

Enantioselective Conversion of Primary Alcohols to α -exo-Methylene γ -Butyrolactones via Iridium-Catalyzed C–C Bond-Forming Transfer Hydrogenation: 2-(Alkoxy carbonyl)allylation

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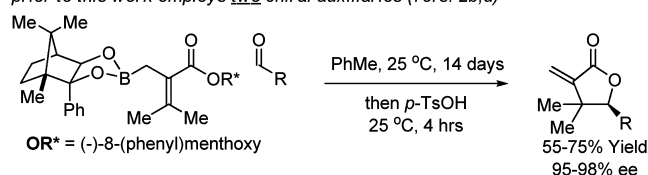
S Supporting Information

ABSTRACT: Upon exposure of acrylic ester **1** to alcohols **2a–i** in the presence of a cyclometalated iridium catalyst modified by (–)-TMBTP, catalytic C–C coupling occurs, providing enantiomerically enriched 5-substituted α -exo-methylene γ -butyrolactones **3a–i**. Bromination of the methylene butyrolactone products followed by zinc-mediated reductive aldehyde addition provides the disubstituted α -exo-methylene γ -butyrolactones **6a** and **6b** with good to excellent levels of diastereoselectivity.

α -exo-Methylene γ -butyrolactones display an enormous array of biological activities and constitute approximately 10% of the >30 000 known natural products.¹ Among methods for their preparation, carbonyl-addition-triggered lactonization reactions involving 2-(alkoxycarbonyl)allylmetal reagents are especially convergent protocols. To date, discrete 2-(alkoxycarbonyl)-allylmetal reagents based on boron,² silicon,³ tin,⁴ zinc,⁵ and nickel⁶ have been utilized in this capacity. Additionally, unpoled reactions of 2-(alkoxycarbonyl)allyl halides promote the formation of α -exo-methylene γ -butyrolactones, including Reformatsky and Nozaki–Hiyama type reactions.⁷ Methods for asymmetric carbonyl addition–lactonization to form α -exo-methylene γ -butyrolactones largely rely upon stoichiometric chirality transfer from auxiliaries.^{2a,b,d,e,l,7i} Furthermore, high enantioselectivities are obtained only when *two* chiral auxiliaries are used in concert.^{2b,d} Remarkably, *related catalytic enantioselective processes for the formation of α -exo-methylene γ -butyrolactones remain an unmet challenge.*⁸ Here we report the first highly enantioselective catalytic 2-(alkoxycarbonyl)-allylations to form α -exo-methylene γ -butyrolactones, which are achieved directly from the alcohol oxidation level under the conditions of iridium-catalyzed C–C bond-forming transfer hydrogenation (Figure 1).⁹

Our earlier work on iridium-catalyzed enantioselective carbonyl allylation¹⁰ revealed that allylic carboxylates incorporating monosubstituted olefins are required. This constraint arises because olefin coordination precedes ionization of the allylic leaving group to form the π -allyl, and the stability of late transition metal–olefin π complex decreases with increasing degree of olefin substitution.¹¹ However, we recently found that enhanced π back-bonding^{12,13} associated with carboxy substitution compensates for such destabilization, enabling vinyl-ogous aldol addition from the alcohol or aldehyde oxidation level.¹⁴ This result supported the feasibility of using acrylic ester **1** as a 2-(alkoxycarbonyl)allylmetal equivalent.

Sole protocol for highly enantioselective carbonyl 2-(alkoxycarbonyl)allylation prior to this work employs *two* chiral auxiliaries (refs. 2b,d)



This work: catalytic enantioselective 2-(alkoxycarbonyl)allylation

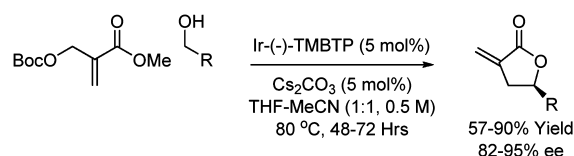


Figure 1. Formation of α -exo-methylene γ -butyrolactones via enantioselective carbonyl 2-(alkoxycarbonyl)allylation.

In preliminary experiments, the catalytic C–C coupling of acrylic ester **1** and alcohol **2b** was explored using the achiral π -allyliridium C,O-benzoate complex derived from [Ir(cod)Cl]₂, 4-chloro-3-nitrobenzoic acid, allyl acetate, and 2,2'-bis-(diphenylphosphino)biphenyl (BIPHEP). This complex, designated as Ir(BIPHEP), was isolated by conventional silica gel chromatography. However, upon exposure of acrylic ester **1** to alcohol **2b** under conditions effective in related vinylogous aldol additions, only trace quantities of the desired butyrolactone **3b** were generated (Table 1, entry 1). The catalyst used in the vinylogous aldol addition was isolated by precipitation and hence may have contained residual cesium carbonate. This hypothesis prompted us to conduct the reaction under the aforementioned conditions in the presence of added cesium carbonate (20 mol %), which promoted generation of butyrolactone **3b** in 31% isolated yield (Table 1, entry 2). Decreased loadings of cesium carbonate (10 and 5 mol %) increased the isolated yield of butyrolactone **3b** (Table 1, entries 3 and 4). Finally, upon adjustment of the reaction temperature, acrylic ester **1** and alcohol **2b** were converted to butyrolactone **3b** in 77% isolated yield (Table 1, entries 5 and 6). The concentration of trace metals in the cesium carbonate had a significant impact on the isolated yield. For the best results, high-grade cesium carbonate (>99.7% purity) with trace metal concentrations of <10 ppm had to be employed.

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Table 1. Selected Optimization Experiments in the C–C Coupling of Ester 1 to Alcohol 2b [R = (CH₂)₂Ph]^a

Entry	Cs ₂ CO ₃ (mol%)	T °C	Yield%
1	0	90	trace
2	20	90	31
3	10	90	54
4	5	90	65
⇒ 5	5	80	77
6	5	70	48

Ir(BIPHEP)

^aYields are of materials isolated by silica gel chromatography. See the Supporting Information for further details.

Under the optimal conditions identified for the conversion of acrylic ester 1 and alcohol 2b to racemic butyrolactone 3b, catalysts modified by diverse axially chiral chelating phosphine ligands were assayed. The chiral ligands assayed included BINAP, Xylyl-BINAP, SEGPHOS, DM-SEGPHOS, C3-TU-NEPHOS, MeO-BIPHEP, Cl₂MeO-BIPHEP, and CTH-PHOS, among others. However, the degree of asymmetric induction was disappointing, with 80% ee or lower in each case. In contrast, the chiral complex modified by (–)-2,2',5,5'-tetramethyl-3,3'-bis(diphenylphosphine)-4,4'-bithiophene [(–)-TMBTP],¹⁵ designated as Ir(TMBTP), provided butyrolactone 3b in 79% yield with 88% ee (Table 2, entry 1). The

Table 2. Selected Optimization Experiments in the Enantioselective C–C Coupling of Ester 1 to Alcohol 2b [R = (CH₂)₂Ph]^a

Entry	Solvent (0.5 M)	Hours	Yield% (ee%)
1	THF	48	79 (88)
2	2-Me-THF	48	68 (77)
3	dioxane	48	33 (72)
4	MeCN	48	31 (92)
5	THF:MeCN (1:1)	48	52 (90)
6	THF:MeCN (1:1)	72	57 (90)

Ir(TMBTP)

^aYields are of materials isolated by silica gel chromatography. Enantiomeric excesses were determined by chiral stationary phase HPLC analysis. See the Supporting Information for further details.

isolated yields and degree of asymmetric induction were both highly solvent-dependent. Whereas reactions performed in 2-Me-THF and dioxane provided butyrolactone 3b in 68% yield with 77% ee and 33% yield with 72% ee, respectively, a 31% yield with 92% ee was obtained in MeCN (Table 2, entries 2–4). To balance the yield and enantioselectivity, reactions were conducted in THF/MeCN mixtures over 3 days (Table 2, entries 5 and 6).

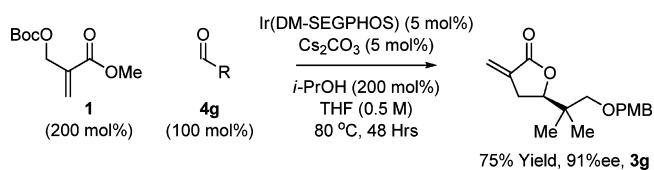
The optimal conditions identified for the enantioselective process were applied to primary aliphatic alcohols 2a–i. The corresponding α -*exo*-methylene γ -butyrolactones 3a–i were produced in good to excellent isolated yields with enantioselectivities ranging from 82 to 95% ee (Table 3). Benzylic alcohols also participated in the 2-(alkoxycarbonyl)allylation, but the enantioselectivities were modest.¹⁶ As illustrated by the

Table 3. Enantioselective 2-(Alkoxycarbonyl)allylation via Iridium-Catalyzed C–C Bond-Forming Transfer Hydrogenation^a

2a, R = (CH ₂) ₇ Me	2b, R = (CH ₂) ₂ Ph	2c, R = (CH ₂) ₂ OPMB	2d, R = (CH ₂) ₃ OBn
2e, R = 5-(2,2-Me ₂ -dioxanyl)	2f, R = <i>c</i> -C ₆ H ₁₁	2g, R = CMe ₂ CH ₂ OPMB	2h, R = 3-(3-Me-oxetanyl)
2i, R = 1-(1-Ph- <i>c</i> -C ₃ H ₅)			
 66% Yield 90% ee, 3a ^b	 57% Yield 90% ee, 3b	 79% Yield 88% ee, 3b ^b	 67% Yield 82% ee, 3d
 65% Yield 94% ee, 3e	 73% Yield 95% ee, 3f	 73% Yield 90% ee, 3i	 84% Yield 87% ee, 3h
 90% Yield 92% ee, 3g ^{b,d}			

^aAs described for Table 2. ^bTHF (0.5 M). ^cThe cyclometalated catalyst derived from 4-CN-3-NO₂-BzOH was used. ^d(*R*)-DM-SEGPHOS was used as the ligand. See the Supporting Information for further details.

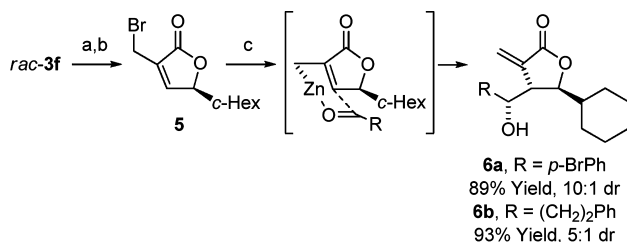
conversion of aldehyde 4g to butyrolactone 3g, 2-(alkoxycarbonyl)allylation can be conducted from the aldehyde oxidation level using isopropanol as a terminal reductant (Scheme 1). Butyrolactones 3a and 3b were previously prepared in optically enriched form and served to corroborate the assignment of absolute stereochemistry for butyrolactones 3a–i.

Scheme 1. Enantioselective 2-(Alkoxycarbonyl)allylation via Iridium-Catalyzed Aldehyde Reductive Coupling via Transfer Hydrogenation^a

^aAs described for Table 2. See the Supporting Information for further details.

To illustrate the potential utility of adducts 3a–i, butyrolactone 3f was converted into allylic bromide 5, which was subjected to zinc-mediated reductive coupling to *p*-bromobenzaldehyde and 3-phenylpropanal (Scheme 2).¹⁷ The corresponding adducts 6a and 6b were generated diastereoselectively, thereby establishing entry to disubstituted α -*exo*-methylene γ -butyrolactones with control of the relative and absolute stereochemistries.

Scheme 2. Conversion of *rac*-3f to Disubstituted α -*exo*-Methylene γ -Butyrolactones 6a and 6b^a



^aReagents: (a) Br₂ (110 mol %), NaOAc (150 mol %), DCM (0.08 M), 25 °C. (b) Li₂CO₃ (500 mol %), LiBr (500 mol %), DMF (0.3 M), 60 °C, 55% yield (2 steps). (c) RCHO (100 mol %), Zn (118 mol %), NH₄Cl (10 μ L, saturated aqueous solution), DMF (0.5 M), 25 °C.

In summary, although α -*exo*-methylene γ -butyrolactones represent a vast family of naturally occurring compounds, the catalytic enantioselective formation of such butyrolactones via carbonyl 2-(alkoxycarbonyl)allylation was hitherto unknown. Here we have reported the first examples of catalytic enantioselective carbonyl 2-(alkoxycarbonyl)allylation through iridium-catalyzed transfer hydrogenative C–C coupling of acrylic ester **1** to alcohols **2a–i**. As illustrated by the formation of adducts **6a** and **6b**, this methodology provides entry to fully substituted α -*exo*-methylene γ -butyrolactones with control of the relative and absolute stereochemistries. Future studies will focus on the application of this methodology to the synthesis of α -*exo*-methylene γ -butyrolactone natural products.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and spectral, HPLC, and GC data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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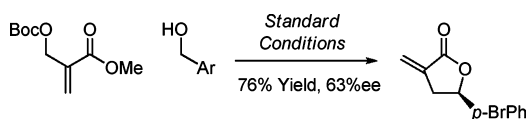
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