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

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ABSTRACT: Rhodium-catalyzed alkyne hydroacylation using alkyl β-S-aldehydes, enantioselective rhodium-catalyzed aryl boronic acid conjugate addition, and sulfi de elimination are combined in sequence to provide β′-aryl enones. The reaction sequence is efi cient 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. 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 diene substrates are either symmetric or feature β,β′-substituents of signifi cant steric and/or electronic variation, 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; (ii) rhodium-catalyzed enantioselective conjugate addition of an aryl boronic acid to enone A; 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 sequences and, as such, speculated that the targeted route, which employs three readily available starting materials, could be achieved in an effi cient and selective manner.

Synthetically useful intermolecular rhodium-catalyzed hydroacylation reactions are dominated by the use of chelating substrates, with aldehydes featuring coordinating groups based on C-, P-, O-, S-, and N-atoms all known. However, for alkyl aldehyde substrates, β-S-substituted examples are most common. Accordingly, we selected a variety of β-S-substituted octenol derivatives as our evaluation substrates and explored their addition to octyne as the fi rst 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 step and diene ligand L1 for the conjugate addition. 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; (ii) rhodium-catalyzed enantioselective conjugate addition of an aryl boronic acid to enone A; 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 sequences and, as such, speculated that the targeted route, which employs three readily available starting materials, could be achieved in an efficient and selective manner.

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Entry 6, in which no additional catalyst was added for the conjugate addition step, confirms that the dpdm-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-methoxynaphthalen-2-carboxylic 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 aryboronic 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 product pairs were obtained by varying the alkyne and boronic acid coupling partners (2i/2j, 2j/2o). In addition, naphthyl and alkylphenylboronic 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–z), phthalimide (2aa), and a ββ′-dimethyl-substituted example (2ab). Notably, products 2w and 2y are the formal monovinylic addition products from symmetrical dienes. 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 αβ-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/sulfoxide elimination sequence, leading to highly functionalized β-aryl-αβ-ununsaturated ketones. The reactions proceed in good yields and provide products with high levels of enantioregion. Key to achieving this transformation was the use of a bulky tert-butyl sulfoxide coordinating group for the hydroacylation step. This method serves as an effective alternative to the monoconjugate addition of aryloboronic acids to dienes 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

![Scheme 3](image)

**Reaction conditions:** Rh(nbd)$_2$BF$_4$ (3 mol%), dpdm (3 mol%), 1a (1.0 equiv), alkene (1.1 equiv), DCE (1.0 M), 55 °C, 1 h; then boronic acid (1.5 equiv), [Rh(L1)Cl$_2$] (2.5 mol%), K$_2$CO$_3$ (1.0 equiv), DCE/MeOH (0.1 M, 9:1), 55 °C, 1.5 h; then filter through a plug of SiO$_2$, CH$_2$Cl$_2$ (0.1 M), m-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), rt, 2.5 h. [Rh(L2)Cl$_2$] was used.

Scheme 4. Variation of the Aldehyde Coupling Partner

![Scheme 4](image)

**Ar = 4-MeO-C$_6$H$_4$. Reaction conditions:** Rh(nbd)$_2$BF$_4$ (3 mol%), dpdm (3 mol%), 1 (1.0 equiv), alkene (1.1 equiv), DCE (1.0 M), 55 °C, 1 h; then boronic acid (1.5 equiv), [Rh(L1)Cl$_2$] (2.5 mol%), K$_2$CO$_3$ (1.0 equiv), DCE/MeOH (0.1 M, 9:1), 55 °C, 1.5 h; then filter through a plug of SiO$_2$, CH$_2$Cl$_2$ (0.1 M), m-CPBA (1.5 equiv), 0 °C, 15 min, then DBU (2.5 equiv), rt, 2.5 h. Reaction stirred at rt for 14 h after addition of DBU. Filter through a plug of mCPBA, toluene (0.1 M), -78 °C, 15 min, then DBU (2.5 equiv), reflux (120 °C), 1.5 h.

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