Asymmetric Catalysis

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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 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 more versatile catalytic systems. The rhodium-catalyzed asymmetric conjugate addition of electron-deficient olefins with arylboronic acids, pioneered by Hayashi, Miyaura, 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.

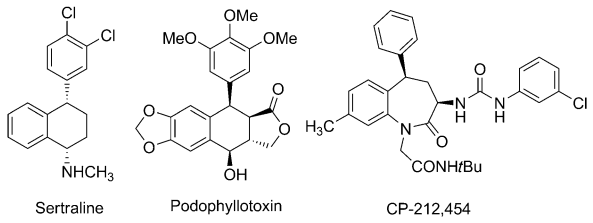
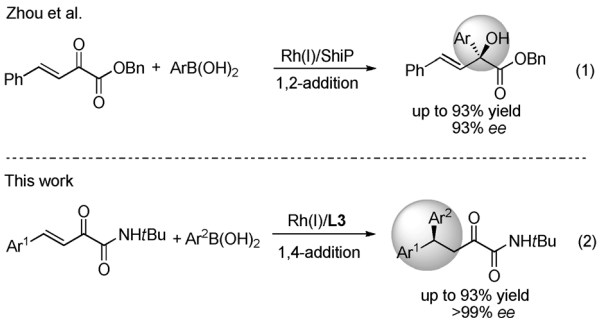


Figure 1. Selected bioactive compounds containing chiral γ,γ-diarylsubstituted carbonyl compounds and derivatives.



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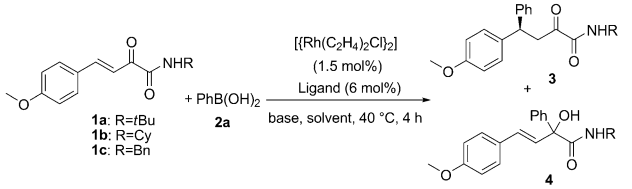
the rhodium-catalyzed arylation of β,γ-unsaturated α-ketoamides with excellent chemo-, regio- and enantioselectivities.

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 $[\{Rh(C_2H_4)_2Cl\}_2]$ 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 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 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 [%]	*ee*[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 (*R*)[15]

[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[\{Rh(C_2H_4)_2Cl\}_2]$ (1.5 mol %), ligand (6.0 mol %), and KOH (50 mol %; 1.0 M in H_2O) 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.

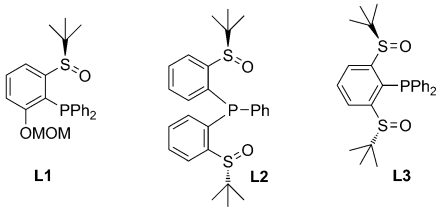
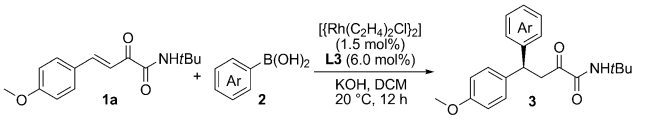
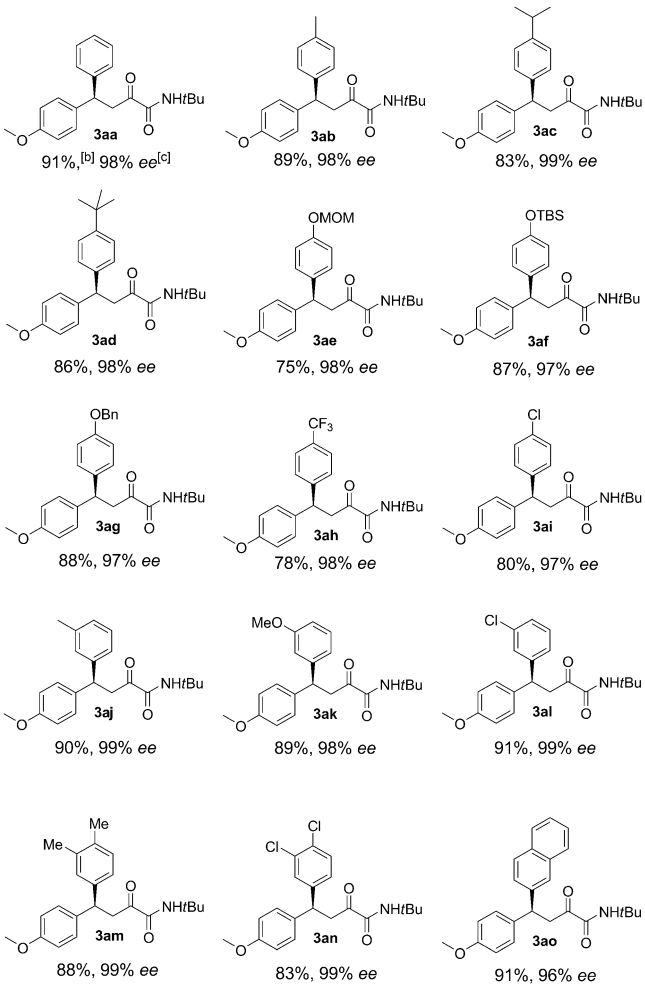


Table 2: Substrate scope for Rh-catalyzed asymmetric 1,4-addition of various arylboronic acids **2** to β,γ-unsaturated α-ketoamide **1a**.[a]



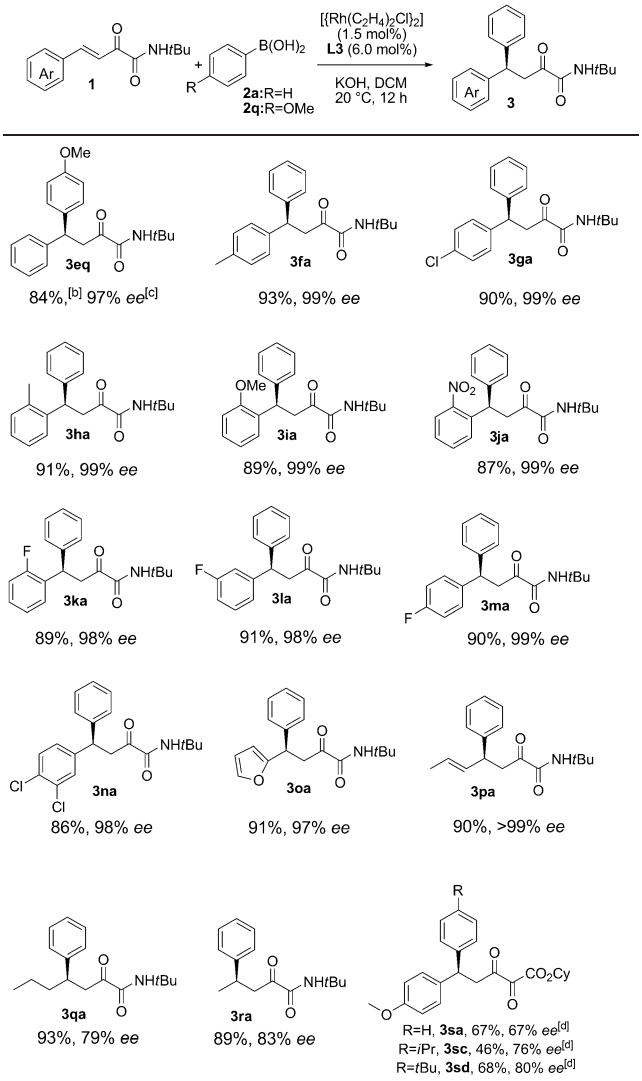


[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $[\{Rh(C_2H_4)_2Cl\}_2]$ (1.5 mol %), **L3** (6.0 mol %), and KOH (50 mol %; 1.0 M in H_2O) in DCM (1.0 mL), 20 °C, 12 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. TBS = *tert*-butyldimethylsilyl.

adducts were prepared from reactions between α-ketoamide **1a** and a variety of arylboronic acids with different stereoelectronic 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*).

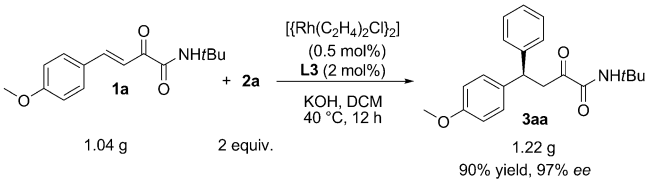
Having established the scope of the arylboronic acid reagent, we turned our attention to the α-ketoamide. The products from the reactions between various β,γ-unsaturated α-ketoamides **1e**–**1r** (see the Supporting Information for structures) and arylboronic acids (**2a** or **2q**) are shown in Table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

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



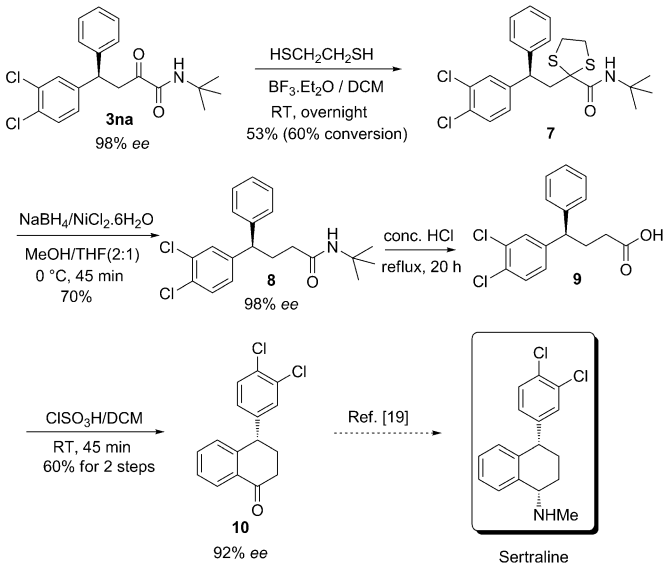
[a] Conditions: **1** (0.2 mmol), **2a**/**2q** (0.4 mmol), [{Rh(C$_2$H$_4$)$_2$Cl}$_2$] (1.5 mol%), **L3** (6.0 mol%), and KOH (50 mol%; 1.0 M in H$_2$O) in DCM (1.0 mL), 20 °C, 12 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] **L1** as ligand, Cy = cyclohexyl.

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 [{Rh(C$_2$H$_4$)$_2$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).

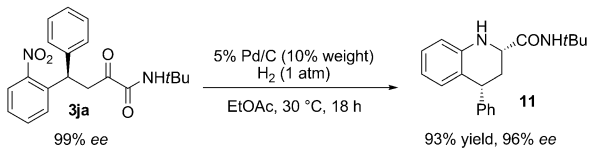


Scheme 2. Gram scale experiment.

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-diarylamide **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 sulfinylphosphine 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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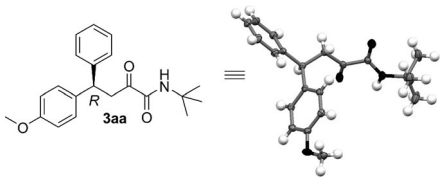
[15] The absolute configuration of **3aa** was determined by single-crystal X-ray crystallography, displacement ellipsoids set at 50% probability. CCDC 995001 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



[16] Selected examples, see: a) S. Song, S. F. Zhu, S. Yang, S. Li, Q. L. Zhou, *Angew. Chem.* **2012**, *124*, 2762; *Angew. Chem. Int. Ed.* **2012**, *51*, 2708; b) K. Tanaka, S. Qiao, M. Tobisu, M. M. C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 9870; c) Y. Kiyotsuka, Y. Katayama, H. P. Acharya, T. Hyodo, Y. Kobayashi, *J. Org. Chem.* **2009**, *74*, 1939; d) T. Magauer, H. J. Martin, J. Mulzer, *Angew. Chem.* **2009**, *121*, 6148; *Angew. Chem. Int. Ed.* **2009**, *48*, 6032; e) D. J. Mans, G. A. Cox, T. V. Rajanbabu, *J. Am. Chem. Soc.* **2011**, *133*, 5776.

[17] M. Amat, O. Bassas, M. Cantò, N. Llor, M. M. M. Santos, J. Bosch, *Tetrahedron* **2005**, *61*, 7693.

[18] 40% of starting material **3na** was recovered from the first step. Wolf–Kishner reduction was used to reduce the ketone and **8** was obtained in high yield (87% yield for two steps). However, the *ee* of **8** decreased to 26% (see Supporting Information for details).

[19] a) G. J. Quallich, *Chirality* **2005**, *17*, S120; b) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345.

[20] R. A. Bunce, D. M. Herron, L. B. Johnson, S. V. Kotturi, *J. Org. Chem.* **2001**, *66*, 2822; For solvent effects on the enantioselectivity of the product, see Supporting Information.

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