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FULL PAPER

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Asymmetric Synthesis of 2,3-Disubstituted Cyclic Ketones by Enantioselective Conjugate Radical Additions

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Happy 60th birthday to *Philippe Renaud*, a great scientist and a dear friend

Enantioselective conjugate radical addition to 2-acyloxymethyl cycloalkenones proceeds in high yield with outstanding diastereoselectivity and excellent enantioselectivity using chiral salen *Lewis* acids. The process provides access to 2,3-disubstituted cycloalkanones, a structural motif present in natural products.

Keywords: enantioselectivity, chiral *Lewis* acids, radical reactions, conjugate additions, cyclic ketones.

Introduction

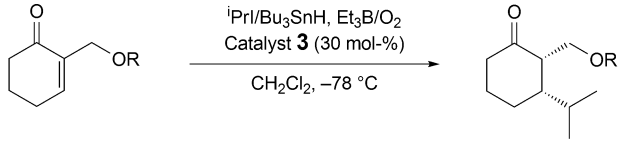
Enantioselective radical chemistry continues to attract interest from the synthetic community.[1] Radical reactions are well suited for the installation of multiple stereocenters in a single operation.[2,3] Enantioselective conjugate radical additions have been extensively investigated using substrates capable of bidentate coordination.[4–18] In contrast, stereoselective reactions with single point binding substrates are more challenging and only a few examples of reactions proceeding with high selectivity have been reported.[19–22] We have previously shown that γ-pyranones possessing a fixed s-*trans* enone geometry undergo highly selective conjugate radical additions.[23] Furthermore, we have also completed a study on enantioselective radical additions to α-alkylidene ketones with a fixed s-*cis* enone geometry.[24] Recently, we reported on enantioselective conjugate radical additions to α-arylidene ketones and lactones also possessing a fixed s-*cis* enone geometry.[25] We have been interested in further extending this chemistry to s-*trans* configured cyclic enones. The methodology has the potential for accessing 2,3-disubstituted cyclic ketones. This is a substitution pattern present in natural products such as penienone, penihydrone, and prostaglandins.[26–30] There are many examples in the literature which report enantioselective addition/trapping experiments with cycloalkenones using ionic chemistry to provide 2,3-disubstituted cycloalkanones. These reactions show selectivities across the spectrum in addition/trapping experiments.[31–38] Reactions with 2-substituted cyclohexenones generally proceed with modest enantio- and/or diastereoselectivity.[39–42] In contrast, there are only scattered examples of radical additions to enones in the literature with most of these transformations in racemic fashion.[43–46] In this his work we report highly efficient and enantioselective conjugate radical additions to 2-hydroxymethyl-cycloalkenones, precursors that are readily available from *Baylis-Hillman* reactions, to yield 2,3-disubstituted cyclopentanones and hexanones in high yield and selectivity. Furthermore, we also show that the nature of the *Lewis* acid activator plays an important role in the stereochemical outcome of the reaction.

Results and Discussion

We began our investigation by examining the effectiveness of conjugate radical addition to cyclohexenone **1** (*Scheme 1*). A variety of chiral *Lewis* acids were evaluated with very limited success with respect to ee of the conjugate addition product ($<40\%$). Conjugate

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.201900223

Table 1. Conjugate radical addition to 2-alkoxymethyl-2-cyclohexenones.



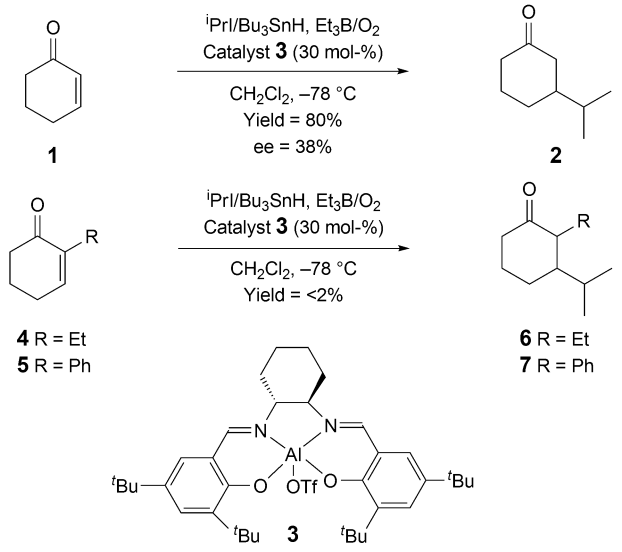
8a – 8d **9a – 9d**

Entry	R	mol-% CLA	Time [h]	Yield [%][a]	dr[b]	ee [%][c]
1	H (**8a**)	100	4	Trace		–
2	Ph–CH_2 (**8b**)	50	1	90	99:1	68
3	4-MeO–C_6H_4–CH_2 (**8c**)	50	1	95	99:1	73
4	4-MeO–C_6H_4–CO (**8d**)	50	2	98	99:1	83

[a] Yield of isolated product. [b] Determined by NMR. The minor isomer could not be detected. [c] Determined by chiral HPLC.

radical additions to 2- substituted-cyclohexenones **4** and **5** were also evaluated in an effort to prepare 2,3-disubstituted cyclic ketones. However, these compounds proved to be very unreactive under a variety of conditions. The electron donating alkyl(aryl) group on the α-carbon deactivate the β-carbon for efficient nucleophilic radical addition.

We have previously shown that acrylate substrates containing an α-hydroxymethyl[47] and α-amidomethyl groups[48] are excellent substrates for conjugate radical addition/enantioselective H-atom transfer reactions. The respective reactions provide access to formaldehyde aldols and β^2-amino acid derivatives in high enantioselectivity. Noting the activation provided by the hydroxymethyl groups, we decided to investigate conjugate radical additions to readily accessible substrate **8**.[49] In these experiments, conjugate radical addition is followed by diastereoselective H-atom transfer.[50–52] Results from these studies are shown in *Table 1*[1]. For initial experiments the chiral salen **3**, a single point binding *Lewis* acid was employed.[53–57] Isopropyl radical addition to the parent compound **8a** was inefficient under a variety of conditions (*Entry 1*). The *O*-benzyl ether (**8b**) was a better substrate giving the addition product in good yield as a single diastereomer and in 68% ee (*Entry 2*). Conjugate addition to the *p*-methoxybenzyl ether (**8c**) did not show any improvement in enantioselectivity (*Entry 3*). The corresponding ester, 4-methoxybenzoate (**8d**) was an excellent substrate and gave the addition product as a single diastereomer in 83% ee (*Entry 4*). These proof of principle experiments demonstrate that enantioenriched 2,3-disubstituted cyclohexanones can be accessed by efficient and highly selective conjugate radical addition.



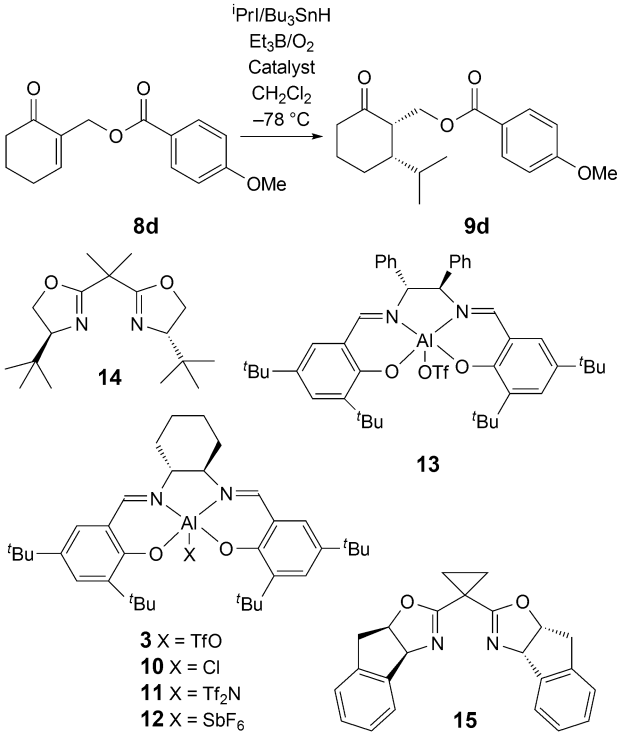
Scheme 1. Enantioselective conjugate radical additions to cyclohexenones.

In an effort to improve the level of enantioselectivity in the addition/H-atom transfer protocol, we set out to investigate the effect of different chiral *Lewis* acids using substrate **8d** and results from these studies are presented in *Table 2*.

Scandium triflate as a *Lewis* acid was very effective under racemic conditions producing the product in high diastereoselectivity (*Entry 1*). The salen *Lewis* acid with a chloride counterion (**10**) was effective in the conjugate addition (*Entry 2*). As noted earlier, the chiral

[1] For the synthesis of starting materials, reaction conditions for radical reactions, ee determination, and product stereochemical analysis see the *Supporting Information*.

Table 2. Evaluation of chiral *Lewis* acids.[a]



Entry	*Lewis* acid, ligand (mol-%)	Time [h]	Yield [%][b]	dr[c]	ee [%][d]
1	$Sc(OTf)_3$ (30%)	0.75	95	99:1	
2	**10** (50%)	1.5	98	99:1	77
3	**3** (50%)	1.5	98	99:1	83
4	**3** (100%)	1.0	98	99:1	83
5	**11** (50%)	1.0	98	99:1	69
6	**12** (50%)	>3.0	50	99:1	70
7	**13** (50%)	2.0	95	99:1	71
8	MgI_2, **14** (50%)	>4.0	65	99:1	3
9	MgI_2, **15** (50%)	>4.0	50	90:10	31 (58)
10	$Mg(ClO_4)_2$, **15** (50%)	1.0	95	62:38	81 (91)

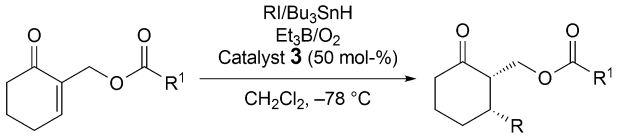
[a] For experimental details see *Supporting Information*. [b] Yield of isolated products. [c] Determined by NMR. For reactions with 99:1 selectivity, the minor isomer could not be detected. [d] Determined by chiral HPLC.

salen with a triflate counterion (**3**) was excellent as a *Lewis* acid furnishing the product **9d** in good yield and selectivity (*Entry 3*). Increasing the catalyst loading to 100 mol% did not result in improvement in selectivity (*Entry 4*). Further changes to the counterion led to a lowering in enantioselectivity (*Entries 5* and *6*). We then decided to explore bidentate binding *Lewis* acids as activators for the reactions. The use of magnesium salts as a *Lewis* acid in combination with bisoxazoline ligands was investigated (*Entries 8–10*). The results from these experiments were quite interesting. Magnesium iodide and **14** as a chiral *Lewis* acid gave the addition/trapping product with high diastereoselectivity, but the product was nearly racemic (*Entry 8*). In contrast, magnesium iodide and **15** gave a mixture of *syn* and *anti* isomers with modest ees (*Entry 9*). The combination of magnesium perchlorate and **15** proved to be very effective giving a mixture of *syn* and *anti* isomers in high enantioselectivity (*Entry 10*). The high selectivity for both diastereomers suggest that initial addition occurs with modest selectivity followed by highly selective matched/mismatched H-atom transfer. The above experiments with mono- and bidentate *Lewis* acids are quite interesting with respect to requirements for substrate-*Lewis* acid interactions which determine the outcome of the stereoselectivity.

Having investigated the effect of the chiral *Lewis* acid, we then evaluated the impact of the acyl group on the enantioselectivity in isopropyl and *tert*-butyl radical additions using **3** as a *Lewis* acid. These results are presented in *Table 3*. It is important to note that the catalyst loading for these experiments is high. This reflects the modest *Lewis* acidity of the catalyst and the steric hinderance at the β-carbon of a relatively unreactive substrate. Additionally, the high catalyst loading suggests that catalyst turnover is slow. Addition to the parent benzoyl compound **8e** gave the addition product in high yield and good selectivity (*Entry 1*). As noted earlier, isopropyl radical addition to **8d** is efficient. The bulkier *tert*-butyl radical gave the addition product with slightly higher enantioselectivity (*Entry 2*). Reactions using a 2-naphthoyl ester **8f** gave the addition products in good yield and selectivity (*Entry 3*). The phenylacetic acid ester **8g** gave the conjugate addition products with the highest selectivity in this series (*Entry 4*). Reactions with **8h** were also effective (*Entry 5*). Overall, the ester group had reasonable impact on selectivity with reactions using **8d** and **8g** being optimal.

The scope of the radical was evaluated next using **8d** as a substrate and **3** as a *Lewis* acid. Results from these experiments are presented in *Table 4*. Addition of primary radicals proceeded with modest chemical efficiency (*Entries 1* and *2*). Although the diastereoselectivity was very high, the level of enantioselectivity was only modest. As was discussed earlier, acyclic secondary (*Entry 3*) and tertiary radicals (*Entry 4*) gave addition products in high yield and selectivity. Reactions with cyclic secondary radicals (*Entries 5* and *6*) also gave conjugate addition products with good selectivity, while the large tertiary radical derived from

Table 3. Effect of the acyl group on reactivity and selectivity.[a]

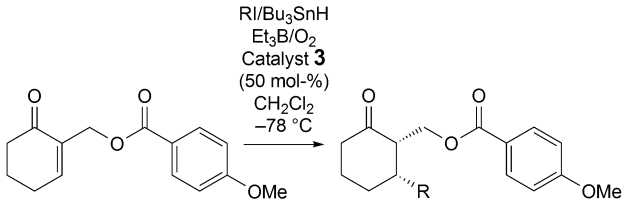


8d – 8h **9d – 9h** R = ^{i}Pr, **9i – 9m** R = ^{t}Bu

Entry	R^1	R = ^{i}Pr Yield [%][b,c]	ee [%][d]	R = ^{t}Bu Yield [%][b,c]	ee [%][d]
1	Ph (**8e**)	90	78	88	80
2	4-MeO-C_6H_4 (**8d**)	98	83	98	89
3	2-Naphthyl (**8f**)	98	85	98	85
4	Benzyl (**8g**)	90	91	85	95
5	2,4,6-Trimethylbenzyl (**8h**)	95	91	90	89

[a] For experimental details, see *Supporting Information.* [b] Yield of isolated products. [c] Diastereoselectivity determined by NMR. For reactions with 99:1 selectivity, the minor isomer could not be detected. [d] Determined by chiral HPLC.

Table 4. Addition of different radicals.[a]



8d **9d**, **9j**, **9n – 9r**

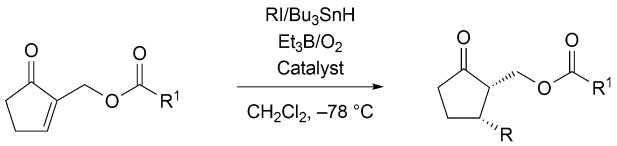
Entry	R–I	Prod.	Time [h]	Yield [%][b]	dr[c]	ee [%][d]
1	Et–I	**9n**	>4.0	70	99:1	51
2	Pr–I	**9o**	>4.0	65	99:1	49
3	^{i}Pr–I	**9d**	2.0	98	99:1	83
4	^{t}Bu–I	**9j**	2.5	98	99:1	89
5	Cyclopentyl–I	**9p**	2.0	98	99:1	77
6	Cylohexyl–I	**9q**	3.0	98	99:1	83
7	1-Adamantyl–I	**9r**	1.5	98	99:1	66

[a] For experimental details, see *Supporting Information.* [b] Yield of isolated products. [c] Diastereoselectivity determined by NMR. For reactions with 99:1 selectivity, the minor isomer could not be detected. [d] Determined by chiral HPLC.

1-adamantyl iodide gave the corresponding addition product with modest ee (*Entry 7*). These experiments demonstrate that there is reasonable scope for the radical precursors allowing access to a variety of 2,3-disubstituted cyclohexanones.

Conjugate radical addition to 2-hydroxymethyl cyclopentenones was investigated next. For these experiments, substrates with three different ester groups (**16a**–**16c**) and three different chiral *Lewis* acids were examined. Results from reactions with isopropyl and *tert*-butyl radicals are presented in *Table 5*. Radical addition to **16a** using **3** as a *Lewis* acid gave the products in high yield and high *syn* diastereoselectivity. The level of enantioselectivity was higher for *tert*-butyl radical addition than for isopropyl radical (*Entry 1*). Reactions of the phenylacetic acid ester **16b** were equally effective giving the addition products in high yield and good enantioselectivity (*Entry 2*). The *p*-methoxybenzoate ester **16c** also gave the addition products in high yield and good selectivity (*Entry 3*). Use of chiral salen **13** in isopropyl radical addition to **16c** gave the product in high yield but only modest enantioselectivity (*Entry 4*). Isopropyl radical addition to **16c** using a chiral *Lewis* acid

Table 5. Addition of different radicals.[a]



Entry	R^1	*Lewis* acid (mol-%)	R = ^{i}Pr		R = ^{t}Bu	
			Yield [%][b][c]	ee [%][d]	Yield [%][b][c]	ee [%][d]
1	Phenyl	**3** (50%)	95	77	90	87
2	Benzyl	**3** (50%)	90	80	90	84
3	4-MeO-Phenyl	**3** (50%)	98	79	98	76
4	4-MeO-Phenyl	**13** (50%)	95	53		
5	4-MeO-Phenyl[d]	$Mg(ClO_4)_2$, **15** (50%)	98	67 (81)		

[a] For experimental details, see *Supporting Information.* [b] Yield of isolated products. [c] Diastereoselectivity determined by NMR. For reactions with 99:1 selectivity, the minor isomer could not be detected. [d] Determined by chiral HPLC.

derived from magnesium perchlorate and **15** gave a mixture of *syn* and *anti* isomers in high yield (*Entry 5*). As was observed with the six-membered analog, the *syn*/*anti* isomers were again formed with good enantioselectivity.

The relative configuration for the conjugate addition products were determined by extensive NOE and decoupling experiments. The major product has *syn* configuration[2]. We have not determined the absolute configuration for the conjugate addition product(s). A model for conjugate addition to **8d** using chiral salen **3** is shown in *Figure 1*[3]. The initial radical addition is controlled by the single point binding chiral *Lewis* acid catalyst. The face selectivity in the subsequent H-atom transfer is determined by the newly formed chiral center with assistance from the still bound catalyst. The electron-withdrawing acyloxy group on the α-carbon facilitates nucleophilic radical addition and its bulk could account for the observed high diastereoselectivity. We are currently working on refining our model to account for the observed selectivity.

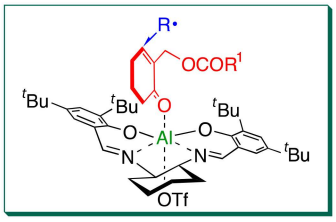


Figure 1. Stereochemical model.

Conclusions

In conclusion, we have demonstrated that enantioselective conjugate radical addition protocols provide ready access to syn-2,3-disubstituted cycloalkanones in excellent chemical yields and high selectivity. During the process two stereocenters are established with a high degree of selectivity. Furthermore, a magnesium salt in combination with a bisoxazoline ligand provides both *syn* and *anti* isomers with high enantioselectivities. Application of the new radical methodology in the synthesis of natural products is underway.

Experimental Section

Representative Experiment

Representative Experimental Procedure for Chiral Lewis Acid-Catalyzed Conjugate Addition of Radicals to 2-Hydroxymethyl Unsaturated Cyclic Ketones. A mixture of chiral Lewis acid (0.05 mmol) and 2-hydroxymethyl unsaturated cyclic ketone (0.1 mmol)

[2] For detailed analysis see the *Supporting Information.*
[3] The tentative absolute stereochemistry shown is based on previous work from our laboratory. For stereochemical models for reactions with chiral salen *Lewis* acids, see [23], [24], and [58].

was stirred vigorously in 5.0 mL of dichloromethane at room temperature 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 1 M solution in hexane) and oxygen (introduced through syringe). The reaction was monitored by TLC (hexane/AcOEt 4:1), and after completion was quenched with silica gel, evaporated, washed with hexanes. Finally, the silica gel (containing product) was washed with AcOEt and the crude product (AcOEt layer) was purified by silica gel chromatography (hexane/AcOEt 4:1). Racemic standards were prepared using $Sc(OTf)_3$ as a Lewis acid in the absence of a chiral ligand.

2-[(Benzyloxy)methyl]-3-(propan-2-yl)cyclohexan-1-one (**9b**). This compound was obtained in 90% yield as colorless oil. Enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 33.2 min (minor); t_R 36.3 min (major) (*Chiralpak ODH* (1.00 cm × 25 cm, from *Daicel Chemical Ind., Ltd.*) hexane/^{i}PrOH, 93:7, 1.0 mL/min) as 68% ee. $[\alpha]_D^{25} = -3.45$ ($c = 0.47$, $CHCl_3$). IR (neat): 3030, 2949, 1673, 1454, 1100, 688. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.88 (*d*, *J* = 5.5, 3 H); 0.91 (*d*, *J* = 5.5, 3 H); 1.20–1.48 (*m*, 2 H); 1.54–1.64 (*m*, 2 H); 1.81–1.83 (*m*, 1 H); 2.03–2.09 (*m*, 1 H); 2.26–2.30 (*m*, 1 H); 2.40–2.50 (*m*, 1 H); 2.93–3.01 (*m*, 1 H); 3.61 (*dd*, *J* = 9.5, 5.5, 1 H); 3.80 (*t*, *J* = 9.7, 1 H); 4.44 (*d*, *J* = 11.3, 1 H); 4.57 (*d*, *J* = 11.3, 1 H); 7.25–7.40 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.8; 21.7; 24.9; 26.1; 29.7; 38.8; 48.5; 53.5; 66.9; 73.1; 127.8; 127.9; 128.6; 138.1; 213.8. HR-MS: 283.1684 ($C_{17}H_{24}NaO_2^+$, $[M + Na]^+$; calc. 283.1674).

2-{[(4-Methoxyphenyl)methoxy]methyl}-3-(propan-2-yl)cyclohexan-1-one (**9c**). This compound was obtained in 95% yield as colorless oil. Enantiomeric purity was determined by HPLC (254 nm, 25 °C) t_R 31.8 min (minor); t_R 35.3 min (major) (*Chiralpak ADH* (1.00 cm × 25 cm; from *Daicel Chemical Ind., Ltd.*) hexane/^{i}PrOH, 93:7, 1.0 mL/min) as 73% ee. $[\alpha]_D^{25} = -5.01$ ($c = 0.52$, $CHCl_3$). IR (neat): 2931, 2859, 1669, 1455, 1256, 1080, 1034, 756. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.86 (*d*, *J* = 6.1, 3 H); 0.90 (*d*, *J* = 6.1, 3 H); 1.43–1.50 (*m*, 4 H); 1.78–1.82 (*m*, 1 H); 2.01–2.06 (*m*, 1 H); 2.22–2.28 (*m*, 1 H); 2.40–2.46 (*m*, 1 H); 2.92–2.96 (*m*, 1 H); 3.58 (*dd*, *J* = 9.5, 5.5, 1 H); 3.74 (*t*, *J* = 9.7, 1 H); 3.79 (s, 3 H); 4.35 (*d*, *J* = 11.3, 1 H); 4.50 (*d*, *J* = 11.3, 1 H); 6.86 (*d*, *J* = 8.5, 1 H); 7.19 (*d*, *J* = 8.5, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): 20.8; 21.7; 24.9; 26.2; 29.7; 38.8; 48.5; 53.4; 55.4; 66.4; 72.7; 113.9; 129.4; 130.2; 159.4; 213.8. HR-MS: 313.1792 ($C_{18}H_{26}O_3Na^+$, $[M + Na]^+$; calc. 313.1780).

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Author Contribution Statement

S. N. carried out all the experiments and *M. P. S.* wrote the manuscript.

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