Published in final edited form as:

J Am Chem Soc. 2012 July 11; 134(27): 11100–11103. doi:10.1021/ja303839h.

Enantioselective Conversion of Primary Alcohols to α -Exo-Methylene γ -Butyrolactones *via* Iridium Catalyzed C-C Bond Forming Transfer Hydrogenation: 2-(Alkoxycarbonyl)allylation

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Abstract

Upon exposure of acrylic ester **1** to alcohols **2a–2i** in the presence of a cyclometallated iridium catalyst modified by (–)-TMBTP, catalytic C-C coupling occurs to provide enantiomerically enriched 5-substituted α -exo-methylene γ -butyrolactones **3a–3i**. 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 tin⁴ and zinc⁵ have been utilized in this capacity. Additionally, unpoled reactions of 2-(alkoxycarbonyl)allylhalides promote formation of α -exo-methylene γ -butyrolactones, including Reformatsky and Nozaki-Hiyama type reactions.⁶ 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,7j} 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 reveals that allylic carboxylates incorporating monosubstituted olefins are required. This constraint arises as 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, recently we found that enhanced π -backbonding^{12,13} associated with carboxy substitution compensates for such destabilization, enabling vinylogous 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.

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

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 BIPHEP [(2,2'-bis(diphenylphosphino)biphenyl)], designated Ir(BIPHEP). The complex 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 contain 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 mol% and 5 mol%) increased the isolated yield of butyrolactone **3b** (Table 1, entries 3 and 4). Finally, by adjusting reaction temperature, acrylic ester **1** and alcohol **2b** could be 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 isolated yield. For the best results, high grade cesium carbonate (>99.7% purity) with trace metal concentrations of <10 ppm should be employed.

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-TUNEPHOS, MeO-BIPHEP, Cl₂MeO-BIPHEP, and CTH-PPHOS among others. However, the degree of asymmetric induction was disappointing, with 80% enantiomeric excess or lower in each case. In contrast, the chiral complex modified by (–)-TMBTP,¹⁵ Ir(TMBTP), provided butyrolactone **3b** in 79% yield and 88% enantiomeric excess (Table 2, entry 1). Isolated yields and the degree of asymmetric induction are both highly solvent dependent. Whereas reactions performed in 2-Me-THF and dioxane provide butyrolactone **3b** in 68% yield and 77% enantiomeric excess and 33% yield and 72% enantiomeric excess, respectively, a 31% yield and 92% enantiomeric excess are obtained in acetonitrile (MeCN) (Table 2, entries 2–4). In order to balance yield and enantioselectivity, reactions were conducted in THF-MeCN mixtures over 3 days (Table 2, entries 5 and 6).

Optimal conditions identified for the enantioselective process were applied to primary aliphatic alcohols **2a–2i**. The corresponding α -exo-methylene γ -butyrolactones **3a–3i** were produced in good to excellent isolated yields with enantioselectivities ranging from 82–95% ee (Table 3). Benzylic alcohols also participate in 2-(alkoxycarbonyl)allylation, but enantioselectivities were modest.¹⁶ As illustrated by the conversion of aldehyde **4g** to butyrolactone **3g**, 2-(alkoxycarbonyl)allylation can be conducted from the aldehyde oxidation level using isopropanol as terminal reductant (Scheme 1). Butyrolactones **3a** and **3b** previously were prepared in optically enriched form and serve to corroborate the assignment of absolute stereochemistry for butyrolactones **3a–3i**.

To illustrate the potential utility of adducts **3a–3i**, butyrolactone **3f** was converted to the allylic bromide **5**, which was subjected to zinc-mediated reductive coupling to *p*-bromobenzaldehyde and 3-phenyl propanal.¹⁷ The adducts **6a** and **6b** are generated diastereoselectively, thereby establishing entry to disubstituted α -exo-methylene γ -butyrolactones with control of relative and absolute stereochemistry.

In summary, although α -exo-methylene γ -butyrolactones represent a vast family of naturally occurring compounds, catalytic enantioselective formation of such butyrolactones *via* carbonyl 2-(alkoxycarbonyl)allylation was hitherto unknown. Here, we report the first example of catalytic enantioselective carbonyl 2-(alkoxycarbonyl)allylation through iridium

catalyzed transfer hydrogenative C-C coupling of acrylic ester **1** to alcohols **2a–2i**. 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 relative and absolute stereochemistry. Future studies will focus on the application of this methodology to the synthesis of α -exo-methylene γ -butyrolactone natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) are acknowledged for partial support of this research. Merck is acknowledged for the generous donation of (–)-TMBTP. The Higher Education Commission of Pakistan is acknowledged for graduate student fellowship support (AH).

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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.
α-Exo-methylene γ-butyrolactones *via* enantioselective carbonyl 2-(alkoxycarbonyl)allylation.

Scheme 1.

Enantioselective 2-(alkoxycarbonyl)allylation *via* iridium catalyzed aldehyde reductive coupling *via* transfer hydrogenation.^a

^aAs described in Table 3. See Supporting Information for further details.

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.

Table 1

Selected optimization experiments in the C-C coupling of ester **1** to alcohol **2b** (R = (CH₂)₂Ph).^a

Entry	Cs₂CO₃ (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

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

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)
5	THF:MeCN (1:1)	72	57 (90)

^aYields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details.

Table 3

Enantioselective 2-(alkoxycarbonyl)allylation *via* iridium catalyzed C-C bond forming transfer hydrogenation.^a

1 (200 mol%)	2a-2i (100 mol%)	3a-3i
2a , R = (CH ₂) ₇ Me 2d , R = (CH ₂) ₃ OBn 2g , R = CMe ₂ CH ₂ OPMB	2b , R = (CH ₂) ₂ Ph 2e , R = 5-(2,2-Me ₂ -dioxanyl) 2h , R = 3-(3-Me-oxetanyl)	2c , R = (CH ₂) ₂ OPMB 2f , R = <i>c</i> -C ₆ H ₁₁ 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

90% Yield 92% ee, 3g^{b,d}	84% Yield 87% ee, 3h	73% Yield 90% ee, 3i

^a As described for Table 2.

^b THF (0.5 M).

^cThe cyclometallated catalyst derived from 4-CN-3-NO₂-BzOH was used.

^d(*R*)-DM-SEGPPOS was used as ligand. See Supporting Information for further details.