Published in final edited form as:

Org Lett. 2017 September 01; 19(17): 4460–4463. doi:10.1021/acs.orglett.7b01994.

Rh-Catalyzed Conjugate Addition of Aryl and Alkenyl Boronic Acids to α -Methylene- β -lactones: Stereoselective Synthesis of *trans*-3,4-Disubstituted β -Lactones

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Abstract

A one-step preparation of 3,4-disubstituted β -lactones through Rh-catalyzed conjugate addition of aryl or alkenyl boronic acids to α -methylene- β -lactones is described. The operationally simple, stereoselective transformation provides a broad range of β -lactones from individual α -methylene- β -lactone templates. This methodology allowed for a direct, final-step C-3 diversification of nocardiolactone, an antimicrobial natural product.

Graphical abstract

β -Lactones are an important class of heterocycles found in many synthetic and natural products of biological interest.¹ They have been explored for anti-obesity,² anticancer,³ and antibacterial⁴ applications and have been utilized as probes in activity-based protein profiling (ABPP).^{1b,5,6} β -Lactones are also versatile intermediates in organic synthesis with a broad range of reactivities.⁷ We recently showed that α -methylene- β -lactones **1** could be used for the synthesis of structurally diverse 3,4-disubstituted β -lactones **2** via cross-metathesis (CM)⁸ to **3** and subsequent reduction (Figure 1a).⁶ While this methodology is attractive for assembling focused libraries of 3,4-disubstituted β -lactones, there are limitations. First, the CM reaction typically requires high catalyst loading (5–10 mol %). Secondly, the 1,4-reduction to access the generally more biologically active *trans* β -lactones suffers from modest diastereoselectivities and yields. We hypothesized that β -lactones **2** could be directly accessed from **1** via conjugate addition, in particular, with organoboron reagents under Rh catalysis (Figure 1b).

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Supporting Information: The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures, analytical and spectral data for all new compounds (PDF).

Notes: The authors declare no competing financial interest.

Rh catalyzed conjugate additions of organoboron reagents to a wide range of activated alkenes have emerged as one of the most powerful approaches to this type of reaction.⁹ There are significant advantages in comparison to other traditional methods, such as organocuprate chemistry. Only catalytic amounts of the metal are used; indeed, catalytic loadings as low as 0.5 mol % have been reported. The reactions can be carried out in water or water/organic solvent mixtures. In addition, more and more aryl and alkenyl boronic acids and esters are commercially available, or they can be readily synthesized. Significantly for us, substrates containing γ - and δ -lactones and α -lactams have been utilized and tolerated.¹⁰ We recognized, however, two critical challenges. First, β -lactones may not be compatible with the most commonly reported basic/aqueous conditions due to facile ring-opening of the starting material or products.⁷ Secondly, the propensity towards β -hydride elimination¹¹ of the anticipated intermediate **A**, giving Heck-type product **3** (Figure 1b) could result. Here, we report an efficient, stereoselective, one-step synthesis of 3,4-disubstituted β -lactones via Rh-catalyzed conjugate addition of organoboron reagents to α -methylene- β -lactones.

Initial studies examined the reaction of α -methylene- β -lactone **1a** with phenylboronic acid in 3:1 toluene/H₂O at 80 °C (Table 1, entry 1) using Wilkinson's catalyst and K₂CO₃ as base. Although complete conversion was observed after 24 h, a 1:1 mixture of conjugate addition **4** and Heck-type product **5** resulted. In addition, there was extensive material decomposition. Lowering the temperature to 60 °C resulted in a very low conversion (entry 2). However, switching the catalyst to [Rh(cod)Cl]₂ afforded a 100% conversion at the lower temperature, although still providing a mixture of Heck and conjugate addition products (2:1 ratio of **4/5**) (entry 3). The competition between Heck-type reaction and conjugate addition has been previously observed and mechanistically rationalized.¹¹ In some previous studies it has been demonstrated that conjugate addition or Heck-type reaction can be selectively achieved by tuning the catalyst, solvent, reactant ratios, and/or additives. For our system, using a strong base, such as KOH, enhanced conjugate addition relative to Heck reaction (entries 4–6). The ratio of **4/5** and the reaction rate were dependent on the amount of KOH (entries 5–8) with 1 equiv providing optimum conversion to **4** (entry 5). The use of 2 equiv KOH (entry 4) gave good selectivity but diminished isolated yield, possibly due to decomposition¹² of the starting material or products. With no base, the reaction essentially did not proceed at 60 °C (entry 8). While screening other catalysts with the optimized base, temperature and solvent (entries 9,10), [Rh(nbd)Cl]₂ proved equally efficient to [Rh(cod)Cl]₂. Subsequent studies on the scope of the reaction employed [Rh(cod)Cl]₂ as the catalyst and KOH (1 equiv) as the base.

With conditions optimized, the scope of the reaction with respect to the β -lactone and organoboron reagents was explored (Scheme 1). A variety of α -methylene- β -lactones reacted with phenylboronic acid to provide the corresponding 3,4-disubstituted β -lactones (**4**, **6–8**) in good to excellent yields with modest to good 3,4-*trans* selectivity.¹³ In general, the lactone diastereomers were separable (see SI). Bulkier substituents at C-4 (see **6**, **13**, **16**, **19**, **22**, **23**) enhanced diastereoselectivity. As previously mentioned, most monocyclic β -lactone natural products and close analogs that have been explored as drugs or probes are *trans* diastereomers.^{1–6,7a,14} Nevertheless, *cis*- β -lactones have been shown to be as potent as

their *trans*-isomers in some cases.¹⁵ Thus, at this stage, access to both diastereomers is advantageous from the standpoint of diversification.

A variety of aryl boronic acids was examined next. As summarized in Scheme 1, both electron rich and electron poor aryl boronic acids reacted efficiently with α -methylene- β -lactones. More importantly, diverse functional groups were tolerated, including, aryl chlorides (**13**), benzyl/phenyl ethers (**14–16**), phenol (**18**), and styrene (**19**). Heterocyclic-containing aryl boronic acids (**20, 21**) also underwent conjugate addition in good yields. Moreover, alkenyl boronic acids were suitable coupling partners, providing C-3 allylated β -lactones (**22, 23**) in good yields. Notably, the alkene geometry of the boronic acid is preserved in the lactone product. Under similar conditions, α -methylene- γ -lactone also underwent conjugate addition to yield α -substituted γ -lactones (**24, 25**) in excellent yields.

Nocardiolactone (Scheme 1), a *trans*-3,4-disubstituted β -lactone, is a natural product isolated from pathogenic *Nocardia strains* and has been found to exhibit antimicrobial activities.^{6b,16,17} Using the developed Rh-catalyzed conjugate addition of boronic acids to a single substrate, a direct, final-stage diversification at C-3 of nocardiolactone was achieved. Nocardiolactone analogs (**26–28**) were obtained in excellent yields.

Having achieved control of conjugate addition vs Heck reaction, future efforts will focus on control of relative and absolute stereochemistry. Catalysts, ligands and bases have all been used to influence both diastereo and enantioselectivity in Rh catalyzed conjugated additions.^{9,10} In our studies a 2:1 *trans/cis* ratio of **4** was seen under all conditions explored using the catalysts noted for the reaction of **1a** and phenylboronic acid (See entries 1, 4, 5, 9 and 10 in Table 1. Also, the same ratio was seen with other bases/reaction conditions not included here). We also determined that this outcome was not dependent on equilibration subsequent to product formation. A 1:1 mixture of *trans/cis*-**4** was subjected to the optimized reaction conditions and was recovered unchanged. A broader range of Rh catalysts and associated ligands will be explored to enhance control of relative stereochemistry. The preparation of enantioenriched α -methylene- β -lactones has been previously reported, and these methods can be used to access enantioenriched 3,4-disubstituted β -lactones.¹⁸

We view α -methylene- β -lactones as masked Morita-Baylis-Hillman (MBH) adducts.^{8,19} Not only are these lactones readily prepared from and returned to MBH products, but α -methylene- β -lactones also undergo reactions that MBH products do not. For example, whether the allylic OH is protected or not, MBH adducts do not readily undergo CM reactions, while α -methylene- β -lactones (and -lactams) have been shown to be superior CM partners.⁸ Navarre *et al.*²⁰ reported that, when MBH adducts were treated with aryl boronic acids under conditions similar to ours, in sharp contrast to our results, trisubstituted alkenes were obtained (see Scheme 2), an outcome that persisted with different rhodium catalysts, solvents and types of organoboron reagent. When the acetate of a MBH adduct was used, lower reactivity was observed, but the result was the same. We confirmed that, under conditions that gave conjugate addition for α -methylene- β -lactones, MBH adduct **29** reacted with phenylboronic acid to give exclusively trisubstituted (*E*)-alkene **30** in 90% yield (Scheme 2). Thus, while conjugate addition products from MBH adducts appear to be inaccessible under Rh catalysis, such products would result from transesterification of the β -

lactone products obtained from Rh-catalyzed conjugate addition of boronic acids to α -methylene- β -lactones.

In summary, we describe the development of a Rh-catalyzed conjugate addition of boronic acids to α -methylene- β -lactones (and γ -lactones) to yield a variety of 3,4-disubstituted β - (and γ)-lactones in excellent yields with moderate to good *trans* selectivities. This methodology is operationally simple with 1 mol % [Rh(cod)Cl]₂, a reaction time of 1 h, and temperature of 60 °C, preventing unwanted ring-opening reactions. Furthermore, the method is compatible with both aryl and alkenyl boronic acids and tolerates a wide range of functionalities, including, aryl chloride, phenol, styrene and heterocycles. Lastly, this method was utilized in a direct diversification of nocardiolactone to construct C-3 analogs. We anticipate that this approach will have broad utility for late-stage diversification of biologically relevant 3,4-disubstituted β -lactones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This paper is based upon work partially supported by the National Institutes of Health (NIH) under Grant: R01 CA193994. Boehringer Ingelheim is acknowledged for financial support (BI Fellowship for C.A.M.).

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Figure 1.

Syntheses of 3,4-disubstituted β -lactones **2** from α -methylene- β -lactones **1**.

(a) Two-step synthesis of 3,4-disubstituted β -lactones from **1** (previous work):

(b) Proposed one-step synthesis of 3,4-disubstituted β -lactones from **1** (this work):

Scheme 1. Scope of Rh-Catalyzed Conjugate Addition of Boronic Acids to α -Methylene- β -lactones^a

^aTypical reaction conditions: α -methylene- β -lactone (0.5 mmol, 1 equiv), boronic acid (0.75 mmol, 1.5 equiv), $[\text{Rh(cod)Cl}]_2$ (1 mol %, 0.01 equiv), KOH (0.5 mmol, 1 equiv) in 10:1 dioxane/ H_2O (2.8 mL) at 60 $^\circ\text{C}$ for 1 h. In all cases the CA:Heck reaction selectivity is >20:1. Values in parenthesis are isolated yields of the combined isomers. Isomers were separable in most cases (see Supporting Information).

Scheme 2.
Reaction of MBH Adduct 29

Table 1
Optimization of Rh-Catalyzed Conjugate Addition (CA) of Phenylboronic Acid to **1a^a**

entry	Rh catalyst	base (equiv)	conv; ^a time	^c 4:5 (% yield 4)
1 ^d	RhCl(PPh ₃) ₃	K ₂ CO ₃ (2)	100%, 24 h	1:1 ^e
2	RhCl(PPh ₃) ₃	K ₂ CO ₃ (2)	<5%, 24 h	–
3	[Rh(cod)Cl] ₂	K ₂ CO ₃ (2)	100%; 1h	2:1
4	[Rh(cod)Cl] ₂	KOH (2)	100%; 1h	20:1 (60) ^e
5	[Rh(cod)Cl] ₂	KOH (1)	100%; 1h	20:1 (92) ^e
6	[Rh(cod)Cl] ₂	KOH (0.5)	100%; 1h	3.5:1
7	[Rh(cod)Cl] ₂	KOH (0.1)	100%; 48h	2:1
8	[Rh(cod)Cl] ₂	none	<5%; 24 h	–
9	RhCl(PPh ₃) ₃	KOH (1)	100%; 24h	2:1 ^e
10	[Rh(nbd)Cl] ₂	KOH (1)	100%; 1h	20:1 (90) ^e

^aReaction conditions: **1a** (0.5 mmol), PhB(OH)₂ (0.75 mmol), Rh catalyst (2 mol % “Rh”); for entries 1–3, solvent = PhCH₃/H₂O (3:1); for entries 4–11, solvent = dioxane/H₂O (10:1). Yields in parentheses are isolated yields of **4**.

^bTime required to obtain 100% consumption of **1a** based on ¹H NMR analysis.

^cRatio of **4**:**5** based on ¹H NMR of crude reaction mixture.

^d80 °C.

^e*Trans:cis* ratio of **4**, 2:1.