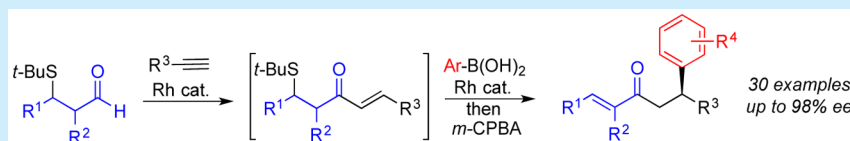


Enantioselective Three-Component Assembly of β' -Aryl Enones Using a Rhodium-Catalyzed Alkyne Hydroacylation/Aryl Boronic Acid Conjugate Addition Sequence

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S Supporting Information



ABSTRACT: Rhodium-catalyzed alkyne hydroacylation using alkyl β -S-aldehydes, enantioselective rhodium-catalyzed aryl boronic acid conjugate addition, and sulfide elimination are combined in sequence to provide β' -aryl enones. The reaction sequence is efficient and delivers highly functionalized products with excellent levels of enantiocontrol. Good variation of the three reaction components is demonstrated. The sequence corresponds to the formal regio- and enantioselective monoconjugate addition of aryl boronic acids to dienones.

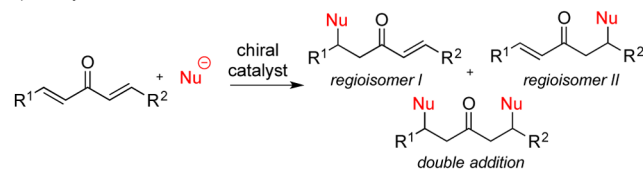
Enantiomerically enriched β' -substituted enones are versatile synthetic building blocks.¹ A simple and conceptually attractive route to these molecules is shown in Scheme 1a and features the catalyst-controlled regio- and enantioselective addition of nucleophiles to dienones. In reality, this approach is plagued by selectivity issues, and unless the dienone substrates are either symmetric^{1b,f} or feature β,β' -substituents of significant steric and/or electronic variation,^{1c-e,2} the formation of two possible regioisomers as well as the double-addition products is likely. To avoid these issues, and to add diversity, we proposed a route to these molecules shown in Scheme 1b. Our design relies on three key operations: (i) rhodium-catalyzed hydroacylative union of an alkyne and a β -substituted alkyl aldehyde to provide β' -substituted enone A;³ (ii) rhodium-catalyzed enantioselective addition of an aryl boronic acid to enone A;⁴ and (iii) elimination of the β -substituent X to provide the target compounds. We have recently established the synthetic utility of combining rhodium-catalyzed hydroacylation and conjugate addition

reactions in one-pot cascade sequences⁵ and, as such, speculated that the targeted route, which employs three readily available starting materials, could be achieved in an efficient and selective manner.

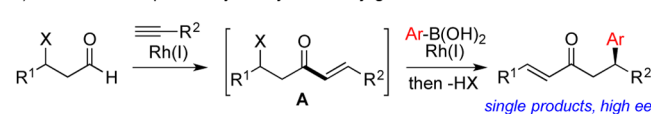
Synthetically useful intermolecular rhodium-catalyzed hydroacylation reactions are dominated by the use of chelating substrates,⁶ with aldehydes featuring coordinating groups based on C-, P-, O-, S-, and N-atoms all known.^{7,8} However, for alkyl aldehyde substrates, β -S-substituted examples are most common.^{5a} Accordingly, we selected a variety of β -S-substituted octenal derivatives as our evaluation substrates and explored their addition to octyne as the first step of our planned sequence (Table 1). Based on earlier studies, we selected the small bite angle ligand dppm as the ligand of choice for use in the hydroacylation step⁹ and diene ligand L1 for the conjugate addition.⁵ Although we could achieve efficient hydroacylation reactions for aldehydes bearing Et-, *i*-Pr-, and *t*-Bu-sulfide substituents, it was only with the sterically demanding *t*-BuS-substituted example that efficient conjugate addition took place (Table 1, entries 1–3).¹⁰ For the experiments in which an efficient conjugate addition was achieved, the final step of the sequence, elimination of the sulfide, was realized by treatment with *m*-CPBA and then DBU. Using this protocol, the combination of *t*-BuS-substituted aldehyde 1a, octyne, and 4-methoxybenzene boronic acid could be achieved in 75% yield and 95% ee, using 3 mol % catalyst loading for the hydroacylation step and 5 mol % catalyst loading for the conjugate addition (entry 3). Two alternative diene ligands (L2 and L3)¹¹ were also evaluated in the conjugate addition step, providing the final product in 94 and –88% ee, respectively (entries 4 and 5).

Scheme 1. Catalyst-Controlled Routes to β' -Substituted Enones

a) Catalyst-controlled additions to dienones

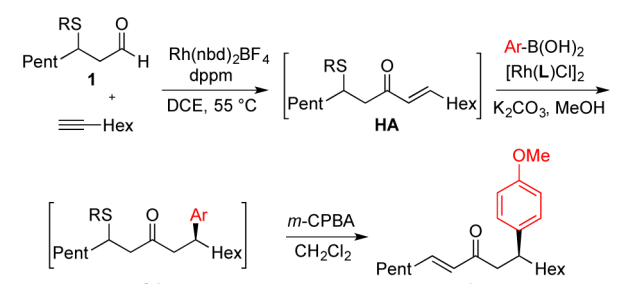


b) **This work:** Sequential hydroacylation/conjugate addition/elimination



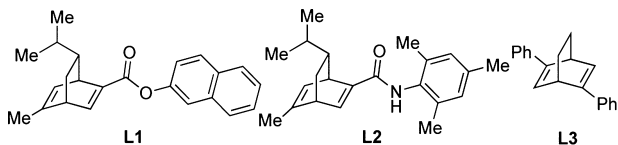
Received: April 11, 2017

Published: May 9, 2017

Table 1. Evaluation of Reaction Conditions for the Formation of Enone 2a^a


entry	R	L	yield (%)	ee ^b (%)
1	Et	L1	0 ^c	
2	<i>i</i> -Pr	L1	0 ^d	
3	<i>t</i> -Bu	L1	75	95
4	<i>t</i> -Bu	L2	73	94
5	<i>t</i> -Bu	L3	75	–88
6 ^e	<i>t</i> -Bu		<5	

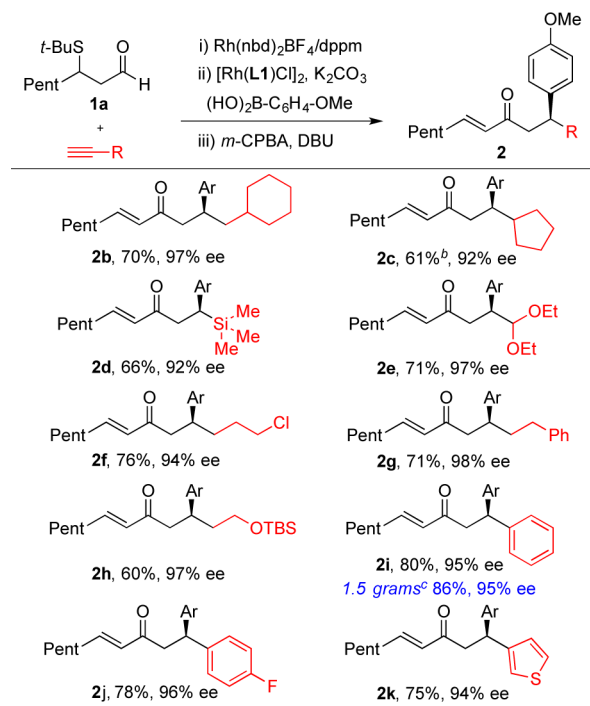
^aReaction conditions: Rh(nbd)₂BF₄ (3 mol %), dppm (3 mol %), aldehyde **1** (1.0 equiv), 1-octyne (1.1 equiv), DCE (1.0 M), 55 °C, 1 h; then 4-MeO-C₆H₄-B(OH)₂ (1.5 equiv), [Rh(L1)Cl]₂ (2.5 mol %), K₂CO₃ (1.0 equiv), DCE/MeOH (0.1 M, 9:1), 55 °C, 1.5 h; then filter through a plug of SiO₂, CH₂Cl₂ (0.1 M), *m*-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), rt, 2.5 h. Isolated yields. ^bMeasured by chiral HPLC. ^c100% conversion to **HA**; 0% conversion to **CA**. ^d100% conversion to **HA**; 34% conversion to **CA**; elimination not performed. ^e[Rh(L1)Cl]₂ not added.



Entry 6, in which no additional catalyst was added for the conjugate addition step, confirms that the dppm-derived hydroacylation catalyst is not an effective catalyst for the conjugate addition step.

Having established the optimal reaction conditions, we next explored the scope of the reaction with respect to the alkyne component; aldehyde **1a** and 4-methoxyphenylboronic acid were held constant (Scheme 2). Alkynes with different steric demand were well-tolerated, yielding the corresponding products in good yields and excellent enantioselectivities (**2b–2d**). A variety of functional groups were successfully tolerated, including acetal (**2e**), chloride (**2f**), phenyl (**2g**), and a silyl-protected alcohol (**2h**). It was also possible to employ arylalkynes in this transformation (**2i**, **2j**). A gram-scale reaction using phenylacetylene was carried out; starting with 5 mmol of aldehyde **1a**, 1.5 g of enone **2i** was obtained in good yield and ee employing only 1 and 2 mol % of catalyst for the hydroacylation and conjugate addition steps, respectively. A thiophene-substituted alkyne was also used successfully, providing product **2k** in 75% yield and 94% ee.

We then directed our attention to the boronic acid reaction component (Scheme 3). Both aryl- and alkyl-substituted alkynes were used in these transformations, with the choice dependent on the ease of separation of the enantiomeric products using chiral HPLC. The reaction was successfully applied to aryl boronic acids bearing both electron-withdrawing (**2m–2o**) and electron-donating (**2p–2r**, **2t**) substituents, which could be placed at all positions of the benzene ring. Notably, enantiomeric

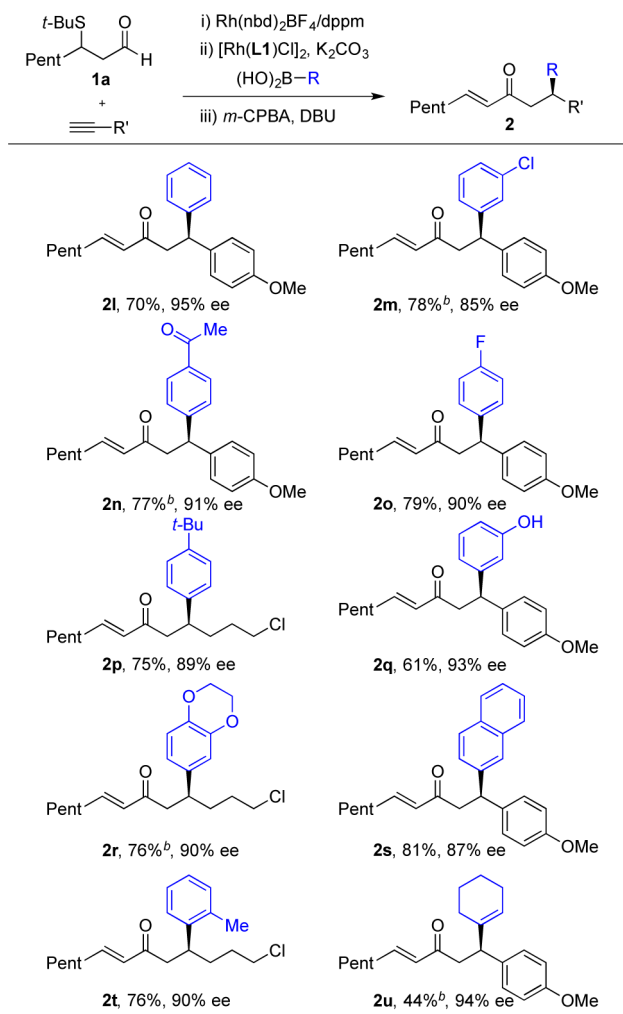
Scheme 2. Variation of the Alkyne Coupling Partner^a

^aAr = 4-MeO-C₆H₄. Reaction conditions: Rh(nbd)₂BF₄ (3 mol %), dppm (3 mol %), **1a** (1.0 equiv), alkyne (1.1 equiv), DCE (1.0 M), 55 °C, 1 h; then boronic acid (1.5 equiv), [Rh(L1)Cl]₂ (2.5 mol %), K₂CO₃ (1.0 equiv), DCE/MeOH (0.1 M, 9:1), 55 °C, 1.5 h; then filter through a plug of SiO₂, CH₂Cl₂ (0.1 M), *m*-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), rt, 2.5 h. ^b[Rh(L2)Cl]₂ was used. ^c5 mmol of **1a**, 1 mol % of Rh(nbd)₂BF₄/dppm, 2 mol % of [Rh(L1)Cl]₂.

product pairs were obtained by varying the alkyne and boronic acid coupling partners (**2i/2l**, **2j/2o**). In addition, naphthyl and alkenyl boronic acids were shown to be effective substrates for this reaction (**2s**, **2u**).

Finally, we evaluated different aldehyde substrates for this transformation (Scheme 4). Aldehydes with a variety of β -substituents were well-tolerated, including alkyl (**2v**, **2w**), aryl (**2x–2z**), phthalimide (**2aa**), and a β,β -dimethyl-substituted example (**2ab**). Notably, products **2w** and **2y** are the formal monoconjugate addition products from symmetrical dienones. α -Substituted aldehydes were also shown to be effective substrates for this reaction, although, in these cases, the elimination step required a longer reaction time (**2ac**, **2ad**). In addition, we succeeded in applying an α,β -disubstituted aldehyde to this transformation, yielding the corresponding cyclohexene-derived ketone (**2ae**).

In conclusion, we have developed a Rh(I)-catalyzed hydroacylation/boronic acid conjugate addition/sulfide elimination sequence, leading to highly functionalized β' -aryl- α,β -unsaturated ketones. The reactions proceed in good yields and provide products with high levels of enantiocontrol. Key to achieving this transformation was the use of a bulky *tert*-butyl sulfide coordinating group for the hydroacylation step. This method serves as an effective alternative to the monoconjugate addition of aryl boronic acids to dienones and employs readily available starting materials and commercially available catalysts. The products obtained, featuring a remaining Michael acceptor, are useful building blocks for further functionalization.

Scheme 3. Variation of the Boronic Acid Coupling Partner^a

^aReaction conditions: $\text{Rh}(\text{nbd})_2\text{BF}_4$ (3 mol %), dppm (3 mol %), **1a** (1.0 equiv), alkyne (1.1 equiv), DCE (1.0 M), 55 °C, 1 h; then boronic acid (1.5 equiv), $[\text{Rh}(\text{L1})\text{Cl}]_2$ (2.5 mol %), K_2CO_3 (1.0 equiv), DCE/MeOH (0.1 M, 9:1), 55 °C, 1.5 h; then filter through a plug of SiO_2 , CH_2Cl_2 (0.1 M), *m*-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), rt, 2.5 h. ^b $[\text{Rh}(\text{L2})\text{Cl}]_2$ was used.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01087.

Experimental procedures and full characterization for all compounds (PDF)

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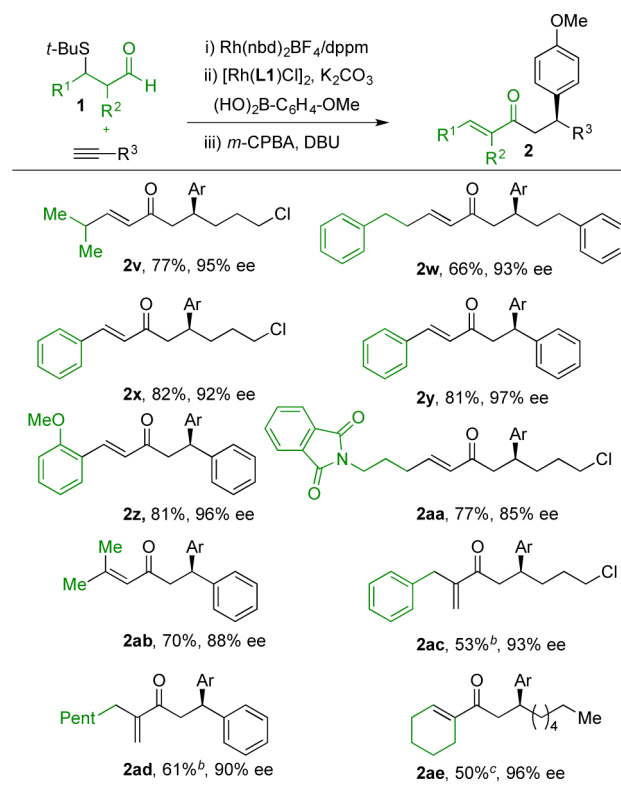
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC for support of this study.

Scheme 4. Variation of the Aldehyde Coupling Partner^a

^aAr = 4-MeO-C₆H₄. Reaction conditions: $\text{Rh}(\text{nbd})_2\text{BF}_4$ (3 mol %), dppm (3 mol %), **1** (1.0 equiv), alkyne (1.1 equiv), DCE (1.0 M), 55 °C, 1 h; then boronic acid (1.5 equiv), $[\text{Rh}(\text{L1})\text{Cl}]_2$ (2.5 mol %), K_2CO_3 (1.0 equiv), DCE/MeOH (0.1 M, 9:1), 55 °C, 1.5 h; then filter through a plug of SiO_2 , CH_2Cl_2 (0.1 M), *m*-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), rt, 2.5 h. ^bReaction stirred at rt for 14 h after addition of DBU. ^cFilter through a plug of SiO_2 , toluene (0.1 M), *m*-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), reflux (120 °C), 1.5 h.

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