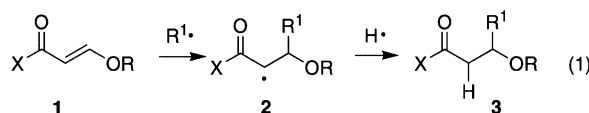


Enantioselective Conjugate Radical Addition to β -Acyloxy Acrylate Acceptors: An Approach to Acetate Aldol-Type Products***Mukund P. Sibi,* Jake Zimmerman, and Tara Rheault*

The aldol reaction remains one of the most important reactions in synthetic organic chemistry. Many traditional ionic routes are currently available for diastereo- and enantioselective aldol reactions.^[1] However, the development of radical methods for the preparation of aldols under neutral conditions is attractive.^[2] With the exception of intramolecular cyclization reactions,^[3] radical approaches towards aldol products remain largely unexplored.^[4] We surmised that nucleophilic radical addition to β -acyloxyenoates using chiral Lewis acid catalysis could provide access to aldol products with high selectivity. A similar strategy using ionic nucleophiles is not possible because of elimination problems.^[5] Herein we demonstrate for the first time an enantioselective intermolecular radical addition strategy for the synthesis of aldol acetates in high yields [Eq. (1)].



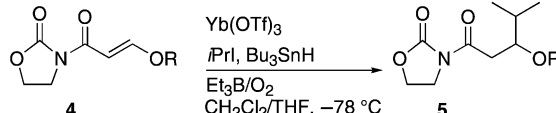
Our experiments began with the evaluation of the β -oxygen substituent in **4** with respect to the ease of radical addition (Table 1).^[6] The addition of an isopropyl radical with and without any Lewis acid additive (100 mol % ytterbium triflate) was studied.^[7] Radical addition to β -alkoxy substrates **4a** or **4b** were inefficient with or without the Lewis acid additive (entries 1 and 2). In contrast, reactions with **4c** containing an acetoxy substituent were moderately effective in the absence of the Lewis acid, and the addition of the Lewis acid resulted in a high yield of **5c** (80%, entry 3). The corresponding benzoate showed slightly higher efficiency (entry 4). In the absence of the Lewis acid, the electronic nature of the benzoyl substituent had an impact on the yield of the conjugate addition product: substrate **4e** with an electron-poor benzoyl group showed higher reactivity than **4f**

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Table 1: Effect of the acyl substituent on reactivity.^[a]


Entry	S.M.	R	Yield, ^[b] no Lewis acid [%]	Yield, Yb(OTf) ₃ (1 equiv) [%]
1	4a	Me	0	< 2
2	4b	Bn	0	< 5
3	4c	COCH ₃	35	80
4	4d	COPh	30	95
5	4e	4-FC ₆ H ₄ CO	40	88
6	4f	4-OMeC ₆ H ₄ CO	12	80
7	4g	2,6-Me ₂ C ₆ H ₃ CO	25	82
8	4h	1-naphthoyl	30	90
9	4i	2-naphthoyl	06	90

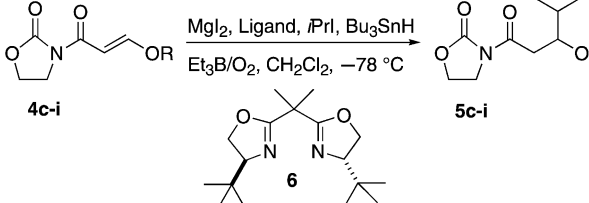
[a] For detailed reaction conditions see Supporting Information.

[b] Yields are for isolated materials purified by column chromatography. S.M. = starting material, Bn = benzyl.

with an electron-rich substituent (compare entries 5 and 6). Other modifications did not lead to large improvements in the yield (entries 7–9). However, in reactions using the Lewis acid, the chemical yields varied only slightly with the nature of the acyloxy group.

Having found a competent acyloxy group for the radical addition, we then undertook a study to identify a chiral Lewis acid system that could provide high enantioselectivity. Magnesium Lewis acids in combination with bisoxazoline ligands were evaluated (Table 2) at two different catalytic loadings.^[8] Although the reactions performed using a 30 mol % catalyst loading were chemically efficient, the enantioselectivity was low, regardless of the β -acyloxy substituent (Table 2). Of the different acyloxy groups examined, the acetate **4c** and the parent benzoate **4d** gave the most promising results (entries 1 and 2). Reactions using stoichiometric amounts of the chiral Lewis acids gave consistently higher levels of enantioselectivity (entries 1–7). These results demonstrate for the first time that acetate aldols can be obtained with *ee* values as high as 93 % using radical chemistry.

A brief study of catalyst stoichiometry using **4d**, **6**, MgI₂, and *i*PrI showed a steady increase in the *ee* value with catalyst loading (50 mol % catalyst: 59 % *ee*; 70 mol % catalyst: 80 % *ee*; 90 mol % catalyst: 85 % *ee*), and reached a maximum with one equivalent (93 % *ee*). These results suggest that either the catalyst turnover is slow^[9] or that a non-catalyzed reaction competes with the catalyzed process. It is interesting to note that increasing the

Table 2: Effect of the acyl group on the enantioselectivity.^[a]


Entry	R	30 mol % Lewis acid ^[b] Yield [%]	30 mol % Lewis acid ^[b] <i>ee</i> ^[c] [%]	100 mol % Lewis acid ^[b] Yield [%]	100 mol % Lewis acid ^[b] <i>ee</i> ^[c] [%]
1	COCH ₃	78	52	70	89
2	COPh	83	58(R)	90	93(R)
3	4-FC ₆ H ₄ CO	88	14	94	62
4	4-OMeC ₆ H ₄ CO	73	58	83	82
5	2,6-Me ₂ C ₆ H ₃ CO	88	31	82	73
6	1-naphthoyl	82	11	87	46
7	2-naphthoyl	83	12	79	80

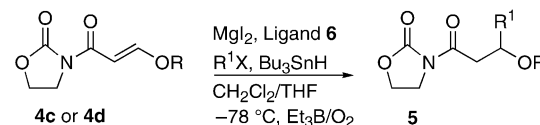
[a] For details of the reaction conditions see the Supporting Information.

[b] Yields are for isolated materials purified by column chromatography.

[c] *ee* values were determined by HPLC on a chiral stationary phase.

catalyst loading to 150 mol % led to a small decrease in the selectivity (86 % *ee*).

We have investigated the scope of the reaction with respect to the nature of the radical precursor (Table 3). The benzoate **4d** was the substrate of choice since it showed the best combination of yield and selectivity. Magnesium iodide in combination with ligand **6** was used as the chiral Lewis acid. In general, different types of radicals were chemically efficient, irrespective of their nature (primary, secondary, or tertiary) or size, with yields ranging from 70–90 % (entries 1–10).^[10] On the other hand, the enantioselectivity varied to some extent depending on the radical precursor. Addition of a primary ethyl radical gave **5j** with a moderate *ee* value at both 30 and 100 mol % catalyst loading (entry 1). Selectivity was

Table 3: Nucleophilic Radical Addition to **4c** or **4d**.^[a]


Entry	Product	R ¹ X	30 mol % Lewis acid Yield ^[b] [%]	30 mol % Lewis acid <i>ee</i> ^[c] [%]	100 mol % Lewis acid Yield ^[b] [%]	100 mol % Lewis acid <i>ee</i> ^[c] [%]
1	5j	CH ₃ CH ₂ I	82	33	90	50
2	5k	CH ₃ OCH ₂ Br	77	04	70	80
3	5d	<i>i</i> PrI	83	58(R)	90	93(R)
4	5l	Cyl	75	52	70	84
5	5m	<i>t</i> BuI	91	46(R)	91	89(R)
6 ^[d]	5n	<i>t</i> BuI	70	30	73	95
7	5o	1-AdI	73	02	76	60
8 ^[d]	5p	1-AdI	92	02	92	57
9	5q	ClCH ₂ CH ₂ CH ₂ (CH ₃) ₂ CBr	71	08	76	50
10 ^[d]	5r	ClCH ₂ CH ₂ CH ₂ (CH ₃) ₂ CBr	75	62	70	89

[a] For details of the reaction conditions see the Supporting Information. [b] Yields are for isolated materials purified by column chromatography. [c] *ee* values were determined by HPLC on a chiral stationary phase. [d] Acetate substrate **4c** was used for this reaction. Cy = cyclohexyl, Ad = adamantyl.

higher in the reaction with the methoxymethyl radical using stoichiometric amounts of the chiral Lewis acid (80% *ee*, entry 2). Acyclic and cyclic secondary radicals gave high selectivity (93 and 84% *ee*, respectively) in the conjugate addition (entries 3 and 4). Bulky tertiary radicals (*tert*-butyl and adamantyl) were equally effective in the conjugate addition. Of these two, the addition of *tert*-butyl radicals gave higher selectivity (compare entries 5 and 7; 89 and 60% *ee*, respectively). The addition of a tertiary radical to the acetate **4c** was investigated to determine if the size of the acyloxy group had an impact on the selectivity. There was a significant improvement in the selectivity of *tert*-butyl radical addition (compare entries 5 and 6) but not of adamantyl radical addition (compare entries 7 and 8). A functionalized tertiary radical amenable for the formation of six-membered rings gave good yields in the conjugate addition (entries 9 and 10). More interestingly, the use of the acetate **4c** gave a dramatic increase in selectivity (compare entries 9 and 10; 50 and 89% *ee*, respectively). These results demonstrate that the acyloxy group can be tuned to provide improvements in reactivity as well as selectivity.

We have determined the absolute stereochemistry of **5d** and **5m** by hydrolysis and conversion into known compounds.^[11] Assuming there is a tetrahedral or *cis*-octahedral geometry around the magnesium center,^[12] the product stereochemistry is consistent with *si*-face radical addition to an *s-cis* conformer of the substrate. This is the same sense of



selectivity as that obtained with oxazolidinone crotonates or cinnamates, which suggests that the rotamer geometry of the differentially substituted enoates is the same. The need for a stoichiometric amount of the chiral Lewis acid to obtain high selectivity with **4** is in contrast to the successful catalytic reactions with crotonates, and is most likely a reflection of the presence of an additional donor atom in the substrate.^[9]

In conclusion we have described a novel radical-based methodology for the synthesis of aldol acetates with high enantioselectivity. Experiments are underway to investigate alternative protocols for carrying out the reactions using catalytic amounts of the Lewis acid and also to extend the methodology to more-complex substrates with α substituents.

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- [9] The aldol product containing donor atoms may not readily dissociate from the chiral Lewis acid and thus compete for coordination with the substrate. This explanation is consistent with the need for stoichiometric amounts of the chiral Lewis acid to obtain high *ee* values. REACT IR studies provide additional support for our explanation. These results will be reported later.
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