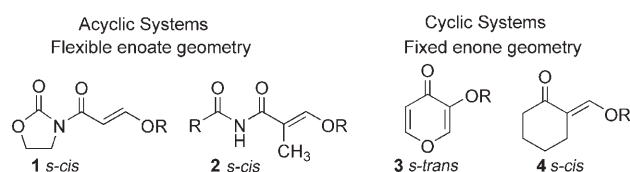


Enantioselective Radical Reactions: Stereoselective Aldol Synthesis from Cyclic Ketones**

Mukund P. Sibi* and Sukanya Nad

Dedicated to Professor Philip Boudjouk on the occasion of his 65th birthday

Stereoselective methods for the preparation of aldol products have been explored extensively through the use of ionic intermediates.^[1,2] In contrast, there are relatively few reports on the use of radical intermediates to synthesize aldols.^[3] Previously it was shown that β -acyloxy acrylates **1** undergo chiral Lewis acid (LA) mediated radical additions to furnish acetate aldol derivatives in high yield and enantioselectivity (Scheme 1).^[4] An enantioselective and diastereoselective



Scheme 1. Enolate and enone geometry.

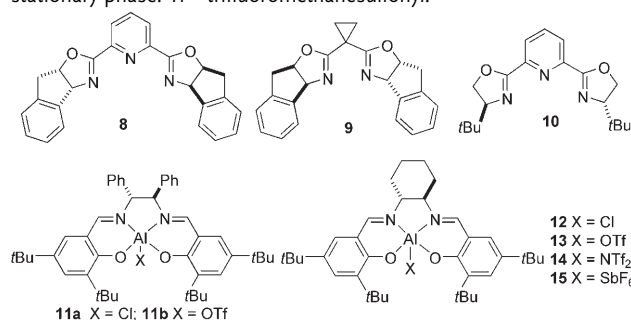
radical method was also developed for accessing *anti*-propionate aldol derivatives by using imide templates **2**.^[5] In these acyclic systems, reactions occur via an *s*-*cis* geometry of the enolate. Recently it was shown that pyrones **3**, with a fixed *s*-*trans* geometry, undergo highly selective conjugate radical additions.^[6] Herein we evaluate the efficiency of **4** with a fixed *s*-*cis* geometry as precursors for the preparation of aldols derived from cyclic ketones.^[7] Furthermore, we demonstrate that **4** and its congeners undergo efficient radical additions to provide cyclic aldols in high yield and excellent diastereo- and enantioselectivity. The process involves enantioselective radical addition followed by a diastereoselective transfer of a hydrogen atom, thus allowing for the establishment of two stereogenic centers in a single operation.

Experimentation began by examining the conjugate addition of an isopropyl radical to the benzoate derivative **5** (Table 1).^[8] This substrate was readily prepared in good overall yield in two steps.^[9] Several combinations of Lewis

Table 1: Optimization of the reaction conditions for radical addition.^[a]

Entry	Lewis acid (%)	Ligand	R-I	t [min]	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	Sc(OTf) ₃ (30)	—	<i>i</i> PrI	30	80	98:2	—
2	Sc(OTf) ₃ (30)	8	<i>i</i> PrI	180	36	≥ 99:1	26
3	Sc(OTf) ₃ (30)	9	<i>i</i> PrI	45	80	≥ 99:1	13
4	Sc(OTf) ₃ (30)	10	<i>i</i> PrI	150	48	≥ 99:1	14
5	11a (30)	—	<i>i</i> PrI	180	75	≥ 99:1	61
6	12 (30)	—	<i>i</i> PrI	60	80	≥ 99:1	73
7	12 (100)	—	<i>i</i> PrI	60	80	≥ 99:1	73
8	13 (30)	—	<i>i</i> PrI	45	80	≥ 99:1	77
9	14 (30)	—	<i>i</i> PrI	40	82	≥ 99:1	60
10	15 (30)	—	<i>i</i> PrI	40	80	≥ 99:1	50
11	13 (30)	—	<i>t</i> BuI	45	78	≥ 99:1	85

[a] For detailed reaction conditions, see the Supporting Information. [b] Yield of isolated products after purification by column chromatography. [c] The diastereomeric ratios were determined by NMR spectroscopy. For reactions with 99:1 selectivity, the minor isomer could not be detected. [d] The *ee* values were determined by HPLC on a chiral stationary phase. Tf = trifluoromethanesulfonyl.



acids and ligands of various strength and coordinating ability were initially evaluated. Scandium triflate in combination with ligands **8–10** gave modest to very good yields of **6**, but the enantioselectivities were low, although excellent diastereoselectivities were achieved in all the cases (Table 1, entries 2–4).

Chiral salen-derived Lewis acids (salen = *N,N'*-bis(salicylidene)ethylenediamine dianion) have proven to be excellent systems for providing good to high enantioselectivity in reactions with single-point donors.^[10] Radical addition to **5**

[*] Prof. M. P. Sibi, Dr. S. Nad
Department of Chemistry and Molecular Biology
North Dakota State University
Fargo, ND 58105 (USA)
Fax: (+1) 701-231-1057
E-mail: mukund.sibi@ndsu.edu

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using 30 mol % of chiral Lewis acid **11a** gave **6** in high yield and diastereoselectivity (Table 1, entry 5). The *ee* value for the product was much higher than that observed with scandium-based Lewis acids. The reaction with chiral salen **12**, which contains a cyclohexanediamine unit, was also facile and gave enhanced enantioselectivity (Table 1, entry 6). Increasing the catalyst loading to 100 mol % did not improve either the chemical yield or the selectivity (Table 1, entry 7). Counterion exchange was carried out in an effort to increase the Lewis acidity of the aluminum center. Catalysts **13–15** were prepared by a rapid exchange of counterions between commercially available **12** and the corresponding silver salts in dichloromethane at room temperature. The chiral Lewis acid with a triflate counterion (**13**) gave the highest enantioselectivity (Table 1, entry 8). Further changes to the counterion to give Lewis acids **14** and **15** did not lead to further improvement (Table 1, entries 9 and 10). The addition of the bulkier *tert*-butyl radical gave enhanced enantioselectivity (Table 1, compare entries 8 and 11). The above experiments demonstrate that cyclic ketone aldols can be synthesized by conjugate radical addition in which two stereocenters are installed in a single step. The aldol products are formed in excellent yields, and the levels of diastereoselectivity and enantioselectivity are high.

In an effort to tune the reactivity and selectivity, a series of substrates were synthesized that contained different acyl groups, and their effectiveness toward radical addition was evaluated (Table 2). The optimal chiral salen catalyst **13** was used, and additions were carried out using both isopropyl and *tert*-butyl radicals. Compound **16**, which contains an electron-rich methoxy benzoate group, showed higher selectivity than the parent benzoate substrate (Table 2, compare entries 1 and 2) for both isopropyl and *tert*-butyl radical additions. The yields were much higher because the methoxy benzoate products **22** and **23** are more resistant to β -elimination; the

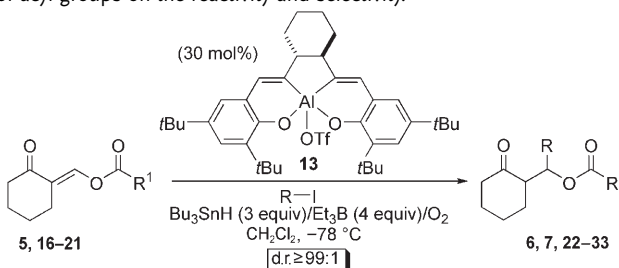
benzoate products **6** and **7** are more sensitive, which causes a reduction in the yield and contamination by the resulting enones. In reactions using substrates **17** and **18**, which contain a bulky mesityl and a benzyl group, respectively, the yields and *ee* values were also superior to those of the parent benzoate substrate (Table 2, compare entries 3 and 4 with entry 1). A dramatic improvement in the selectivity was observed with substrate **19** compared to that with the parent benzoate substrate (Table 2, entry 5), which suggests that steric effects play an important role in the conjugate radical addition. With substrates **20** and **21**, the yields and *ee* values were only slightly better than those obtained with the parent benzoate substrate (Table 2, entries 6 and 7). It is noteworthy that reactions with the bulky *tert*-butyl radical consistently proceeded with higher selectivity than did those with the less bulky isopropyl radical. This trend parallels that observed previously in the synthesis of *anti*-propionate aldol derivatives.^[5]

Three cyclic ketones were investigated, which differed in ring size (5–7), in an effort to broaden the scope of the aldol products available (Table 3). For these reactions the *p*-methoxy benzoate was used because it had previously given the best yields and the most stable products (Table 2). Enantioselectivity was poor with the five-membered substrate **34** when catalyst **13** was used (Table 3, entry 1). Surprisingly, good selectivity and excellent yields were achieved for both isopropyl and *tert*-butyl radical addition using the alternative salen catalyst **11b** that had a triflate counterion (Table 3, entry 2). As discussed earlier, reactions were efficient with six-membered ring substrate **16**. The enantioselectivity was high for the seven-membered ring **35**, but yields were poor when 30 mol % of catalyst **13** was used (Table 3, entry 4). Increasing the catalyst loading to 50 mol % gave the desired product in excellent yield and high selectivity (Table 3, entry 5). A rationale for this difference in reactivity

with respect to catalyst loading is not clear. The diastereoselectivity in all of the above reactions was excellent (*d.r.* $\geq$ 99:1). It is noteworthy that isopropyl radical addition was most enantioselective with the seven-membered ketone (Table 3, compare entry 4 with entries 2 and 3). The same trend was not present for *tert*-butyl radical addition, where the six-membered ring gave slightly higher selectivity (Table 3, compare entries 3 and 4). These experiments indicate that radical conjugate additions can provide access to aldols from cyclic ketones of various ring size.^[11]

The scope of radicals that can be used was also evaluated (Table 4). For these experiments **16** was used as the substrate and 30 mol % of **13** was used as the catalyst. In general, primary, sec-

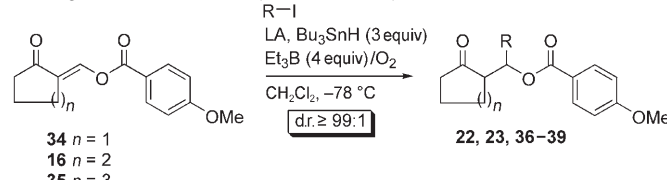
Table 2: Effect of acyl groups on the reactivity and selectivity.



Entry	R ¹ (starting material)	R = Isopropyl ^[a]			R = <i>tert</i> -Butyl ^[a]		
		prod.	yield [%] ^[b]	<i>ee</i> [%] ^[c]	prod.	yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	phenyl (5)	6	80	77	7	78	85
2	4-methoxyphenyl (16)	22	95	84	23	90	95
3	2,4,6-trimethylphenyl (17)	24	85	82	25	70	90
4	benzyl (18)	26	90	93	27	80	91
5	2,4,6-trimethylbenzyl (19)	28	85	94	29	75	97
6	1-naphthyl (20)	30	85	84	31	80	91
7	2-naphthyl (21)	32	86	83	33	80	94

[a] For detailed reaction conditions see the Supporting Information. The diastereoselectivity was determined by NMR spectroscopy. For reactions with 99:1 selectivity, the minor isomer could not be detected. [b] Yield of isolated products after purification by column chromatography. [c] The *ee* values were determined by HPLC on a chiral stationary phase.

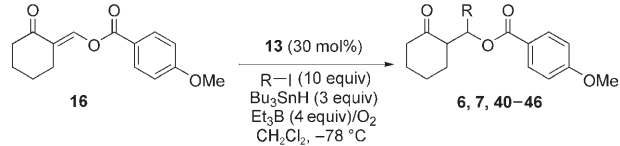
Table 3: Effect of ring size on the reactivity and selectivity.



Entry	SM	Lewis acid (%)	R = Isopropyl ^[a]			R = <i>tert</i> -Butyl ^[a]		
			prod.	yield [%] ^[b]	ee [%] ^[c]	prod.	yield [%] ^[b]	ee [%] ^[c]
1	34 (<i>n</i> = 1)	13 (30)	36	95	15	37	78	14
2	34	11b (30)	36	95	75	37	90	83
3	16 (<i>n</i> = 2)	13 (30)	22	95	84	23	70	95
4	35 (<i>n</i> = 3)	13 (30)	38	35	89	39	30	91
5	35	13 (50)	38	90	89	39	88	91

[a] For detailed reaction conditions see the Supporting Information. The diastereoselectivity was determined by NMR spectroscopy. For reactions with 99:1 selectivity, the minor isomer could not be detected. [b] Yield of isolated products after purification by column chromatography. [c] The *ee* values were determined by HPLC on a chiral stationary phase. SM = starting material.

Table 4: Effect of radical precursors on the reactivity and selectivity.



Entry	R-I ^[a]	Prod.	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	CH ₃ CH ₂ CH ₂ -I	40	98	≥ 99:1	75
2	CH ₂ =CHCH ₂ CH ₂ CH ₂ -I	41	98	≥ 99:1	75
3	CH ₃ OCH ₂ -Br	42	95	97:3	69
4	<i>i</i> Pr-I	6	95	≥ 99:1	84
5	cyclopentyl-I	43	95	≥ 99:1	71
6	cyclohexyl-I	44	95	≥ 99:1	77
7	<i>t</i> Bu-I	7	90	≥ 99:1	95
8	ClCH ₂ CH ₂ CH ₂ (CH ₃) ₂ -I	45	85	≥ 99:1	83
9	1-Ad-I	46	85	≥ 99:1	5

[a] For detailed reaction conditions see the Supporting Information. [b] Yield of isolated products after purification by column chromatography. [c] Diastereomeric ratios were determined by NMR spectroscopy. For reactions with 99:1 selectivity, the minor isomer could not be detected. [d] The *ee* values were determined by HPLC on a chiral stationary phase.

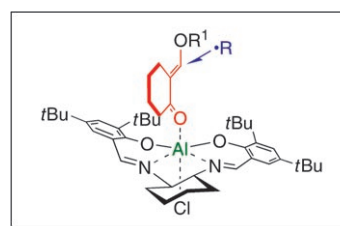
ondary, or tertiary radicals all gave high yields (85–98 %) and excellent diastereoselectivity. That primary radicals add in such high yields, without competition from ethyl addition, suggests very long and efficient radical chains. Only a single diastereomer was detected in most cases. It is noteworthy that the reaction with 1-iodo-4-pentene did not give any cyclized product, even though the radical adduct is poised to undergo a 6-*exo* cyclization following the initial radical addition (Table 4, entry 2). The enantioselectivity in these reactions depended on the nature of the radical. The enantioselectivities obtained with primary radicals, were only good (highest *ee* value of 75 %; Table 4, entries 1–3). The acyclic secondary radicals gave higher enantioselectivity than cyclic secondary radicals (Table 4, compare entry 4 with entries 5 and 6). Both simple and functionalized tertiary radicals effected the

conjugate addition reaction (Table 4, entries 7–9). Acyclic tertiary radicals provided excellent selectivity (Table 4, entries 7 and 8), while the adamantyl radical gave very poor enantioselectivity (Table 4, entry 9). The above results clearly demonstrate that a variety of aldols from cyclic ketones can be synthesized in high efficiency and in all cases with outstanding diastereoselectivity. The levels of enantioselectivity were good to excellent with a single exception.

The relative stereochemistry of **6** was determined by converting it into a known compound.^[12] The absolute stereochemistry of **6** was established by comparing its HPLC retention time with that of a known

compound. Results from these experiments clearly establish that the *anti* aldol adducts are formed in radical additions and that the absolute stereochemistry for the product is 1*S*,2*S*.

A tentative model to explain the stereochemical outcome in these radical reactions is proposed (Figure 1). The Lewis acid coordinates to the lone pair of electrons on the oxygen


Figure 1. Model for explaining the stereochemical outcome in conjugate radical addition followed by transfer of a hydrogen atom.

atom which is in the *anti* position. The bulky OR¹ group orients away from the axial hydrogen atoms on the cyclohexane ring leaving the *si* face more open to nucleophilic radical addition. Subsequent hydrogen transfer to the α -carbon atom is apparently controlled not by the chiral ligand, but by the newly formed β -stereocenter, with the radical R group shielding the *si* face, thus resulting in an overall *anti* addition of R' and an H atom.

Experimental Section

A mixture of chiral salen Lewis acid (0.03 mmol) and α -methylene cyclic ketone (0.1 mmol) in dichloromethane (5.0 mL) was stirred vigorously at RT for 45 min, and then cooled at -78°C for 20 min. The reaction was initiated by sequential addition of alkyl halide (0.5 mmol), tributyltin hydride (0.3 mmol), triethylborane (0.4 mmol, 1M solution in hexane), and oxygen (introduced by syringe). The reaction was monitored by TLC (hexanes/EtOAc 4:1), and after completion was quenched with silica gel, evaporated, and washed with hexanes (average of 1 h for the five- and six-membered ketones; 3 h for the seven-membered ketone). Finally, the silica gel (containing

the product) was washed with ethyl acetate and the crude product (ethyl acetate layer) was purified by chromatography on silica gel (hexane/EtOAc 4:1). Racemic standards were prepared using Sc(OTf)₃ as a Lewis acid in the absence of a chiral ligand.

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