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The Role of the Achiral Template in Enantioselective Transformations. Radical Conjugate Additions to α-Methacrylates Followed by Hydrogen Atom Transfer

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Abstract: We have evaluated various achiral templates (**1a**−**g**, **10**, and **16**) in conjunction with chiral Lewis acids in the conjugate addition of nucleophilic radicals to α-methacrylates followed by enantioselective H-atom transfer. Of these, a novel naphthosultam template (**10**) gave high enantioselectivity in the H-atom-transfer reactions with ee's up to 90%. A chiral Lewis acid derived from $MgBr_2$ and bisoxazoline (**2**) gave the highest selectivity in the enantioselective hydrogen-atom-transfer reactions. Non-C_2 symmetric oxazolines (**20**−**25**) have also been examined as ligands, and of these, compound **25** gave optimal results (87% yield and 80% ee). Insights into rotamer control in α-substituted acrylates and the critical role of the tetrahedral sulfone moiety in realizing high selectivity are discussed.

Introduction

The development of new synthetic methodology for the preparation of enantiomerically pure compounds (EPC) is an important goal.[1] In contrast to the large amount of literature available on ionic and neutral methods for the synthesis of EPCs, only in the past couple of years have methodologies for absolute stereocontrol using radical intermediates been reported.[2] A majority of them involve C−C bond formations using chiral Lewis acids.[3] Another area of focus, although less actively pursued, is H-atom-transfer reactions. In principle, these reactions can be carried out in two distinct ways: (1) by H-atom transfer from a chiral reagent to a radical or (2) alternatively by H-atom transfer from an achiral reagent to a radical complexed to a chiral source. Curran,[4a] Metzger,[4b,c] Roberts,[4d] and Schiesser[4e] have reported examples of reactions using chiral H-atom-transfer reagents. On the other hand, only a few examples of H-atom transfer to chiral Lewis acid-complexed radicals have been noted in the literature.[5] We have recently reported that chiral Lewis acid-complexed protected glycine radicals undergo H-atom transfer with good to excellent selectivity.[6]

In the past couple of years, we[7] and others[8] have reported examples of enantioselective conjugate radical additions using catalytic amounts of chiral Lewis acids. The enantioselectivity in our work employing bisoxazolines as chiral ligands was as high as 97% using 30 mol % of the catalyst. With the success of the bisoxazoline-derived chiral Lewis acid system at controlling the β center, a logical progression would be an attempt to establish the stereochemistry of the α-methyl group in an appropriately chosen α-methacrylate substrate. Selectivity could in principle be achieved through the addition of a nucleophilic radical to the terminal olefinic carbon followed by an enantioselective hydrogen atom transfer (Figure 1).

The high enantioselectivity observed in the radical conjugate additions can be attributed to the control of the various rotamers of the starting material with reaction occurring from one reactive conformation. In contrast, preferred conformations in α-alkyl-substituted systems such as **A** (Figure 1) are not so easily predicted.[9] Will an s-cis (**A**), an s-trans (**B**), or a strongly twisted conformer predominate? X-ray analysis by Giese on a pyrrolidinone methacrylamide showed strong twisting.[10] Similarly,

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(6) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1263. For a review on free radical reactions in the synthesis of amino acids see: Easton, C. J. *Chem. Rev.* **1997**, *97*, 53.

(7) For a review on enantioselective conjugate additions including radical reactions see: Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

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(9) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.

10.1021/ja016839b CCC: $22.00

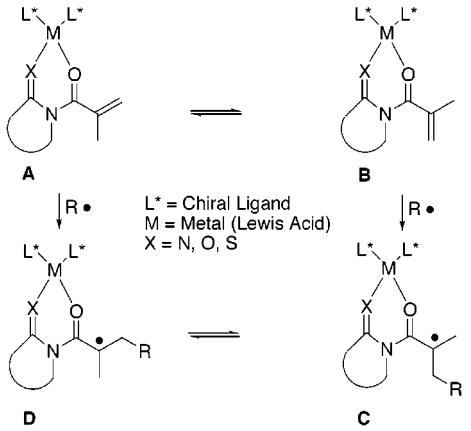

Figure 1.

crystal structure analyses of α-methacryloyl camphor sultam[9] and α,*β*-dimethylacryloyl camphor sultam show significant deviation of the alkene from planarity.[11] The relief of steric strain in the substrate apparently overcame any additional stabilization otherwise obtained by π conjugation. Non-coplanarity of the α,*β*-unsaturated fragment could manifest itself in reduced reactivity toward nucleophilic additions.[12]

In the system shown in Figure 1, after conjugate addition, H-atom transfer to the intermediate chiral Lewis acid complexed radical should occur from one reactive conformation to realize high selectivity. Additionally, conformational interconversion (**C** to **D**, Figure 1)[13] of the radical intermediate should be slower than intermolecular hydrogen atom transfer. Since hydrogen atom transfer from tributyltin hydride occurs with high rates,[14] we were hopeful that conformer interconversion of the intermediate radical may not be an issue. Thus maximum face shielding from a substrate−chiral Lewis acid complex and reactions occurring from one ground-state conformer should provide for high selectivity in conjugate radical addition followed by H-atom-transfer experiments.

Several groups have reported important results on the preferred conformation in α-methacrylates in diastereoselective transformations. The seminal work of Oppolzer[15] and Curran[16] with chiral sultams is of relevance. Additional support for the preference for s-trans rotamer of the α-methacrylate fragment comes from the work of Murahashi and co-workers[17] who have examined the Pd(II)-catalyzed asymmetric acetalization of the terminal olefin carbon of a number of Evans oxazolidinones.[18] The sense of stereoinduction suggests that the reaction occurs from an s-trans rotamer.[19] This was further supported by CAChe calculations at the MM2 level.

Giese[10] and Taber[20] have independently shown that using pyrrolidinone auxiliaries highly diastereoselective H-atom-transfer reactions are indeed possible in α-methacrylate systems. Diastereoselective H-atom-transfer reactions to captodative radicals derived from *N*-acylamido acrylates in both acyclic[21] and cyclic[22] systems have also been investigated, and they proceed with moderate to good selectivity. A few examples of enantioselective H-atom transfer to chiral Lewis acid-complexed prochiral radicals with achiral donors are known;[5,6] however, none involve α-methacrylate systems.

Evaluation of the effect of achiral templates on reactivity and/or selectivity in stereoselective transformations has been reported in the literature but only in a sporadic nature.[23] The diastereoselective H-atom-transfer reactions described above with α-methacrylates suggested that development of enantioselective variants might indeed be possible. Our goal was to examine a series of achiral templates, which are used as anchors for the acrylate fragment, with the expectation of controlling the reactive conformers. By systematic change of the ring size and nature of the achiral template (variation of heteroatoms in the ring) we surmised that additional space for either the α-methyl group or the methylene could be available. Alterations in the steric environment, it was hoped, would also assist in providing rotamer control for the olefin side chain.

This paper details the evaluation of various achiral templates in conjunction with chiral Lewis acids in the conjugate addition of nucleophilic radicals to α-methacrylates followed by enantioselective H-atom transfer. Of these, a novel sultam template gave high enantioselectivity in the H-atom-transfer reactions with ee's up to 90%. Insights into rotamer control in α-substituted acrylates and the critical role of the tetrahedral sulfone moiety in realizing high selectivity are discussed below.

Results and Discussion

Our work began with the screening of a series of templates attached to the α-methacryloyl group. The required side chain was attached to the templates using standard conditions. The initial goals were to identify templates that would provide good reactivity and selectivity. Reactions were carried out under a set of standard conditions: addition of nucleophilic isopropyl radical at −78 °C employing magnesium bromide as the Lewis acid and the cyclopropyl bisoxazoline (**2**) as the chiral ligand

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(12) Curran has carried out several relative reactivity studies of α-methacryloyl systems. These clearly show reduced reactivity for α-alkylacrylates. See ref 9.
(13) Only two conformers are shown. It is quite likely that the actual conformation is an intermediate of these two extreme structures.
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(22) (a) Axon, J. R.; Beckwith, A. L. J. *J. Chem. Soc., Chem Commun.* **1995**, 549. (b) Goodal, K.; Parsons, A. F. *Tetrahedron Lett.* **1997**, *38*, 491. (c) Goodal, K.; Parsons, A. F. *Tetrahedron* **1996**, *52*, 6739. (d) Chai, C. L. L.; King, A. R. *Tetrahedron Lett.* **1995**, *36*, 4295. (e) Manzoni, L.; Belvisi, L.; Scolastico, C. *Synlet* **2000**, 1287. (f) Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 2815. For reactions at a center remote to the carbonyl see: Beaulieu, F.; Arora, J.; Veith, U.; Taylor, N. J.; Chapell, B. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 8727. Pyne, S. G.; Schafer, K. *Tetrahedron* **1998**, *54*, 5709. For reactions with lactones see: Piber, M.; Leahy, J. W. *Tetrahedron Lett.* **1998**, *39*, 2043.
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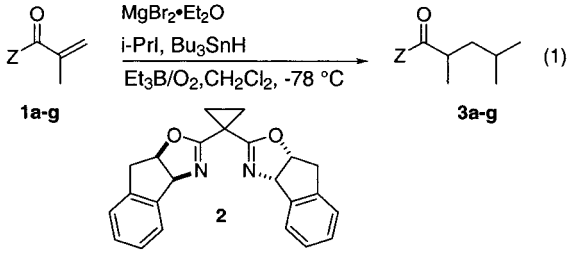
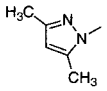
Table 1. Investigation of Various Templates



Entry	Comp	Z	Yield, %[a]	ee, % (Config)
1	**1a**		52	15[b] (R)
2	**1b**		54	38[b] (R)
3	**1c**		66	15[b] (R)
4	**1d**		54	15[c] (S)
5	**1e**		80	65[c] (S)
6	**1f**		76	42[c] (S)
7	**1g**		67	28[c] (S)

[a] Isolated yield. [b] ee determined by optical rotation of the hydrolysis product: see Supporting Information. [c] ee determined by chiral HPLC analysis.

and tributyltin hydride as a H-atom donor and chain carrier. We have previously established that conjugate radical additions using chiral Lewis acids derived from bisoxazolines and Mg or Zn Lewis acids proceed with high selectivity.[24]

Three templates, pyrazole, 3,5-dimethylpyrazole, and indazole, capable of forming five-membered chelates with the Lewis acid were chosen for the initial study (eq 1). These results are shown in Table 1. All of these templates showed moderate reactivity and low selectivity (entries 1−3) in radical addition reactions.[25] The stereochemistry for the conjugate product **3b** was determined to be (*R*) by hydrolysis to a known acid.[26] We have previously shown that 3,5-dimethylpyrazole is a good template for enantioselective conjugate addition.[27] Thus the low selectivity for reactions with **1a**−**c** is most likely due to poor rotamer control.

We then examined templates capable of forming six-membered chelates. Readily available four- and five-membered heterocycles were selected for the study. Commercially available 2-azetidinone as a template was examined first. Curran and Porter have previously shown that radical addition to *N*-acryloyl-2-azetidinone is very facile.[28] In our experiments, 2-(α-methacryloyl)azetidinone was also extremely reactive and the noncatalyzed reaction occurred at a similar rate as the Lewis acid-catalyzed reaction. The enantioselectivity obtained with this template was disappointing (entry 4). Our laboratory has shown that oxazolidinone-derived templates can indeed provide high levels of both diastereoselectivity[29] and enantioselectivity[30] in free radical chemistry. The readily available 2-oxazolidinone was chosen as the next template for study. In the absence of a Lewis acid, the reaction does proceed, but at a much slower rate. The enantioselective additions using this template were encouraging providing the best enantioselectivity at 65% (entry 5). The stereochemistry of the addition product was shown to have (*S*) configuration by hydrolysis of **3e** to the known acid. Thus templates which lead to five-membered chelates give enantiomeric products in contrast to templates which form six-membered chelates with the chiral Lewis acid.[31] Isopropyl radical addition to the pyrrolidinone derived substrate **1f** was also facile, and the product **3f** was isolated in 76% yield (entry 6). The observed enantioselectivity was lower than that for the oxazolidinone template (compare entries 5 and 6). Hydrolysis of **3f** to the known acid[23] indicated that the *S* isomer was formed in these reactions as well. One additional template, the commercially available *N*-phenylpyrazolone, was examined. The nitrogen at the 3-position was appealing since it could have an impact on the rotamer population of the side chain. However, radical addition to **1g** proceeded with poor selectivity (entry 7). On the basis of the above results, templates **1e** and **1f** were chosen for more detailed scrutiny.

Reactions aimed at determining which Lewis acid would offer the best combination of yield and enantioselectivity for the addition of isopropyl radical to substrate **1e** was undertaken (eq 2, Table 2). In the absence of a Lewis acid, the reaction does proceed, but at a much slower rate (entry 1). Zinc based Lewis acids failed in both respects; the yields and enantioselectivities were unacceptable (entries 2 and 3). Of the magnesium Lewis acids, the counterion was important with $MgBr_2 \cdot Et_2O$ providing the best enantioselectivity at 65% (entry 6). After establishing that $MgBr_2 \cdot Et_2O$ as a Lewis acid of choice, the next series of experiments were undertaken in an attempt to discern if the size of the attacking radical exhibited any effect on the selectivity of the reaction. A series of nucleophilic radicals that differed in size were examined. No definitive trend was observed (entries 6−9). The above results suggest that oxazolidinone is an ineffective template in controlling the stereochemistry at the α-carbon.

Results from radical additions to the pyrrolidinone derived acrylate **1f** (eq 3) are shown in Table 3. Different radicals were

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(25) We have carried out extensive studies on all the templates shown in Table 1. For brevity, only the most pertinent results are shown. The reader should consult the following for additional information: Sausker, J. B. MS thesis, North Dakota State University, Fargo, 2001.
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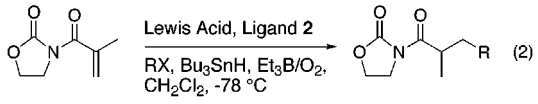
(27) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955.
(28) Curran, D. P.; Qi, H.; Porter, N. A.; Su, Q.; Wu, W.-X. *Tetrahedron Lett.* **1993**, *34*, 4489.
(29) (a) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (b) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190. (c) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517.
(30) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800.
(31) We have previously hypothesized that formation of enantiomeric products from pyrazole and oxazolidinone derived templates is most likely due to changes in the geometry of the reactive complex: trans octahedral for pyrazoles and cis octahedral for oxazolidinone. For a review on reversal of stereochemistry see: Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719.

Table 2. Radical Additions to 2-Oxazolidinone α-Methacrylate[a]



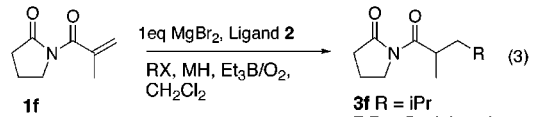
1e

3e R = *i*-Pr
4 R = Cyclohexyl
5 R = t-Butyl
6 R = Acetyl

entry	product	Lewis acid[b]	yield,[c] %	ee,[d] %
1	**3e**	none	27	0
2	**3e**	$ZnBr_2$	48	7
3	**3e**	$Zn(OTf)_2$	50	4
4	**3e**	MgI_2	85	10
5	**3e**	$Mg(OTf)_2$	98	2
6	**3e**	$MgBr_2 \cdot Et_2O$	80	65
7	**4**	$MgBr_2 \cdot Et_2O$	65	20
8	**5**	$MgBr_2 \cdot Et_2O$	75	38
9	**6**	$MgBr_2 \cdot Et_2O$	57	50

[a] Reactions were performed on a 0.2 mmol scale at −78 °C. [b] Stoichiometric amount of chiral Lewis acid. [c] Isolated yield. [d] ee's determined from chiral HPLC analysis.

Table 3. Reactions on the 2-Pyrrolidinone α-Methacrylate[a]



1f

3f R = iPr
7 R = Cyclohexyl
8 R = CH_2OMe
9 R = Acetyl

entry	product	temp, °C	hydride	yield,[c] %	ee,[d] %
1	**3f**	−78	Bu_3SnH	76	42
2	**7**	−78	Bu_3SnH	92	45
3	**8**	−78	Bu_3SnH	75	40
4	**9**	−78	Bu_3SnH	75	75
5	**7**	−40	Bu_3SnH	82	34
6	**7**	0	Bu_3SnH	75	0
7	**7**	−78	$(MeSi)_3SiH$	trace	0
8	**7**	−40	$(MeSi)_3SiH$	35 (55)[e]	−39
9	**7**	0	$(MeSi)_3SiH$	45 (47)[e]	−35
10	**9**	0	$(MeSi)_3SiH$	53 (43)[e]	−20

[a] Reactions were performed on a 0.2 mmol scale. [b] Stoichiometric amount of chiral Lewis acid. [c] Isolated yield. [d] ee's were determined from chiral HPLC analysis. [e] Numbers in parentheses indicate recovered starting material.

screened utilizing a stoichiometric amount of magnesium bromide as the Lewis acid, which provided good yields of the desired reaction products. Enantioselectivity varied on the basis of the choice of the radical precursor. Alkyl radicals gave only moderate levels of enantioselectivity between 40 and 45% (entries 1 and 2). Heteroatom functionalized radicals such as methoxymethyl and acetyl could be added in good yields (entries 3 and 4). The addition of acetyl radical gave the product with the highest level of enantioselectivity (entry 4). This is similar to the results observed with the oxazolidinone template where the acetyl radical again provided good selectivity. The limited success with the addition of cyclohexyl and acetyl radicals to **1f** led us to modify reaction conditions with respect to Lewis acid, temperature, and H-atom donor. The addition of acetyl radical to **1f** was carried out using two other Lewis acids, $Zn(OTf)_2$ and $Mg(OTf)_2$. Both of these gave nearly racemic products (data not shown in table). Temperature had an adverse effect on selectivity. Increasing the reaction temperature from −78 to −40 °C for the cyclohexyl radical addition to **1f** led to a small decrease in ee (compare entry 2 with 5). Further increase in temperature to 0 °C gave racemic material (entry 6). Results from these studies suggest that there is very little rotamer control at higher temperatures or a poorly organized structure for the complex derived from Lewis acid + ligand + substrate.

A more interesting result was obtained by altering the H-atom donor from Bu_3SnH to tris(trimethylsilyl)silane (TTMSS); the opposite enantiomeric product was obtained (compare entry 2 with entry 8).[32] This inversion of stereochemistry based solely on H-atom donor was completely unexpected. The stronger Si−H bond as compared to the Sn−H bond could potentially allow for a slower trap of the radical intermediate. This in turn could provide the radical enough time to interconvert to a more stable conformation. Unfortunately, the reaction was unsuccessful at −78 °C (entry 7). The reaction was extremely slow, and at the higher temperature of −40 °C (entry 8), 35% of the cyclohexyl conjugate addition product was obtained along with 55% yield of recovered starting material after 8 h. As temperature was increased further to 0 °C (entry 9), the yield improved to 45%. Starting material was still recovered in these reactions. Enantioselectivity was highest at −40 °C (entry 8). This phenomenon was not unique to cyclohexyl radical addition. The addition of acetyl radical experienced this strange effect as well (entry 10). At this time, we have no explanation for these unexpected results.

It appeared that achieving practical levels of enantioselectivity utilizing templates that form six-membered chelates with the chiral Lewis acid would be difficult. One final modification to these types of templates was initiated in the hope of solving the problem of obtaining synthetically useful levels of enantioselectivity. Alteration of the geometry of substrate−Lewis acid−ligand superstructure by replacing the sp^2 carbon of the template carbonyl with an sp^3 center was envisaged. To maintain the possibility of two-point binding in the template, it was decided to utilize a sulfone oxygen as the second Lewis basic site.[33]

The application of sultams as chiral auxiliaries has been well established by Oppolzer.[34] In contrast, there are only limited reports on the use of sulfones as templates in enantioselective transformations.[35] Wada and Kanemasa have shown that α,β-unsaturated ketones appended with a phenyl sulfonyl group undergo highly selective Diels−Alder reactions.[36] The two sulfonyl oxygens in differentially substituted sulfones are enantiotopic. Wada and Kanemasa hypothesized on the preferential coordination of one of the sulfonyl oxygen to the chiral Lewis acid and for the phenyl group to provide face selectivity.

(32) Chatgilialoglu, C.; Ferreri, C.; Gimisis, T. Tris(trimethylsilyl)silane in organic synthesis. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, U.K., 1997; Vol. 2, Chapter 25, p 1539. Also see: Chatgilialoglu, C. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinhem, Germany, 2001; Chapter 1.3.

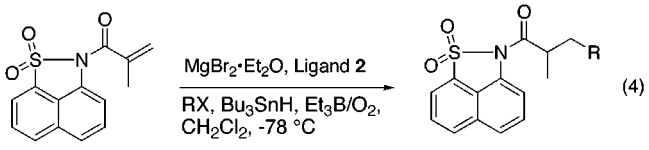
(33) For an excellent review on sultam derived acrylates and issues related to geometry and reactivity see: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293.

(34) References 13, 14, and 33. Sultams have been used as an auxiliary in a variety of transformations including radical reactions. For the use of Oppolzer sultam 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. For the use of sulfones in diastereoselective reactions see: (d) Marcantoni, E.; Cingolani, S.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1998**, *63*, 3624. (e) Marino, J. P.; Viso, A.; Lee, J.-D. *J. Org. Chem.* **1997**, *62*, 645. (f) Enders, D.; Muller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 879. (g) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1741.

(35) (a) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637. (b) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 145.

(36) Wada, E.; Pei, W.; Kanemasa, S. *Chem. Lett.* **1994**, 2345.

Table 4. Reactions on the 1,8-Naphthosultam Template[a]



10

11 R = *i*-Pr
12 R = *t*-Butyl
13 R = Cyclohexyl
14 R = CH_2OMe
15 R = Acetyl

entry	product	temp, °C	Lewis acid (eqiv)	hydride	yield,[c] %	ee,[d] %
1	**11**	−78	none[b]	Bu_3SnH	<5	0
2	**11**	−78	$MgBr_2$·Et_2O (1.0)	Bu_3SnH	90	78
3	**11**	−78	$MgBr_2$·Et_2O (0.3)	Bu_3SnH	80	80[e]
4	**11**	−40	$MgBr_2$·Et_2O (0.3)	Bu_3SnH	71	59
5	**11**	0	$MgBr_2$·Et_2O (0.3)	Bu_3SnH	52	5
6	**11**	−78	$MgBr_2$·Et_2O (1.0)	Ph_3SnH	59	88
7	**11**	−78	$MgBr_2$·Et_2O (0.3)	Ph_3SnH	55	80
8	**11**	−40	$MgBr_2$·Et_2O (1.0)	Ph_3SnH	51	42
9	**12**	−78	$MgBr_2$·Et_2O (1.0)	Bu_3SnH	91	80
10	**12**	−78	$MgBr_2$·Et_2O (0.3)	Bu_3SnH	84	89[e]
11	**12**	−78	$MgBr_2$·Et_2O (1.0)	Ph_3SnH	32	78
12	**13**	−78	$MgBr_2$·Et_2O (1.0)	Bu_3SnH	96	89
13	**13**	−78	$MgBr_2$·Et_2O (0.3)	Bu_3SnH	71	82[e]
14	**13**	−78	$MgBr_2$·Et_2O (1.0)	Ph_3SnH	72	83
15	**14**	−78	$MgBr_2$·Et_2O (1.0)	Bu_3SnH	91	86
16	**14**	−78	$MgBr_2$·Et_2O (0.3)	Bu_3SnH	89	90
17	**14**	−78	$MgBr_2$·Et_2O (1.0)	Ph_3SnH	95	87
18	**14**	−78	$MgBr_2$·Et_2O (0.3)	Ph_3SnH	93	88
19	**15**	−78	$MgBr_2$·Et_2O (1.0)	Bu_3SnH	<25	18

[a] Reactions were performed on a 0.2 mmol scale. [b] No Lewis acid was added. [c] Isolated yields. [d] ee's were determined from chiral HPLC analysis. [e] Reactions were performed on a 0.5 mmol scale with 30 mol % of the chiral Lewis acid.

Porter has shown that radical additions to acrylates attached to an achiral cyclic sultam proceeds in good yields.[37] Recently, Hiroi has reported an interesting example of enantiocontrol in radical cyclization using sulfones.[38] The selectivity in the cyclization was attributed to the coordination of one of the enantiotopic sulfonyl oxygen to the chiral Lewis acid. An additional example on the use of sulfones in radical reactions was recently reported by Toru and co-workers.[39] We surmised that the formation of one of the two possible diastereomeric complexes between enantiotopic sulfonyl oxygen in *N*-acyl sultams and the chiral Lewis acid could allow for conformer control of the acyl side chain. This in turn could allow for selectivity in H-atom-transfer reactions.

A commercially available achiral template that would meet our needs was the 1,8-naphthosultam. This offered advantages as a potential achiral template. Both the starting material and the desired products were UV-active, simplifying isolation. The radical addition compounds were considerably less polar than the other templates investigated thus far, again simplifying isolation of the product from polar organotin reaction byproducts. This new template was tested with the addition of isopropyl radical and the enantioselectivity of the product was measured (eq 4, Table 4). We were pleased by the results for radical additions to this template. In the absence of a Lewis acid, isopropyl radical addition did not occur (NMR spectrum of the crude reaction product indicated the formation of less than 5% of the product (entry 1)). In contrast, addition of isopropyl radical occurred with both high yield and excellent selectivity in the presence of $MgBr_2$·Et_2O (1 equiv) and ligand **2** (entry 2). The product ee of 78% was the highest yet obtained for these addition/H-atom-transfer reactions. Catalytic reactions were attempted using 30 mol % of the chiral Lewis acid and at this loading, the yield and ee were similar (entry 3). Increasing the temperature to −40 °C (entry 4) or 0 °C (entry 5) led to deterioration in both yield and selectivity. An alternate H-atom donor, triphenyltin hydride, was examined. The chemical efficiency with this reagent was slightly lower as compared to tributyltin hydride; however, the enantioselectivity was quite similar (compare entry 2 with 6 and 3 with 7). As was the case with tributyltin hydride, reaction at −40 °C gave lower selectivity with triphenyltin hydride also (compare entry 3 with 4 and 7 with 8). TTMSS was ineffective in reactions with **10**.

Other alkyl radicals that are reasonably nucleophilic add efficiently using stoichiometric or catalytic amounts of the Lewis acid (entries 9, 10, 12, and 13). The enantioselectivities in these experiments were quite good ranging between 80 and 89%. Methoxymethyl radical addition followed by H-atom transfer occurred with exceptionally high selectivity (entries 15 and 16). Triphenyl and tributyltin hydrides showed similar efficiency in H-atom-transfer selectivity, although chemical yields differed from substrate to substrate (entries 11, 14, 17, and 18). The addition of acetyl radical (entry 19) was extremely slow and ethyl radical did not add under any of the reaction conditions utilized (data not shown).

The absolute configuration of the isopropyl radical addition product **11** was determined by hydrolysis. The sign of the optical rotation for the product acid was compared with that reported in the literature[23] and was determined to be (*S*). The absolute stereochemistry for the isopropyl radical addition product was identical for the various templates which form a six-membered chelate with the magnesium Lewis acids.

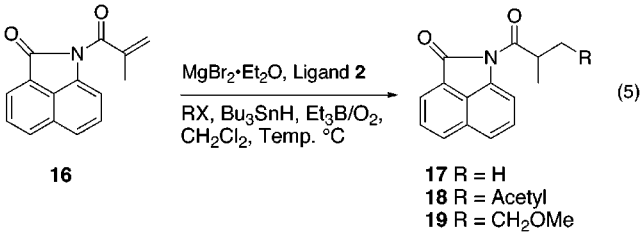
Control experiments were in order to probe the importance of the tetrahedral nature of the sulfone group and reactions with a template in which SO_2 group is replaced by a trigonal CO group were undertaken. The 1,8-naphtholactam is also a commercially available compound, and the required substrate (**16**) was prepared uneventfully. This template proved to be much more reactive than the naphthosultam, and this caused a small problem (eq 5, Table 5). Due to its enhanced reactivity, the reduced starting material, **17**, contaminated the conjugate addition products, especially when alkyl radicals were used. However, it was possible to separate **17** from the products resulting from the addition of the more polar heteroatom containing radicals (entries 1−3, Table 5). The data in the table clearly indicate that the lactam template is ineffective in providing even marginal levels of selectivity. This is in marked contrast to the high levels of selectivity observed with the sultam template.

Other Chiral Ligands

Until now the only class of ligands we have investigated in some detail in enantioselective radical reactions are the C_2 symmetric bisoxazolines. Two working models with the magnesium Lewis acid in a tetrahedral or an octahedral environment have been formulated to explain results obtained in conjugate

(37) Porter, N. A.; Carter, R. L.; Mero, C. L.; Roepel, M. G.; Curran, D. P. *Tetrahedron* **1996**, *52*, 4181.
(38) Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, *41*, 7071.
(39) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981.

Table 5. Reactions on the 1,8-Naphtholactam Template[a]

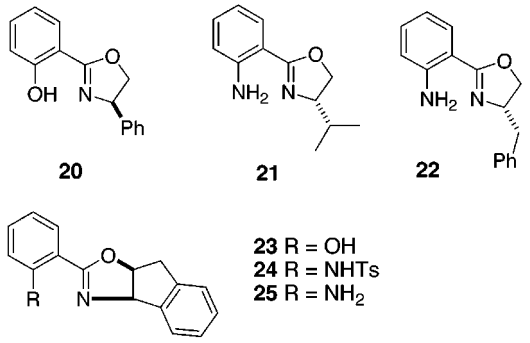


entry	product	Lewis acid[b]	temp, °C	yield,[c] %	ee,[d] %
1	**18**	$MgBr_2$	−78	55 (36)	22
2	**19**	$MgBr_2$	−78	61 (27)	6
3	**18**	$MgBr_2$	−40	00 (86)	0
4	**19**	$Mg(ClO_4)_2$	−78	31 (62)	6

[a] Reactions were performed on a 0.2 mmol scale. [b] Stoichiometric amount of chiral Lewis acid utilized. [c] Isolated yield. Numbers in parentheses represent reduced starting material **17**. [d] ee's determined from chiral HPLC analysis.

additions. To gain further insight into the nature of the geometry around the Lewis acid, we decided to explore alternative ligands. Fujisawa[40] has reported on the use of chiral complexes of 2-arylsulfonyloxazoline-based ligands for enantioselective Diels−Alder reactions. In these reactions, the chiral Lewis acid was formed in situ, via the addition of Grignard reagents to solutions of the ligand. Fujisawa postulated an octahedral Mg complex in the Diels−Alder reaction between cyclopentadiene and an oxazolidinone acrylate to account for the high selectivity.

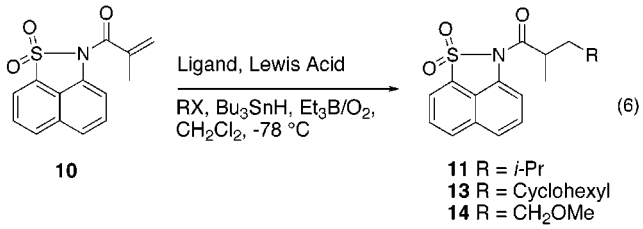
We hoped that reaction of **10** catalyzed by Mg complexes derived from ligands **20**−**25** would serve two purposes: (1) offer a new ligand system for selective H-atom-transfer reactions and (2) provide us with additional information on ligand + Lewis acid + substrate superarchitecture.



A series of ligands **20**−**25** were prepared following literature procedures.[41] The chiral Lewis acids were prepared by the addition of methyl Grignard reagents to the aryl oxazoline of interest. This solution was then cooled to −78 °C, and **10** was added. Results from conjugate addition of nucleophilic radicals to **10** followed by H-atom transfer are tabulated in Table 6 (eq 6). From the results a number of trends are apparent. The Mg Lewis acid that is formed in situ by the addition of the MeMgI to ligands **20** and **23** are quite successful in activating the substrate for conjugate addition (entries 2 and 5). Unfortunately, the enantioselectivity was poor. The chiral catalyst formed by the reaction of the amine containing ligands **21** and **22** gave lower yields and also suffered from low enantioselectivity

(40) Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *J. Org. Chem.* **1997**, *62*, 7937.
(41) See Supporting Information for experimental details.

Table 6. Enantioselective H-Atom Transfers Catalyzed by Acyloxazoline Complexes



entry	ligand	Lewis acid	compd[a]	yield,[b] %	ee,[c] %
1	**2**	$MgBr_2$•Et_2O	**11**	90	78
2	**20**	MeMgI	**11**	85	34
3	**21**	MeMgI	**11**	62	9
4	**22**	MeMgI	**11**	68	10
5	**23**	MeMgI	**11**	85	18
6	**24**	MeMgI	**11**	60	8
7	**25**	MeMgI	**11**	87	80
8	**25**	MeMgI[d]	**11**	80	75
9	**25**	MeMgI[e]	**11**	76	68
10	**25**	MeMgBr	**11**	88	14
11	**25**	MeMgCl	**11**	72	0
12	**25**	MeMgI	**13**	87	75
13	**25**	MeMgI	**14**	77	35

[a] Reaction performed on 0.3 mmol scale. [b] Isolated yield. [c] ee's obtained from chiral HPLC analysis. [d] Reaction performed with 50 mol % chiral Lewis acid, 0.5 mmol scale. [e] Reaction performed with 30 mol % chiral Lewis acid, 0.5 mmol scale.

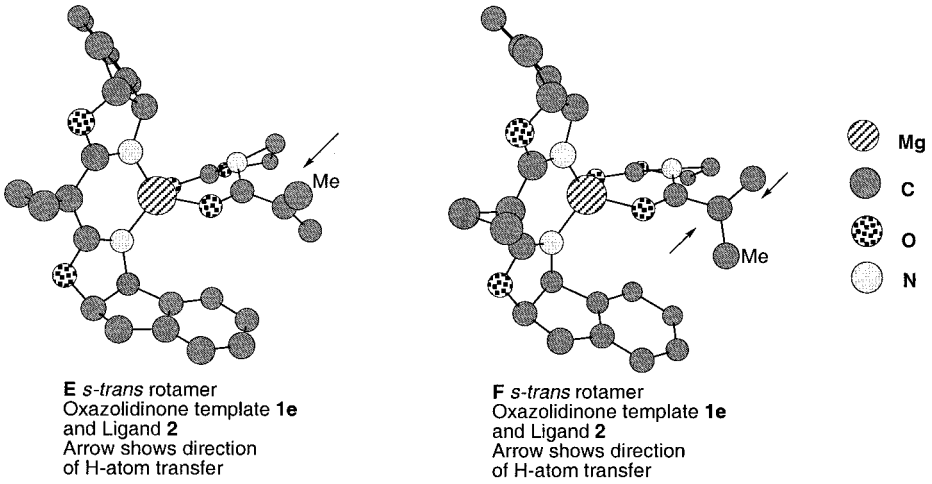
(entries 3 and 4). Fujisawa noted in his Diels−Alder reactions that sulfonamides similar to ligand **21** furnished superior yield and enantioselectivity. Unfortunately when ligand **24** (entry 6) was utilized, the same effect was not observed. The yield was moderate, and enantioselectivity was poor.

Surprisingly, the parent compound **25**, catalyzed the H-atom-transfer reaction quite well (entries 7−13). In fact, the observed 80% ee (entry 7) was similar to that with ligand **2** (entry 1). With a highly selective ligand for H-atom-transfer reactions, attempts to further optimize the reaction were undertaken. With ligand **25**, a pronounced counterion effect was observed with iodide > bromide ≫ chloride (entries 9−11). All of the counterions tested showed good ability to activate the substrate with excellent yields of the product **11** obtained in all cases. An examination of the enantioselectivity shows that ee's drop rapidly as the size of the counterion decreases. The stereochemistry for the addition product **11** was determined to be (*R*) (note: ligand **25** has the 1*R*,2*S* stereochemistry; opposite to that in ligand **2**). Thus the sense of stereoinduction in the addition reaction leading to **11** is the same with ligands **2** and **25**.

Stereochemical Model for Selectivity

Radical reactions are known to proceed by an early transition state, and thus its structure closely resembles that of the starting material (complex). In our analysis (vide infra) it is assumed that the H-atom transfer occurs rapidly in relation to any rotamer interconversion, and thus precursor geometry impacts on product stereochemistry. Thus the enoate conformation in the Lewis acid-coordinated complex is critical to determining product stereochemistry.

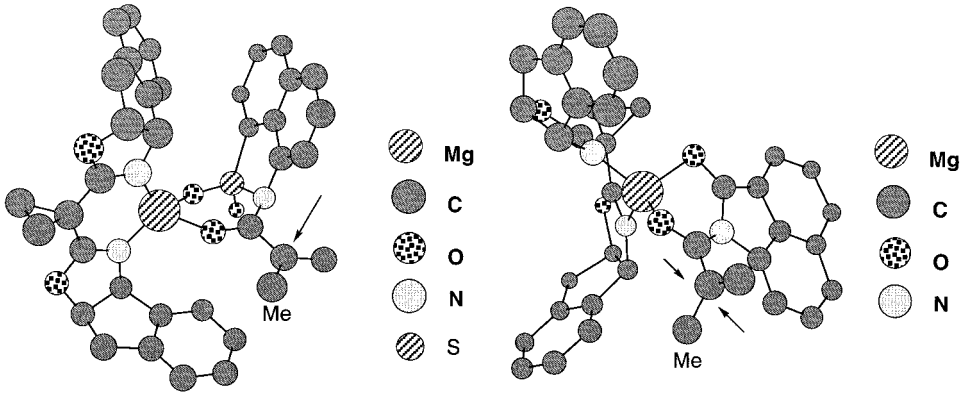
Oxazolidinone and Pyrrolidinone Templates. None of the traditional templates were successful in providing good to high levels of selectivity. Literature precedents for predominance of s-trans rotamer geometry in α-methacryloyl amides and the formation of the (*S*) enantiomer allow us to propose stereo-



E *s-trans* rotamer
Oxazolidinone template **1e**
and Ligand **2**
Arrow shows direction
of H-atom transfer

F *s-trans* rotamer
Oxazolidinone template **1e**
and Ligand **2**
Arrow shows direction
of H-atom transfer

Figure 2.



s-trans rotamer
G Sultam template **10**
and Ligand **2**
Arrow shows direction
of H-atom transfer

s-trans rotamer
H Lactam template **16**
and Ligand **2**
Arrow shows direction
of H-atom transfer

Figure 3.

chemical models for the H-atom-transfer reactions with **1e** and **1f**. Assuming a tetrahedral Mg(II) species and a bidentate coordination of the substrate, the enoate resides in a twisted s-trans conformation to minimize adverse steric interactions.[42] The enoate can twist in either a clockwise (**E**, Figure 2) or an anticlockwise (**F**, Figure 2) manner (from an ideal s-trans conformer) to relieve steric strain, and both rotamers seem reasonable. The relative ease of conjugate addition to the oxazolidinone methacrylate suggests that the deviation of the O═CC═C dihedral angle from 180° is not large. The β-carbon is easily accessible for conjugate addition. In the subsequent H-atom-transfer step, both faces of the intermediate radical are open, with a small preference for *re* face addition. This accounts for the moderate selectivity observed with templates **1e** and **1f**.

Sultam and Lactam Templates. The high selectivities with the sultam template raises questions related to enoate geometry. Molecular models indicate that both s-trans and s-cis rotamers are relatively free from steric interactions in a tetrahedral Mg chelate with the substrate (**G**, Figure 3). The tetrahedral nature of the sulfone also imparts a near planarity to the enoate portion of the substrate with the nitrogen atom slightly above this plane. The facility of conjugate additions to **10** lends support to this conclusion. The single bond of the enoate is also restricted in its motion in the complex. For example, clockwise motion is less sterically encumbered than an anticlockwise rotation. This is in contrast to the rotamers postulated with the oxazolidinone and pyrrolidinone templates.

Product stereochemistry analysis suggests that the reaction should occur from conformer **G** (Figure 3) with H-atom transfer taking place from the *re* face of the radical intermediate. The reasons for the preference for this rotamer are not apparent. Models suggest that higher selectivities may be possible with the s-cis rotamer.

In the case of the lactam-based template **16**, coordination to the Lewis acid results in the carbonyls again aligning syn to one another. To remove unfavorable steric interactions, the olefin assumes an s-trans geometry (**H**, Figure 3). The methyl group twists up and rotates clockwise to move the methylene further away from the hydrogen atom of the naphthalene ring system. However, unlike the sultam, the trigonal nature of the CO group in the lactam system pushes the naphthalene ring system into a planar arrangement with the CONCO atoms (chelated ring). The rotation of the enoate opens the back face to attack by both the

(42) Other geometries, such as cis octahedral structures, are also possible. We have been unable to arrive at an exact geometry for the ternary complex in these radical reactions. Experiments are underway to gain a better understanding

incoming radical and to the H-atom donor. The exposed nature of the olefin should result in a nonselective reaction. The results substantiate this hypothesis. Comparison of the results for the addition of methoxymethyl radical to both the lactam and the sultam (Table 4, entry 4 and Table 5, entry 16) clearly suggests the requirement for the sulfone group for high selectivity.

Conclusions

In conclusion, an effective enantioselective H-atom-transfer reaction has been developed by the utilization of the 1,8-naphthosultam achiral template. Reactions with this template could be conducted with catalytic amounts of the chiral Lewis acid and maintain the high levels of enantioselectivity. Other templates that formed six-membered chelates with the chiral Lewis acid were unsuccessful in providing high levels of enantioselectivity. Pyrazole-based templates that form a five-membered chelate offered products with the opposite configuration for the newly formed chiral center, but with reduced levels of enantioselectivity. A series of new chiral aryloxazoline-based ligands were found to be effective for the addition of alkyl radicals to the 1,8-naphthosultam template. Achieving high levels of enantioselectivity for H-atom-transfer reactions is more difficult than for radical conjugate addition reactions.

Experimental Section

For general experimental details, see Supporting Information.

General Procedure for the Chiral Lewis Acid Mediated Intermolecular α-Selective Hydrogen Atom Transfer Reaction Utilizing Chiral Ligand 2 at −78 °C (2/Lewis Acid/Substrate = 1:1:1). A solution of the substrate (0.20 mmol), Lewis acid (0.20 mmol), ligand (71 mg, 0.20 mmol), and CH_2Cl_2 (3 mL) under N_2 was allowed to stir at room temperature for 30 min. The solution was cooled to −78 °C in a dry ice acetone bath. To the solution was added the radical precursor RX [passed through basic alumina] (1.0 mmol), Bu_3SnH (116 mg, 0.40 mmol), and Et_3B (1 M in hexane, 1 mL, 1 mmol) at −78 °C. A 5 mL aliquot of O_2 was then added via syringe over 2 h. 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 crude product was purified by flash column chromatography to yield the alkylated products.

***N*-(2-Methylpropenoyl)-1,8-naphthosultam (10).** A suspension of 1,8-naphthosultam (10.26 g, 50 mmol) in THF (200 mL) and under N_2 atmosphere was cooled to 0 °C in an ice bath. To this suspension was added NaH (3.0 g, 75 mmol, 60% in mineral oil) portionwise over a period of 20 min. The solution bubbled upon the addition of NaH, and the dark brown suspension turned clear and was allowed to stir at room temperature for 1.5 h. A solution of freshly distilled methacryloyl chloride (7.6 mL, 75 mmol) was added dropwise over 10 min. After stirring at room temperature overnight, the solution was carefully quenched by the slow addition of saturated aqueous NH_4Cl (30 mL). The mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was a brown solid and was purified by recrystallization using EtOAc:hexanes (11.89 g, 87%, brown solid); mp 160−162 °C. $R_f = 0.40$ (30% EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 5.78−5.80 (m, 1H), 5.96 (s, 1H), 7.67−7.81 (m, 3H), 7.94 (d, $J = 7.2$ Hz, 1H), 7.97 (d, $J = 7.2$ Hz, 1H), 8.15 (d, $J = 8.3$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4, 114.7, 119.5, 120.1, 122.5, 123.7, 128.1, 129.5, 129.7, 130.7, 131.8, 131.9, 139.6, 169.3. Anal. Calcd for $C_{14}H_{11}NSO_3$: C, 61.53; H, 4.07; N, 5.12. Found: C, 61.26; H, 4.44; N, 5.08.

(2*S*)-*N*-(2,4-Dimethy1pentanoyl)-1,8-naphthosultam (11). According to the general procedure outlined above, **10** was alkylated to provide **11** (yield, 90%; yellow solid); mp 63−65 °C. $R_f = 0.55$ (30% EtOAc: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 1.72−1.80 (m, 1H), 2.22−2.29 (m, 1H), 2.92−2.98 (dd, $J = 16.5$, 8.7 Hz, 1H), 3.14−3.18 (dd, $J = 16.3$, 4.7 Hz, 1H), 7.62−7.69 (m, 2H), 7.75−7.79 (dd, $J = 8.2$, 7.4 Hz, 1H), 7.98 (d, $J = 7.4$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.25−8.27 (dd, $J = 7.4$ Hz, 0.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.0, 18.6, 20.3, 32.3, 35.5, 41.0, 113.8, 119.5, 122.1, 127.9, 128.8, 130.0, 130.6, 132.0, 132.2, 170.9. $[\alpha]_D^{26}$: +23.2 (*c* 0.66 CH_2Cl_2). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.55; H, 6.42; N, 4.65. ee 78% (*S*) by HPLC (Chiralcel OJ, hexanes: propan-2-ol = 9:1 (0.4 mL/min), 254 nm). (Absolute configuration determined by hydrolysis to the acid and comparison of the sign of the optical rotation to that reported in the literature; see below.)

Hydrolysis of 11 to (2*S*)-2,4-Dimethylpentanoic Acid. To a flask containing **11** (111 mg, 0.35 mmol), tetrahydrofuran (THF) (5 mL), and H_2O (5 mL) under N_2 was added H_2O_2 (30%, 0.16 mL, 1.4 mmol) at 0 °C. $LiOH{\cdot}H_2O$ (29 mg, 70 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; removal of achiral template). 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 (2*S*)-2,4-dimethylpentanoic acid (34 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83−0.88 (overlapping doublets, 6H), 1.12 (d, $J = 7.25$ Hz, 3H), 1.17−1.25 (m, 1H), 1.52−1.64 (m, 2H), 2.43−2.54 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5, 22.6, 22.7, 26.0, 37.7, 42.9, 183.4; $[\alpha]_D^{26}$: +17.1 (*c* 0.99 Et_2O) [lit.[23] $[\alpha]_D^{26}$: −21.86 (*c* 5.39, Et_2O) (*R*) isomer].

General Procedure for Enantioselective H-Atom-Transfer Reactions Catalyzed by Aryl Oxazoline Ligands. A solution of the desired ligand (0.15 mmol) in 3 mL of CH_2Cl_2 was cooled to 0 °C in an ice bath. To the solution was added the appropriate methyl Grignard reagent (0.05 mL (0.15 mmol) of 3.0 M Et_2O). The solution bubbled and changed from clear to pale yellow and was allowed to stir at 0 °C for 30 min. The flask was transferred to a dry ice acetone bath and cooled to −78 °C. The substrate, **18,** was added as a solution in 2 mL of CH_2Cl_2 followed by the radical precursor RX [passed through basic alumina] (1.0 mmol), Bu_3SnH (88 mg, 0.30 mmol), and Et_3B (1 M in hexane, 1 mL, 1 mmol) at −78 °C. A 5 mL aliquot of O_2 was then added via syringe over 2 h. 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 crude compound was purified by flash column chromatography to furnish the alkylated product.

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Supporting Information Available: Characterization data for compounds **1**−**25** and experimental procedures. See any current masthead page for ordering information and Web access instructions.

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