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Enantioselective Synthesis of α-*exo*-Methylene γ-Butyrolactones via Chromium Catalysis

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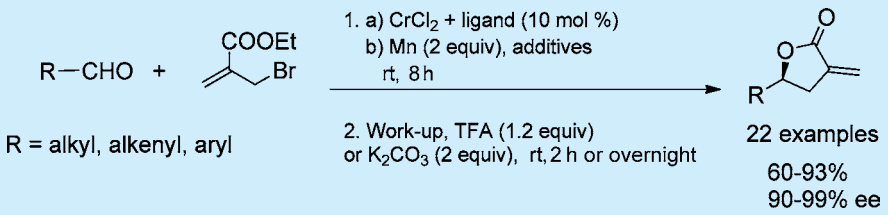
Supporting Information



ABSTRACT: Enantioenriched α-*exo*-methylene γ-butyrolactones have been obtained via a two-step sequence consisting of a highly enantioselective chromium-catalyzed carbonyl 2-(alkoxycarbonyl)allylation and lactonization. A variety of functional groups are compatible under the mild reaction conditions. The synthetic utility of this methodology was demonstrated by two short derivatization transformations and the enantioselective synthesis of (+)-methylenolactocin.

α-*exo*-Methylene-γ-butyrolactones have been observed in more than 3000 known natural products with diverse useful biological activities (Figure 1). They have attracted broad research interests

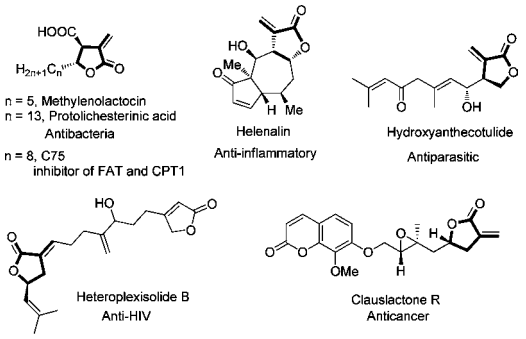


Figure 1. Representative natural products.

from different areas including natural product chemistry, biology, pharmacology, and synthetic organic chemistry.[1] For their preparation, carbonyl allylation–lactonization based on the 2-(alkoxycarbonyl)allyl reagent represents one of the most convergent approaches. To date, a variety of allyl reagents made from boron,[2] silicon,[3] tin,[4] zinc,[5] nickel,[6] indium,[7] magnesium,[8] and ruthenium[9] have been successfully applied to this task, mainly in stoichiometric and racemic versions. In some cases, high enantioselectivity could be achieved when two chiral auxiliaries are present.[2] To the best of our knowledge, the only known catalytic asymmetric versions of this carbonyl allylation–lactonization approach was reported by Krische in an elegant iridium-catalyzed conversion of acrylic ester and alcohol to α-*exo*-methylene-γ-butyrolactones with high enantioselectivity.[10] Given the wide occurrence of this type of molecular skeleton, new catalytic systems for asymmetric preparation of α-*exo*-methylene-γ-butyrolactones under mild reaction conditions with tolerance of broad and sensitive functionalities are still highly desired.

Chromium-mediated Grignard-type addition of carbohalides to aldehyde, well-known as the Nozaki–Hiyama–Kishi reaction when a catalytic amount of Ni salt was employed, has proven to be one of the most powerful synthetic methods for carbon–carbon bond formation.[11,12] Chromium-mediated addition of 2-(alkoxycarbonyl)allyl halide to aldehyde to provide racemic α-*exo*-methylene-γ-butyrolactones has been documented.[13] However, a catalytic asymmetric version of this transformation has not been reported.

During the last two decades, several classes of chiral ligand have been identified to induce high stereoselectivity in chromium-catalyzed asymmetric transformations such as allylation, 2-haloallylation, and 2-methylallylation.[14] Our own interest in this important research area leads us to investigate the impact of these chiral ligands on the chromium-catalyzed asymmetric synthesis of α-*exo*-methylene-γ-butyrolactones. Herein, we report a highly enantioselective 2-(alkoxycarbonyl)-allylation reaction with carbazole-based bisoxazoline first developed by Nakada,[14i] as chiral ligand. The resulting homoallylic alcohols were treated with proper acid or base, providing synthetically useful α-*exo*-methylene γ-butyrolactones with preservation of optical purity. This reaction exhibits broad functional group compatibility and mild reaction conditions. Furthermore, our modified ligand synthesis provides a practical access to this important class of chiral "pincer" ligands.[15]

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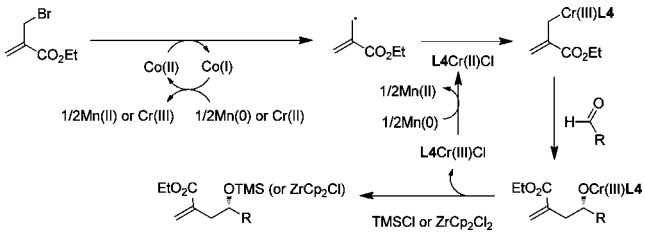
To begin our study, the reaction between dihydrocinnamaldehyde and ethyl 2-(bromomethyl) acrylate was chosen as the model reaction. A catalytic cycle with the functions of reagents and additives is shown in Scheme 1.[13] A general experimental

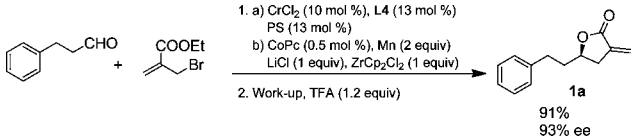
Scheme 1. Proposed Catalytic Cycle



procedure includes the following: (1) a complexation step in which a suspension of $CrCl_2$ in THF was treated with chiral ligand and Proton Sponge at rt to in situ generate the corresponding chromium catalyst; (2) an allylation step in which the catalyst solution was transferred to a mixture of Mn (reduing agent), $ZrCp_2Cl_2$ (or TMSCl) (dissociating agent), and additives, followed by the addition of dihydrocinnaldehyde and ethyl 2-(bromomethyl) acrylate; (3) and a lactonization step in which the resulting homoallylic alcohol was treated with 1.2 equiv of TFA to give *α-exo*-methylene-*γ*-butyrolactone **1a** as the final product. Triethylamine could serve as base in the first step as well, but Proton Sponge is chosen due to its stronger deprotonation capability and solid form for easier handling.

The effects of a variety of chiral ligands on the reaction are summarized in Table 1. Salen ligand **L1** (Figure 2) led to the

Table 1. Evaluation of Chiral Ligands and Other Reaction Parameters



entry[a]	deviation from the standard conditions	yield[b] (%)	ee[c] (%)
1	none	91	93
2	L1	62	10
3	L2	88	38
4	L3	70	79
5	L5	66	30
6	L6	83	82
7	L7	89	85
8	L8	80	83
9	L9	88	89
10	5% $CrCl_2$, 7% L4	78	85
11	$CrCl_3$[d,e]	87	93
12	without CoPc	50	93
13	without LiCl	75	90
14	TMSCl instead of $ZrCp_2Cl_2$	81	90
15	without $CrCl_2$	trace	
16	1 mmol of aldehyde	90	93

[a]The reactions were carried out on a 0.2 mmol scale unless noted otherwise. [b]Isolated yield. [c]Determined by chiral HPLC analysis; absolute configuration was assigned by comparison of the specific rotation to literature value (see the Supporting Information). [d]Et_3N was used instead of PS; 1 equiv of Mn was added for the complex formation. [e]Complexation took 8 h. PS = Proton Sponge.

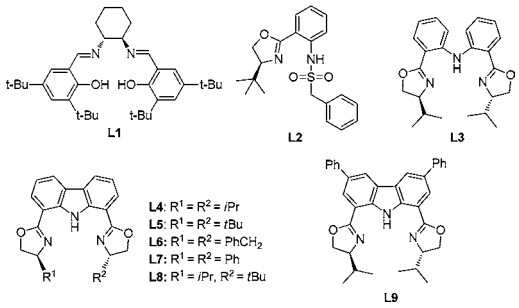


Figure 2. Tested ligands.

desired product **1a** in 62% yield with only 10% ee (Table 1, entry 1). Sulfonamide ligand **L2** developed by Kishi was also tested,[14f−h] **1a** was obtained in 88% yield with 38% ee (Table 1, entry 2). Then we turned our attention to easily accessible C2 symmetric bisoxazoline ligand **L3** developed by Guiry.[14n] To our delight, a dramatic increase of enantioselectivity was observed, and **1a** was obtained in 70% yield with 79% ee (Table 1, entry 3). In order to increase the rigidity compared to **L3**, we developed a three-step synthesis of carbazole-based bisoxazoline ligands **L4**−**L7**.[17] Ligand **L4** was the best one to give **1a** in 91% yield with 93% ee (Table 1, entry 4). Ligand **L5** with sterically demanding *t*-Bu groups was not effective for this reaction; **1a** was obtained in 66% yield with 30% ee (Table 1, entry 5). Ligand **L6** with benzyl groups and **L7** with phenyl groups gave slightly lower enantioselectivity (82% ee and 85% ee, respectively; Table 1, entries 6 and 7). Unsymmetrical ligand **L8** was also prepared and tested, but a diminished yield and ee were observed (Table 1, entry 8).[18] The known **L9** gave a result comparable to that with **L4**, as **1a** was obtained in 88% yield with 89% ee (Table 1, entry 9).[19]

The impact of various deviations from the standard reaction conditions was also evaluated. Lower catalyst loading ($CrCl_2$ 5 mol %, **L4** 7 mol %) resulted in decreased yield and ee (78% yield, 85% ee, Table 1, entry 10). Cheaper and easy handling $CrCl_3$ could also be directly used (87% yield, 93% ee, Table 1, entry 11). The presence of CoPc and LiCl is critical to the efficiency of the coupling reaction, as the yield of **1a** decreased under conditions without either of these two components. However, enantioselectivity essentially remained the same (Table 1, entries 12 and 13). CoPc were reported to significantly increase the rate of Cr-catalyzed process by facilitating the formation of allyl species,[20] and LiCl have similar functions to increase the rate of transmetalation to the chiral chromium complex.[14f−h,21] Both TMSCl[22] and $ZrCp_2Cl_2$[23] worked well as dissociating agents of chromium alkoxides. In this case, TMSCl gave a slightly lower enantiomeric excess (Table 1, entry 14). It is worth pointing out that no allylation took place in the absence of $CrCl_2$, indicating the formation of products through allylcobalt and allylzirconium species is less likely (Table 1, entry 15). Notably, the reaction scale could be increased to 1 mmol with maintenance of the efficiency (Table 1, entry 16).

This highly enantioselective synthesis of **1a** can also be expanded to reactions with a broad range of aldehydes, and high enantioselectivity (90−99% ee) was obtained (Scheme 2). Representative aliphatic aldehydes including cyclohexyl carboxyaldehyde, heptaldehyde, and cyclopropyl carboxyaldehyde participated in this two-step sequence efficiently; the corresponding *γ*-butyrolactones **1b**−**d** were isolated in high yield with excellent enantiomeric excess (93−95% ee). Reaction of 4-TBDPSO-1-butaldehyde proceeded smoothly to give product **1e**

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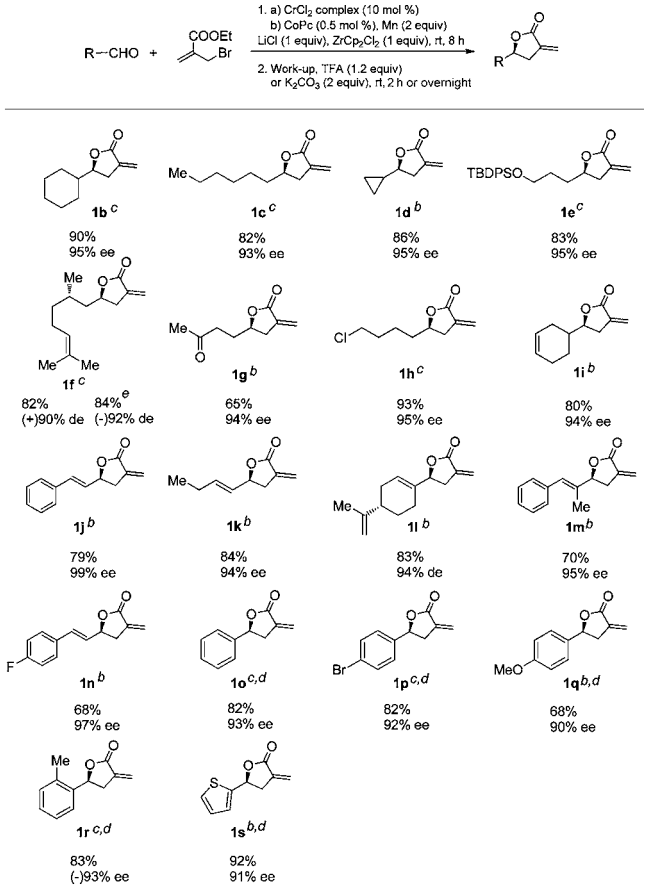
Scheme 2. Substrate Scope Studies[a]



[a]All reactions carried out on a 1 mmol scale under the standard conditions; ligand (*S*)-**L4** was used unless otherwise noted. [b]K_2CO_3/*t*-BuOH was utilized for lactonization. [c]TFA/DCM was utilized for lactonization. [d]20 mol % of ligand was employed. [e]Ligand (*R*)-**L4** was used.

with a protected hydroxyl group in 83% yield with 95% ee. A naturally occurring aldehyde (−)-citronellal bearing a chiral methyl group β to the carbonyl group exhibited a negligible catalyst−substrate mismatching profile, as reactions using either (*S*)-**L4** or (*R*)-**L4** gave products in 82% yield with (+) 90% ee and 84% yield with (−) 92% ee, respectively. For substrates containing both ketone and aldehyde functionalities, this chromium-catalyzed 2-(alkoxycarbonyl)allylation selectively took place on the aldehyde to give **1g** in 65% yield with 94% ee. A terminal chloro group is also compatible under the reaction conditions, giving product **1h** in 93% yield with 95% ee. This reaction also tolerates olefins as **1i** was formed in 80% yield with 94% ee. A range of α,β-unsaturated aldehydes including (−)-perillaldehyde were also tested, providing the corresponding products in high enantiomeric excess. Among those, **1j** from the reaction of cinnaldehyde was obtained in 99% ee.

It is worth noting that this allylation−lactonization protocol works equally well with various aryl aldehydes to produce the corresponding 5-arylated γ-butyrolactones in moderate to good yields with excellent enantiomeric excess (90 to 93% ee). For aryl aldehydes, a 20 mol % ligand loading had to be employed for the best result. The 13 mol % ligand loading led to products with about 80% ee. A preinstalled bromo group on the benzene ring allows further functionalization through standard cross-coupling reactions. Interestingly, 2-methylbenzaldehyde gave product **1r** with opposite optical rotation probably due to an altered conformational preference. Furthermore, heterocycles such as thiophene were also compatible under the current reaction conditions, giving product **1s** in 92% yield with 91% ee.

A transition state was proposed to account for the preferential formation of the (*S*)-enantiomer of the product (Figure 3).

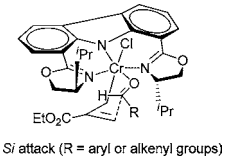
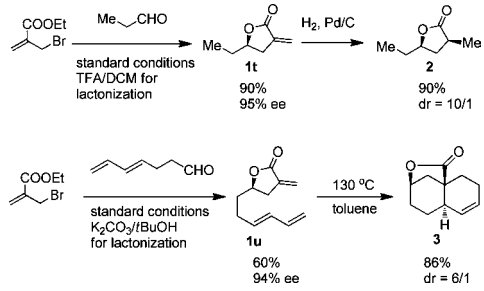


Figure 3. Proposed transition state.

To demonstrate the synthetic potential of our methodology, two short transformations were carried out (Scheme 3). The

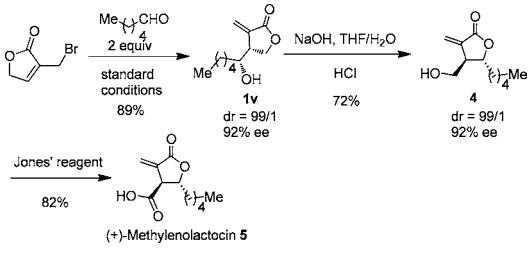
Scheme 3. Synthetic Utilities of α-*exo*-Methylene-γ-butyrolactones



allylation and lactonization of propionaldehyde under standard conditions proceeded smoothly to give compound **1t** in 90% yield with 95% ee. Subsequent hydrogenation delivered compound **2** in 90% yield with 10/1 dr, which was the advanced intermediate in the synthesis of a family of natural products curvularides A−E.[24] This protocol could be applied to aldehyde with a terminal diene moiety to generate lactone **1u** in 60% yield with 94% ee. Heating **1u** in toluene, an intramolecular D−A reaction took place to deliver product **3** in 86% yield with 6/1 dr.[25] The bridged lactone segment has been observed in several naturally occurring compounds such as levatin.[26]

Trans β,γ-disubstituted α-*exo*-methylene-γ-butyrolactones are widely present in biologically active natural products including methylenolactocin (Figure 1). Recently, a concise synthesis of (±)-methylenolactocin through a chromium-catalyzed Barbier-type coupling of 3-(bromomethyl)furan-2(5*H*)-one with hexanal was reported.[27] We tested this reaction under our optimal conditions. To our delight, as shown in Scheme 4, the corresponding β-substituted lactone **1v** was obtained in 89%

Scheme 4. Approach for the Synthesis of (+)-Methylenolactocin



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yield with 99/1 dr and 92% ee. The next translactonization proceeded smoothly to give β,γ-disubstituted lactone **4** with preservation of dr and ee.[28] The Jones' oxidation delivered the (+)-methylenolactocin **5** in 82% yield.

In conclusion, a highly enantioselective synthesis of α-*exo*-methylene γ-butyrolactones has been achieved through asymmetric chromium-catalyzed 2-(alkoxycarbonyl)allylation of aldehydes and lactonization. The synthetic utilities are demonstrated by two short transformations and enantioselective syntheses of (+)-methylenolactocin. Future work will focus on expanding this catalytic system to other chromium-mediated transformations and applying this protocol to the synthesis of complex molecules with biological and medicinal significance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02597.

(PDF)

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Notes

The authors declare no competing financial interest.

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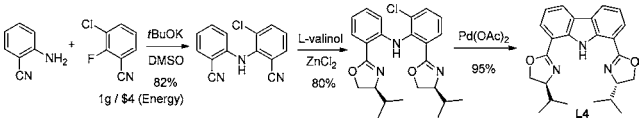

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