Higher Selectivity at Higher Temperatures! Effect of Precursor Stereochemistry on Diastereoselectivity in Radical Allylations. Insight into the Role of the Lewis Acid

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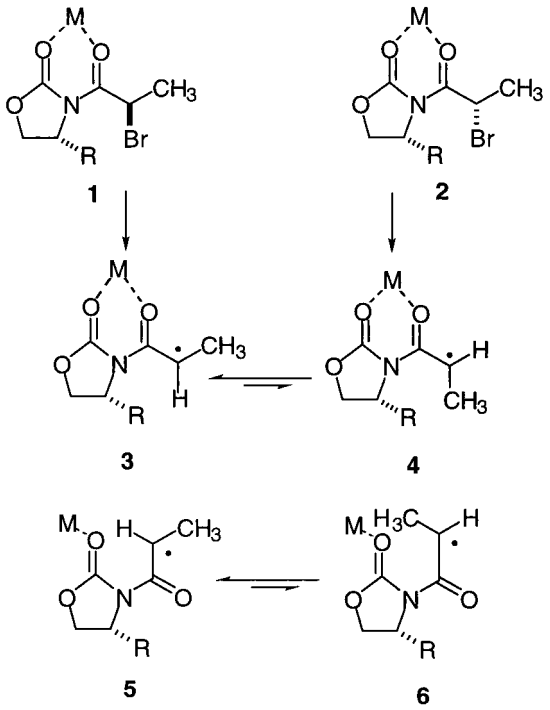
Abstract: A detailed investigation of the effects of Lewis acid, temperature, and trapping efficiency of functionalized allylstannanes on diastereoselective radical allylation reactions of α-bromooxazolidinone imides **1** and **2** was conducted. Results indicate that despite the addition of Lewis acids, a bidentate chelated radical intermediate **21** may be accessible from only one diastereomer of starting material due to steric interactions in **20** that are not present in chelated intermediate **17**. It is shown that application of the appropriate Lewis acid, increasing temperatures, and slower allylstannane traps all facilitate formation of **21**. Thus highly stereoselective radical allylations (>50:1, Tables 2 and 3) can be performed at room temperature as well as low temperatures.

Construction of carbon−carbon bonds with high selectivity in acyclic systems by radical processes has been the subject of investigation in many laboratories.[2,3] A major driving force in the recent success of such processes was the realization that Lewis acids can be effectively used to control the conformations of either the radical intermediate or the radical trap and also enhance the reactivity of certain substrates for radical addition.[4] The dogma in free radical chemistry is that the precursor configuration has little or no impact on the levels of stereoinduction in diastereoselective transformations and this is often cited as an advantage over ionic processes. The reason for this conclusion is that a prochiral radical intermediate generated is generally planar or slightly tetrahedral with a very low barrier for interconversion, and thus it has no memory of its origin. As part of an ongoing program toward understanding the basis for diastereoselectivity in Lewis acid-mediated radical reactions, we became interested in exploring the issue of precursor stereochemistry on the levels of selectivity in radical allylations. The basic postulate we wished to examine was whether diastereomeric bromides **1** and **2** will lead to the same conformationally locked radical intermediate **3** or whether non-Lewis acid (or singly bound) controlled rotamers **5** or **6** play a role in the diastereoselective outcome of these allylations.[5] In addition, we wished to probe whether variations in temperature and/or tuning of allylstannane reactivity by appropriate functionalization would have an impact on which reactive rotamer is finally trapped. The evaluation of this hypothesis is the focus of this paper.



Generally, increasing reaction temperatures has a dramatic effect on stereoselectivity in that higher temperatures lead to decreased levels of stereocontrol. However, there have been sporadic reports in the literature illustrating an inverse relation-

(1) This material is based upon work supported under a National Science Foundation Graduate Fellowship.

(2) For monographs and leading review articles, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (c) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. (d) Smadja, W. *Synlett* **1994**, 1.

(3) For selected recent reports on stereoselective allylation, see: (a) Renaud, P.; Moufid, N.; Kuo, L. H.; Curran, D. P. *J. Org. Chem.* **1994**, *59*, 3547. (b) Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421. (c) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029. (d) Porter, N. A.; Wu, J. H.; Zhang, G.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702. (e) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713. (f) Fhal, A.-R.; Renaud, P. *Tetrahedron Lett.* **1997**, *38*, 2661. (g) Rosenstein, I. J.; Tynan, T. A. *Tetrahedron Lett.* **1998**, *39*, 8429.

(4) For a recent review, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562. For Lewis acid-mediated enantioselective conjugate additions, see: Sibi, M. P.; Ji, J.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. For a discussion on Lewis acid-assisted atom-transfer reactions of α-halo amides, see: Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155.

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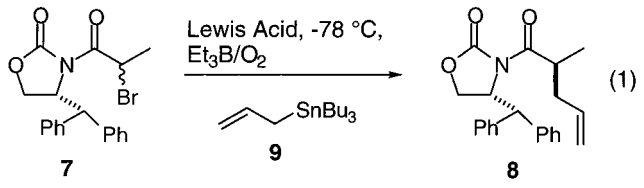
Table 1. Effect of Lewis Acid on ρ-Diastereoselectivity[a]



7 9 8

entry	lewis acid	reaction conditions	yield,[b] %	ratio (*RS*:*RR*)[c]
1	none	−78 °C, CH_2Cl_2, 3 h	93	1:1.8
2	BF_3·OEt_2	−78 °C, CH_2Cl_2, 2.5 h	85	1:1.4
3	$MgBr_2$	−78 °C, CH_2Cl_2, 2 h	94	39:1
4	$Yb(OTf)_3$[d]	−78 °C, CH_2Cl_2/THF (1:1), 2 h	64 (14)[e]	5:1

[a] Two equivs of Lewis acid was used in all reactions unless otherwise noted. [b] Yield of isolated product. [c] Diastereomer ratios were determined by ^1H NMR (400 MHz). [d] 1 equiv of the Lewis acid was used. [e] Yield of the reduced product.

ship between temperature and stereoselectivity.[6] In this work we show a consistent pattern of higher temperatures leading to significantly increased levels of diastereoselectivity.

Results

We have previously reported on the allylation of oxazolidinones of the type **7** under radical conditions using allyltributyltin and triethylborane−oxygen as an initiator at −78 °C. Salient results from this study are tabulated in Table 1.[7] General conclusions from this study are (1) the allylations are nonselective in the absence of Lewis acid additives (entry 1), (2) single point binding Lewis acids such as BF_3·Et_2O gave the allylated product with low selectivity, (3) Lewis acids capable of coordinating to both the carbonyl oxygens gave high selectivity (entry 3, data with other Lewis acids not shown), (4) the use of ytterbium triflate, which was the best Lewis acid for conjugate additions, gave only moderate selectivity (entry 4), and (5) the chiral oxazolidinone derived from diphenylalaninol[8] was found to be optimal for obtaining high selectivity (compared to oxazolidinone auxiliaries derived from phenylglycinol or phenylalaninol). The absolute configuration of the newly formed stereocenter was established as *S* by hydrolysis and comparison of the sign of rotation with that of a known compound.[9] This result agrees with the model shown in Figure 1where the *si* face of the molecule is blocked by the bulky portion of the chiral auxiliary, leaving the *re* face exposed to trap the allyltin. The sense of stereoinduction in the radical mediated allylation was

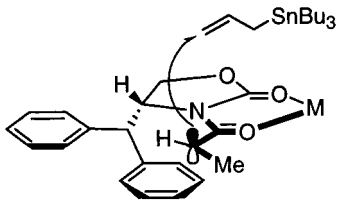
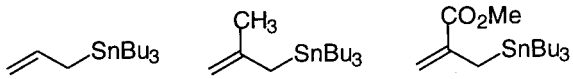


Figure 1.

the same as that of enolate allylation and the two reactions provide comparable diastereoselectivity.[10]

Commencing our study of diastereoselective radical allylations, three readily accessible allylstannanes were chosen: **9**, **10**, and **11**. The relative reactivity of the three different



9 **10** **11**

allylstannanes toward the electrophilic radical intermediate (generated from either **1** or **2**) was assessed qualitatively through competitive experiments. Control experiments using equal molar amounts of two allylstannanes in trapping the intermediate radical established the reactivity in the following order **11** > **10** > **9**, with a relative reactivity ratio of 25:5:1.[11]

To probe the dependence of selectivity on precursor stereochemistry, we undertook a detailed study of reactions of **1** and **2** with each allylstannane (**9**−**11**), various Lewis acids, and various temperatures. Diastereomerically pure starting materials were prepared by acylation of the chiral auxiliary with racemic 2-bromopropionyl bromide under standard conditions (*n*-BuLi, THF, −78 °C) followed by column chromatographic separation of the diastereomers.[12] With the pure compounds in hand, two Lewis acids, $MgBr_2$·Et_2O and $Yb(OTf)_3$, were chosen for the study. Initial reactions conditions employed were −78 °C, Et_3B/O_2, and 2.5 equivs of the allylating agent. Results from these experiments are presented in Tables 2 and 3.

Allylation of either **1** or **2** with allyltributyl tin (**9**) using 2 equivs of $MgBr_2$ at −78 °C gave the allylated product **8** in good yield and ∼40:1 selectivity (Table 2, entries 1 and 2).[13] The stereochemistry of the product was the same regardless of the starting geometry, i.e., starting from either **1** or **2** gave **8** of the same configuration. The observed high selectivity suggests the following: (1) both diastereomers produce the same radical intermediate, (2) the intermediate radical is chelated to the Lewis acid as an s-cis rotamer and approach of the reagent occurs from the face opposite to the bulky chiral auxiliary, (3) assuming that bromine atom abstraction may or may not occur from a chelated form of the substrate **1** and **2**, rotation across the radical-carbonyl ($COCHCH_3$) bond (structures **4**→**3**) as well as

(5) For limited examples of selectivity dependence on precursor stereochemistry, see: (a) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554. (b) Gerster, M.; Audergon, L.; Moufid, N.; Renaud, P. *Tetrahedron Lett.* **1996**, *35*, 6335. (c) Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507.

(6) For examples describing an inverse relationship between temperature and stereoselectivity, see the following references. Asymmetric decarboxylation: Musart, J.; Hénin, F.; Aboulhoda, S. J. *Tetrahedron: Asymmetry* **1997**, *8*, 381. Hydrogenation: Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. Oxazaborolidine reductions: Zhang, Y.-W.; Shen, Z.-X.; Liu, C.-L.; Chen, W.-Y. *Synth. Commun.* **1995**, *25*, 3407. Stone, G. *Tetrahedron*: *Asymmetry* **1994**, *5*, 465. Asymmetric protonation using SmI_2: Takeuchi, S.; Miyoshi, N.; Hirata, K.; Hayashida, H.; Ohgo, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2001. Asymmetric addition of Grignards to aldehydes: Markó, I. E.; Chesney, A.; Hollinshead, D. M. *Tetrahedron: Asymmetry* **1994**, *5*, 569.

(7) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190.

(8) (a) For synthesis of the auxiliary, see: Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J.; Christensen, J. W. *Tetrahedron Lett.* **1995**, *36*, 8961. (b) Sibi, M. P. *Aldrichim. Acta* **1999**, *32*, 93. This chiral auxiliary is now available commercially from Aldrich Chemical Co.

(9) On hydrolysis with $LiOH/H_2O_2$ **8** gave (*S*)-2-methyl-4-butenoic acid $[\alpha]^{26}_D = 10.5°$ (*c* 1.15, $CHCl_3$); lit. $[\alpha]^{26}_D = 10.5°$ ($CHCl_3$). Riley, R. G.; Silverstein, R. M. *Tetrahedron* **1974**, *30*, 1171.

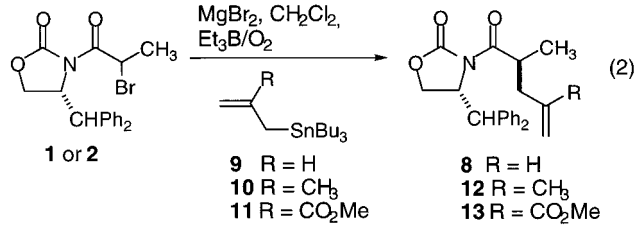
(10) Enolate allylation of 3-(1-oxopropyl)-4-(diphenylmethyl)-2-oxazolidinone gave **8** in 63% yield with >99% de. Sibi, M. P.; Deshpande, P. K.; Ji, J. *Tetrahedron Lett.* **1995**, *36*, 8965.

(11) Allyltributyl tin is commercially available. Methylallylstannane and carbomethoxyallylstannane were prepared by known procedures, see: (a) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B.; Robertson, J. *Tetrahedron* **1991**, *47*, 5901. (b) Schwartz, W. T., Jr.; Post, H. W. *J. Organomet. Chem.* **1964**, *2*, 357. For similar competitive experiments, see: Landais, Y.; Planchenault, D. *Tetrahedron* **1995**, *44*, 12 097. Renaud, P.; Gerster, M.; Ribezzo, M. *Chimia* **1994**, *48*, 366.

(12) Absolute configuration of α-bromoimides **1** and **2** were determined by hydrolysis with $LiOH/H_2O_2$ and comparison of the optical rotation with commercially available (*S*)-2-bromopropionic acid.

(13) Two equivalents of $MgBr_2$ were used in order to ensure that at least one equivalent was indeed the Lewis acid in case of possible contamination by oxidation products.

Table 2. Effect of Substrate Stereochemistry and Reaction Temperature on Product Diastereoselectivity



1 or **2**

9 R = H
10 R = CH_3
11 R = CO_2Me

8 R = H
12 R = CH_3
13 R = CO_2Me

entry	substrate stereochem	temp	R	% yield[a,b]	ratio[c]
1	(*R*)	−78 °C	H	70	39:1 (*S*)
2	(*S*)	−78 °C	H	91	39:1 (*S*)
3	(*R*)	0 °C	H	90	>50:1 (*S*)
4	(*S*)	0 °C	H	92	>50:1 (*S*)
5	(*R*)	RT	H	82	>50:1 (*S*)
6	(*S*)	RT	H	88	>50:1 (*S*)
7	(*R*)	−78 °C	Me	78	24:1 (*S*)
8	(*S*)	−78 °C	Me	92	12:1 (*S*)
9	(*R*)	0 °C	Me	78	>50:1 (*S*)
10	(*S*)	0 °C	Me	95	20:1 (*S*)
11	(*R*)	RT	Me	75	>50:1 (*S*)
12	(*S*)	RT	Me	95	30:1 (*S*)
13	(*R*)	−78 °C	CO_2Me	25(50)	3:1 (*S*)
14	(*S*)	−78 °C	CO_2Me	90(10)	1:1
15	(*R*)	0 °C	CO_2Me	72	43:1 (*S*)
16	(*S*)	0 °C	CO_2Me	70	23:1 (*S*)
17	(*R*)	RT	CO_2Me	80	40:1 (*S*)
18	(*S*)	RT	CO_2Me	68(27)	20:1 (*S*)

[a] Yield of isolated product. [b] Yield of recovered starting material in parentheses. [c] Diastereomer ratios were determined by ^1H NMR spectroscopy (400 MHz).

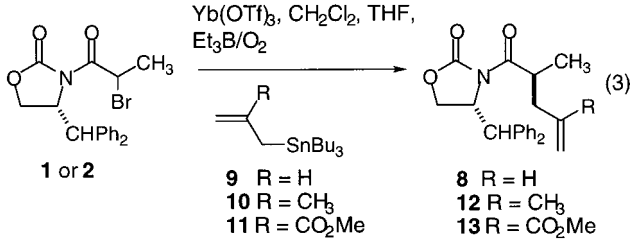
rotation across the *N*-carbonyl (NCO) bond (structures **5** or **6**→**3**) in the intermediate is facile in comparison to its trapping with allyltin. Surprisingly, increasing the reaction temperature (entries 3−6) led to substantial improvements in selectivity as compared to −78 °C experiments irrespective of precursor stereochemistry.

The next set of experiments used (2-methylallyl)tributyltin (**10**) as the trapping agent. Based on our model, we assigned the stereochemistry of products **12** and **13** by analogy, assuming the chelated radical intermediate will trap allyltin compounds predominantly from the *re* face. In comparison to the parent system, this trap gave lower levels of selectivity (compare entry 1 with 7). More interestingly, the two diastereomeric starting materials furnished **12** with a large difference in level of selectivity: 24:1 for **1** and 12:1 for **2** (entry 7 and 8). However, the product configuration was the same in both cases. Of the two diastereomeric starting materials, the *R*,*S* isomer **2** was found to be more reactive and less selective.[14] A similar trend as in the case of the parent allyltin (**9**) was also observed for the 2-methylallyltin system **10**: increasing reaction temperature led to higher selectivity (entries 9−12).

As before, the acrylate tin reagent **11** was examined as the allylating agent. Unlike the previous two allyl tins (**9** and **10**), reactions with compound **11** at −78 °C were nonselective with either diastereomer **1** or **2** (compare entry 1 or 7 with 13 and 14). However, increasing the reaction temperature led to dramatic changes in levels of selectivity with a maximum of 43:1 for the *R*,*R* isomer **1** at room temperature (entry 15). The configuration of product **13** was the same starting from **1** or **2**. A similar trend in precursor geometry−selectivity was observed for both **11** and **10** in that the *R*,*R* isomer **1** was more selective than the *R*,*S* isomer **2** at all temperatures (for example, compare entry 7 with 8; 9 with 10; 15 with 16; 17 with 18).

(14) This is based on recovered starting material when a 3:1 diastereomeric mixture was used as the reactant and reactions were stopped after partial conversion.

Table 3. Effect of Substrate Stereochemistry and Reaction Temperature on Product Diastereoselectivity



1 or **2**

9 R = H
10 R = CH_3
11 R = CO_2Me

8 R = H
12 R = CH_3
13 R = CO_2Me

entry	substrate stereochem	temp	R	% yield[a,b]	ratio[c]
1	(*R*)	−78 °C	H	46 (49)	2:1 (*S*)
2	(*S*)	−78 °C	H	90	5:1 (*S*)
3	(*R*)	0 °C	H	95	50:1 (*S*)
4	(*S*)	0 °C	H	93	50:1 (*S*)
5	(*R*)	RT	H	92	>50:1 (*S*)
6	(*S*)	RT	H	95	>50:1 (*S*)
7	(*R*)	−78 °C	Me	81	1:1
8	(*S*)	−78 °C	Me	93	1:1
9	(*R*)	0 °C	Me	88	>50:1 (*S*)
10	(*S*)	0 °C	Me	86	22:1 (*S*)
11	(*R*)	RT	Me	71	>50:1 (*S*)
12	(*S*)	RT	Me	95	20:1 (*S*)
13	(*R*)	−78 °C	CO_2Me	41 (45)	1:2 (*R*)
14	(*S*)	−78 °C	CO_2Me	70 (23)	1:2 (*R*)
15	(*R*)	0 °C	CO_2Me	81	4:1 (*S*)
16	(*S*)	0 °C	CO_2Me	95	4:1 (*S*)
17	(*R*)	RT	CO_2Me	70	5:1 (*S*)
18	(*S*)	RT	CO_2Me	76	4:1 (*S*)

[a] Yield of isolated product. [b] Yield of recovered starting material in parentheses. [c] Diastereomer ratios were determined by ^1H NMR spectroscopy (400 MHz).

Lanthanide triflates have proven to be a versatile class of Lewis acids.[15] We have successfully used these Lewis acids in conjugate radical reactions.[16] Ytterbium triflate was chosen as a representative Lewis acid and results from its use in allylations are tabulated in Table 3. A parallel series of experiments with magnesium bromide was undertaken (eq 3). Because of limited solubility in CH_2Cl_2, reactions with $Yb(OTf)_3$ as a Lewis acid used a mixed solvent system (CH_2Cl_2/THF 2:1).

Reaction of **1** or **2** with allyltin **9** and 1 eq of $Yb(OTf)_3$ as a Lewis acid at −78 °C was only moderately selective (entries 1 and 2). This is in contrast to the high selectivity observed with magnesium bromide as a Lewis acid. Temperature had a significant effect on the selectivity (entries 3−6). Reactions at room temperature gave >50:1 starting with either **1** or **2**. Reactions with allyltin **10** showed a similar dependency in that higher temperatures gave higher selectivity. Additionally, the *R*,*R* diastereomer **1** gave higher selectivity (>50:1, entry 9) compared to the *R*,*S* diastereomer **2** (22:1, entry 10). Reactions with the allyltin reagent **11** were very different and were essentially nonselective at low temperature (entries 13 and 14); increase in temperature led to only marginal improvement in selectivity (entries 15−18).

The low selectivity with $Yb(OTf)_3$ at all temperatures for the acrylate tin **11** implied that the α,β-unsaturated carbonyl compound sequestered the Lewis acid from the less Lewis basic

(15) For a recent review, see: Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 1. Also see: Kobayashi, S *Synlett* **1994**, 689.

(16) (a) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (c) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274. (d) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7717.

Table 4. Effect of Lewis Acid on Substrate Epimerization[a]

entry	temp	pure (*RR*)**1** $MgBr_2$ (*RR*:*RS*)	pure (*RS*)**2** $MgBr_2$ (*RR*:*RS*)	pure (*RS*)**2** $Yb(OTf)_3$ (*RR*:*RS*)
1	−78 °C	13:1	1:12	0:100
2	0 °C	8:1	1:5	0:100
3	RT	3:1	3:1	0:100

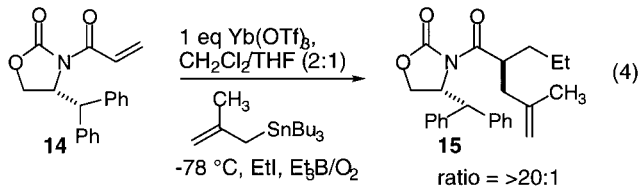
[a] Diastereomerically pure starting materials were stirred with the Lewis acid for 2 h and the amount of epimerization was determined by ^1H NMR spectroscopy (400 MHz).

α-bromo substrates (**1** or **2**).[17] In such a case, no Lewis acid would be left over to chelate the substrate (**1** or **2**) and hence no facial selectivity would be provided for diastereoselective trapping by the allyltin. To ensure that uncomplexed Lewis acid would remain to coordinate to the substrate, 6 equivs of $Yb(OTf)_3$ were used. Employing these reaction conditions at room temperature led to product **13** with diastereoselective ratios of 45:1 and 49:1 (*R*,*S*:*R*,*R*) for reactions using substrates **1** and **2**, respectively.

To rule out any competition from ionic reactions, control experiments were performed. The allylation was not possible in the absence of the radical initiator triethylborane/oxygen using either $MgBr_2$ or $Yb(OTf)_3$ as a Lewis acid. Conducting the allylation in the presence of a radical inhibitor, galvinoxyl, led to no reaction and thus provides additional support for a radical pathway.

The formation of product with *S* configuration starting from either diastereomeric starting material and the variation in level of selectivity with precursor stereochemistry led us to explore if there was epimerization during the reaction.[18] Diastereomerically pure starting materials were stirred in the presence of the Lewis acids ($MgBr_2$ or $Yb(OTf)_3$) at different temperatures for 2 h and the amount of epimerization was determined by NMR. It was found early on that $MgBr_2$ epimerized **1** and **2** to different extents at different temperatures (Table 4). At low temperatures the epimerization was very slow (entry 1), but at higher temperatures it occurred readily (entry 3). In contrast, experiments with $Yb(OTf)_3$ showed no epimerization over the same time period regardless of the temperature. Initially, it appeared that the amount of substrate epimerization positively correlated with the diastereoselectivity of the allylation. However, high levels of selectivity are achieved with $Yb(OTf)_3$ and the *R*,*S* diastereomer of substrate (**2**) at 0 °C and room temperature, even though substrate epimerization is not a factor (Table 3, entries 3−6 and 9−12). These results suggest that substrate epimerization and resultant radical generation exclusively from **1** is not responsible for the seemingly contradictory high selectivity at higher temperatures.

The lack of selectivity with $Yb(OTf)_3$ at low temperatures with any of the three traps was puzzling. We wanted to demonstrate that a similar radical intermediate, generated in an alternate fashion from a substrate precomplexed with the Lewis acid $Yb(OTf)_3$, could be selectively trapped at low temperatures.[19] As acrylate **14** is a better donor than the bromides **1** or **2**, it will chelate $Yb(OTf)_3$ and generate the radical in the desired *s-cis* conformation. Thus addition of ethyl radical to acrylate **14** in the presence of 1 equiv of $Yb(OTf)_3$ followed by trapping with methylallyl stannane (**10**) was carried out (eq 4). This



(4)

example shows that the intermediate radical, if generated from a precomplexed precursor, can be trapped with high selectivity even at low temperatures (see Scheme 1, path D).

The main facts which emerge from the data presented in the results section are as follows: (1) higher temperatures lead to higher selectivity in allylations, (2) the *R*,*R* starting material is more selective and less reactive, (3) 2-carboxymethylallylstannane is the most reactive trap, followed by 2-methylallylstannane and last by the simple allylstannane, (4) magnesium bromide epimerizes the starting material slowly at low temperatures and the rate increases at higher temperatures, (5) no epimerization occurs with $Yb(OTf)_3$, (6) reactions with $MgBr_2$ as a Lewis acid are selective at low temperature in contrast to nonselective reactions using $Yb(OTf)_3$, and (7) tandem addition/allylation with a precomplexed substrate is highly selective.

Discussion

Initially, our goal was to use different allylstannanes as trapping reagents for the allylation of **1** and **2** under the optimal conditions established for reactions with allyltributyltin. It was assumed that both diastereomers **1** and **2** should form chelated intermediates and that the product radical formed from either diastereomer of starting material should be identical due to the trigonal planar nature of radical intermediates. To this end our initial experiments were conducted on a diastereomeric mixture of the α-bromoimides (epimeric at the α-carbon) using substituted allyltributyltin **10** and **11** as the trap. Careful analysis of the reaction mixture including unreacted starting material suggested that our initial assumption *was incorrect: the two diastereomers reacted at different rates and different selectivity*. This contrasts with the indiscriminate trapping by the parent allyltributyl tin **9**. This result revived questions regarding the reactive radical conformation and rotamer issues thought previously solved by the addition of chelating Lewis acids. In addition, relative reactivity differences of the functionalized traps compared to the parent allylstannane needed to be carefully reconsidered.

The major issue we needed to address involved the relative orientation, syn vs anti, of the two carbonyl oxygens present in the substrate. In the absence of chelating Lewis acids, dipole−dipole interactions favor an anti ground-state orientation with respect to the two carbonyl oxygens (**16** and **19**). Recently, Lewis acids have been employed in such systems in order to hold the two carbonyl oxygens in a syn fashion, thus providing rotamer control for pending asymmetric manipulations. Even though the rotamer issues surrounding oxazolidinone systems appear resolved by the addition of chelating Lewis acids, it is possible that subtle differences in the Lewis acids themselves as well as steric interactions that may arise in the chelated form of one diastereomer (**17** vs **20**) may also play a role in the stereochemical outcome of these reactions (Scheme 1).[5]

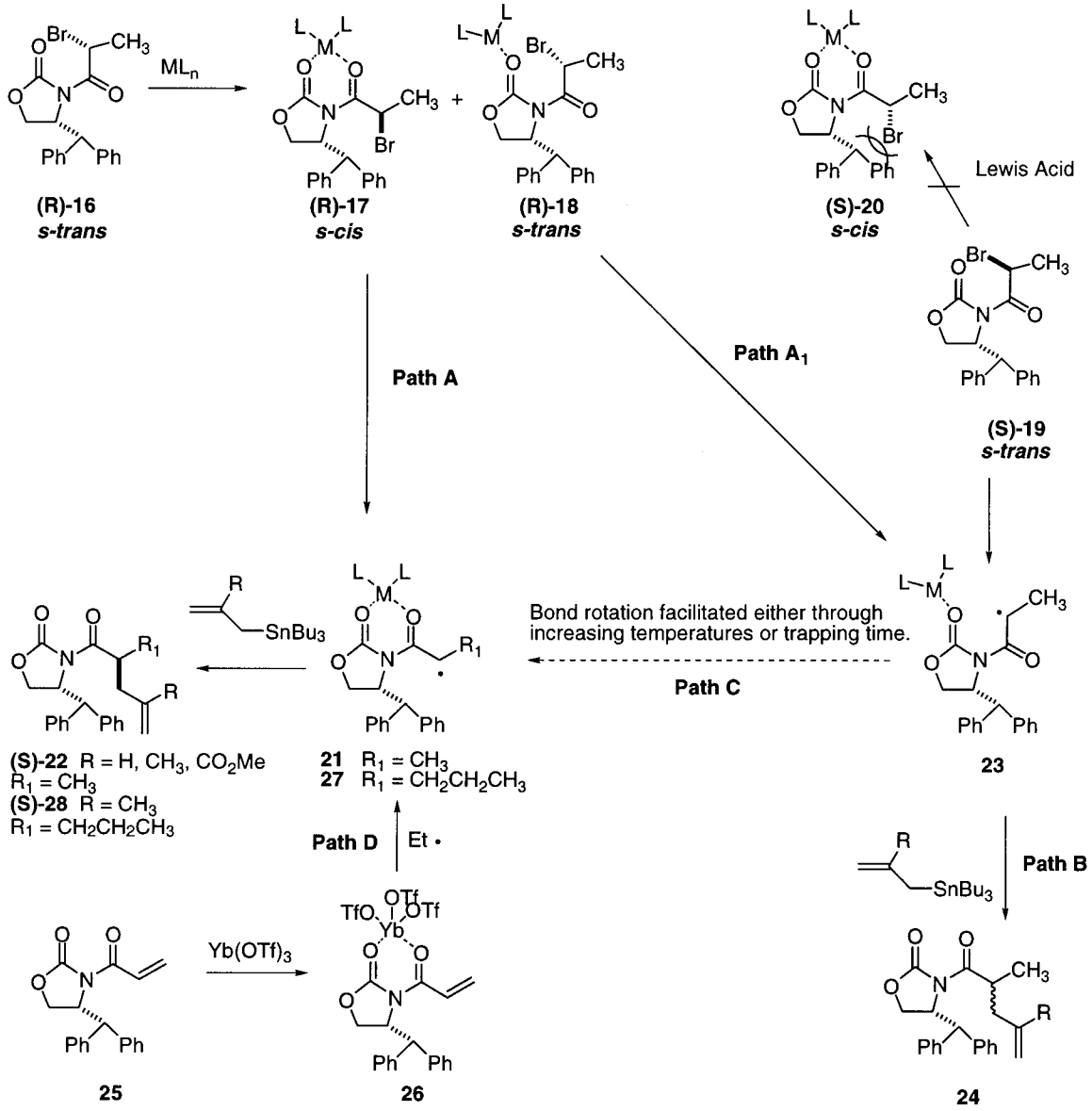
Scheme 1 takes into account all of our observations. Of the two diastereomers (*R*,*R* and *R*,*S*), only *R*,*R* is capable of forming a chelate with a Lewis acid prior to radical generation (compare **17** and **20**). However, only a portion of the *R*,*R* substrate will exist in a conformation which is predisposed to form a chelate with minimal energy constraints. This scenario renders the *R*,*R*

(17) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067.

(18) For examples using epimerization of α-halo esters in dynamic kinetic resolution processes, see: Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. *J. Org. Chem.* **1998**, *63*, 3117. Koh, K.; Durst, T. *J. Org. Chem.* **1994**, *59*, 4683. Durst, T.; Koh, K.; Ben, R. N. *Tetrahedron Lett.* **1993**, *34*, 4476.

(19) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090.

Scheme 1



substrate only partially chelated at low temperatures. Reaction occurs through path A, leading to product **22** with high levels of selectivity, and alternatively reaction can also occur through path A_1, where increasing the trapping time through variation in the allylstannane leads to higher levels of selectivity. On the other hand, in order for the Lewis acid to form a chelated intermediate with the *R*,*S* diastereomer **19**, it must adopt a sterically hindered conformation **20**, as a result of steric interactions that arise between the bromide and the bulky diphenylmethyl substituent of the of the oxazolidinone chiral auxiliary. Rotamer **20** is not energetically accessible, disfavoring a chelated intermediate and resulting in loss of facial discrimination and little or no diastereoselectivity in the products (path B to product **24**).

Contrary to convention, increasing reaction temperatures led to higher diastereoselectivity with maximum selectivity being achieved not at −78 °C but at 0 °C or room temperature. Higher temperatures allow enough energy for the nonchelated (monocoordinated) radical intermediate **23** to undergo bond rotation followed by chelation to form the rigid intermediate **21** (path C). It is this chelated intermediate **21** which can then be selectively trapped by the functionalized allylstannane. The most important factor in determining the diastereoselectivity of the functionalized allylstannane additions is the bond rotation, which allows the nonchelated (monocoordinated) radical intermediate **23** to form the chelated intermediate **21**. Increasing reaction temperatures, slower radical traps, and the appropriate choice of Lewis acid all function to facilitate this bond rotation and lead to selective trapping through intermediate **21**.

Starting with the *R*,*S* substrate **19**, this follows with Scheme 1 in that at low temperatures where epimerization is not an issue (see Table 4, entry 1), the substrate is unable to form a chelate with either Lewis acid before radical generation. As a result, uncomplexed or singly bound substrate will react with tributyltin radical to form intermediate radical **23**. If the trap is too fast, as it is in the case with R = CO_2Me, then radical **23** is trapped indiscriminately to form equal amounts of diastereomeric products (Table 2, entries 13 and 14). With a slightly slower trap, **10**, the bond rotation and formation of chelated intermediate **21** is not complete and both **21** and **23** are trapped, leading to products enriched in the *R*,*S* diastereomer resulting in a ratio of 12:1 (Table 2; entry 8). Finally, using the slowest trap, simple allylstannane, enough time is available for formation of the bidentate complex **21** and trapping results in highly diastereo-

selective products irrespective of the starting diastereomer used, **16** or **19**. Conversely, selectivities starting with the *R,R* substrate **16** are almost always higher since at least a portion of the radical generation occurs through a substrate precomplexed with the Lewis acid.

An explanation for the observed differences in selectivity with changes in Lewis acid also involves differing abilities to access the chelated complex **21**. At −78 °C ytterbium triflate provides minimal selectivity (Table 3, entries 1, 2, 7, and 8), indicating that much of the radical is trapped from a nonchelated form. While the selectivity for the chelate-derived *S*-product increases as the trap speed decreases, it never exceeds 5:1 even with the slowest allylstannane trap. The failure of ytterbium triflate to form the chelate easily at low temperatures results from the presence of THF solvent,[20] which is required for solubility reasons. The starting bromide (**16** or **19**) is a poorer Lewis base than THF (the electronegativity of the bromine weakens the carbonyl basicity).[21] As a result, only a small population of bromide substrate is initially coordinated to ytterbium triflate, and most of the radical is formed without coordinated Lewis acid. At low-temperature dynamic equilibration is too slow to enable the ligand exchange and complex reorganization required to form a chelate **21**. In contrast, magnesium bromide in the nondonor solvent CH_2Cl_2 has no choice but to complex the bromide; even if some of the radical is formed in a nonchelated form, the rate of equilibration from a monodentate complex to the bidentate chelate is able to compete with all but the most reactive traps. In the case of ytterbium triflate, as the temperature increases, the rate of equilibration from the free radical **23** to the chelated complex **21** increases rapidly (more so than does the rate of trapping), and trapping of the chelated radical intermediate provides high selectivity.

The reason that ytterbium triflate gives high selectivity in the addition−trapping experiment of acrylate **25** even at low temperature is because the radical is generated in the chelated form **21**. Addition predominantly occurs to the preactivated acrylate−ytterbium triflate chelate. Radicals that are monocoordinated to ytterbium triflate, or not coordinated at all, are unlikely, and so no complex equilibration is required.

In conclusion, the application of Lewis acids in radical reactions to control rotamer populations is a more complex situation than previously hypothesized. Several factors need to be carefully examined including the interactions of the Lewis acid with the substrate (or solvent), the reactive conformation required to obtain high selectivity and the variations in how to access this conformation, the time scale of the reaction, and finally the temperature dependence of all the above. Realization of these intricacies has provided access to functionally allylated products with excellent diastereoselectivity (>50:1) and yield (>90%) even at room temperature.

Experimental Section

For general experimental see ref 16d.

Preparation of *N*-(α-bromopropionyl)-2-oxazolidinones 1 and 2. Typical Procedure. To a flask containing 4-(diphenylmethyl)-2-oxazolidinone (1.265 g, 5 mmol) and THF (20 mL) under N_2 was added *n*-BuLi (2.5 M) (2.0 mL, 5 mmol) at −78 °C dropwise. After complete addition, the solution was stirred for 10 min at −78 °C. A solution of 2-bromopropionyl bromide (1.296 g, 6 mmol) in 5 mL of THF was then added dropwise at −78 °C over 10 min and the mixture was stirred at −78 °C for 0.5 h. The reaction was quenched with 1 mL of saturated NH_4Cl solution and extracted with ethyl acetate (3 × 30 mL). The organic extracts were combined, washed with brine (2 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The product *N*-(α-bromopropionyl)-2-oxazolidinone (a diastereomeric mixture of **1** and **2**) was purified by chromatography on silica gel using hexane/ethyl acetate (4:1) as the eluent, yield 1.59 g (82%).

1: R_f = 0.3 (80:20 hexane/ethyl acetate); mp 120−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.09 (m, 10 H), 5.61 (q, J = 6.7 Hz, 1 H), 5.32 (q, J = 5.4 Hz, 1 H), 4.75 (d, J = 4.8 Hz, 1 H), 4.47 (d, J = 5.6 Hz, 2 H), 1.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.4, 152.5, 139.5, 137.8, 129.6, 129.0, 128.9, 128.4, 128.0, 127.3, 64.9, 56.5, 50.4, 38.2, 20.8; $[\alpha]^{26}_D$ = −152.2° (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{19}H_{18}BrNO_3$: C, 58.78; H, 4.67, N, 3.61. Found: C, 58.55; H, 4.42; N, 3.60.

2: R_f = 0.6 (80:20 hexane/ethyl acetate); mp: 162−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.09 (m, 10 H), 5.55 (q, J = 6.7 Hz, 1 H), 5.36−5.30 (m, 1 H), 4.65 (d, J = 6.7 Hz, 1 H), 4.47 (dd, J = 7.8, 9.6 Hz, 1 H), 4.39 (dd, J = 2.4, 9.4 Hz, 1 H), 1.64 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.3, 152.7, 139.2, 137.8, 129.2, 129.2, 128.8, 128.5, 128.2, 127.3, 65.8, 57.1, 51.5, 38.8, 21.1; $[\alpha]^{26}_D$ = −88.9° (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{19}H_{18}BrNO_3$: C, 58.78, H, 4.67, N, 3.61. Found: C, 58.60; H, 4.33; N, 3.53.

Lewis Acid-Mediated Radical Allylations of 1. To a flask containing **1** (78 mg, 0.2 mmol), $MgBr_2$ (103 mg, 0.4 mmol), and CH_2Cl_2 (4 mL) under N_2 were added (2-methylallyl)tributyl tin (173 mg, 0.5 mmol) and Et_3B (1M in hexane) (0.4 mL, 0.4 mmol) at −78 °C. Two milliliters of O_2 was then added via syringe at once. 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 **8** was purified by chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluent, yield 57 mg (78%)

8: R_f = 0.6 (80:20 hexane/ethyl acetate); mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08−7.33 (m, 10 H), 5.6 (m, 1 H), 5.29 (m, 1 H), 5.01 (m, 2 H), 4.66 (d, J = 6.6 Hz, 1 H), 4.35 (d, J = 5.1 Hz, 2 H), 3.62 (m, 1 H), 2.28 (m, 1 H), 1.89 (m, 1 H), 1.05 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 176.1, 153.0, 139.5, 138.1, 135.5, 129.2, 128.9, 128.6, 128.4, 128.3, 127.8, 127.0, 117.0, 64.9, 56.5, 51.2, 37.3, 16.0; $[\alpha]_D^{26}$ = −111.9° (*c* 0.35, CH_2Cl_2). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.34, H, 6.82, N, 4.24.

Hydrolysis of 8. Typical Procedure. To a flask containing **8** (174.5 mg, 0.5 mmol) was added THF (5 mL), H_2O (5 mL), and H_2O_2 (30%) (0.226 mL, 2 mmol) at 0 °C under N_2. $LiOH{\cdot}H_2O$ (41 mg, 1 mmol) was added to the reaction mixture; it was stirred at 0 °C for 1 h. After completion (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). Finally, The aqueous solution was acidified with HCl (3M) to pH ∼1 and reextracted with CH_2Cl_2 (4 × 15 mL). The organic solution was dried ($MgSO_4$) and concentrated to yield (*S*)-2-methyl-4-butenoic acid (45 mg, 88%). $[\alpha]^{26}_D$ = 10.5° (*c* 1.15, $CHCl_3$) [lit. $[\alpha]^{26}_D$ = 10.5° ($CHCl_3$). Riley, R. G.; Silverstein, R. M. *Tetrahedron* **1974**, *30*, 1171]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.72 (m, 1 H), 5.18−5.05 (m, 2 H), 2.62−2.56 (m, 1 H), 2.48−2.42 (m, 1 H), 2.26−2.18 (m, 1 H), 1.20 (d, J = 7.0 Hz, 3 H).

Products from Allylation of 1 with 10 and 11. 12: R_f = 0.6 (80:20 hexane/ethyl acetate); mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.11 (m, 10 H), 5.32 (q, J = 5.7 Hz, 1 H), 4.79 (s, 1 H), 4.75−4.68 (m, 2 H), 4.39 (d, J = 5.4 Hz, 2 H), 3.89−3.80 (m, 1 H), {[2.40 (dd, J = 7.4, 13.5 Hz)], [2.30 (dd, J = 7.4, 13.5 Hz)], 1 H}, {[1.99 (dd, J = 7.0, 14.2 Hz)], [1.81 (dd, J = 7.0, 14.2 Hz)], 1 H}, {[1.72 (s)], [1.68 (s)], 3 H}, {[1.05 (d, J = 6.8 Hz)], [0.94 (d, J = 6.8 Hz)], 3 H}; ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.7, 153.2, 142.9, 139.7, 138.1, 129.4, 128.9, 128.7, 128.5, 127.9, 127.1, 112.9, 68.1, 64.9, 56.6, 51.1, 41.6, 35.6, 25.7, 22.0, 16.2; $[\alpha]^{26}_D$ = −130.9° (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.66; H, 6.64; N, 4.09.

13: R_f = 0.3 (80:20 hexane/ethyl acetate); oil; ^{1}H NMR (400 MHz,

(20) For the use of THF (or alkyl ethers) coordinated lanthanides in synthesis, see: Aspinall, H. C.; Browning, A. F.; Greeves, N.; Ravenscroft, P. *Tetrahedron Lett.* **1994**, *35*, 4639; Aspinall, H. C.; Dwyer, J. L. M.; Greeves, N.; McIver, E. G.; Woolley, J. C. *Organometallics* **1998**, *17*, 1884. Aspinall, H. C.; Greeves, N.; Lee, W.-M.; McIver, E. G.; Smith, P. M. *Tetrahedron Lett.* **1997**, *38*, 4679.

(21) (a) Wu, J. H.; Zhang, G.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067. (b) Hunt, I. R.; Rogers, C.; Woo, S.; Rauk, A.; Keay, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 1049.

$CDCl_3$) δ 7.36−7.09 (m, 10 H), {[6.21 (d, J = 1 Hz)], [6.17 (d, J = 1 Hz)], 1 H}, {[5.56 (d, J = 1 Hz)], [5.54 (d, J = 1 Hz)], 1 H}, 5.31 (m, 1 H), {[4.75 (d, J = 4.8 Hz)], [4.69 (d, J = 4.8 Hz)], 1 H}, 4.48−4.36 (m, 2 H), 3.99−3.80 (m, 1 H), {[3.78 (s)], [3.72 (s)], 3 H}, 2.63 (dd, J = 7.2, 13.8 Hz), {[2.39 (dd, J = 7.2, 13.8 Hz)], [2.27 (dd, J = 7.2, 13.8 Hz)], 1 H}, {[1.10 (d, J = 6.7 Hz)], [0.96 (d, J = 6.7 Hz)], 3 H}; ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.2, 167.3, 153.1, 139.7, 138.0, 137.8, 129.4, 129.0, 128.8, 128.5, 127.9, 127.4, 127.1, 64.9, 56.6, 52.1, 50.9, 36.8, 35.0, 17.2; $[\alpha]^{26}_D = -104.8°$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75, H, 6.18, N, 3.44. Found: C, 70.43; H, 6.27; N, 3.55.

15: R_f = 0.7 (80:20 hexane/ethyl acetate); mp 104−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.09 (m, 10 H), 5.35−5.30 (m, 1 H), 4.80 (s, 1 H), 4.77−4.72 (m, 3 H), 4.43−4.36 (m, 2 H), 4.01−3.94 (m, 1 H), 2.32 (dd, J = 7.2, 13.7 Hz, 1 H), {[2.07 (dd, J = 7.3, 13.8 Hz)], [1.94 (dd, J = 7.3, 13.8 Hz)], 1 H}, {[1.74 (s)],[1.70 (s)], 3 H}, 1.61−1.52 (m, 1 H), 1.44−1.21 (m, 3 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.2, 153.2, 143.2, 139.8, 138.1, 129.5, 128.9, 128.8, 128.5, 127.9, 127.1, 112.8, 64.7, 56.7, 50.9, 40.7, 40.4, 33.8, 22.2, 20.6, 14.2; $[\alpha]^{26}_D = -183.3°$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{25}H_{29}NO_3$: C, 76.70, H, 7.47, N, 3.58. Found: C, 76.67; H, 7.52; N, 3.65.

Competition Experiment for Determination of Relative Rates for Allylstannane Trapping. Typical Procedure. The same procedure was used as in the preparation of **8** except that in addition to 2 equivs of allylstannane, 2 equivs of either **10** or **11** were added and allowed to compete for the 1 equiv of substrate **1** or **2**. Each combination of substrate, allylstannane and Lewis acid was tested and crude product ratios were determined by ^{1}H NMR (400 MHz).

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