Free Radical-Mediated Intermolecular Conjugate Additions. Effect of the Lewis Acid, Chiral Auxiliary, and Additives on Diastereoselectivity

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Abstract: We have developed a highly diastereoselective method for the conjugate addition of carbon radicals to chiral α,β-unsaturated *N*-enoyloxazolidinones using Bu_3SnH as chain carrier and Et_3B/O_2 as radical initiator. Lewis acids have been screened, and $Yb(OTf)_3$ proved to give optimized results for both chemical yield (88% for **1a** and 94% for **1b**) and diastereoselectivity (25:1 for **1a** and 46:1 for **1b**). The selectivity is solvent-dependent, CH_2Cl_2-THF being an ideal combination. Scrupulously dry solvents or reaction conditions were not required. Substoichiometric amounts of $Yb(OTf)_3$ provided efficient reaction with minimal sacrifice in diastereoselectivity. Carbon radicals with reasonable nucleophilicity were generally successful, including functionalized radicals such as acetyl or methoxymethyl. Electrophilic radicals were not successful. A model which accounts for most of our observations is presented.

Formation of a carbon−carbon bond by addition to an α,β-unsaturated system is one of the premiere reactions in synthetic organic chemistry.[1] In the majority of these reactions, the carbon nucleophile is an ionic species and most often an organocopper reagent. A large number of chiral auxiliaries and chiral ligands have been described which provide good to excellent diastereoselectivity and enantioselectivity, respectively, in anionic conjugate additions to acyclic α,β-unsaturated systems.[2,3]

Intermolecular conjugate additions of free radicals to enones and enoates have been reported in the literature.[4] However, stereoselective addition to nonterminal alkenes has met with limited success. Only in the last several years have successful examples of diastereoselective radical conjugate additions been reported. In one notable example, Curran used a complex auxiliary derived from Kemp's triacid to obtain excellent levels of diastereoselectivity.[5] Other examples include methyl radical addition to an enoate with a sugar-derived template,[6] alkyl radicals to α-ketosulfoxides,[7] and ketyl radicals addition to enoates with high selectivity have also been reported.[8] However, a general solution to the problem of acyclic diastereoselection[9] in β-radical additions remained elusive until 1995 when we demonstrated highly diastereoselective conjugate reactions using simple and readily available oxazolidinones as chiral auxiliaries.[10] After this initial study, several other examples of highly diastereoselective conjugate additions[11] as well as their enantioselective variants have been reported.[12]

When we initiated this study, oxazolidinone auxiliaries had found limited application in radical reactions. Crich had used an ephedrine-derived oxazolidinone under non-Lewis acid conditions with limited selectivity in an alkylation/trapping reaction.[13] We felt that the low selectivity was due to a lack of appropriate rotamer control with *N*-acyloxazolidinones. Several rotamers are available for free *N*-acyloxazolidinones (Figure 1). High stereoselectivity requires a dominant reactive rotamer in which one face is effectively blocked, but in ground state conformer, **C** the R group is too far away for effective face shielding. We hypothesized that a chelating Lewis acid additive could enforce predominant reaction via rotamer **A** so that with an appropriate R group in the auxiliary facial shielding in the β-addition of radicals could be possible. The increasing application of Lewis acids in radical reactions[14] and the excellent diastereofacial control in Lewis acid-mediated Diels−Alder

(1) For an excellent monograph, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, U.K., 1992. For a recent review, see: Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051.

(2) For a recent review on conjugate additions using copper reagents, see: Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 184.

(3) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771 and references therein.

(4) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403.

(5) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007.

(6) Rück, K.; Kunz, H. *Synthesis* **1993**, 1018.

(7) Toru, T.; Watanabe, Y.; Tsusaka, M.; Ueno, Y. *J. Am. Chem. Soc.* **1993**, *115*, 10464.

(8) For seminal contributions, see: Molander G.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. Kawatsura, M.; Deckura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501.

(9) For a discussion of acyclic diastereoselection in radical reactions, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1995. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (c) Smadja, W. *Synlett* **1994**, 1.

(10) For a preliminary communication, see: Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779.

(11) (a) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (b) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 2274. (c) Toru, T.; Watanabe, M.; Mase, N.; Tsusaka, Y.; Hayakawa, T.; Ueno, Y. *Pure Appl. Chem.* **1996**, *68*, 711. (d) Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794. (e) Nishida, M.; Ueyama, E.; Hayashi, H.; Ohtake, Y.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *J. Am. Chem. Soc.* **1994**, *116*, 6455. (f) Nishida, M.; Hayashi, H.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1995**, *36*, 269. (g) Badone, D.; Bernassau, J. M.; Cardamone, R.; Guzzi, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 535. (h) Piber, M.; Leahy, J. W. *Tetrahedron Lett.* **1998**, *39*, 2043. (i) Merlic, C. A.; Walsh, J. C. *Tetrahedron Lett.* **1998**, *39*, 2083.

(12) For a recent account, see: Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. For examples of enantioselective free radical conjugate additions, see: (a) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067. (b) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576.

(13) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, *28*, 4205.

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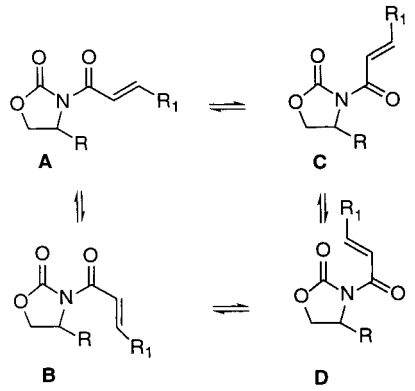


Figure 1.

reactions of *N*-enoyloxazolidinones[15] (involving a type **A** rotamer) supported our approach. We also anticipated that Lewis acids should greatly enhance the electrophilicity of the β-carbons, obviating the problems normally associated with the slow addition of radicals to nonterminal alkenes.[16] We also recognized that, if the reaction proceeds exclusively via rotamer **A**, the distance between the reactive β-center and the chiral carbon is still significant; thus we assumed that the R groups familiar from Evans chemistry (isopropyl, benzyl, phenyl) might prove too small and that a larger substituent might be necessary for high selectivity.

In this paper we describe a comprehensive investigation on diastereoselective free-radical additions to enoyl oxazolidinones. The use of a novel oxazolidinone auxiliary was found to be superior to the traditional Evans auxiliaries. High selectivity required the use of a two-point binding Lewis acid. We detail the effect of Lewis acid, solvent, and radical precursors on the facility of the reaction as well as the levels of diastereoselectivity. A model which accounts for most of our observations is presented.

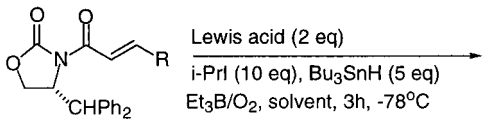
Results

Effect of Lewis Acids and Solvent on Diastereoselectivity. We began our study by examining radical additions to the crotonate and cinnamate derived from 4-(diphenylmethyl)-2-oxazolidinone, a new chiral auxiliary introduced by our group.[17] The required starting materials **1a** and **1b** were prepared by standard acylation protocols. We originally screened a variety of different Lewis acids for their ability to mediate diastereoselective and high-yielding addition of isopropyl radical (eq 1, Table 1). Reactions were conducted at −78 °C, using Bu_3SnH as the radical chain carrier and triethylborane/oxygen as the radical initiator.[18] In the standard Lewis acid screening experiment, two equivalents of Lewis acid was used relative to the substrate. As discussed later, substoichiometric quantities of Lewis acid also proved quite satisfactory under optimized conditions. The solvent, substrate, and Lewis acid were always premixed at room temperature; the solution was then cooled, the isopropyl iodide and Bu_3SnH were added at −78 °C,[19] and the Et_3B was then rapidly added last to initiate the reaction. Oxygen was added at 30 min intervals to reinitiate radical reaction, and the screening reactions were worked up after 3 h. The solvent varied depending on Lewis acid. Dichloromethane was used for soluble Lewis acids, but THF or ether was often included to solubilize Lewis acids that were otherwise insoluble. During the evaluation of the Lewis acids, we used large excesses of isopropyl iodide, tributyl tin hydride, and triethylborane in order to give maximum opportunity for reaction. These quantities in eq 1 do not reflect those necessary under optimized conditions.

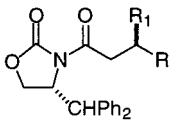
Table 1. Effect of Lewis Acids and Solvents on Diastereoselective Conjugate β-Radical Addition[a]

entry	substrate	Lewis acid	solvent	product	yield (%)[b]	ratio[c]
1	(*R*)-**1a**	none	CH_2Cl_2	**2a**	30[d,e]	1.3:1
2	(*R*)-**1a**	$Yb(OTf)_3$	CH_2Cl_2/THF (4:1)	**2a**	93[f]	25:1
3	(*R*)-**1b**	$Yb(OTf)_3$	CH_2Cl_2/THF (4:1)	**2b**	94[f]	45:1
4	(*R*)-**1a**	$Y(OTf)_3$	CH_2Cl_2/THF (4:1)	**2a**	88[f]	24:1
5	(*R*)-**1a**	$Sm(OTf)_3$	CH_2Cl_2/THF (4:1)	**2a**	90[f]	18:1
6	(*R*)-**1a**	$Sc(OTf)_3$	CH_2Cl_2/THF (4:1)	**2a**	82[f]	9:1
7	(*R*)-**1a**	$La(OTf)_3$	CH_2Cl_2/THF (4:1)	**2a**	93[f]	7:1
8	(*R*)-**1a**	$ZrCl_4$	CH_2Cl_2/THF (4:1)	**2b**	90	7:1
9	(*R*)-**1a**	$MgBr_2{\cdot}OEt_2$	CH_2Cl_2/THF (4:1)	**2a**	90	6:1
10	(*R*)-**1a**	$MgBr_2{\cdot}OEt_2$	CH_2Cl_2/ether	**2a**	90	6:1
11	(*R*)-**1a**	MgI_2	CH_2Cl_2/Et_2O (4:1)	**2a**	80	6:1
12	(*R*)-**1a**	$ZnCl_2$ (2)	CH_2Cl_2/Et_2O (4:1)	**2a**	90	6:1
13	(*R*)-**1a**	$ZnCl_2$ (2)	CH_2Cl_2	**2a**	30[d,g]	1.3:1
14	(*R*)-**1a**	$ZnCl_2$ (2)	CH_2Cl_2/THF (4:1)	**2a**	20[d]	1.3:1
15	(R)-**1a**	$Zn(OTf)_2$ (2)	CH_2Cl_2/Et_2O (4:1)	**2a**	50 (20)	3:1
16	(R)-**1a**	$MeAlCl_2$	CH_2Cl_2	**2a**	20 (80)	5:1
17	(R)-**1a**	Et_2AlCl	CH_2Cl_2	**2a**	70 (20)	4:1
18	(R)-**1a**	$SnCl_4$ (2)	CH_2Cl_2	**2a**	30 (60)	3:1
19	(R)-**1a**	$Yb(OTf)_3$	CH_2Cl_2	**2a**	50[d,g]	1.3:1
20	(R)-**1a**	Bu_2SnCl_2	CH_2Cl_2	**2a**	90[d]	1.3:1
21	(R)-**1a**	$BF_3.Et_2O$	CH_2Cl_2	**2a**	80 (5)	1.3:1
22	(R)-**1a**	$TiCl_4$	CH_2Cl_2	**2a**	−(90)	−
23	(R)-**1a**	Bu_2BOTf	CH_2Cl_2	**2a**	−(70)	−
24	(R)-**1b**	$MgBr_2{\cdot}OEt_2$	CH_2Cl_2/ether	**2b**	90	20:1
25	(R)-**1b**	$La(OTf)_3$	CH_2Cl_2/THF (4:1)	**2b**	80	12:1
26	(R)-**1b**	$ZnCl_2$ (2)	CH_2Cl_2/Et_2O (4:1)	**2b**	70	9:1

[a] Two equivalents of the Lewis acid, 10 equiv of ^{i}Pr−I, 5 equiv of Bu_3SnH, and 10 equiv of Et_3B were used at −78 °C. [b] Yields were determined by NMR integration, except when purified yields are indicated. Yields in parentheses are for the alkene reduction product. [c] Diastereomer ratios were determined by ^{1}H NMR (400 MHz). [d] Starting material accounted for most of the remaining mass balance. [e] Sixty percent of the starting material was recovered. [f] Purified yield. [g] The Lewis acid was insoluble.



1a R = Me
1b R = Ph



(1)

2a R = Me, R_1 = i-Pr
2b R = Ph, R_1 = i-Pr
2c R = Me, R_1 = Et

In the control reaction in which no Lewis acid additive was present, a nonselective 1.3:1 diastereomeric mixture of **2a** formed in low yield (entry 1).[20] The reaction was extremely sluggish, as is typical for radical additions to nonterminal alkenes.[16] Most of the remaining mass was recovered starting material. The yield without added Lewis acid could be boosted to 60%, but only by using large excesses of isopropyl iodide

(14) For an excellent recent review, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562.

(15) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(16) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

(17) This auxiliary is now commercially available from Aldrich chemical company. For its synthesis, see: Sibi, M. P.; Deshpande, P. K.; LaLoggia, A. J.; Christensen, J. W. *Tetrahedron Lett.* **1995**, *36*, 8961.

(18) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Soc. Chem. Jpn.* **1989**, *62*, 143.

and tributyltin hydride, using multiple additions of initiator, and conducting the reaction for 12 h. It is worth noting that, even in the absence of added Lewis acid, Bu_3SnI forms as a byproduct and may function as a weak but noncoordinating Lewis acid.[21]

The best Lewis acid proved to be $Yb(OTf)_3$, which gave essentially quantitative yields and diastereoselectivities of 25:1 (crotonate **1a,** entry 2) and 45:1 (cinnamate **1b,** entry 3).[22] We emphasize that these *diastereoselectivities are comparable to or better than those available using ionic reaction conditions*![23] Other Lewis acids generally gave good conversion, confirming the importance of alkene activation. Starting material was recovered only when the Lewis acid was insoluble and thus ineffective (entries 13, 19). Ether or THF was often added to the dichloromethane solvent mixture in order to solubilize the Lewis acid. There are many reactions in which Lewis acid solubility is not a necessity, but since radicals are relatively short-lived reactants, it is probable that Lewis acid solubility is a necessity in radical reactions.

When very strong Lewis acids were used (entries 15−18, 21−23), alkene reduction (H−H addition instead of R−H addition) was observed. In a control reaction using $EtAlCl_2$, alkene reduction was also observed even when radical initiator (Et_3B/O_2) was omitted. We surmise that, when the Lewis acid is relatively strong, the crotonate is sufficiently activated so that tin hydride may serve as an ionic hydride source.[24] Optimal results thus require that the Lewis acid be soluble and strong enough to activate radical addition but not strong enough to activate direct reaction with tin hydride.[25]

A trace side product formed in variable yields was ethyl addition compound **2c**. The use of Et_3B/O_2 as radical initiator generates ethyl radical, which can add to the substrate. The amount of ethyl addition was 0.5−2.0% when $Yb(OTf)_3$ was used as Lewis acid. Although the quantities were too small to quantify carefully by NMR, we have qualitatively observed that ethyl addition is minimized when reactivity is maximum. When weaker Lewis acids ($ZnCl_2$), less reactive substrates, or less reactive radicals were used (vide infra) the amount of ethyl transfer product was sometimes as high as 5−10%. This observation is consistent with the expectation that short radical chains require more initiation events and provide more opportunities for ethyl addition. In the case of $Yb(OTf)_3$-mediated addition of isopropyl radical to the crotonate **1a**, it appears that the radical chain has an average chain length of between 50 and 200.

Table 2. Effect of Rare Earth Lewis Acid on Diastereoselective Conjugate β-Radical Addition

		(*R*)-**1a** → **2a**		(*R*)-**1b** → **2b**	
entry	Lewis acid[a]	yield (%)[b]	dr[c]	yield (%)[b]	dr[c]
1	$Sc(OTf)_3$	82	8.6:1	90	8.0:1
2	$Y(OTf)_3$	88	24:1	88	37:1
3	$La(OTf)_3$	93	3.5:1	87	5:1
4	$Ce(OTf)_3$	82	6.4:1	85	7.5:1
5	$Pr(OTf)_3$	90	7:1	88	11:1
6	$Nd(OTf)_3$	85	7:1	90	18:1
7	$Sm(OTf)_3$	93	10:1	93	32:1
8	$Eu(OTf)_3$	88	20:1	85	36:1
9	$Gd(OTf)_3$	93	18:1	96	32:1
10	$Tb(OTf)_3$	96	23:1	95	46:1
11	$Dy(OTf)_3$	90	23:1	95	17:1
12	$Ho(OTf)_3$	96	23:1	90	29:1
13	$Er(OTf)_3$	93	25:1	87	36:1
14	$Tm(OTf)_3$	90	24:1	87	41:1
15	$Yb(OTf)_3$	88	25:1	94	46:1
16	$Lu(OTf)_3$	90	20:1	90	50:1

[a] One equivalent of the Lewis acid, 5 equiv of ^{i}Pr−I, 2 equiv of Bu_3SnH, and 2 equiv of Et_3B were used at −78 °C. [b] Yields are for isolated and column-purified materials. [c] Diastereomer ratios were determined by ^{1}H NMR (400 MHz).

In terms of diastereoselectivity, Table 1 shows that in general lanthanide and pre-lanthanide triflates gave the best results (entries 2−7). Lewis acids incapable of simultaneously binding both substrate carbonyls gave low selectivity. For example, $BF_3{\cdot}Et_2O$ gave high chemical reactivity but essentially no higher selectivity than was observed in the Lewis acid-free control reaction (entry 21). Chelating Lewis acids capable of binding both substrate carbonyls consistently showed improved diastereoselectivity relative to the control but surprisingly gave a wide range of selectivities; with the crotonate **1a**, for example, $Yb(OTf)_3$ gave 25:1 selectivity whereas $MgBr_2$ and $ZnCl_2$ gave only 6:1 ratios (entries 2, 9−12).

Since lanthanide triflates appeared to give the best results we hoped to gain a better appreciation of what factors influence the magnitude of selectivity. We have conducted a systematic study of the dependence of selectivity on lanthanide and prelanthanide triflates as Lewis acid (Table 2). Yields were consistently high. The general pattern observed is that the late lanthanide triflates gave higher selectivity than the earlier lanthanides. Within the Sc−Y−La period, yttrium triflate gave much higher selectivity than either the scandium or lanthanum analogue and came close to matching the selectivity obtained with ytterbium. Moving from the early to late lanthanides both reduces the ionic radii ("the lanthanide contraction") and also increases the Lewis acidity of the ions. The ionic radius is probably the more critical influence on selectivity in the present reaction. If selectivity simply increased with increasing Lewis acidity, then $Sc(OTf)_3$ should have given higher selectivity than $Y(OTf)_3$, contrary to observation. Ytterbium and yttrium ions have similar ionic radii (∼0.9 Å),[26] so their similar selectivity is in agreement with the dependence of stereoselectivity on ionic radii. Lewis acids such as $MgBr_2$, $ZnCl_2$, $ZrCl_4$, and $Sc(OTf)_3$ are probably too small; early lanthanides such as $La(OTf)_3$ and $Ce(OTf)_3$ are probably too big.

The dependence of the reaction on solvent is shown in Table 3. As discussed previously, dichloromethane was a poor solvent because of its inability to dissolve $Yb(OTf)_3$ (entry 1). The results and selectivity in dichloromethane were fairly similar to reaction run in the absence of any Lewis acid additive. Use

(19) Bu_3SnH often reacted at room temperature with substrate−Lewis acid complexes.

(20) No regioisomeric product, that is, the product arising from addition to the α-carbon, was detected in the reaction. Belokon et al. report the formation of α-addition products in their work on electrophilic radical addition to oxazolidinone cinnamates in the absence of Lewis acids: Tararov, V. I.; Kuzentanov, N. Yu.; Bakhmutov, V. I.; Ikonnikov, N. S.; Bubnov, Y. N.; Khrustalev, V. N.; Saveleva, T. F.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans 1* **1997**, 3101.

(21) The Bu_3SnI generated in situ in the reaction may conceivably serve as a Lewis acid. See: Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063; Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702.

(22) $Yb(OTf)_3$ was purchased from Aldrich Chemical company and contained ∼0.5−1% water by mass. The use of anhydrous $Yb(OTf)_3$ did not lead to improvement in selectivity.

(23) For conjugate addition to chiral *N*-enoyl oxazolidinones under ionic conditions using copper nucleophiles, see: Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766. For a comparative study of chiral auxiliaries, see: Andersson, P. G.; Schink, H. E.; Österlund, K. *J. Org. Chem.* **1998**, *63*, 8067.

(24) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2585.

(25) We have observed that adding THF as a cosolvent minimized the problem of direct reduction with several Lewis acids.

(26) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th 5d.; Wiley: New York, 1988; p 955.

Table 3. Effect of Solvent and $Yb(OTf)_3$ Stoichiometry on Selectivity[a]

entry	Lewis acid (equiv)	solvent[b]	yield (%)[c]	dr[d]
1	$Yb(OTf)_3$ (2)	CH_2Cl_2	50 (40)[e]	1.3:1
2	$Yb(OTf)_3$ (2)	CH_2Cl_2/Et_2O (4:1)	90	9:1
3	$Yb(OTf)_3$ (2)	toluene/THF (4:1)	90	11:1
4	$Yb(OTf)_3$ (2)	THF	90	15:1
5	$Yb(OTf)_3$ (2)	CH_2Cl_2/THF (4:1) H_2O (6 equiv.)	90	20:1
6	$Yb(OTf)_3$ (2)	CH_2Cl_2/THF[a] (4:1)	93	25:1
7	$Yb(OTf)_3$ (2)	CH_2Cl_2/THF (4:1) H_2O (30 equiv.)	60	1.7:1
8	$Yb(OTf)_3$ (2)	CH_2Cl_2/THF (4:1)	93	25:1
9	$Yb(OTf)_3$ (1)	CH_2Cl_2/THF (4:1)	90	25:1
10	$Yb(OTf)_3$ (0.3)	CH_2Cl_2/THF (4:1)	90	20:1
11	$Yb(OTf)_3$ (0.1)	CH_2Cl_2/THF (4:1)	88	16:1

[a] Five equivalents of ^{i}Pr−I, 2 equiv of Bu_3SnH, and 2 equiv of Et_3B were used at −78 °C. [b] Commercial THF and CH_2Cl_2 were used without any attempt to predry or predistill them. [c] Yields are for isolated and column-purified materials. [d] Diastereomer ratios were determined by ^{1}H NMR (400 MHz). [e] The yield in parentheses is for the reduction product.

of ether instead of THF (entry 2), toluene instead of CH_2Cl_2 (entry 3), or THF only (entry 4) all gave good yields but reduced selectivity. Moderate quantities of water did little harm (entry 5). The ability to use $Yb(OTf)_3$ under slightly wet conditions is of tremendous practical impact. Many other Lewis acids are acutely moisture-sensitive and must be handled in scrupulously dry solvents using drybox or syringe techniques. By contrast, we were able to routinely weigh $Yb(OTf)_3$ in the air, and our $Yb(OTf)_3$ bottles showed no sign of deterioration over months of usage despite not using glovebox procedures. We also found that it was unnecessary to predry our solvents (entry 6); when CH_2Cl_2 and THF were used "straight from the bottle" the reaction results were not compromised![27] A large excess of water[28] did appear to deactivate the $Yb(OTf)_3$, however (entry 7), even though $Yb(OTf)_3$ has been found to be active in aqueous solvent in other applications.[29]

We have also evaluated the use of lesser excesses of tributyltin hydride and isopropyl iodide. With 2 equiv of tributyltin hydride, 2 equiv of isopropyl iodide, and 1 equiv of $Yb(OTf)_3$, the yield of **2a** was 84%. With 1.2 equiv of tributyltin hydride, 1.2 equiv of isopropyl iodide, and 1 equiv of $Yb(OTf)_3$, the yield dropped slightly to 75%. The diastereoselectivities were not affected. When tributyltin hydride was replaced by $(Me_3Si)_3SiH$ or Ph_2SiH_2, very low yields of **2a** resulted, combined with complex mixtures of unreacted starting material **1a**, ethyl addition product **2c**, silane addition products, and unidentified side products.

The dependence of the selectivity on the $Yb(OTf)_3$ stoichiometry is also shown in Table 3 (entries 8−11). The use of 10% $Yb(OTf)_3$ resulted in only a modest reduction in selectivity and minimal increase in the time required for completion (6 h). Successful catalysis shows that $Yb(OTf)_3$ transfers readily from adduct **2a** to reactant substrate **1a**. This is in keeping with the typically facile ligand exchange kinetics of lanthanide Lewis acids, and with the observations that α,β-unsaturated carbonyls are normally more basic than saturated analogues.[30] The catalytic

Table 4. Effect of Additives on Diastereoselectivity in Isopropyl Radical Addition to **1b** Using 0.1 Equivalent $Yb(OTf)_3$[a]

entry	additive (equiv)	yield (%)[b]	dr[c]
1	none	82	10:1
2	HMPA (0.1)	90	8:1
3	DMSO (0.1)	92	10:1
4	$H_3COCH_2CH_2OCH_3$ (0.1)	89	8:1
5	12-Crown-4 (0.1)	82	3:1
6	15-Crown-5 (0.1)	81	10:1
7	18-Crown-6 (0.1)	76	4:1
8	$(H_3C)_2NCH_2CH_2N(CH_3)_2$ (0.1)	61	1.4:1
9	Methanol (0.2)	92	22:1
10	$HOCH_2CH_2OH$ (0.1)	92	23:1
11	2,3-Butanediol (0.1)	91	21:1
12	Pinacol (0.1)	92	17:1
13	Catechol (0.1)	89	14:1
14	$HO(CH_2CH_2O)_2OH$ (0.1)	90	10:1
15	$HO(CH_2CH_2O)_3OH$ (0.1)	88	4:1
16	$HO(CH_2CH_2O)_4OH$ (0.1)	90	3:1
17	$HO(CH_2CH_2O)_5OH$ (0.1)	75	6:1
18	$HOCH_2CH_2OH$ (0.2)	95	18:1
19	$HOCH_2CH_2OH$ (0.3)	86	6:1
20	$HOCH_2CH_2OH$ (0.4)	60	7:1

[a] For typical reaction conditions (5 equiv of ^{i}Pr−I, 2 equiv of Bu_3SnH, 4 equiv of Et_3B, 4:1 CH_2Cl_2/THF, −78 °C); see experimental section. A total of 2.5 mL was used for 0.1 mmol scale reaction. [b] Yields are for isolated and column-purified materials. [c] Diastereomer ratios were determined by ^{1}H NMR (400 MHz).

potential of the reaction was obviously appealing because it suggested to us that chiral Lewis acids could mediate enantioselective conjugate addition reactions on achiral substrates; we have already reduced this possibility to practice.[31]

It is well-known that the exact complexation environment of lanthanide ions is extremely complex.[32] Additives can influence ion pairing to counterions, Lewis acidity, steric volume, and the redox chemistry of lanthanide reagents. As background to other investigations of enantioselective reactions involving chiral lanthanides, we have tested the effect of several additives on $Yb(OTf)_3$-catalyzed radical addition to cinnamate **1b** (Table 4). Good Lewis bases such as HMPA, DMSO, and DME had little effect relative to the reference reaction (entries 1−4), crown ethers reduced the selectivity somewhat (entries 5−7), and TMEDA was very harmful for both reactivity and selectivity (entry 8). Methanol and simple diol additives, however, had a generally favorable impact on both yield and selectivity (entries 9−13). Poly(ethylene glycol) had a negative impact on selectivity (entries 14−17), as did increasing amounts of ethylene glycol (entries 18−20). It was qualitatively observed that there was a correlation between selectivity and reaction speed. We believe that those additives that reduced selectivity did so by sequestering the $Yb(OTf)_3$, such that the slower reactions and increased production of minor isomer resulted from nonselective reaction by "free" substrate competing with reaction of $Yb(OTf)_3$-bound substrate. The simple alcohols and diols may have enhanced the selectivity by modestly enhancing the reactivity of the substrate−Lewis acid complex for reasons we do not yet

(27) 99.6% CH_2Cl_2 from Aldrich chemical company, listed as <0.02% water; 99.5% THF, listed as <0.02% water.

(28) Triethylborane is stable to water and is capable of initiating radical reactions under aqueous conditions. See: Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604.

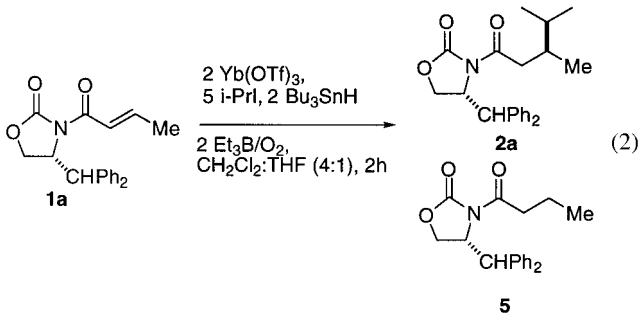
(29) (a) Kobayashi, S. *Synlett* **1994**, 689 and references therein. (b) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15. (c) Keller, E.; Feringa, B. L. *Tetrahedron Lett.* **1996**, *37*, 1879.

(30) Hunt, I. R.; Rogers, C.; Woo, S.; Rauk, A.; Keay, B. *J. Am. Chem. Soc.* **1995**, *117*, 1049.

(31) (a) Sibi, M. P.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (c) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955.

(32) For modification of lanthanide reactivity and or structure by addition of ligands, see: Aspinall, H. C.; Dwyer, J. L. M.; Greeves, N.; McIver, E. G.; Wooley, J. C. *Organometallics* **1998**, *17*, 1884. Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283. Greeves, N.; Aspinall, H. C.; Browning, A. F.; Ravenscroft, P. *Tetrahedron Lett.* **1994**, *35*, 4639. Lacote, E.; Renaud, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2259. Fukuzaka, S.-I.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.

Table 5. Effect of Temperature on Diastereoselectivity



(2)

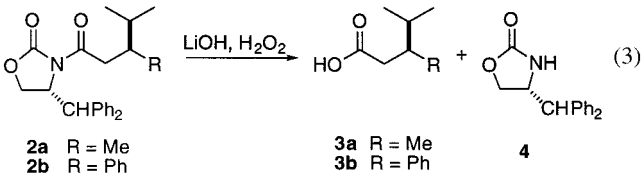
entry	temp (°C)	yield (%)[a]	dr[b]
1	−78	93	25:1
2	−40	90	15:1
3	0	80 (15%)[c]	5:1
4	25	30 (65%)[c]	4:1

[a] Yields are for isolated and column-purified materials. Five equivalents of ^{i}Pr−I, 2 equiv of Bu_3SnH, and 2 equiv of Et_3B were used. [b] Diastereomer ratios were determined by ^{1}H NMR (400 MHz). [c] The yield in parentheses is the yield of the reduction product **5**.

understand. The success of the reaction in the presence of these miscellaneous additives also suggests good compatibility with a wide variety of functionality.

The $Yb(OTf)_3$-mediated alkylation of crotonate **1a** was found to be significantly compromised at temperatures higher than −78 °C (Table 5, eq 2). The stereoselectivity diminished appreciably, and at room temperature, direct reduction of the alkene became the predominant reaction pathway, just as in −78 °C reactions with very strong Lewis acids (Table 1).

The newly created stereocenter in the major diastereomer of **2a** and **2b** had the S configuration shown (eq 3). The absolute



(3)

stereochemistry of the products was established by hydrolysis (LiOH, H_2O_2) to give known optically active carboxylic acids **3a** and **3b**.[33] The chiral auxiliary can be easily recovered in essentially quantitative yield.

Relationship between Chiral Auxiliary and Diastereoselectivity. Optically active oxazolidinone auxiliaries are readily derived from amino acids and have been widely applied to control stereoselectivity in a host of synthetic methods, such as α-alkylation reactions, aldol reactions, and Diels−Alder reactions.[34] The most commonly used optically active oxazolidinones are the "Evans auxiliaries", in which the R_1 group is phenyl, benzyl,[35] or isopropyl. We have screened the ability of these auxiliaries to control the stereoselectivity of radical conjugate additions under our $Yb(OTf)_3$-activated conditions, and the results are shown in Table 6 (eq 4). Chemical yields were good in all cases. The results show that traditional oxazolidinone auxiliaries (R_1 = Ph, benzyl, i-Pr) give modest but not useful levels of stereocontrol (= 3:1, entries 2−4, 6−8), unlike our much bulkier auxiliary (R_1 = $CHPh_2$, entries 1, 5). In the absence of Lewis acid, substrates **1c**−**e** reacted sluggishly and nonselectively.

We have shown elsewhere that our serine-derived auxiliary also induces outstanding stereoselectivity in aldol reactions, alkylation reactions, Diels−Alder reactions, and radical α-allylation reactions.[36] In all of these reactions, the diastereoselectivity observed using diphenylmethyl-substituted oxazolidinones was equal to or superior to that of benzyl, isopropyl, or phenyl-substituted oxazolidinones. The superiority of the diphenylmethyl-substituted oxazolidinone auxiliary is particularly striking in the present conjugate addition context, however. The majority of chiral oxazolidinone applications have involved chemistry *alpha* to the carbonyl, where even the isopropyl and benzyl groups are close enough to provide efficient face-shielding (so long as the conformation of the acyloxazolidinone is controlled). Conjugate addition is a much more demanding reaction, however, because the reactive *beta* carbon is one bond further removed from the oxazolidinone stereocenter; thus effective face shielding requires a significantly larger blocking group. While the isopropyl, benzyl, and phenyl groups are too small, the larger steric volume of the diphenylmethyl group evidently has sufficient extension to block one face of the beta carbon. As a general note, it may be that conjugate additions may serve as a nice test reaction to discriminate between chiral auxiliaries. It may also be that the diphenylmethyl-substituted chiral auxiliary may be of common value for "tough cases", in applications where simpler oxazolidinone auxiliaries provide inadequate selectivity.

The Effect of Radical Precursors. A wide range of organohalides serve as radical precursors and undergo addition cleanly and with good selectivity under our optimized conditions (Table 7, eq 5). We generally used iodides, but entry 2 shows that isopropyl bromide gave the same yield and selectivity as the iodide, demonstrating that the halogen used as the proradical species does not impact the selectivity. Primary and secondary alkyl groups added effectively and easily (entries 1−4, 8−10).[37] Addition of *tert*-butyl radical was sluggish at −78 °C but proceeded efficiently at −40 °C, although with accordingly reduced selectivity (entries 5, 11). The lesser reactivity of the *tert*-butyl radical was surprising, since tertiary alkyl radicals are considered to be relatively nucleophilic and normally show good reactivity toward addition.[38] This may reflect a sensitivity to steric size.

The β-substituent of the enoyl group had a significant impact on the diastereoselectivity of the radical addition. Under identical reaction conditions, isopropyl radical addition to **1b** gave 45:1 selectivity as compared to 25:1 for **1a** (entries 1 vs 9). Ethyl and cyclohexyl additions to the cinnamate **1b** were also more selective than their additions to the crotonate **1a** (entries 3, 4 vs 8, 10).[39]

Of special note is the efficient addition of alkoxyalkyl radicals and especially acyl radicals (entries 6, 7, 12, 13). The ability to introduce functionalized organic moieties such as acyl groups under radical conditions highlights one of the advantages of

(33) The absolute stereochemistry of the products was established by hydrolysis: Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235. Lardicci, L.; Salvadori, P.; Caporusso, A. M.; Menicagli, R.; Belgodere, E. *Gazz. Chim. Ital.* **1972**, *102*, 64.

(34) For a recent monograph, see: Ager, D. A.; East, M. B. *Asymmetric Synthetic Methodology*, CRC: Boca Raton, FL, 1996.

(35) Gage J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.

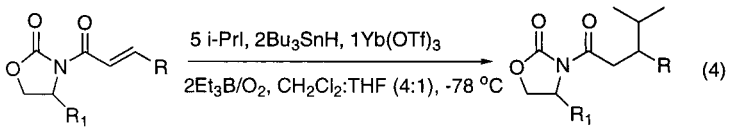
(36) Aldol: Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848. Alkylation: Sibi, M. P.; Deshpande, P. K.; LaLoggia, A. J. *Synlett* **1996**, 343. Diels−Alder: Sibi, M. P.; Deshpande, P. K.; Ji, J. *Tetrahedron Lett.* **1995**, *36*, 8965. α-allylation: Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190.

(37) The configuration of **2c**−**l** is assumed by analogy to **2a** and **2b** to be *S*.

(38) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Synthesis*; Wiley: New York, 1995; pp 49−71.

(39) We have not carried out careful kinetic studies, but in general, the cinnamate was qualitatively observed to be less reactive than the crotonate.

Table 6. Relationship between Chiral Auxiliary and Diastereoselectivity



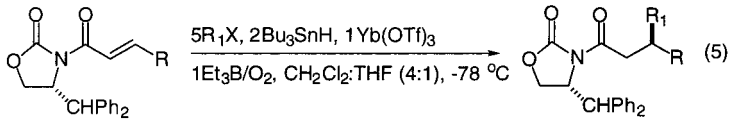
1a R_1 = $CHPh_2$, R = Me
1b R_1 = $CHPh_2$, R = Ph
1c R_1 = Ph, R = Me
1d R_1 = CH_2Ph, R = Me
1e R_1 = i-Pr, R = Me
1f R_1 = Ph, R = Ph
1g R_1 = CH_2Ph, R = Ph
1h R_1 = i-Pr, R = Ph

2a R_1 = $CHPh_2$, R = Me
2b R_1 = $CHPh_2$, R = Ph
2r R_1 = Ph, R = Me
2s R_1 = CH_2Ph, R = Me
2t R_1 = i-Pr, R = Me
2u R_1 = Ph, R = Ph
2v R_1 = CH_2Ph, R = Ph
2w R_1 = i-Pr, R = Ph

entry	substrate	R_1	R_2	product	yield (%)[a]	dr[b]	entry	substrate	R_1	R_2	product	yield (%)[a]	dr[b]
1	(*R*)-**1a**	$CHPh_2$	Me	**2a**	90	25:1	5	(*R*)-**1b**	$CHPh_2$	Ph	**2b**	94	45:1
2	(*S*)-**1c**	Ph	Me	**2r**	82	3:1	6	(*R*)-**1f**	Ph	Ph	**2u**	92	2.2:1
3	(*S*)-**1d**	CH_2Ph	Me	**2s**	81	2:1	7	(*S*)-**1g**	CH_2Ph	Ph	**2v**	85	2.2:1
4	(*S*)-**1e**	i-PrI	Me	**2t**	82	3:1	8	(*S*)-**1h**	i-Pr	Ph	**2w**	90	3.4:1

[a] Yields are for isolated and column-purified materials. [b] Diastereomer ratios were determined by ^{1}H NMR (400 MHz).

Table 7. Effect of Radical Precursors on Conjugate Additions



1a R = Me
1b R = Ph

2a R = Me, R_1 = i-Pr
2b R = Ph, R_1 = i-Pr
2c R = Me, R_1 = Et
2d R = Ph, R_1 = Et
2e R = Me, R_1 = cyc-C_6H_{11}
2f R = Me, R_1 = t-Bu
2g R = Me, R_1 = CH_2OMe
2h R = Me, R_1 = COMe
2i R = Ph, R_1 = cyc-C_6H_{11}
2j R = Ph, R_1 = t-Bu
2k R = Ph, R_1 = CH_2OMe
2l R = Ph, R_1 = COMe
2m R = Me, R_1 = Ph
2n R = Me, R_1 = Me
2o R = Me, R_1 = allyl
2p R = Me, R_1 = CH_2Ph
2q R = Me, R_1 = CH_2OAc
2r R = Me, R_1 = CH_2CO_2Et

entry	substrate	R_3X	Lewis acid (equiv)	product	yield (%)[a]	dr[b]	entry	substrate	R_3X	Lewis acid (equiv)	product	yield (%)[a]	dr[b]
1	(*R*)-**1a**	i-PrI	$Yb(OTf)_3$ (1)	**2a**	90	25:1	11	(*R*)-**1b**	*tert*-ButylI	$Yb(OTf)_3$ (1)	**2j**	90	9:1[c]
2	(*R*)-**1a**	i-PrBr	$Yb(OTf)_3$ (1)	**2a**	90	25:1	12	(*R*)-**1b**	$MeOCH_2Br$	$Yb(OTf)_3$ (1)	**2k**	81	10:1
3	(*R*)-**1a**	EtI	$Yb(OTf)_3$ (1)	**2c**	84	12:1	13	(*R*)-**1b**	MeCOBr	$Yb(OTf)_3$ (1)	**2l**	84	8:1
4	(*R*)-**1a**	c−$C_6H_{11}I$	$Yb(OTf)_3$ (1)	**2e**	92	16:1	14	(*R*)-**1a**	PhI	$Yb(OTf)_3$ (1)	**2m**	<5%[d]	
5	(*R*)-**1a**	*tert*-ButylI	$Yb(OTf)_3$ (1)	**2f**	82	14:1[c]	15	(R)-**1a**	MeI	$Yb(OTf)_3$ (1)	**2n**	<5%[d]	
6	(*R*)-**1a**	$MeOCH_2Br$	$Yb(OTf)_3$ (1)	**2g**	84	14:1	16	(R)-**1a**	allyl-I	$Yb(OTf)_3$ (1)	**2o**	<5%[d]	
7	(*R*)-**1a**	MeCOBr	$Yb(OTf)_3$ (1)	**2h**	85	7:1	17	(R)-**1a**	$PhCH_2I$	$Yb(OTf)_3$ (1)	**2p**	<5%[d]	
8	(*R*)-**1b**	EtI	$Yb(OTf)_3$ (1)	**2d**	80	20:1	18	(R)-**1a**	$AcOCH_2Br$	$Yb(OTf)_3$ (1)	**2q**	<5%[d]	
9	(*R*)-**1b**	i-PrI	$Yb(OTf)_3$ (1)	**2b**	94	45:1	19	(R)-**1a**	$BrCH_2CO_2Bn$	$Yb(OTf)_3$ (1)	**2r**	<5%[d]	
10	(*R*)-**1b**	c−$C_6H_{11}I$	$Yb(OTf)_3$ (1)	**2i**	88	26:1							

[a] Yields are for isolated and column-purified materials. [b] Diastereomer ratios were determined by ^{1}H NMR (400 MHz). [c] Reactions were conducted at −40 °C. [d] The product mixtures from entries 14−19 were analyzed by ^{1}H NMR only.

radical procedures relative to ionic methods.[40] We were also delighted to find that simple acyl bromides functioned as convenient acyl radical precursors under our reaction conditions.[41] Methoxymethyl and acetyl radical additions were qualitatively observed to react faster than simple alkyl radicals,[42] in keeping with their nucleophilic character.[43]

Several organohalides did not undergo addition. Phenyl, methyl, allyl, and benzyl iodide, bromomethyl acetate, and benzyl bromoacetate all failed to react with crotonate **1a** under the standard conditions (entries 14−18).[44] Aryl radicals are known to react fairly rapidly with THF and some THF radical addition was observed when PhI was used, so we conclude that, under our reaction conditions, the Ph$^\bullet$ radical is hydrogenated by Bu_3SnH/THF too quickly to allow clean addition. That allyl and benzyl radicals have low reactivity is well-known, so their failure to add is not at all surprising.[45] When benzyl iodide was used, some dibenzyl was observed in addition to mostly toluene. The use of $(Me_3Si)_3SiH$ or syringe pump addition of Bu_3SnH did not make reaction of benzyl iodide successful. We believe that the radicals $AcOCH_2^\bullet$ and $^\bullet CH_2CO_2Bn$ are "mismatched"

(40) We have also found that haloalkyl radicals derived from reagents such as CH_2ICl and CH_3CHBr_2 add very efficiently to provide halogenated products (unpublished results).

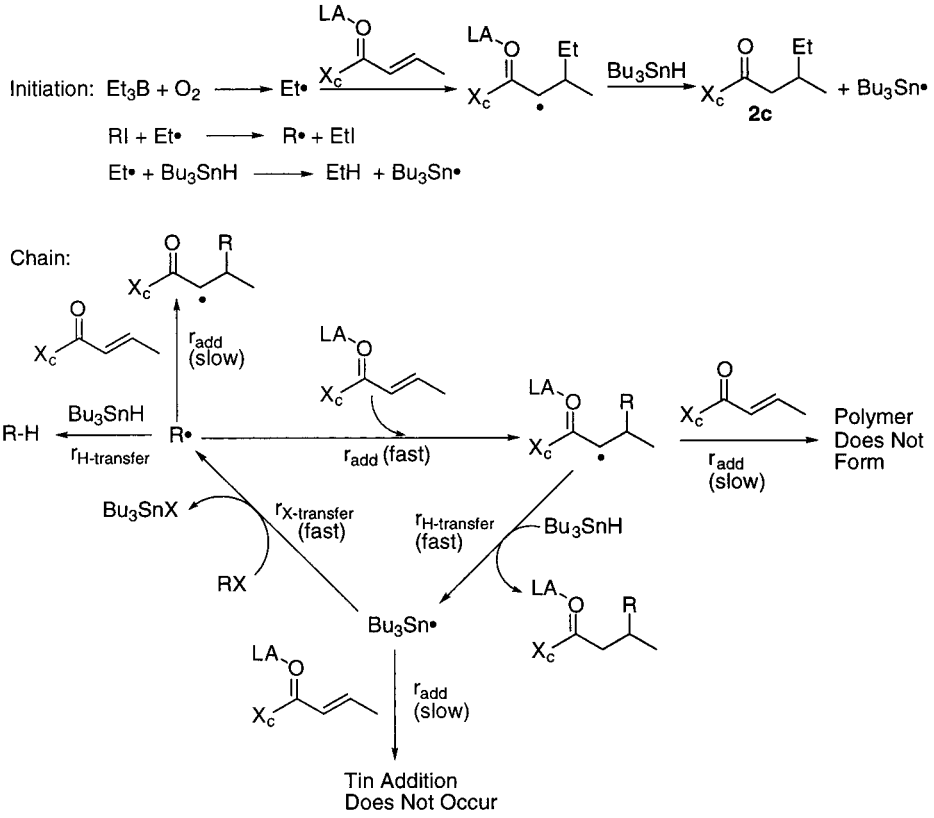
(41) Acyl radicals have usually been prepared from acyl selenides. See: Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429.

(42) While the results in the table reflect standard reaction times, TLC analysis showing reactions involving methoxymethyl bromide or acetyl bromide were complete within 15 min. NMR analysis of crude reaction mixtures also showed no indication of ethyl addition, indicating long, efficient radical chains; 1−3% ethyl addition was often observed when simple alkyl radicals were used.

(43) Alkoxyalkyl radicals are "nucleophilic". See: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, U.K., 1986, Chapter 2. Giese, B.; Dupuis, J.; Haβkerl, T.; Meixner, J. *Tetrahedron Lett.* **1983**, *24*, 703. Acyl radicals are also nucleophilic; see ref 41.

(44) The reactions were analyzed by ^{1}H NMR only. No further attempt was made to characterize the products.

Scheme 1



with the electrophilic Lewis acid-complexed enamides such that addition is apparently too slow to compete with radical hydrogenation. It appears that, while the addition is efficient for radicals of reasonable reactivity and nucleophilicity, reactivity problems occur under our conditions when electrophilic radicals, highly stabilized radicals, or too highly reactive radicals (aryl radicals) are used.

Mechanism and Model. The probable mechanism for the reaction is shown in Scheme 1. Initiation indirectly generates an alkyl radical R• that adds to the Lewis acid-activated alkene. Lewis acid activation is crucial for this addition step; in the absence of Lewis acid addition is slow, so that radical hydrogenation to give R−H occurs preferentially. The competition between radical addition and hydrogenation explains why the Lewis acid must be soluble, so that there is a substantial concentration of activated alkene. The competition between addition and hydrogenation also explains why electrophilic or benzylic radicals fail to add; in these cases addition evidently becomes slower than hydrogenation (even though the rate of hydrogenation is also reduced when radicals are stabilized by conjugation). This explanation is supported by the observation that no tributyltin hydride remained (based on GC or I_2 titration) following reaction with benzyl iodide, methyl iodide, or benzyl 2-bromoacetate. Additionally, in reactions with benzyl iodide and benzyl 2-bromoacetate, the reduced products toluene and benzyl acetate were found in the crude reaction mixtures. We consider the competition between radical addition and hydrogenation to be the most significant limitation to our procedure. If structural modifications in either the radical or the alkene result in significant reductions in the rate of addition, it may become increasingly difficult for addition to win over hydrogenation. While it is reasonable that the use of a less reactive hydrogen donor will prevent hydrogenation, our initial attempts to use $(Me_3Si)_3SiH$ as a chain carrier have failed.

Following radical addition to the Lewis acid activated alkene, the adduct radical then reacts with tin hydride. It is significant that we did not observe any polymerization when soluble Lewis acids were used. The kinetic partitioning is balanced such that a nucleophilic radical selectively adds to the Lewis acid-activated substrate, faster than it abstracts hydrogen from Bu_3SnH; however the adduct radical reacts with Bu_3SnH much faster than it adds to another substrate. This reversal in chemoselectivity reflects that the substrate is electrophilic and reacts faster with a nucleophilic isopropyl radical than with electrophilic radicals. As discussed earlier, when the radical *R*• is electrophilic, then addition to the activated alkene is too slow and the electrophilic radical instead abstracts hydrogen atom from Bu_3SnH. It is also notable that we saw no evidence for the addition of the Bu_3Sn• radical, halogen transfer apparently remaining much faster. This was true even when only 1.2 equiv of isopropyl iodide was used or when isopropyl iodide was replaced by isopropyl bromide.

That a radical mechanism was operative under our standard procedure is supported by the observation that, when Et_3B was omitted, no reaction proceeded and starting materials could be recovered. When Bu_3SnH was omitted, no product **2a** formed, although some side reactions (including ethyl transfer)[46] were observed.

The nature of the radical chain initiation involves the reaction of triethylborane with molecular oxygen to produce ethyl radical. The ethyl radical can initiate the chain in any of three ways. Since use of iodoethane gave alkylation in high yield, it is evident that ethyl radical adds effectively to the activated alkene under our conditions, regardless of whether the ethyl radical is

(45) We have recently found that benzyl radicals add to the more reactive chiral fumarates in good yields.

(46) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic: London, U.K., 1988.

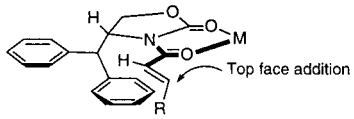


Figure 2.

produced from iodoethane or from triethylborane. Iodine atom transfer[4] may also be important but is not necessary, on the basis of the observation that replacement of isopropyl iodide with isopropyl bromide did not inhibit the reaction or complicate the product mixture. Additionally, hydrogen atom abstraction from tinhydride could also participate. If initiation involves ethyl addition, the formation of some ethyl addition product **2c** is a necessary consequence of using triethylborane as initiator. The absence of significant quantities of ethyl addition product **2c**, however, implies that radical chains are long under our standard conditions.

The high diastereoselectivity observed in the β-radical addition can be explained by a chelation model (Figure 2). Upon Lewis acid chelation, the orientations of the two carbonyls are fixed. Radical addition to the chelated substrate then takes place from the face opposite of the bulky diphenylmethyl substituent. Because the reactive beta carbon is fairly distant from the chiral carbon in the chiral auxiliary, the oxazolidinone substituent must be very large to afford adequate face shielding. Thus replacement of the diphenylmethyl group by the smaller phenyl, benzyl, or isopropyl groups gives unacceptable diastereoselectivity. The dependence of stereoselectivity on the lanthanide or prelanthanide triflate suggests that ytterbium's ionic radius of about 0.9 Å is nearly optimal for radical additions. A shorter ionic radius may "pull" the enoyl carbonyl away from the diphenylmethyl group and thus expose the back face of the reactive beta carbon toward radical addition. We had anticipated that a longer ionic radius would enhance selectivity by "pushing" the enoyl portion further over the blocking group, but the results contradicted this notion. For Lewis acids whose ionic radii are too long, distortions from planarity may occur that either block the top face or somehow expose the bottom face.

The significantly higher selectivity observed for cinnamate **1b** as compared to crotonate **1a** (Table 7) is puzzling. This observation, combined with the decreased selectivity in the presence of toluene (Table 3, entries 3 vs 7), raises the possibility that π-stacking may play a role in organizing the orientation of the diphenylmethyl group relative to the enoyl portion.[47] If so, perhaps the π-stacking is more effective for cinnamate than crotonate because the former is more highly conjugated, and toluene reduces the stereoselectivity because it disrupts the auxiliary-enoyl π-stack.

With good chelating Lewis acids under stoichiometric conditions, we believe that the reaction proceeds primarily from the Lewis acid−substrate complex; the minor isomer probably results from radical addition to the "wrong" face of the complex rather than from competing nonselective addition to substrate in which only one or neither carbonyl is bound to Lewis acid. NMR studies in CD_3CN show very strong binding between acyloxazolidinone substrates and chelating Lewis acids.[48] In the case of $MgBr_2$, replacement of ether with the more Lewis-basic THF did not reduce the selectivity (Table 1, entries 9 and 10), as would have been expected if the solvent was competing with the substrate for Lewis acid binding sites. Only minimal reduction in selectivity was observed when the amount of Yb(OTf)$_3$ was reduced from 2 to 1 to 0.3 equiv, and selectivity was still good using only 10 mol % (Table 3, entries 8−11). Free substrate is also inherently less reactive than Lewis acid-complexed substrate (see Table 1, entry 1) and thus unlikely to provide a major competing pathway unless present in substantial quantities.

(47) Jones, G. J.; Chapman, B. J. *Synthesis* **1995**, 475.
(48) Unpublished results.

Summary

We have developed a highly diastereoselective method for the conjugate addition of carbon radicals to chiral α,β-unsaturated *N*-enoyloxazolidinones using Bu_3SnH as chain carrier and Et_3B/O_2 as radical initiator. Lewis acids have been screened, and Yb(OTf)$_3$ proved to give optimized results for both chemical yield and diastereoselectivity. The virtue of the Yb(OTf)$_3$ lies in its ability to chelate both substrate carbonyls and thus control the conformation of the reactive substrate; in its ionic radius, which is neither too long nor too short; and in its Lewis acidity, which is strong enough to greatly activate the substrates but not so strong that hydrogenation of the substrate interferes at −78 °C. Chemical yields were outstanding, especially given the normally sluggish reactivity of nonterminal alkenes toward radical addition, and no competing polymerization was observed. The diastereoselectivity observed is comparable to or better than that observed in analogous conjugate additions using ionic methods.

The selectivity is solvent-dependent, CH_2Cl_2−THF being an ideal combination. Scrupulously dry solvents or reaction conditions were not required. Substoichiometric amounts of Yb(OTf)$_3$ provided efficient reaction with minimal sacrifice in diastereoselectivity. Our diphenylmethyl-substituted oxazolidinone auxiliaries gave greatly superior selectivity compared to phenyl-, benzyl-, or isopropyl-substituted oxazolidinones. Carbon radicals with reasonable nucleophilicity were generally successful, including functionalized radicals such as acetyl or methoxymethyl. Electrophilic radicals were not successful.

Experimental Procedures

All reagents were used as received from the supplier. Tetrahydrofuran, ether, and 1,2-dimethoxyethane were distilled from sodium benzophenone/ketyl prior to use. Chloroform, hexane, and CH_2Cl_2 were distilled from calcium hydride. Standard benchtop techniques were employed for handling air-sensitive reagents, and all reactions were carried out under nitrogen. Flash column chromatography was performed using Merck 60 silica gel, 230−400 mesh. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 (400) and 65 MHz, respectively. Chiral HPLC analysis were performed using a Chiralcel OD column (Chiral Technologies, Inc.) on a ISCO system comprising of a 2360 pump, 2350 gradient programmer, and a variable wavelength UV detector. Rotations were recorded on a JASCO-DIP-370 instrument. Elemental analyses were performed in house on a Perkin-Elmer instrument.

Lewis Acid-Mediated Intermolecular β-Selective Radical Addition to 1a: Scale-up Procedure for Product Characterization. The following conditions differ slightly from the typical reaction conditions stated in the text. The selectivity using this procedure is identical to that listed in the text under standard conditions. To a flask containing **1a** (160 mg, 0.5 mmol) Yb(OTf)$_3$ (210 mg, 0.5 mmol), THF (5 mL), and CH_2Cl_2 (5 mL) under N_2 was added i-PrI (425 mg, 2.5 mmol), Bu_3SnH (730 mg, 2.5 mmol), and Et_3B (1 M in hexane) (1 mL, 1 mmol) at −78 °C. Five milliliters of O_2 was then added via syringe over 2 min. The reaction mixture was stirred at −78 °C for 2 h. After completion (TLC), Et_2O (20 mL) was added to the reaction mixture. It was then washed with brine (3 × 3 mL) and dried with $MgSO_4$. The product **2a** was purified by chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent, yield 170 mg (93%).

2a. mp 67−70 °C; R_f = 0.75 (80:20 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 7.3 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 1.50−1.63 (m, 1H), 1.98−2.12 (m, 1H),

2.73 (dd, $J = 16.1, 9.6$ Hz, 1H), 3.04 (dd, $J = 16.1, 4.3$ Hz, 1H), 3.36 (d, $J = 9.3$ Hz, 1H), 3.80 (dd, $J = 9.3, 2.2$ Hz, 1H), 4.66 (d, $J = 5.9$ Hz, 1H), 4.86−4.95 (m, 1H), 6.80−7.10 (m, 10H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 15.8, 18.3, 20.5, 32.3, 35.2, 40.3, 51.8, 56.8, 65.6, 127.5, 128.3, 128.9, 129.1, 129.4, 129.6, 138.6, 140.1, 173.3; $[\alpha]_D^{26}$ +107.7 (*c* 0.545, CH_2Cl_2). Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45. Found: C, 75.76, H, 7.45.

2b. mp 173−175 °C; $R_f = 0.8$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H), 1.84−1.99 (m, 1H), 2.90−3.04 (m, 2H), 3.55−3.66 (m, 1H), 4.16 (t, $J = 8.8$ Hz, 1H), 4.28 (dd, $J = 9.5, 2.2$ Hz, 1H), 4.64 (d, $J = 5.9$ Hz, 1H), 5.05−5.12 (m, 1H), 7.05−7.45 (m, 15H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 20.8, 21.3, 33.4, 38.9, 48.8, 51.5, 56.9, 65.5, 126.7, 127.5, 128.3, 128.5, 128.8, 128.9, 129.0, 129.3, 129.6, 138.6, 140.0, 143.5, 153.9, 172.6; $[\alpha]_D^{26}$ −142.4 (*c* 0.460, CH_2Cl_2). Anal. calcd for $C_{28}H_{29}NO_3$: C, 78.66, H, 6.84. Found: C, 78.97, H, 7.05.

Typical Procedure using Ethylene Glycol as an Additive. To a solution of $Yb(OTf)_3$ (0.01 mmol) in 4:1 CH_2Cl_2/THF (2.5 mL) was added ethylene glycol (0.01 mmol), and the mixture was stirred for 5 min. This was followed by addition of substrate **1b** (0.1 mmol) and *i*-PrI (0.5 mmol), and the reaction was cooled to −78 °C. Bu_3SnH (0.2 mmol) and triethylborane (0.4 mmol) were added in sequence, and the reaction was initiated by oxygen. After completion (TLC), normal workup gave **2b**.

Hydrolysis of 2a. Typical Procedure. To a flask containing **2a** (256 mg, 0.7 mmol) THF (5 mL) and H_2O (5 mL) under N_2 was added H_2O_2 (30%) (0.317 mL, 2.8 mmol) at 0 °C. $LiOH\cdot H_2O$ (57 mg, 1.4 mmol) was then added, and the reaction mixture was stirred at 0 °C for 1 h. After completion of the reaction (TLC), most of the THF was evaporated. The aqueous solution (pH = 12) was extracted with CH_2Cl_2 (3 × 10 mL) (recovery of chiral auxiliary). The aqueous solution was acidified with HCl (3 M) until pH ∼1 and extracted again with CH_2Cl_2 (4 × 15 mL). The organic solution was dried ($MgSO_4$) and concentrated to yield (*S*)-3,4-dimethyl-pentanoic acid (85 mg, 93%).

(*S*)-3,4-Dimethylpentanoic Acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, $J = 6.5$ Hz, 3H), 0.92 (d, $J = 7$ Hz, 3H), 0.94 (d, $J = 6.4$ Hz, 3H), 1.62−1.67 (m, 1H), 1.88−1.94 (m, 1H), 2.14 (dd, $J = 15.1, 9.1$ Hz, 1H), 2.44 (dd, $J = 15.1, 4.8$ Hz, 1H); $[\alpha]_D^{26}$ −10.7 (*c* 0.55, benzene). {lit: $[\alpha]_D^{21}$ −6.9 (*c* 1.18, benzene); Enders, D.; Rendenbach, B. E. M. *Tetrahedron* **1986**, *42*, 2235}.

(*S*)-3-Phenyl-4-methylpentanoic Acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, $J = 6.5$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 1.82−1.90 (m, 1H), 2.62 (dd, $J = 15.6, 9.6$ Hz, 1H), 2.80 (dd, $J = 15.1, 5.4$ Hz, 1H), 2.82−2.90 (m, 1H), 7.20−7.32 (m, 5H); $[\alpha]_D^{26}$ −33.6 (*c* 3.77, $CHCl_3$) or $[\alpha]_D^{26}$ −41.0 (*c* 0.405, benzene). {lit:$[\alpha]_D^{25}$ −34.4 (*c* 4.06, $CHCl_3$); Lardicci, L.; Salvadori, P.; Caporusso, A. M.; Menicagli, R.; Belgodere, E. *Gazz. Chim. Ital.* **1972**, *102*, 64}.

Ethyl Radical Addition to 1a. Product 2c. Yield 83%; white solid; mp 58−60°; $R_f = 0.43$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84−0.87 (m, 6H), 1.00−1.36 (m, 2H), 1.78−1.90 (m, 1H), 2.58−2.64 (dd, $J = 16.4, 8.1$ Hz, 1H), 2.77−2.82 (dd, $J = 16.2, 4.0$ Hz, 1H), 4.34−4.41 (m, 2H), 4.67−4.68 (d, $J = 6.2$ Hz, 1H), 4.72−4.74 (d, $J = 5.6$ Hz, min), 5.31−5.36 (m, 1H), 7.36−7.11 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 19.2, 29.3, 31.0, 42.2, 51.3, 56.4, 65.2, 127.1, 127.9, 128.5, 129.0, 138.3, 139.7, 153.5, 172.5; $[\alpha]_D^{26}$ −110.09 (*c* 1.09, CH_2Cl_2). Anal. calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.05; H, 7.20; N, 3.91.

Ethyl Radical Addition to 1b. Product 2d. Yield 80%; white solid; mp 140−142°; $R_f = 0.38$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74−0.79 (t, $J = 7.2$ Hz, 3H), 1.54−1.65 (m, 2H), 2.91−3.02 (m, 2H), 3.35−3.42 (dd, $J = 16.5, 8.3$ Hz, 1H), 4.18−4.22 (t, $J = 8.1$ Hz, 1H), 4.27−4.29 (dd, $J = 9.1, 2.4$ Hz, 1H), 4.53−4.54 (d, $J = 4.8$ Hz, min), 4.63−4.64 (d, $J = 5.9$ Hz, 1H), 5.12−5.16 (m, 1H), 5.22−5.26 (m, min), 7.06−7.36 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 29.3, 41.5, 43.1, 56.5, 65.2, 126.4, 127.1, 127.8, 127.9, 128.4, 128.7, 129.0, 129.3, 129.4, 138.2, 139.6, 144.1, 153.5, 171.8; $[\alpha]_D^{26}$ −106.7 (*c* 0.52, $CHCl_3$). Anal. calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.35; H, 6.54; N, 3.46.

Cyclohexyl Radical Addition to 1a. Product 2e. Yield 87%; white solid; mp 114−116°; $R_f = 0.40$ (70:30 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84−1.29 (m, 9H), 1.59−1.71 (m, 5H), 2.03−2.11 (m, 1H), 2.77−2.83 (dd, $J = 16.1, 9.1$ Hz, 1H), 3.06−3.11 (dd, $J = 16.1, 9.1$ Hz, 1H), 3.35−3.39 (dt, $J = 17.5, 7.7, 1.9$ Hz, 1H), 3.79−3.82 (dd, $J = 9.1, 2.4$ Hz, 1H), 4.70−4.71 (d, $J = 5.9$ Hz, 1H), 4.90−4.94 (m, 1H), 6.83−6.85 (m, 2H), 6.93−7.07 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 26.6, 26.7, 26.8, 28.7, 30.5, 34.3, 42.6, 51.2, 56.4, 65.2, 127.1, 127.9, 128.5, 128.7, 129.0, 129.3, 138.2, 139.7, 153.5, 172.9, 173.0; $[\alpha]_D^{26}$ −93.82 (*c* 0.534, $CHCl_3$). Anal. calcd for $C_{26}H_{31}NO_3$: C, 77.00; H, 7.70; N, 3.45. Found: C, 76.74; H, 7.36; N, 3.82.

***tert*-Butyl Radical Addition to 1a. Product 2f.** Yield 82%; white solid; mp 75−83°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72−0.74 (d, $J = 6.7$ Hz, min), 0.77−0.79 (d, $J = 6.7$ Hz, 3H), 0.85 (s, min), 0.86 (s, 9H), 1.71−1.85 (m, 1H), 2.50−2.57 (dd, $J = 16.1, 6.4$ Hz, min), 2.58−2.64 (dd, $J = 15.8, 5.9$ Hz, 1H), 2.82−2.87 (dd, $J = 16.5, 2.1$ Hz, 1H), 2.92−2.97 (dd, $J = 17.1, 2.4$ Hz, min), 4.29−4.42 (m, 2H), 4.66−4.67 (d, $J = 5.5$ Hz, 1H), 4.71−4.72 (d, $J = 5.6$ Hz, min), 5.32−5.36 (m, 1H), 7.11−7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 32.9, 38.2, 38.7, 51.4, 56.5, 65.3, 127.2, 127.9, 128.5, 128.7, 129.0, 129.3, 138.3, 139.7, 153.5, 173.4; $[\alpha]_D^{26}$ −248.83 (*c* 0.512, $CHCl_3$). Anal. calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69.

Methoxymethyl Radical Addition to 1a. Product 2g. Yield 84%; white solid; mp 81−82°; $R_f = 0.18$ (70:30 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.88 (d, $J = 6.7$ Hz, min), 0.90−0.91 (d, $J = 6.8$ Hz, 3H), 2.19−2.31 (m, 1H), 2.53−2.59 (dd, $J = 16.9, 7.4$ Hz, min), 2.67−2.73 (dd, $J = 16.9, 7.5$ Hz, 1H), 2.86−2.92 (dd, $J = 16.9, 5.9$ Hz, 1H), 2.98−3.04 (dd, $J = 16.6, 5.9$ Hz, min), 3.24−3.14 (m, 2H), 3.28 (s, min), 3.32 (s, 3H), 4.32−4.46 (m, 2H), 4.62−4.64 (d, $J = 6.4$ Hz, min), 4.67−4.68 (d, $J = 5.9$ Hz, 1H), 5.30−5.34 (m, 1H), 7.10−7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 29.7, 39.4, 51.3, 56.4, 58.9, 65.2, 77.3, 127.2, 127.9, 128.5, 128.8, 129.0, 129.3, 138.3, 139.7, 153.6, 172.1; $[\alpha]_D^{26}$ −123.80 (*c* 1.0, CH_2Cl_2). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.56; H, 6.85; N, 3.80.

Acetyl Radical Addition to 1a. Product 2h. Yield 88%; clear solid; mp 115−119°; $R_f = 0.15$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12−1.14 (d, $J = 7.5$ Hz, min), 1.15−1.17 (d, $J = 5.1$ Hz, 3H), 2.20 (s, min), 2.25 (s, 3H), 2.67−2.72 (dd, $J = 18.5, 3.8$ Hz, min), 2.79−2.84 (dd, $J = 18.5, 3.8$ Hz, 1H), 3.00−3.09 (m, 1H), 3.32−3.40 (dd, $J = 18.5, 9.8$ Hz, min), 3.38−3.45 (dd, $J = 18.5, 9.9$ Hz, 1H), 4.34−4.36 (dd, $J = 9.3, 2.4$ Hz, min), 4.41−4.49 (m, 2H), 4.64−4.65 (d, $J = 5.6$ Hz, min), 4.69−4.70 (d, $J = 4.6$, 1H), 5.28−5.22 (m, 1H), 7.05−7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 28.6, 39.0, 41.9, 49.8, 56.0, 64.7, 127.1, 127.9, 128.3, 128.8, 128.9, 129.7, 137.9, 139.7, 153.4, 171.8, 211.1; $[\alpha]_D^{26}$ −248.83 (*c* 0.512, $CHCl_3$). Anal. calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.02; H, 6.57; N, 3.69.

Cyclohexyl Radical Addition to 1b. Product 2i. Yield 85%; white solid; mp. 169−173°; $R_f = 0.40$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73−1.85 (m, 11H), 2.90−3.00 (m, 2H), 3.51−3.59 (m, 1H), 4.08−4.13 (app. t, $J = 8.3$ Hz, 1H), 4.23−4.26 (dd, $J = 9.1, 2.1$ Hz, 1H), 4.37−4.39 (m, min), 4.48−4.49 (d, $J = 4.3$ Hz, min), 4.59−4.61 (d, $J = 5.9$ Hz, 1H), 5.01−5.05 (m, 1H), 5.15−5.19 (m, min), 7.03−7.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 26.5, 30.8, 31.2, 38.2, 42.7, 47.6, 51.0, 56.6, 65.1, 126.3, 127.1, 127.9, 128.1, 128.4, 128.5, 128.7, 129.0, 129.3, 138.2, 139.6, 143.3, 153.9, 172.3; $[\alpha]_D^{26}$ −130.0 (*c* 1.00, CH_2Cl_2). Anal. calcd for $C_{31}H_{33}NO_4$: C, 76.99; H, 6.86; N, 2.90. Found: C, 77.13; H, 6.78; N, 3.11.

***tert*-Butyl Radical Addition to 1b. Product 2j.** Yield 90%; white solid; mp 194−195°; $R_f = 0.40$ (70:30 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 2.82−2.88 (dd, $J = 15.5, 3.2$ Hz, 1H), 2.99−3.02 (dd, $J = 11.5, 3.0$ Hz, 1H), 3.74−3.81 (dd, $J = 17.2, 11.5$ Hz, 1H), 4.16−4.18 (t, $J = 5.6$ Hz, 1H), 4.24−4.27 (dd, $J = 11.8, 2,4$ Hz, 1H), 4.58−4.59 (d, $J = 6.2$ Hz, 1H), 4.63−4.64 (d, $J = 5.6$ Hz, min), 5.02−5.04 (m, 1H), 5.10−5.15 (m, min), 6.99−7.35 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 33.8, 35.9, 51.1, 55.5, 56.5, 65.2, 126.4, 127.1, 127.8, 127.9, 128.5, 128.7, 129.0, 129.3, 138.2, 139.6, 142.1, 153.7, 172.4; $[\alpha]_D^{26}$ −117.3 (*c* 1.10, CH_2Cl_2). Anal. calcd for $C_{29}H_{31}NO_3$: C, 78.89; H, 7.08; N, 3.17. Found: C, 78.54; H, 7.28; N, 3.18.

Methoxymethyl Radical to 2b. Product 2k. Yield 84%; white solid; mp 153−155°; $R_f = 0.27$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14−3.53 (m, 5H), 3.33 (s, 3H), 4.27−4.42 (m, 2H), 4.55−

4.54 (d, $J = 5.1$ Hz, min), 4.66−4.67 (d, $J = 6.2$ Hz, 1H), 5.16−5.20 (m, 1H), 5.25−5.29 (m, min), 7.05−7.12 (m, 4H), 7.18−7.36 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4, 41.2, 50.8, 56.4, 58.9, 65.1, 76.5, 126.9, 127.1, 127.9, 128.0, 128.4, 128.6, 128.7, 129.0, 129.3, 138.1, 137.9, 141.7, 153.5, 171.5; $[\alpha]_D^{26}$ −130.8 (*c* 0.52, CH_2Cl_2). Anal. calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.48; H, 6.34; N, 3.26.

Acetyl Radical Addition to 1b. Product 2l. Yield, 84%: mp. 110−113°; $R_f = 0.26$ (70:30 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, min), 2.17 (s, 3H), 2.86−2.92 (dd, $J = 18.3$, 3.5, 1H), 3.00−3.05 (dd, $J = 18.8$, 3.5 Hz, 1H), 3.81−3.88 (dd, $J = 9.8$, 10.6 Hz, min), 3.88−3.95 (dd, $J = 18.8$, 10.7 Hz, 1H), 4.26−4.29 (dd, $J = 10.7$, 3.5 Hz, 1H), 4.35−4.37 (dd, $J = 9.1$, 2.4 Hz, min), 4.42−4.43 (m, 2H), 4.62−4.63 (d, $J = 5.9$ Hz, min), 4.75−4.76 (d, $J = 4.0$ Hz, 1H), 7.06−7.07 (d, $J = 7.5$ Hz, 2H), 7.18−7.20 (d, $J = 7.5$ Hz, 1H), 7.22−7.41 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 39.1, 49.6, 54.0, 56.0, 64.5, 127.1, 127.8, 127.9, 128.3, 128.5, 128.8, 128.9, 129.3, 129.8, 137.3, 137.9, 139.8, 153.2, 171.6, 206.9; $[\alpha]_D^{26}$ −297.7 (*c* 0.997, CH_2Cl_2). Anal. calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.27. Found: C, 75.92; H, 6.24; N, 3.28.

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Supporting Information Available: Characterization data for compounds **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, and **2r**, **2s**, **2t**, **2u**, **2v**, and **2w**. This material is available free of charge via the Internet at http://pubs.acs.org.

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