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Enantioselective H-Atom Transfer Reaction: A Strategy to Synthesize Formaldehyde Aldol Products

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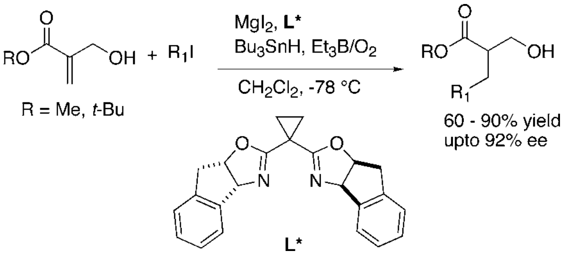
ABSTRACT



Enantioselective radical alkylation of Baylis–Hillman adducts furnished aldol products in good yield and selectivity. The results illustrate that the selectivity in the hydrogen atom transfer is dependent on the size of the ester substituent, with smaller substituents providing better enantioselectivity.

The aldol reaction constitutes one of the most important carbon−carbon bond forming reactions.[1] Enantiopure aldol products can be synthesized in numerous ways,[2] and can be converted to substructures that are widely present in biologically interesting targets such as β-lactones,[3] β-lactams, and various other derivatives. The use of radical reactions[4] for generating sensitive aldol products is relatively underdeveloped,[5] even though the mild, neutral conditions seem well suited. Our group was the first to report enantioselective intermolecular radical additions to synthesize acetate aldols, in which the products are chiral at the β-carbon but not the α-carbon.[6] Stereochemistry was generated in the alkylation step but not the ensuing hydrogen atom transfer step. While a number of enantioselective alkylations have been developed, only a few enantioselective hydrogen atom transfer reactions have been reported, with the controlling factors not well understood. We recently described a highly efficient tandem alkylation−hydrogen atom transfer reaction to synthesize β^2-amino acids (**2**) from N-protected α-aminomethyl acrylate (**1**), where the stereodetermining step involves enantioselective hydrogen atom transfer (eq 1).[7] The reduc-

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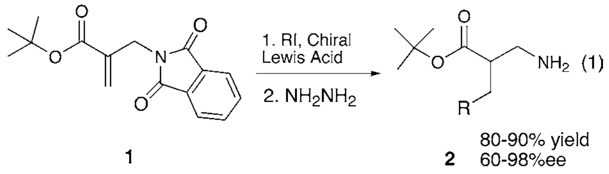
tion[8] of such carbonyl-substituted radicals can be viewed as being complementary to enantioselective protonation of enolates.[9] In this paper, we report related radical alkylation of simple α-hydroxy acrylates (**3**), which are readily available as Baylis−Hillman reaction adducts.[10] Under radical conditions, substrates **3** can react in their free alcohol form without need for protection providing access to enantioenriched aldol products **4** (eq 2).



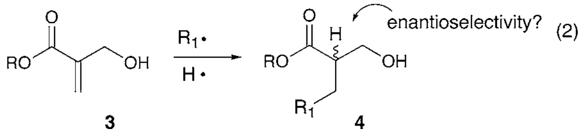
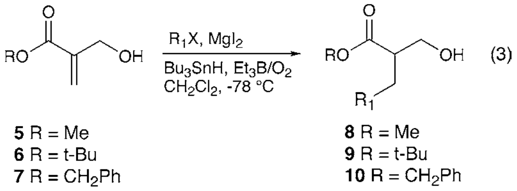


Table 1. MgI_2-Catalyzed H-Atom Transfer Reactions[a,b]



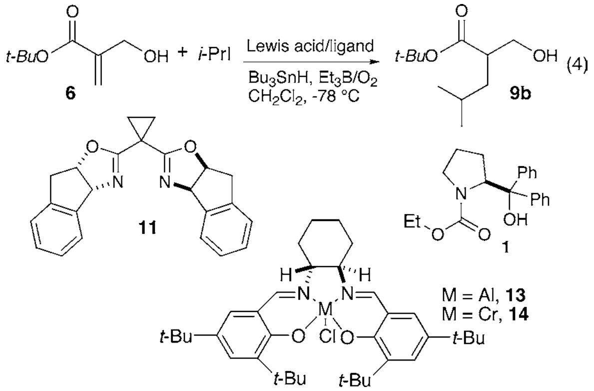
entry	R	R_1X	compd	yield (%)[c]
1	Me	ethyl-I	**8a**	53
2	Me	*i*-Pr-I	**8b**	52
3	Me	cyclohexyl-I	**8c**	60
4	Me	*t*-Bu-I	**8d**	68
5	*t*-Bu	ethyl-I	**9a**	68
6	*t*-Bu	*i*-Pr-I	**9b**	53
7	*t*-Bu	cyclohexyl-I	**9c**	61
8	*t*-Bu	*t*-Bu-I	**9d**	52
9	Bn	ethyl-I	**10a**	92
10	Bn	*i*-Pr-I	**10b**	95
11	Bn	cyclohexyl-I	**10c**	88

[a] Typical reaction conditions: For 1 equivalent of substrate, 10 equivalents of radical precursor, 3.6 equivalents of Bu_3SnH, and 3.6 equivalents of Et_3B were used. For more details see the Supporting Information. [b] 1 equiv of Lewis acid used. [c] Isolated yield after column purification.

Our experimental work began by investigating additions to α-hydroxymethyl acrylates **5**−**7**[11] under achiral conditions (Table 1). The reactivity was high, and good yields were obtained at −78 °C even in the absence of any Lewis acid.[12] With MgI_2 as the representative Lewis acid,[13] moderate yields were observed for methyl- and *tert*-butyl-substituted esters **5** and **6**, irrespective of the size of radical added (entries 1−8). On the other hand, excellent yields were obtained when benzyl ester **8** was used (entries 9−11). It appears that some acrylate polymerization interferes when methyl and *tert*-butyl esters **5** and **6** were used, but was less significant with the benzyl ester **7**.

Chiral Lewis acids were then screened[14] for enantioselective alkylation−hydrogenation, using isopropyl iodide as rad-

Table 2. Effect of Chiral Lewis Acid on Enantioselectivity[a]



entry	Lewis acid[b]	ligand[b]	yield (%)[c]	ee (%)[d]
1	MgI_2	**11**	53	55
2	$Zn(OTf)_2$	**11**	52	24
3	$Sm(OTf)_3$	**12**	61	21
4	$Yb(OTf)_3$	**12**	65	25
5	Al-Salen	**13**	45	21
6	Cr-Salen	**14**	40	23

[a] For reaction details see the Supporting Information. [b] 1 equiv of chiral Lewis acid used. [c] Isolated yield after column purification. [d] Determined with chiral GC.

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(7) Sibi, M. P.; Patil, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1235.

(8) For examples of H-atom transfer reactions mediated by chiral Lewis acids, see: (a) Sugimoto, H.; Nakamura, S.; Watanabe, Y.; Toru, T. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3043. (b) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984. (c) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293. (d) Murakata, M.; Tsutsui, H.; Takeuchi, N.; Hoshino, O. *Tetrahedron* **1999**, *55*, 10295. (e) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576. For selected examples of enantioselective reductions with chiral H-atom transfer reagents, see: (f) Zeng, L.; Perchyonok, T.; Schiesser, C. H. *Tetrahedron*: *Asymmetry* **2004**, *15*, 995. (g) Dakternieks, D.; Perchyonok, V. T.; Schiesser, C. H. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3057. (h) Blumenstein, M.; Lemmler, M.; Hayen, A.; Metzger, J. O. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3069. (i) Dakternieks, D.; Dunn, K.; Perchyonok, V. T.; Schiesser, C. H. *Chem. Commun.* **1999**, 1665. (j) Blumenstein, M.; Schwarzkopf, K.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 235. (k) Nanni, D.; Curran, D. P. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2417.

(9) For a review on enantioselective protonations see: Eames, J.; Weerasooriya, N. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1. For non free radical methods involving reductive alkylation of acrylates with enantioselective protonation see: (a) Reetz, M. T.; Moulin, D.; Gosburg, A. *Org. Lett.* **2001**, *3*, 4083. (b) Chapman, C. J.; Wadsworth, K. J.; Frost, C. G. *J. Organomet. Chem.* **2003**, *680*, 206. (c) Chapman C. J.; Frost, C. G. *Adv. Synth. Catal.* **2003**, *345*, 353. (d) Huang, T.-S.; Li, C.-J. *Org. Lett.* **2001**, *3*, 2037. (e) Moss, R. J.; Wadsworth, K. J.; Chapman, C. J.; Frost, C. G. *Chem. Commun.* **2004**, 1984. For Co-mediated reduction/protonation, see: Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron*: *Asymmetry* **2003**, *14*, 967.

(10) For recent reviews on Baylis−Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201.

(11) For the synthesis of substrates, see the Supporting Information. For benzyl substituent, see: O'Leary, B. M.; Szabo, T.; Svenstrup, N.; Schalley, C. A.; Lutzen, A.; Schafer, M.; Rebek J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 11519.

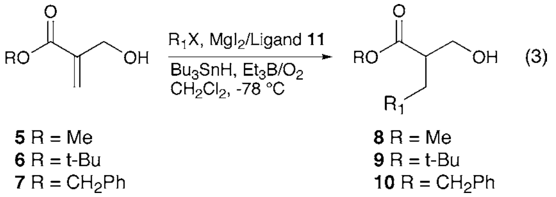
(12) Reaction of **6** with different radicals at −78 °C in the absence of any Lewis acid gave products in good yields; EtI (78%), *i*-Pr-I (51%), cyclopentyl-I (79%), cyclohexyl-I (74%), *t*-Bu-I (62%). Compound **5** showed similar results.

(13) Other Lewis acids such as $Yb(OTf)_3$, $Mg(ClO_4)_2$, and $Sm(OTf)_3$ gave similar yields. Use of 30 mol % of the Lewis acid gave similar yields. Since we had used MgI_2 for synthesizing β-amino acids, the same Lewis acid has been used for obtaining the aldol products.

ical precursor and *tert*-butyl ester **6** as substrate (Table 2). Three different classes of ligands were tested, namely the bisoxazoline, proline, and salen ligands (see **11**−**14**). MgI_2 with bisoxazoline ligand **11** showed the best enantioselectivity (entry 1). With $Zn(OTf)_2$ and the same ligand the enantioselectivity deteriorated, although the chemical yield was unaffected (entry 2). It has been reported by our group that lanthanide Lewis acids with proline ligand **12** provide good enantioselectivity in radical additions to oxazolidinone cinnamates;[15] however, only low enantioselectivity was obtained upon alkylation−hydrogenation of substrate **6** (entries 3 and 4). Commercially available aluminum and chromium salen Lewis acids provided moderate selectivity for the H-atom transfer reaction (entries 5 and 6). Several H-atom donors with size or reactivity differing from that of tributyltin hydride were also screened but were not found to be beneficial.[16]

Table 3 shows results for a series of enantioselective additions to esters **5**−**7**, using various acyclic and cyclic radicals and using MgI_2-ligand **11** as the chiral Lewis acid.

Table 3. Enantioselective H-Atom Transfer Reactions with Various Radical Precursors[a,b]



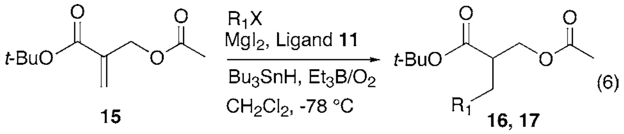
entry	R	R_1X	compd	yield (%)[c]	ee (%)[d]
1	Me	ethyl-I	**8a**	51	75[e]
2	Me	*i*-Pr-I	**8b**	69	88[e]
3	Me	cyclopentyl-I	**8e**	82	90[e]
4	Me	cyclohexyl-I	**8c**	52	78[e]
5	Me	*t*-Bu-I	**8d**	77	92[e]
6	*t*-Bu	ethyl-I	**9a**	58	−62[e]
7	*t*-Bu	*i*-Pr-I	**9b**	53	−55[e]
8	*t*-Bu	cyclopentyl-I	**9e**	62	−69[e]
9	*t*-Bu	cyclohexyl-I	**9c**	75	−71[e]
10	*t*-Bu	*t*-Bu-I	**9d**	80	−53[e]
11	Bn	ethyl-I	**10a**	85	40
12	Bn	*i*-Pr-I	**10b**	94	44
13	Bn	cyclopentyl-I	**10e**	81	48
14	Bn	cyclohexyl-I	**10c**	97	41

[a] For reaction details see the Supporting Information. [b] 1 equiv of chiral Lewis acid used. [c] Isolated yield after column purification. [d] Determined with chiral HPLC. [e] ee determined for benzoate derivative.

Methyl ester **5** consistently gave the best enantioselectivity (entries 1−5). While a primary radical gave moderate enantioselectivity (entry 1), the addition of larger secondary or tertiary alkyl groups resulted in good enantioselectivity (78−92% ee, entries 2−5). The medium sized benzyl ester **7** gave much inferior enantioselectivity (entries 11−14) with all the radicals irrespective of their size, although the sense of induction was the same as that with the methyl ester **5**. By contrast ester **6** with the bulky *tert*-butyl substituent gave the opposite sense of stereoinduction (entries 6−10).[17] The absolute configuration of **8c** was determined to be (*S*) whereas for **9c** it was (*R*), based on conversion to a known compound.[18] The stereochemistries of **8b** and **9b** were also shown to be complementary, based on conversion to a common compound. Thus a remarkable dependence on the size of the ester substituent, with the small methyl ester substituent leading to relatively high (*S*) configuration, the bulky *tert*-butyl ester substituent leading to the reversed (*R*) configuration, albeit with lesser selectivity, and the intermediate-sized benzyl substituent giving intermediate selectivity.

With free alcohols **5**−**7**, Lewis-acid chelation should involve six-membered rings. In our protected β^2-amino acid work (see eq 1), we had observed high enantioselectivity when eight-membered-ring Lewis acid complexes were involved. Thus the free alcohol **6** was converted to acetate **15**,[19] which seemed likewise capable of eight-membered-ring chelation. Radical additions to the acetate **15** in the absence of a Lewis acid gave the products in good yields (Table 4, entries 1 and 3). However, when the same MgI_2-**11** catalyst that was successful with free alcohols **5** and **6** and in our β^2-amino acid project was used, the enantioselectivity of the hydrogen atom transfer was quite low (Table 4, entries 2 and 4).

Table 4. Enantioselective H-Atom Transfer Reactions to Acetates[a,b]



entry	R_1X	product	yield (%)[c]	ee (%)[d]
1[e]	cyclohexyl-I	**16**	59	
2	cyclohexyl-I	**16**	90	34[f]
3[e]	*i*-Pr-I	**17**	84	
4	*i*-Pr-I	**17**	89	36[f]

[a] For reaction details see the Supporting Information. [b] 1 equiv of chiral Lewis acid used. [c] Isolated yield after column purification. [d] Determined with chiral HPLC. [e] Reaction in the absence of a Lewis acid. [f] ee for the products was determined by converting them to the corresponding benzoate derivative.

We do not have a definitive model to explain the surprising reversal of enantioselectivity between methyl ester **5** and *tert*-butyl ester **6**. At least several possibilities may apply. One

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(14) Various other chiral Lewis acids were investigated and the best results are shown here. Chiral Lewis acid reactions were also performed on methyl ester. Since the results were similar, they are not shown here.

(15) Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, *4*, 2929.

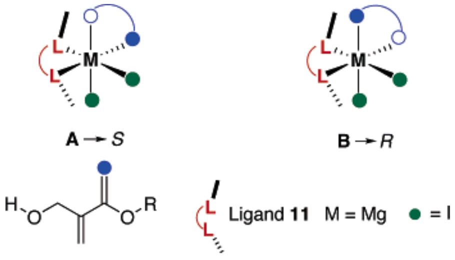
(16) Radical reactions with Ph_3SnH and $(TMS)_3SiH$ (TMS = trimethylsilyl) were not clean.

(17) 30 mol % chiral Lewis acid-catalyzed reactions provided ee values in the range of 20−25% for most of the substrates with the radical precursors shown.

(18) Imogai, H.; Larcheveque, M. *Tetrahedron*: *Asymmetry* **1997**, *8*, 965. Also see the Supporting Information.

(19) Reactions of methyl ester substituted acetate provided polymerized products.

is that the methyl ester **5** reacts via an octahedral magnesium complex, while for steric reasons the bulkier *tert*-butyl ester reduces the coordination number for magnesium such that reaction proceeds via a tetrahedral complex instead. A second more likely possibility is that all three substrates **5**, **6**, and **7** react via octahedral magnesium complexes, but that the substrates can coordinate in either of two orientations, depending on the size of the ester substituent. With a methyl ester **5**, Dreiding model analysis suggests that the ester carbonyl coordinates trans to one of the ligand nitrogens (Figure 1, complex **A** in the simplified conceptual diagram).



5-7

Figure 1. Models to explain stereochemistry

With the bulky *tert*-butyl substituent, however, it appears that the chiral cavity is not well suited for coordination of substrate **6** in orientation **A**. We believe that the *tert*-butyl ester **6** instead reverses its orientation and reacts via complex **B**, in which the hydroxy group rather than the ester carbonyl occupies the position trans to a ligand nitrogen. This reversal of orientation would accommodate the observed reversal in enantioselectivity. With methyl ester **5**, enantioselectivities as high as 92% were obtained, so the preference for reaction via orientation **A** must be fairly high. While the sense of selectivity with *tert*-butyl substrate **6** is reversed, the level of enantioselectivity is never as high (53−71% ee). It is possible that while substrate **6** reacts primarily via complex **B**, that stereochemical erosion results from significant competing reaction via complex **A**. With the medium-sized benzyl ester **7**, presumably reaction occurs largely via complex **A**, but with too much reaction via orientation **B** to allow useful selectivity. A third possibility is that the reversal of enantioselectivity between substrates **5** and **6** simply reflects local conformational effects that result from the differing sizes of the ester substituents. The presence of the sp^3-hybridized carbon in the substrate backbone provides considerable flexibility in a six-membered-ring chelate with the Lewis acid.

In summary, we have developed an interesting route to α-substituted aldol products from simple Baylis−Hillman α-hydroxymethyl acrylates. Under the mild radical conditions the alkylation−hydrogenation reaction requires no protection of the hydroxyl group. An unexpected reversal in enantioselectivity is observed between methyl and *tert*-butyl esters. The results provide additional examples of enantioselective hydrogen atom transfer reactions.

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Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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