio obtained being about 70/30.

(16) Curran, D. P.; Kim, D.; Ziegler, C. *Tetrahedron* **1991**, *47*, 6189.
(17) Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *47*, 6171.
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(21) Mero, C. L.; Porter, N. A., to be published.

The difficulty in all of the enantioselective atom-transfer reactions is in forming a 1:1:1 complex of substrate/Lewis acid/chiral ligand that both is formed preferentially to a 1:1 complex of substrate and Lewis acid and is capable of promoting the reaction to a significant extent over any background reaction. Scandium, for example, is an excellent Lewis acid for oxazolidinone auxiliaries as long as there are no species present (e.g., ligand **16**) capable of competing for complexation. Zinc triflate, although not as effective a Lewis acid in the diastereoselective reactions, appears to strike the necessary balance of affinity for oxazolidinone carbonyls and the ligand nitrogens so that 1:1:1 complexes are formed. Additionally, solubility factors work in favor of 1:1:1 complex formation, as only the combination of all three elements can solubilize the majority of the zinc present; zinc triflate and **16** alone are insufficient (compare to the solubility of Sc(OTf)$_3$ and **16**). Unfortunately, the resulting complex does not render the substrate electron-deficient enough to substantially alter its reactivity compared to the uncomplexed substrate in the reactions studied.

Conclusions

The use of Lewis acids in free radical chemistry shows tremendous promise: the examples reported here of atom-transfer addition to simple alkenes opens the door for construction of complex structures by the use of simple and efficient transformations. The advantages of Lewis acid-promoted atom-transfer reactions are several:

(i) Atom-transfer reactions with both monosubstituted and 1,2-disubstituted alkenes are possible. Atom-transfer additions with internal (and perhaps cyclic) alkenes, typically difficult to achieve except with Curran's iodomalononitrile systems, are possible with Lewis acid-promoted reactions. In effect, Lewis acids activate radicals monosubstituted with an amide such that their reactivity mirrors the malononitriles of Curran.[1−4]

(ii) Mild reaction conditions and short reaction times are possible with Lewis acid-promoted atom-transfer reactions.

(iii) Bromine atom-transfer reactions are possible rather than just iodine atom transfers. The often necessary step of reducing or functionalizing the halogenated product is no longer required, given the added stability of brominated products vs iodinated ones. The bromine also provides an excellent synthetic "handle" for further chemistry.

(iv) Excellent stereoselectivities can be achieved with commercially available and easily removable and recyclable chiral auxiliaries.

The work presented here lays the foundation for further studies and provides an excellent starting point for continued expansion into the subject of Lewis acid-promoted atom-transfer reactions.

Experimental Section

Typical Atom-Transfer Reaction. In a 10-mL round-bottom flask, 0.225 mmol of the α-bromo oxazolidinone amide and 5 mL of solvent were mixed. Lewis acid was added and the mixture stirred for 15 min. The mixture was brought to temperature for 15 min, and alkene and 0.5 equiv of Et$_3$B (1 N in hexanes) were added sequentially. The flask was capped with a drying tube and stirred for 1 h. The mixture was diluted with 100 mL of ether, washed with 75 mL of saturated ammonium chloride solution, dried with anhydrous magnesium sulfate, and filtered, and volatiles were removed by rotary evaporation. Determinations of yield were made by NMR analysis of crude product mixture with 1 equiv of dichloromethane standard added to the NMR sample.

Typical Tris(trimethylsilyl)silane Reduction of Bromide Products.[20] In a 25-mL round-bottom flask under argon, the bromide products were dissolved in 5 mL of degassed benzene. Approximately 1.3 equiv of tris(trimethylsilyl)silane was added and the mixture warmed to 75 °C. Approximately 15 mg of AIBN dissolved in 250 μL of benzene was added and the mixture heated for 2 h. The reaction was quenched with 100 mL of ammonium chloride solution and extracted with 100 mL of ether, dried with anhydrous magnesium sulfate, filtered, and concentrated. Analysis of reduced products was performed by gas chromatography.

4-Bromooctanoyl 2-Oxazolidinone Amide (2): ^{1}H NMR δ 4.4 (t, 2H), 4.1 (m, 1H), 4.0 (t, 2H), 3.1 (t, 2H), 2.2 (m, 1H), 2.1 (m, 1H), 1.8 (m, 2H), 1.5 (m, 1H), 1.4 (m, 1H), 1.3 (m, 2H), 0.8 (t, 3H); ^{13}C NMR δ 172.4, 153.4, 62.1, 57.1, 42.4, 38.9, 33.3, 33.2, 29.6, 22.0, 13.8; HRMS calcd for (MH$^+$) C$_{11}$H$_{19}$^{79}BrNO$_3$ 292.0548, found 292.0546.

Octanoyl 2-Oxazolidinone Amide (2H): ^{1}H NMR δ 4.3 (t, 2H), 3.9 (t, 2H), 2.8 (m, 2H), 1.6 (m. 2H), 1.3 (m, 10H), 0.8 (t, 3H); ^{13}C NMR δ 173.5, 153.5, 61.9, 42.4, 35.0, 31.6, 29.0, 28.9, 24.1, 22.5, 14.0; MS (MH$^+$) 214.

4-Bromo-3-ethylhexanoyl 2-Oxazolidinone Amide (3) (Mixture of Diastereomers): ^{1}H NMR δ 4.4 (t, 2H), 4.2 (m, 1H), 4.0 (t, 2H), 3.0 (m, 2H), 2.2 (m, 1H), 1.8 (m, 2H), 1.5 (m, 2H), 1.0 (t, 3H), 0.9 (m, 3H); ^{13}C NMR δ 172.61, 172.58, 153.37, 64.94, 63.86, 62.03, 61.98, 42.64, 42.54, 41.83, 41.56, 37.35, 36.8, 30.04, 29.46, 25.92, 23.09, 13.09, 12.91, 11.86, 11.38; HRMS calcd for (MH$^+$) C$_{11}$H$_{19}$^{79}BrNO$_3$ 292.0548, found 292.0548.

3-Ethylhexanoyl 2-Oxazolidinone Amide (3H): ^{1}H NMR δ 4.4 (t, 2H), 4.0 (t, 2H), 2.8 (d, 2H), 1.9 (m, 1H), 1.3 (m, 6H), 0.8 (m, 6H); ^{13}C NMR δ 173.4, 153.5, 61.9, 42.6, 39.2, 35.6, 35.3, 26.2, 19.7, 14.3, 10.8; HRMS calcd for (MH$^+$) C$_{11}$H$_{20}$NO$_3$ 214.1443, found 214.1453.

4-Bromo-3-propylheptanoyl 2-Oxazolidinone Amide (4) (Mixture of Diastereomers): ^{1}H NMR δ 4.4 (t, 2H), 4.2 (m, 1H), 4.0 (m, 2H), 3.0 (m, 2H), 2.2 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H), 1.6 (m, 1H), 1.3 (m, 4H), 0.9 (m, 6H); ^{13}C NMR δ 172.5, 174.4, 153.4, 153.3, 62.9, 62.0, 61.9, 61.8, 42.6, 42.5, 39.7, 39.7, 38.7, 38.2, 37.7, 36.9, 35.2, 32.3, 21.3, 21.2, 20.3, 19.9, 14.1, 13.9, 13.3; HRMS calcd for (MH$^+$) C$_{13}$H$_{23}$^{81}BrNO$_3$ 322.0840, found 322.0842.

3-Propylheptanoyl 2-Oxazolidinone Amide (4H): ^{1}H NMR δ 4.4 (t, 2H), 4.0 (t, 2H), 2.8 (d, 2H), 2.0 (m, 1H), 1.3 (m, 10H), 0.8 (t, 6H); ^{13}C NMR δ 173.3, 153.5, 61.8, 42.5, 39.6, 36.1, 33.8, 33.4, 28.7, 22.9, 19.7, 14.3, 14.0; HRMS calcd for (MH$^+$) C$_{13}$H$_{24}$NO$_3$ 242.1756, found 242.1759.

4-Bromo-4-ethylhexanoyl 2-Oxazolidinone Amide (5): ^{1}H NMR δ 4.4 (t, 2H), 4.0 (t, 2H), 3.1 (m, 2H), 2.1 (m, 2H), 1.8 (m, 4H), 0.9 (t, 6H); ^{13}C NMR δ 172.6, 153.4, 78.2, 62.0, 42.5, 35.6, 35.0, 31.6, 9.6; HRMS calcd for (MH$^+$) C$_{11}$H$_{19}$^{81}BrNO$_3$ 294.0536, found 294.0514.

4-Ethylhexanoyl 2-Oxazolidinone Amide (5H): ^{1}H NMR δ 4.4 (t, 2H), 4.0 (t, 2H), 2.8 (m, 2H), 1.5 (m, 2H), 1.3 (m, 5H), 0.8 (t, 6H); ^{13}C NMR δ 173.8, 153.4, 61.9, 42.5, 39.8, 32.6, 27.1, 25.0, 10.7; HRMS calcd for (MH$^+$) C$_{11}$H$_{20}$NO$_3$ 214.1444, found 214.1452.

4-Bromo-3,4-dimethylhexanoyl 2-Oxazolidinone Amide (6) (Mixture of Diastereomers): ^{1}H NMR δ 4.4 (t, 2H), 4.0 (t, 2G), 3.3 (m, 1H), 3.0 (m, 1H), 2.4 (m, 1H), 2.0 (m, 1H), 1.8 (m, 1H), 1.7 (s, 1.5H), 1.6 (s, 1.5H), 1.1 (t, 3H), 1.0 (d, 3H); ^{13}C NMR δ 172.5, 172.4, 153.4, 62.0, 42.6, 40.2, 39.6, 39.5, 39.2, 36.6, 35.6, 28.7, 27.5, 16.5, 15.9, 10.1, 10.0; GCMS for (MH$^+$) 292, 294.

3,4-Dimethylhexanoyl 2-Oxazolidinone Amide (6H) (Mixture of Diastereomers): ^{1}H NMR δ 4.4 (t, 2H), 4.0 (t, 2H), 2.9 (m, 1H), 2.7 (m, 1H), 2.1 (m, 1H), 1.4 (m, 2H), 1.1 (m, 1H); ^{13}C NMR δ 173.5, 173.3, 61.9, 42.6, 42.5, 40.1, 39.4, 38.7, 38.4, 33.8, 33.0, 27.2, 25.7, 16.8, 15.7, 14.4, 14.2, 12.1, 12.0; HRMS calcd for (MH$^+$) C$_{11}$H$_{20}$NO$_3$ 214.1444, found 214.1442.

4-Bromo-2-methyl-octanoyl 2-Oxazolidinone Amide (9) (Mixture of Diastereomers): HRMS calcd for MH$^+$ (C$_{12}$H$_{21}$^{79}BrNO$_3$ + H$^+$) 306.0704, found 306.0707. After separation by HPLC (33% ethyl acetate in hexanes), first-eluting diastereomer: ^{1}H NMR δ 4.4 (t, 2H), 4.1 (m, 1H), 4.0 (m, 2H), 3.9 (m, 1H), 2.3 (m, 1H), 1.8 (m, 3H), 1.5 (m, 1H), 1.3 (m, 3H), 1.2 (d, 3H), 0.9 (t, 3H); ^{13}C NMR δ 176.3, 152.8, 61.9, 55.9, 42.7, 42.3, 39.3, 36.6, 29.6, 22.1, 18.3, 13.9. Second-eluting diastereomer: ^{1}H NMR δ 4.4 (t, 2H), 4.0 (m, 4H), 2.3 (m, 1H), 1.9 (m, 1H), 1.8 (m, 2H), 1.5 (m, 1H), 1.3 (m, 3H), 1.2 (d, 3H), 0.9 (t, 3H); ^{13}C NMR δ 176.7, 153.0, 61.8, 55.2, 42.8, 42.0, 39.1, 36.3, 29.5, 22.0, 17.2, 13.9.

4-Bromo-2-methyloctanoyl (5(S)-Benzyl-2-oxazolidone) Amide (12) (Mixture of Major Diastereomers): ^{1}H NMR δ 7.2 (m, 5H), 4.6 (m, 1H), 4.2 (m, 2H), 4.0 (m, 2H), 3.3 (m, 1H), 2.7 (m, 1H), 2.4 (m, 1H), 1.9 (m, 3H), 1.5 (m, 1H), 1.3 (m, 3H), 1.2 (2 d, 3H), 0.9 (t, 3H); ^{13}C NMR δ 176.7, 176.3, 152.9, 152.7, 153.4, 153.2, 129.4, 129.3, 129.0, 128.9, 127.4, 127.3, 66.0, 65.9, 55.8, 55.5, 55.3, 55.1, 42.5, 42.0, 39.2, 39.1, 37.0, 36.7, 29.7, 29.6, 22.2, 22.1, 18.2, 17.3, 13.9; HRMS calcd for (MH$^+$) $C_{19}H_{27}^{79}BrNO_3$ 396.1174, found 398.1181.

4-Bromo-2-methyloctanoyl (5(S)-Isopropyl-2-oxazolidone) Amide (13) (Mixture of Major Diastereomers): ^{1}H NMR δ 4.4 (m, 1H), 4.3 (m, 1H), 4.2 (m, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 2.3 (m, 2H), 1.8 (m, 3H), 1.5 (m, 1H), 1.3 (m, 2H), 1.2 (d, 1.5H), 1.1 (d, 1.5H), 0.9 (m, 9H); ^{13}C NMR δ 176.5, 176.2, 153.5, 153.3, 63.0, 62.9, 58.6, 58.5, 55.6, 55.0, 42.6, 42.1, 39.2, 38.9, 36.9, 36.6, 29.7, 29.6, 28.3, 28.2, 22.1, 18.1, 18.0, 17.9, 17.1, 14.6, 14.5, 13.9; HRMS calcd for (MH$^+$) $C_{15}H_{27}^{81}BrNO_3$ 350.1174, found 350.1160.

2-Methyloctanoyl (5(S)-Benzyl-2-oxazolidone) Amide (12H). Synthesis of (S,S,S) diastereomer: In a 100-mL round-bottom flask under argon, 943 mg (3.1 mmol, 1 equiv) of **45** was dissolved in 25 mL of tetrahydrofuran and cooled to −78 °C. Once at temperature, 3.4 mL (3.4 mmol, 1.1 equiv) of NaHMDS (1 M solution in tetrahydrofuran) was added and the mixture stirred for 30 min. Methyl iodide (1.0 mL, 15.5 mmol, 5 equiv) was added and stirred for 3 h. The reaction was quenched with 75 mL of saturated ammonium chloride solution and extracted with 100 mL of ether, dried with anhydrous magnesium sulfate, filtered, concentrated, and chromatographed on silica with 10% ethyl acetate in hexanes. Upon concentration, 748 mg (2.4 mmol, 76% yield) of a colorless oil was obtained: ^{1}H NMR δ 7.3 (m, 5H), 4.6 (m, 1H), 4.1 (m, 2H), 3.7 (m, 1H), 3.2 (d of d, 1H), 2.7 (d of d, 1H), 1.7 (m, 1H), 1.4 (m, 1H), 1.3 (m, 8H), 1.2 (d, 3H), 0.8 (t, 3H); ^{13}C NMR δ 177.3, 153.0, 135.3, 129.4, 128.9, 127.3, 65.9, 55.3, 37.9, 37.7, 33.4, 31.7, 29.3, 27.2, 22.5, 17.3, 14.0; HRMS calcd for $C_{19}H_{27}NO_3$ 317.1991, found 317.1985.

2-(S)-Methyloctanoyl Methyl Ester ((S)-14). In a 50-mL round-bottom flask, 640 mg (2.02 mmol) of (S,S,S)-**42** and 11 mL of 4:1 tetrahydrofuran/H_2O were mixed and cooled to 0 °C. To this solution, 915 μL of 30% H_2O_2 was added and the mixture stirred for 5 min, followed by addition of a solution of 136 mg of LiOH/H_2O in 7.5 mL of H_2O. The mixture was stirred for 30 min at 0 °C and 1 h at room temperature. Excess peroxides were quenched with a solution of 1.1 g of sodium sulfite in 5 mL of H_2O. Hydrolyzed auxiliary was removed by bringing up the solution in 75 mL of 0.25 M NaOH and washing with two 50-mL portions of dichloromethane. The desired acid was isolated by acidifying with 4 N HCl until strongly acidic and extracting with three 300-mL portions of ethyl acetate. The extracts were dried with anhydrous magnesium sulfate, filtered, and concentrated. An ethereal solution of 2-(S)-methyloctanoic acid was prepared and esterified with excess diazomethane generated from Diazald with Diazald kit. Excess diazomethane was removed by blowing a stream of argon over the ethereal solution until it was colorless. The solution was dried with anhydrous magnesium sulfate, filtered, and concentrated. No further purification was required. ^{1}H and ^{13}C NMR spectra were compared to literature values for racemic **14**. Chiral GC analysis was performed at 65 °C isothermal with 5 psi head pressure of helium.

2-Iodopropionyl 2-Oxazolidone Amide (17). A mixture of 1.29 g (5.8 mmol) of **15**, 75 mL of acetone, and 2.0 g (13.3 mmol) of NaI was refluxed overnight in a 100-mL round-bottom flask. The solution was washed with 75 mL of water and extracted with two 50-mL portions of dichloromethane. The organic extracts were washed with 50 mL of saturated sodium thiosulfate solution, dried with anhydrous magnesium sulfate, filtered, and concentrated. The material was chromatographed on silica with 33% ethyl acetate/hexanes to give 1.1 g (4.12 mmol, 71% yield) of a pale yellow crystalline solid: ^{1}H NMR δ 5.8 (m, 1H), 4.4 (m, 2H), 4.0 (m, 2H), 2.0 (d, 3H); ^{13}C NMR δ 171.5, 152.5, 62.0, 42.8, 22.3, 12.6; HRMS M$^+$ calcd 269.9627, found 269.9628.

Typical Zn/HOAc Dehalogenation Procedure (19). To the crude atom-transfer product mixture, 1.0 mL (17 mmol) of acetic acid was added, followed by 1.0 g (15 mmol) of zinc powder. The mixture was stirred overnight. Workup consisted of diluting with 50 mL of H_2O and extracting with two 50-mL portions of dichloromethane. The organic extracts were washed with 50 mL of sodium bicarbonate solution, dried with anhydrous magnesium sulfate, filtered, concentrated, and chromatographed on silica with 33% ethyl acetate/hexanes. Chiral GC analysis of **19** was performed at 145 °C isothermal at 5 psi head pressure.

Supporting Information Available: Experimental procedures and characterization data for compounds **8**, and compounds prepared for assignment of product stereochemistry via Evans enolate chemistry (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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