

Rhodium-Catalyzed Asymmetric Arylation of β,γ -Unsaturated α -Ketoamides for the Construction of Nonracemic γ,γ -Diarylcarbonyl Compounds**

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Abstract: A highly regio- and enantioselective rhodium-catalyzed 1,4-addition of arylboronic acids to β,γ -unsaturated α -ketoamides using a simple new chiral sulfinylphosphine ligand is described. This transformation provides an attractive approach to construct chiral nonracemic γ,γ -diarylsubstituted carbonyl compounds, as exemplified in the concise syntheses of sertraline and tetrahydroquinoline-2-carboxylamide.

Chiral nonracemic γ,γ -diarylsubstituted carbonyl units and their derivatives are typical scaffolds present in a number of natural products, pharmaceuticals, and bioactive compounds (Figure 1).^[1] Many synthetic methods for the construction of

more versatile catalytic systems. The rhodium-catalyzed asymmetric conjugate addition of electron-deficient olefins with arylboronic acids, pioneered by Hayashi, Miyauchi, and co-workers,^[4] is one straightforward method to construct chiral *gem*-diaryl alkanes.^[5] Nevertheless, the asymmetric route to access enantioenriched γ,γ -diarylsubstituted carbonyl compounds remains a significant challenge.^[6] Herein, we report the first enantioselective Rh-catalyzed 1,4-selective conjugate addition of arylboronic acids to β,γ -unsaturated α -ketoamides (Scheme 1), and demonstrate the synthetic utility of the method with a concise formal synthesis of sertraline.

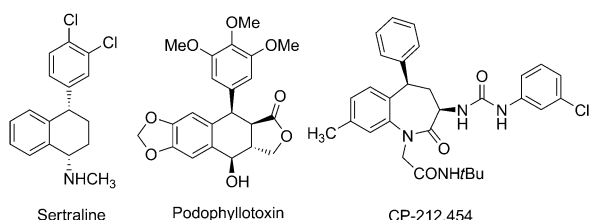
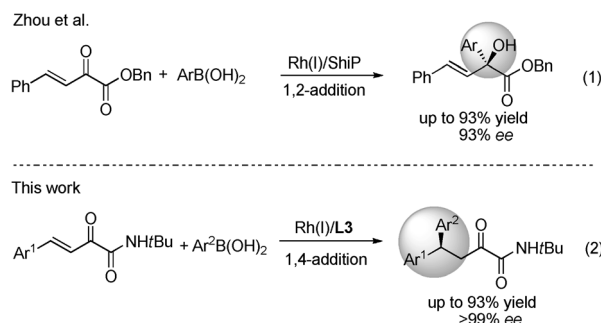


Figure 1. Selected bioactive compounds containing chiral γ,γ -diarylsubstituted carbonyl compounds and derivatives.

enantioenriched γ,γ -diarylsubstituted carbonyl compounds have been developed; however, these compounds are generally prepared through the transformation of optically pure precursors.^[2] Although routes involving asymmetric catalysis provide an attractive alternative, the current methods tend to be limited in scope^[3] and thus require the development of



Scheme 1. Rhodium-catalyzed asymmetric arylation of β,γ -unsaturated α -ketocarbonyl compounds. ShiP = aryl(1,1'-spirobiindane-7,7'-diyl)-phosphite.

Although β,γ -unsaturated α -ketocarbonyl compounds are widely used in aldol, Diels–Alder, Friedel–Crafts, and other reactions,^[7] they have seldom served as Michael acceptors in transition-metal-catalyzed additions^[8] of organometallic reagents. Alexakis et al. used the highly reactive AlMe_3 as the Michael donor to achieve a remarkable Cu-catalyzed asymmetric 1,4-addition to β,γ -unsaturated α -ketoesters,^[8a] as well as β,γ -unsaturated α -ketoamides.^[8b] However, these substrates are particularly challenging for rhodium-catalyzed asymmetric conjugate additions, owing to the high reactivity of the α -keto moiety, which promotes 1,2-addition.^[9] For instance, Zhou and co-workers demonstrated a rhodium-catalyzed asymmetric addition of arylboronic acids to (*E*)-benzyl-2-oxo-4-phenylbut-3-enoate using a spirophosphine ligand, to furnish the 1,2-addition products with excellent yields and enantioselectivities (Scheme 1, Equation 1).^[9c] Another challenge with these substrates is their ability to undergo sequential 1,4- and 1,2-addition, which might complicate the reaction system. To this end, we report a new sulfinylphosphine ligand, which controls the 1,4-selectivity in

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the rhodium-catalyzed arylation of β,γ -unsaturated α -ketoamides with excellent chemo-, regio- and enantioselectivities.

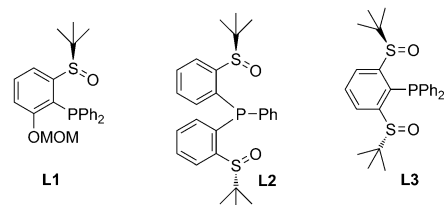
We have previously demonstrated that chiral sulfinylphosphine ligands effectively promoted Rh-catalyzed arylation of arylboronic acids to nitro-styrenes and chalcones, and provide chiral *gem*-diarylalkanes in high yield and enantiomeric excess.^[10] To examine the feasibility of this strategy, phenylboronic acid **2a** was added to the β,γ -unsaturated α -ketoamides (**1a–c**)^[8b] and ligand **L1**^[11] with $[\{\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}\}_2]$ as catalyst, in the presence of aqueous KOH in dichloromethane (DCM) at 40 °C (Table 1, entries 1–3). Amides (**1a–c**) provide the 1,4-adduct **3** as product in more than 86 % yield with excellent 1,4-selectivity (93/7 to 94/6) and enantioselectivities (92–93 % *ee*). The reaction also demonstrated excellent chemoselectivity, in which no double arylation products were detected.^[12] In addition, the nature of the amide (*tert*-butyl-, cyclohexyl-, and benzyl-) does not influence the regio- and enantioselectivity of the reaction (entries 1–3).

Encouraged by the preliminary studies with the sulfinylphosphine ligand **L1**, we tested other ligands (Table 1).^[13] Interestingly, the bifunctional sulfinylphosphine ligand **L2**, which was recently introduced by our group,^[14] did not afford any of the desired product (entry 4). However, the sulfinylphosphine **L3** proved an efficient ligand for this reaction, providing the desired 1,4-adduct **3** in 91 % yield and with 98 % enantiomeric excess (entry 5). The increase of *ee* value from **L1** to **L3** might be attributed to the more appropriate chiral environment provided by the additional *tert*-butylsulfinyl

Table 1: Conditions screening for Rh-catalyzed asymmetric 1,4-addition of phenylboronic acid **2a** to β,γ -unsaturated α -ketoamides (**1a–c**).^[a]

entry	L	1	Ratio ^[b] of 3/4	Yield ^[c] of 3 [%]	<i>ee</i> ^[d] of 3 [%]
1	L1	1a	94/6	90	93
2	L1	1b	93/7	90	92
3	L1	1c	93/7	86	92
4	L2	1a	n.d. ^[e]	trace	n.d. ^[e]
5	L3	1a	94/6	91	98
6 ^[f]	L3	1a	96/4	91	98 (<i>R</i>) ^[15]

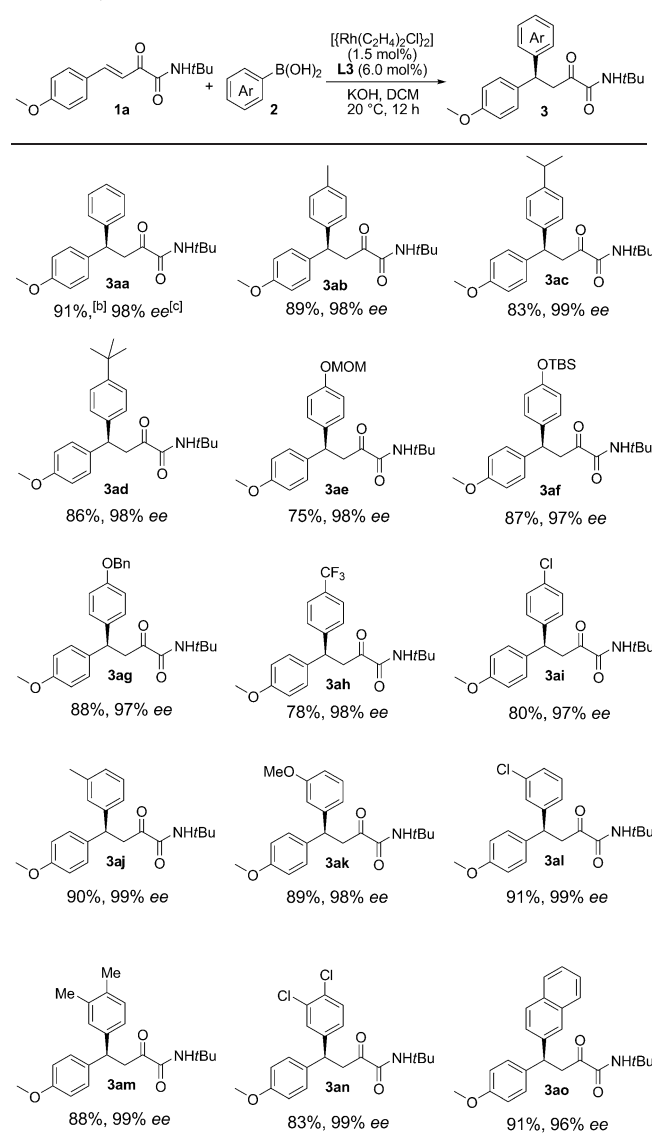
[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[\{\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}\}_2]$ (1.5 mol%), ligand (6.0 mol%), and KOH (50 mol%; 1.0 M in H₂O) in DCM (1.0 mL), 40 °C, 4 h. [b] Determined by crude ¹H NMR spectroscopic analysis. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis. [e] n.d.: not determined. [f] At 20 °C for 12 h. MOM = methoxymethyl.



moiety in **L3**. Importantly, **L3** can be readily prepared by a concise two-step synthetic route via a key intermediate, 1,3-bis(*tert*-butylsulfinyl)benzene **6**, starting from 1,3-dibromobenzene **5** (see Supporting Information). After a systematic screening of the other reaction conditions, such as solvent, base, and the ligand/Rh ratio, a mixture of dichloromethane/potassium hydroxide with a 2:1 ligand/metal ratio proved optimal (see Supporting Information). The best regio- and enantioselectivity and the highest yield of isolated product were achieved for the reaction at 20 °C for 12 hours (entry 6).

Having established the optimal reaction conditions, we examined the scope of potential substrates. Table 2 shows a range of 1,4-adducts **3aa–3ao**, isolated in 75–91 % yield and with excellent enantioselectivities (96–99 % *ee*). These

Table 2: Substrate scope for Rh-catalyzed asymmetric 1,4-addition of various arylboronic acids **2** to β,γ -unsaturated α -ketoamide **1a**.^[a]

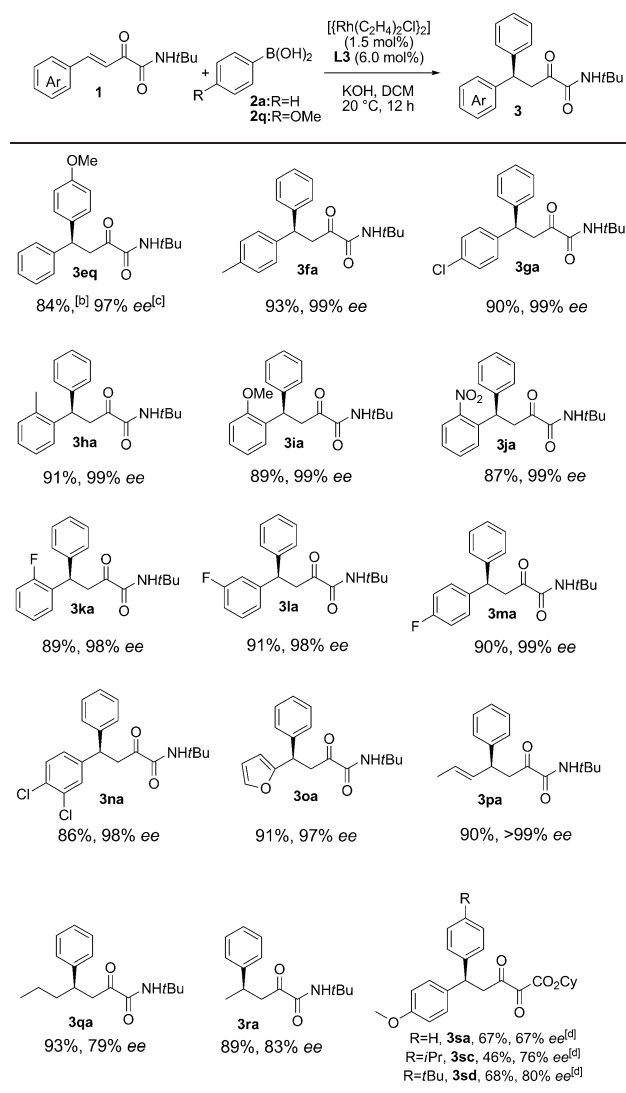


[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $[\{\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}\}_2]$ (1.5 mol%), **L3** (6.0 mol%), and KOH (50 mol%; 1.0 M in H₂O) in DCM (1.0 mL), 20 °C, 12 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. TBS = *tert*-butyldimethylsilyl.

adducts were prepared from reactions between α -ketoamide **1a** and a variety of arylboronic acids with different stereo-electronic properties (electron-rich and electron-poor). Note, in addition to monosubstituted derivatives, 3,4-disubstituted phenylboronic acids **2m** and **2n** react efficiently with **1a** to furnish **3am** and **3an**. For *ortho*-substituted derivatives, *ortho*-methoxyphenylboronic acid was unreactive, however the reaction with 2-naphthylboronic acid proceeded efficiently to yield **3ao** (91 % yield, 96 % *ee*).

Having established the scope of the arylboronic acid reagent, we turned our attention to the α -ketoamide. The products from the reactions between various β,γ -unsaturated α -ketoamides **1e–1r** (see the Supporting Information for structures) and arylboronic acids (**2a** or **2q**) are shown in Table 3. Interestingly, the stereoelectronic properties of the γ -aryl groups in **1e–1n** do not affect the overall efficiency and

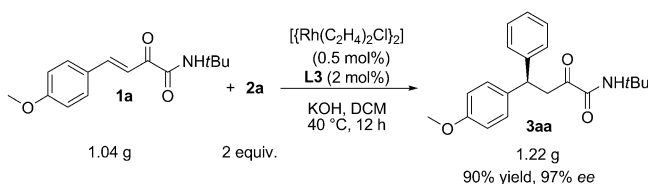
Table 3: Substrate scope for Rh-catalyzed asymmetric 1,4-addition of phenylboronic acid **2a** to various β,γ -unsaturated α -ketoamides.^[a]



[a] Conditions: **1** (0.2 mmol), **2a/2q** (0.4 mmol), $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (1.5 mol%), **L3** (6.0 mol%), and KOH (50 mol%; 1.0 M in H_2O) in DCM (1.0 mL), 20 °C, 12 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] **L1** as ligand, Cy = cyclohexyl.

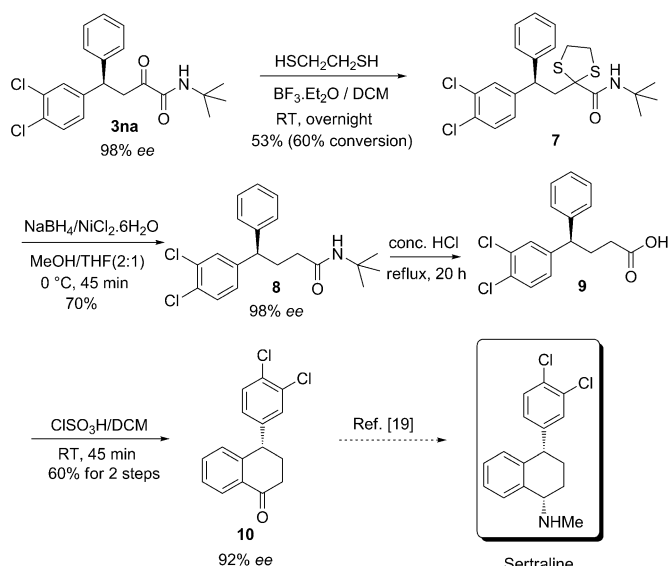
selectivity of this transformation. Gratifyingly, bulky γ -aryl groups with *ortho*-substituents readily undergo reaction to form products **3ha–3ka** with good yields and excellent enantioselectivities (up to 99% *ee*), in contrast to the arylboronic acid substrate limitation. The γ -dichlorophenyl- and γ -furyl-substituted **3na** and **3oa** were also readily prepared by this method. Using the conjugated diene **1p** as substrate, functional crotyl-substituted 1,4-adduct **3pa** was obtained in 90% yield and more than 99% *ee*. In this reaction, no 1,6-addition product was observed. Note, this methodology also provided a general route for the synthesis of enantiomerically enriched γ -alkyl- γ -aryl (particularly, γ -methyl- γ -aryl) carbonyl compounds from γ -alkyl- β,γ -unsaturated α -ketoamides.^[8a,b,16] For example, the reaction between phenylboronic acid **2a** and γ -methyl- and γ -propyl- β,γ -unsaturated α -ketoamides (**1q** and **1r**) proceeded smoothly in the rhodium-catalyzed 1,4-arylation to provide **3qa** and **3ra** in good yields and in enantiomeric excess. In addition, β,γ -unsaturated α -ketoesters were employed in the catalytic system (using **L1** as the ligand) and were readily transformed to their corresponding products **3sa**, **3sc**, and **3sd** with 46–68% yields and 67–80% *ee*. In this case, lower yields were observed because of the partial decomposition of substrates and products under the basic reaction conditions.

The performance of the new rhodium/sulfinylphosphine catalyst in the enantioselective 1,4-addition reaction was also undertaken on a gram scale, using 0.5 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ and the β,γ -unsaturated α -ketoamide **1a** (1.04 g, 3.84 mmol), with 2 equivalents of phenylboronic acid **2a** at 40 °C for 12 hours. This reaction afforded the 1,4-adduct **3aa** in excellent yield (1.22 g, 90%) and without loss of enantioselectivity (97% *ee*, Scheme 2).

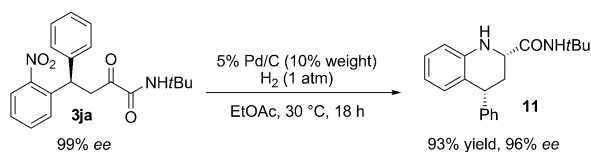


Scheme 2. Gram scale experiment.

The utility of this methodology is demonstrated in a concise formal synthesis^[2a–c] of sertraline (Scheme 3), an important pharmaceutical agent for the treatment of depression. The 1,4-adduct **3na** (98% *ee*) was converted into 1,3-dithiolane **7** and then reduced^[8b,17] to form γ,γ -diarylamine **8**, without the loss of enantiomeric excess.^[18] The amide **8** was hydrolyzed by heating under reflux in concentrated HCl for 20 hours to afford **9**. Product **9** was then subjected to an acid-catalyzed cyclization^[2b] to provide the tetralone **10** in 60% yield and 92% enantiomeric excess for 2 steps (overall yield 22%). The tetralone **10** can be readily converted into sertraline by a known procedure.^[19] Furthermore, to exploit the carbonyl group of the α -ketoamide product (Scheme 4), the adduct *N*-*tert*-butyl-4-(2-nitrophenyl)-2-oxo-4-phenylbutanamide (**3ja**) was exposed to an atmosphere of hydrogen (1 atm) in the presence of Pd/C as catalyst (5 %).^[20] Product



Scheme 3. Synthesis of sertraline from 1,4-adduct **3 na**.



Scheme 4. Catalytic hydrogenation of 1,4-adduct **3 ja** to prepare tetrahydroquinoline-2-carboxylamide.

11, one of a new class of tetrahydroquinoline-2-carboxyl derivatives, was isolated in 93 % yield and 96 % *ee*.^[21]

In summary, we have developed a new chiral sulfenylphosphine ligand **L3**, which promotes, for the first time, the rhodium-catalyzed 1,4-addition of arylboronic acids to β,γ -unsaturated α -ketoamides. This methodology proceeds with excellent chemo-, regio- and enantioselectivities in high yield (up to 93 %) and high enantiomeric excess (up to 99 % *ee*). The procedure provides a convenient approach to access important chiral γ,γ -diarylsubstituted carbonyl compounds. Additionally, the synthetic utility of this methodology was demonstrated in a concise formal synthesis of sertraline and the synthesis of a tetrahydroquinoline-2-carboxyl derivative. Studies to apply enantioenriched γ,γ -diarylsubstituted carbonyl compounds in useful organic syntheses are underway in our laboratory.

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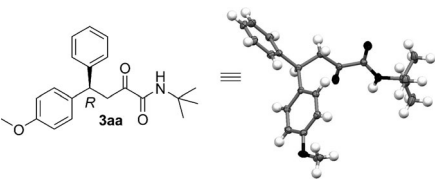
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