Synlett C. Zhao, M. P. Sibi Letter

Enantioselective and Diastereoselective Conjugate Radical Additions to α-Arylidene Ketones and Lactones

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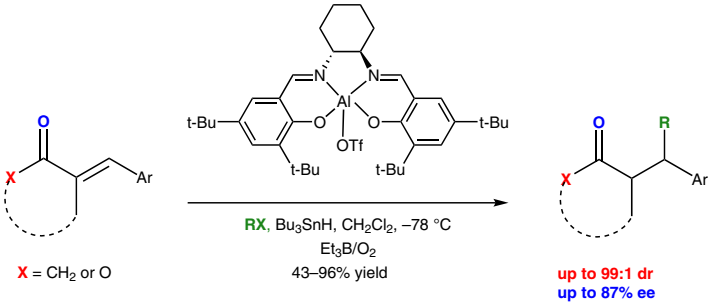
Dedicated to Prof. Victor Snieckus on his 80th birthday



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Abstract A highly stereoselective conjugate radical addition to arylidene ketones and lactones has been developed. The conjugate radical additions using chiral salen Lewis acids proceeds with up to 99:1 dr and 87% ee in good to excellent chemical yields.

Key words enantioselective radical reaction, arylidene ketones and lactones, diastereoselectivity, conjugate addition, chiral salen Lewis acid

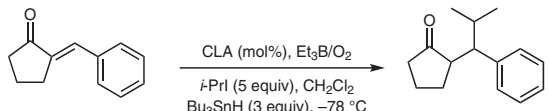
Development of new methods for the installation of contiguous chiral centers with control over relative as well as absolute stereochemistry is sought after in synthetic organic chemistry.[2] In general, neutral reactions such as cycloadditions or ionic reactions are often the methods of choice for such processes. In the last two decades, reactions with radical intermediates have reached prominence for the development of enantioselective processes.[3] Taking lessons from stereoselective ionic and cycloaddition methods, initial development of enantioselective radical reactions utilized chiral Lewis acids.[4] Most of the substrates used in these studies provided a well-organized chelate with the chiral Lewis acid for controlling face selectivity.[5] In the last decade, radical processes with organocatalysts have made spectacular advances for a variety of C–C and C–X bond-forming reactions.[6] In this regard, reactions with photoredox reagents have overcome certain limitations associated with radical reactions such as the use of toxic tin reagents and the need for large excess of reagents.[7]

In contrast to many reports on enantioselective radical reactions with bidentate substrates, reactions with monodentate substrates such as aldehydes, ketones, or esters have received less scrutiny.[8] This is partly due to the difficulty in discriminating the binding mode of these functional groups with chiral activators. Reactions with monodentate starting materials are attractive in that they avoid the need for the attachment and detachment of achiral templates or additional manipulations required to arrive at carbonyl or carboxylic acid functionalities. In this work, we demonstrate that nucleophilic radical addition to α-arylidene ketones and lactones mediated by chiral salen Lewis acids[9] proceeds in good yields, high diastereoselectivity, and good to high enantioselectivity while establishing two contiguous chiral centers.[10]

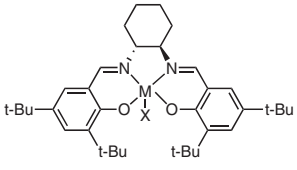
Our work began with finding optimal conditions for nucleophilic radical addition to enones[11] under chiral Lewis acid activation. The following conditions were used for initial Lewis acid screening. α-Benzylidene cyclopentanone (**1**) was used as the test substrate, and the reactions were carried out using isopropyl iodide (4 equiv), tributyltin hydride (3 equiv) in methylenechloride at –78 °C. Triethylborane/oxygen was used for radical initiation.[12] A variety of chiral Lewis acids were screened (see Table S1 for data) with variable success.[13] We[14] and others[15] have previously shown that chiral aluminum Lewis acids are excellent activators for monodentate substrates. We set out to evaluate readily available and inexpensive chiral salen Lewis acids. Data from these investigations are shown in Table 1. The reaction using the commercially available aluminum salen catalyst **3** gave the conjugate addition product **2** in high yield and diastereoselectivity (Table 1, entry 1). The ee for the product was good. Increasing the catalyst loading did not lead to improvement in ee for the product (Table 1, entries 2 and 3). Replacing the chloride counterion in **3** with a triflate (**4**) showed a small improvement in ee while maintaining the diastereoselectivity for the reaction (Table 1, compare entry 1 with 4). Increasing the catalyst loading of **4** did not lead to improvement in selectivity (Table 1, entries 5 and 6). Further changes to the counterion[13] (catalysts **5** and **6**) did not lead to any improvement in reaction efficien-

cy (Table 1, entries 7 and 8). Use of chromium salen Lewis acids (**7** and **8**) gave modest yields of the product with low ee values (Table 1, entries 9 and 10).

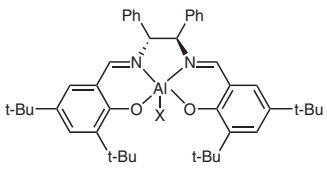
Table 1 Evaluation of Different Chiral Lewis Acids in Conjugate Addition of Isopropyl Radical to α-Benzylidene Cyclopentanone.



1 **2**



3 M = Al, X = Cl
4 M = Al. X = OTf
5 M = Al, X = NTf_2
6 M = Al, X = SbF_6
7 M = Cr, X = Cl
8 M = Cr, X = OTf



9 M = Al, X = Cl
10 M = Al, X = OTf
11 M = Al, X = SbF_6

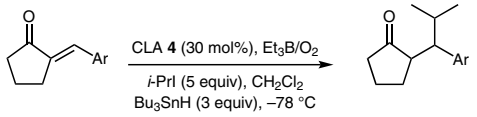
Entry	CLA (mol%)	Yield (%)[a]	dr[b]	ee (%)[c]
1	**3** (30)	96	99:1	73
2	**3** (50)	92	99:1	70
3	**3** (100)	85	99:1	73
4	**4** (30)	81	99:1	75
5	**4** (70)	90	99:1	70
6	**4** (100)	88	99:1	70
7	**5** (30)	85	99:1	70
8	**6** (30)	89	99:1	73
9	**7** (30)	60	95:5	20
10	**8** (30)	60	92:8	5
11	**9** (30)	89	99:1	36
12	**10** (30)	93	99:1	31
13	**11** (30)	91	99:1	46

[a] Isolated yield after column purification.
[b] Determined by NMR spectroscopy.
[c] Determined by chiral HPLC analysis.

Catalysts **9–11** gave the product in high yields but low ee values (Table 1, entries 11–13). From these studies, we identified the use of chiral Lewis acids derived from (1*R*,2*R*)-(–)-1,2-diaminocyclohexane, commercially available catalyst **4** (30 mol%) as the optimal catalyst for the conjugate additions.[16]

We next investigated isopropyl radical addition to arylidene cyclopentanones to assess the impact of aryl substituents on reactivity and selectivity using salen catalyst **4**. This data is tabulated in Table 2. Replacing a phenyl group with a more electron-rich *p*-methoxyphenyl group reduced the efficiency of the reaction but with little impact on stereoselectivity (Table 2, compare entry 1 with 2).

Table 2 Conjugate Radical Addition to α-Arylidene Cyclopentanones



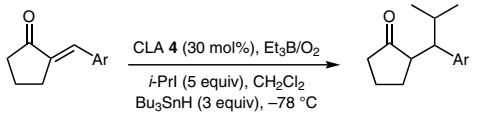
Entry	SM	Product	Yield (%)[a]	dr[b]	ee (%)[c]
1	**1** Ar = Ph	**2** Ar = Ph	81	99:1	75
2	**12** Ar = 4-$MeOC_6H_4$	**13** Ar = 4-$MeOC_6H_4$	63	99:1	70
3	**14** Ar = 1-naphthyl	**15** Ar = 1-naphthyl	94	99:1	66
4	**16** Ar = 2-naphthyl	**17** Ar = 2-naphthyl	75	99:1	79

[a] Isolated yield after column chromatography.
[b] Determined by NMR spectroscopy.
[c] Determined by chiral HPLC analysis.

Reactions with naphthyl-substituted enones were also efficient and had a slight improvement in ee for the 2-naphthyl group (Table 2, entries 3 and 4). The above results demonstrate that various α-arylidene cyclopentanones are competent substrates in conjugate radial addition providing the products in good yields and selectivities.[17]

The effect of ring size on stereoselectivity of isopropyl radical addition was assessed next using an aryldiene cyclohexanone as a substrate. These results are shown in Table 3. Isopropyl radical addition to α-benzylidene cyclohexanone (**18**) using catalyst **4** gave the addition product in good yield and selectivity (Table 3, entry 1). The ee for the product using six-membered cyclohexanone as a substrate was similar to that observed for the five-membered analogue (compare entry 1 in Tables 2 and 3). Changing the arylidene substituent from a phenyl to either a *p*-methoxyphenyl (**20**) or a naphthyl group (**22**) had minimal impact on the overall efficiency of the conjugate addition (Table 3, entries 2 and 3).

Table 3 Conjugate Radical Addition to α-Arylidene Cyclohexanones



Entry	SM	Product	Yield (%)[a]	dr[b]	ee (%)[c]
1	**18** Ar = Ph	**19** Ar = Ph	77	93:7	73
2	**20** Ar = 4-$MeOC_6H_4$	**21** Ar = 4-$MeOC_6H_4$	91	98:2	74
3	**22** Ar = 2-naphthyl	**23** Ar = 2-naphthyl	75	97:3	79

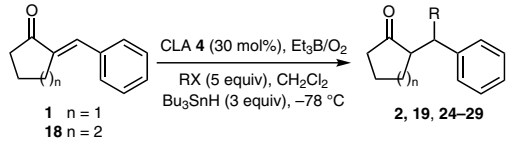
[a] Isolated yield after column chromatography.
[b] Determined by NMR spectroscopy.
[c] Determined by chiral HPLC analysis.

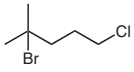
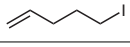
The above results demonstrate that conjugate radical addition to arylidene cyclopentanones and -hexanones proceeds with good efficiency. Furthermore, ring size or the nature of the aryl substituent has minimal impact on stereoselectivity of the conjugate addition products.

The scope of the chiral-salen-mediated enantioselective conjugate radical addition to enones (**1** and **18**) was assessed next using various radicals of differing nucleophilicities. These results are shown in Table 4. As discussed earlier, isopropyl radical addition to five- and six-membered enones using **4** as a catalyst proceed with good efficiency (Table 4, entries 1 and 2). Reactions with cyclic secondary radicals were investigated next. Cyclopentyl radical addition to both benzylidene cyclopentanone and -hexanone proceeded with good efficiency (Table 4, entries 3 and 4). The products were formed with excellent diastereoselectivity and the highest enantioselectivities observed in the present study. Cyclohexyl radical was also effective in the conjugate addition and gave product **26** in good yield and selectivity (Table 4, entry 5) similar to that observed for reaction with cyclopentyl radical. Addition of the more nucleophilic tertiary radical to **1** was also effective and gave the product in good yield and selectivity (Table 4, entry 6). Reaction of **1** with a functionalized tertiary radical (chloro bromoalkane) was also successful furnishing product **28** in good yield and a slightly lower ee compared to reaction with *tert*-butyl radical (Table 4, entry 7). The addition of 4-pentenyl radical to **1** was also evaluated (Table 4, entry 8). The addition of the less nucleophilic primary radical gave the product in low yield but good stereoselectivity. A product from a 5-*exo* cyclization of the intermediate α-carbonyl radical was not observed.

Conjugate addition of isopropyl radical to five- and six-membered benzylidene lactones were investigated next using catalyst **4**. These results are shown in Table 5. Isopropyl radical addition to **30** (n = 1) using 30 mol% of **4** gave product **31** is modest yield and good selectivity (Table 5, entry 1). Increasing the catalyst loading to 100% led to higher yield of the product with a very slight improvement in ee (Table 5, compare entry 2 with 1). Reaction with the six-membered lactone **32** was also effective and gave the product in good yield and selectivity (Table 5, entries 3 and 4). These results show that arylidene lactones are also competent substrates in enantioselective conjugate radical additions.

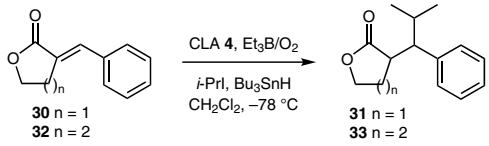
Table 4 Conjugate Addition of Different Radicals to α-Benzylidene Cycloalkenones



Entry	SM	RX	Product	Yield (%)[a]	dr[b]	ee (%)[c]
1	1		2	81	99:1	75
2	18		19	77	93:7	73
3	1		24	93	99:1	85
4	18		25	68	99:1	87
5	1		26	75	99:1	83
6	1		27	89	99:1	81
7	1		28	48	99:1	72
8	1		29	48	65:35	82

[a] Isolated yield after column chromatography.
[b] Determined by NMR spectroscopy.
[c] Determined by chiral HPLC analysis.

Table 5 Conjugate Radical Addition to α-Benzylidene Lactones



Entry	SM	CLA 4 (mol%)	Yield (%)[a]	dr[b]	ee (%)[c]
1	30	30	43	99:1	73
2	30	100	66	99:1	78
3	32	30	58	99:1	75
4	32	100	66	99:1	75

[a] Isolated yield after column chromatography.
[b] Determined by NMR spectroscopy.
[c] Determined by chiral HPLC analysis.

In this work, we have demonstrated that enantioselective conjugate radical addition to α-arylidene ketones and lactones proceed in good yields, very high diastereoselectivities, and good to high enantioselectivities.[18,19] The methodology shows good scope for the acceptors as well as the nucleophilic radicals. The methodology also showcases the use of readily available and cheap chiral salen Lewis acids as activators for monodentate substrates. The use of chiral salen Lewis acids in other transformations of significance are underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590930.

References and Notes

(1) Beijing Pharmin Technology Company Limited, Room 202, Unit 2, Huilongsen Park, No 99, Kechuang 14th Street, Beijing Economic-Technological Development Area, Beijing, 101111, P. R. of China.

(2) (a) *Asymmetric Synthesis II: The Essentials*, 2nd ed.; Christmann, M.; Bräse, S., Eds.; Wiley-VCH: Weinheim, **2007**. (b) *Asymmetric Synthesis II*, 2nd ed; Christmann, M.; Bräse, S., Eds.; Wiley-VCH: Weinheim, **2012**. (c) *Fundamentals of Asymmetric Catalysis*; Walsh, P. J.; Kozlowski, M. C., Eds.; University Science Books: Sausalito, CA, **2009**.

(3) (a) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, **2001**. (b) *Stereochemistry of Radical Reactions*; Curran, D. P.; Porter, N. A.; Giese, B., Eds.; VCH: Weinheim, **1995**. (c) *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C.; Studer, A., Eds.; Wiley-VCH: Weinheim, **2012**.

(4) (a) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (b) Zimmerman, J.; Sibi, M. P. *Top. Curr. Chem.* **2006**, *263*, 107. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (e) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263.

(5) For selected examples, see: (a) Sibi, M. P.; Ji, J. G.; Wu, J. H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (b) Sibi, M. P.; Ji, J. G. *J. Org. Chem.* **1997**, *62*, 3800. (c) Sibi, M. P.; Zimmerman, J. *J. Am. Chem. Soc.* **2006**, *128*, 13346. (d) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452. (e) Zhang, L.; Meggers, E. *Acc. Chem. Res.* **2017**, *50*, 320. (f) Sibi, M. P.; Nie, X.; Shackleford, J. P.; Stanley, L. M.; Bouret, F. *Synlett* **2008**, 2655.

(6) (a) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Berkessel, A.; Gröger, H., Eds.; Wiley-VCH: Weinheim, **2005**. (b) *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 2563.

(7) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898.

(8) For selected examples, see: (a) Hepburn, H. B.; Melchiorre, P. *Chem. Commun.* **2016**, *52*, 3520. (b) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768. (c) Guo, H.; Herdweck, E.; Bach, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7782. (d) Vallavoju, N.; Selvakumar, S.; Jockusch, S.; Sibi, M. P.; Sivaguru, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 5604. (e) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735. (f) Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *Chem. Commun.* **1996**, 579. (g) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392. (h) Lee, S.; Kim, S. *Tetrahedron Lett.* **2009**, *50*, 3345. (i) Jang, D. O.; Kim, S. Y. *J. Am. Chem. Soc.* **2008**, *130*, 16152.

(9) For selected recent reviews, see: (a) Park, J.; Hong, S. *Chem. Soc. Rev.* **2012**, *41*, 6931. (b) Shaw, S.; White, J. D. *Synthesis* **2016**, *48*, 2768. (c) Also see: Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511. (d) Wu, S.; Tang, J.; Han, J.; Mao, D.; Liu, X.; Gao, X.; Yu, J.; Wang, L. *Tetrahedron* **2014**, *70*, 5986.

(10) For the installation of contiguous chiral centers in radical reactions, see: (a) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (b) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390. (c) He, L.; Srikanth, G. S. C.; Castle, S. L. *J. Org. Chem.* **2005**, *70*, 8140. (d) Banerjee, B.; Capps, S. G.; Kang, J.; Robinson, J. W.; Castle, S. L. *J. Org. Chem.* **2008**, *73*, 8973. (e) Lee, J. Y.; Kim, S.; Kim, S. *Tetrahedron Lett.* **2010**, *51*, 4947. (f) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494.

(11) All the starting enones and lactones used in this study are known in the literature, see Supporting Information.

(12) (a) Yorimitsu, H.; Oshima, K. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**, 11. (b) Renaud, P. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C.; Studer, A., Eds.; Wiley: New York, NY, **2012**, 601. (c) Curran, D. P.; McFadden, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 7741.

(13) A variety of 3^+ and 2^+ chiral Lewis acids were screened with modest success; see Supporting Information for details.

(14) Sibi, M. P.; Nad, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 9231.

(15) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576.

(16) For an example of conjugate addition of achiral copper reagent to α-alkylidene cyclopentanone see: Borner, C.; Dennis, M. R.; Sinn, E.; Woodward, S. *Eur. J. Org. Chem.* **2001**, 2435.

(17) We have not established the relative stereochemistry of the major isomer. As noted in ref. 14, we speculate that the newly formed chiral center controls the stereochemistry of the H-atom-transfer step.

(18) For stereochemical models of single-point binding substrates to chiral salens, see: (a) Ref. 14. (b) Sibi, M. P.; Zimmerman, J. *J. Am. Chem. Soc.* **2006**, *128*, 13346. (c) Hutson, G. E.; Turkman, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 4988.

(19) **Representative Procedure for Radical Addition**
To a 6 dram vial were added substrate (0.3 mmol) and Lewis acid **4** (0.09 mmol, 30 mol%). The vial was sealed with a septum, the air was removed from the vial via a vacuum pump, nitrogen was charged. To the mixture was then charged solvent (CH_2Cl_2, 8 mL), the mixture was stirred at r.t. for 20 min. Then the mixture was cooled to –78 °C, radical precursor (1.5 mmol, 5 equiv), triethylborane solution (1.0 M in hexane, 1.2 mL, 4 equiv), tributyltin hydride (0.24 mL, 0.9 mmol, 3 equiv), and oxygen gas (10 mL) were added successively via syringe. The reaction was stirred at –78 °C for 2–3 h until TLC analysis indicated disappearance of starting material. To the mixture was added silica gel (3.6 g), the solvent was removed under reduced pressure, the residue was first washed with hexanes (100 mL),

then Et_2O (100 mL). To the ether solution was added silica gel (1.8 g), the solvent was removed under reduced pressure. The residue was subjected to flash chromatography using hexane/EtOAc (9:1) as eluent to afford the conjugate addition product.

2-(2-Methyl-1-phenylpropyl)-cyclopentanone (2)

88 mg (0.5 mmol), yield 81%, dr 99:1, ee 75% by HPLC (210 nm, 25 °C, OJ-H column Chiralcel, 0.46cm × 25 cm, from Daicel Chemical Ind., Ltd., 1% i-PrOH/hexanes, 0.5 mpm, t_R (major) = 18.5 min; t_R (minor) = 14.4 min). $[\alpha]_D$ +71.3 (*c* 0.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.65 (d, *J* = 6.4 Hz, 3 H), 0.95 (t, *J* = 6.8 Hz, 3 H), 1.56–2.46 (m, 8 H), 2.61 (dd, *J* = 10.4, 3.6 Hz, 1 H), 7.11–7.25 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 22.0, 22.1, 26.9, 29.7, 39.4, 52.7, 53.8, 126.4, 128.5, 128.8, 144.2, 220.3. IR: 3062, 3029, 2960, 2894, 2871, 1733, 1493, 1470, 1407, 1385, 1273, 1152 cm^{-1}. HRMS: *m/z* calcd for $C_{15}H_{20}ONa^+$: 239.1406; found: 239.1400.