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Highly Regioselective Introduction of Aryl Substituents via Asymmetric 1,4-Addition of Boronic Acids to Linear α,β,γ,δ-Unsaturated Ketones

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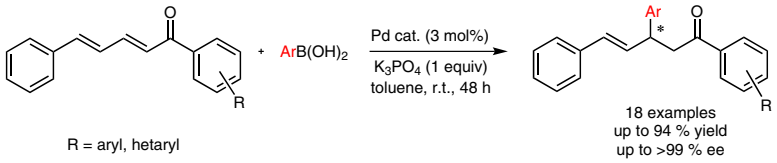

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Abstract An efficient palladium(II)-catalyzed regioselective asymmetric 1,4-conjugate addition of arylboronic acids to linear α,β,γ,δ-unsaturated ketones is developed using phosphapalladacycle catalysts. The relevant 1,4-products were obtained exclusively with perfect regioselectivity, appreciable yields, and enantioselectivities. A wide range of dienone substrates as well as substituted arylboronic acids are tolerated in this protocol which proceeds at room temperature.

Key words asymmetric catalysis, regioselectivity, phosphapalladacycle, boronic acid, conjugate addition

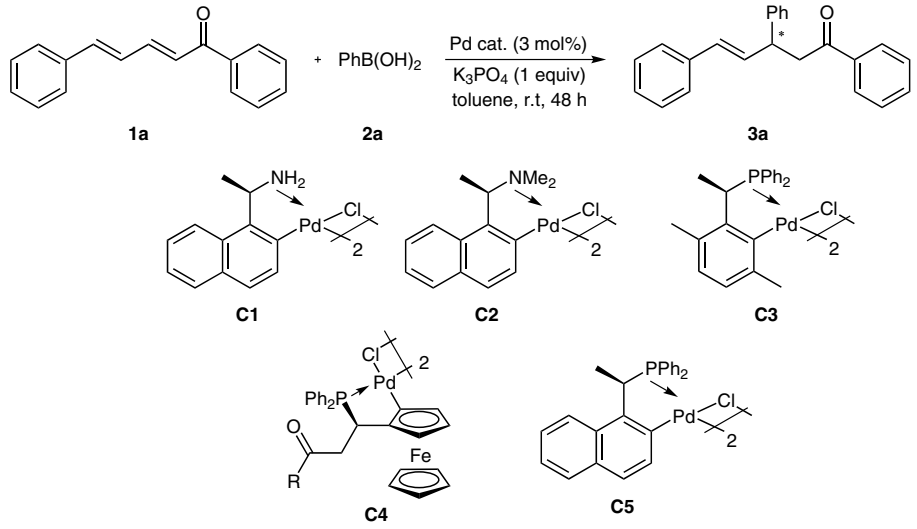
Enantioselective 1,4-addition of C-nucleophiles to α,β-unsaturated enones serves as a powerful synthetic tool toward asymmetric C–C bond formation.[1–3] Despite the substantial progress achieved in this area, reports on the analogous asymmetric addition of C-nucleophiles to polyconjugated substrates such as α,β,γ,δ-unsaturated enones have been relatively limited due to the difficulty in simultaneously controlling both the regioselectivity (1,2- vs. 1,4- vs. 1,6-addition) as well as the enantioselectivity of the reaction. For α,β,γ,δ-unsaturated cyclic enones, highly efficient protocols relying on copper-based catalysts have been reported by Alexakis et al., employing Grignard reagents which can selectively yield 1,4-adducts[4a] as well as a regiodivergent method employing trialkylaluminium reagents which provides access to 1,6-adducts.[4c] For linear α,β,γ,δ-unsaturated enones, selective 1,6-additions of Grignard, trialkylaluminium, and zinc-based C-nucleophiles have been reported with copper-, rhodium-, and iridium-based catalytic systems.[5] Furthermore, reports by Hayashi et al. have established iridium–chiral diene catalyzed protocols that selectively yield 1,6-adducts in an enantioselective manner when employing boroxines.[6]

When compared to the aforementioned, a highly regioselective methodology for the selective 1,4-addition of alkyl or aryl substituents on conjugated α,β,γ,δ-unsaturated enones is rare. Zhang et al. have recently reported a copper-catalyzed methodology using Grignard reagents which proceeds at –70 °C utilizing a ferrocenyl monophosphinooxazoline ligand.[7] However, the attempted addition of a benzyl moiety using the methodology led to poor yields and enantiomeric excesses.

Therefore, a protocol which allows the simultaneous control of both regio- and stereoselectivity during the course of the 1,4-addition of aryl substituents onto linear α,β,γ,δ-unsaturated enones when employing air- and moisture-stable reagents under facile conditions is highly desirable.

We have recently disclosed the efficacy of phosphapalladacycles as catalysts toward the addition of arylboronic acids to linear and cyclic α,β-unsaturated enones, thus providing a viable alternative to existing rhodium(I) and copper(I)/(II) catalysts for the preparation of synthetically relevant C-chiral skeletons.[8] These results prompted us to further explore the potential of chiral palladacycles as catalysts for a regioselective addition protocol involving linear polyconjugated enones using cheap and easily accessible arylboronic acids. Of particular interest would be the regioselectivity pattern exhibited by these catalysts in the case of a conjugated substrate.

We initiated our study by choosing the reaction of (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**1a**) with two equivalents of phenylboronic acid (**2a**) as our model (Scheme 1). We proceeded to screen a range of palladacycles, **C1**–**5** to analyze their catalytic efficacy. While the C–N-type palladacycles **C1** and **C2** were ineffective toward the addition reaction (Table 1, entries 1 and 2), their phosphapalladacycle analogues **C3**–**5** provided more encouraging results. This is in agreement with previous observations



Scheme 1 Optimization of conditions for the 1,4-addition phenylboronic acid (**2a**) to linear polyconjugated enone **1a**

that N–C palladacycles are typically inactive in this scenario due to their innate tendency to preferentially undergo reductive elimination.[9] A preliminary analysis of the results obtained revealed that phosphapalladacycle **C5** was the most effective, furnishing the desired 1,4-adduct in a highly regioselective manner with a 40% nonoptimized yield and 53% enantiomeric excess with no 1,2- or 1,6-addition products observed on the crude ^{1}H NMR spectrum (Table 1, entry 5). The structural attributes of this catalyst, which allows it to effectively relay stereocontrol to the reaction centers on palladium(II), has been previously described.[10] The influence of the boron source was subsequently analyzed. Use of both phenylboroxine $(PhBO)_3$ and phenyl potassium trifluoroborate salt ($K^+PhBF_3^-$), however, did not result in a substantial increase in yield and enantiomeric excess (Table 1, entries 6 and 7). We then proceeded to study the impact of the tandem increase in boronic acid concentration and catalyst loading (5 equiv and 3 mol% vs. 2 equiv and 2.5 mol%). These modifications led to an appreciable increase in yield to 87% and selectivity to 76% when the addition was conducted over 48 hours at room temperature. Lowering the reaction temperature to 0 °C did not provide considerable improvement in selectivity but the yield deteriorated significantly (Table 1, entry 8 vs. 9).

Using the chosen phosphapalladacycle **C5** and adopting the optimized conditions as in Table 1, entry 8, we proceeded to screen the addition of **2a** to various derivatives of dienone **1a** obtained by variation of the R moiety at the carbonyl carbon. This yielded the addition products **3a**–**k** (Scheme 2) in satisfactory yields (60–94%), perfect regioselectivity, and moderate enantiomeric excess (66–80%).[13] Interestingly, although the phenylation of 2-furyl- and 2-thienyl-functionalized ketones proceeded smoothly yielding **3b** and **3c**, no product was observed when the 2-pyridyl-functionalized conjugated ketone was employed. The reaction proved robust when relatively bulky naphthyl and substituted benzyl substrates were used (**3d**–**f**). Furthermore, the electronic influence of the *para* substituent on reactivity was clearly evident when results obtained with **3g** and **3h** were compared. With an electron-donating group (4-MeO), a moderate yield of 60% with 66% enantiomeric excess was obtained. However, with an electron-withdrawing group (4-F_3C), high yield of 86% and 79% enantiomeric excess was achieved. This addition procedure can also be extended to 4-halogenated aromatic substrates **3i**–**k**. In these cases,

Table 1 Optimization of Conditions for the 1,4-Addition of Phenylboronic Acid (**2a**) to Linear Polyconjugated Enone **1a**[a]

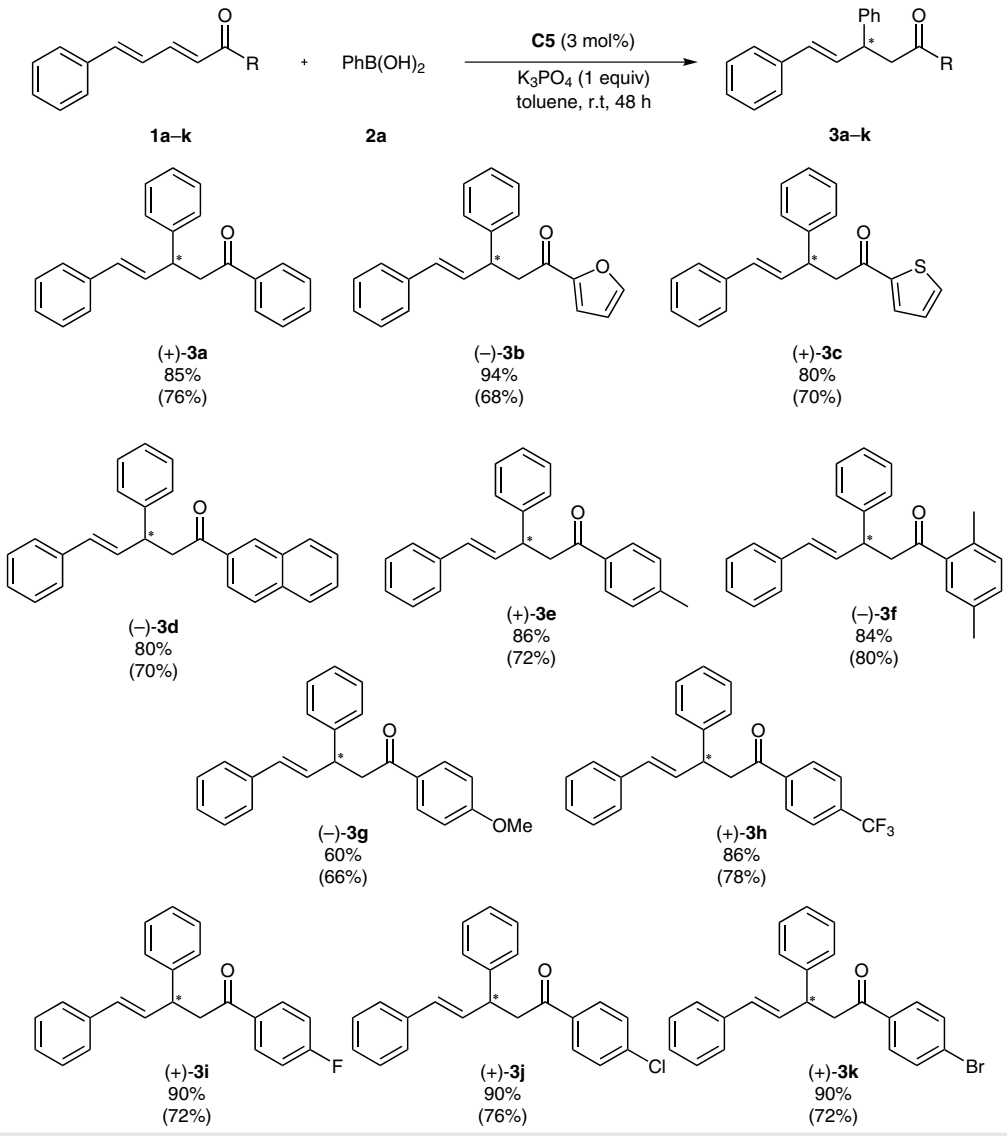
Entry	Cat. (mol%)	**2a** (equiv)	Temp	Yield (%)[b]	ee (%)[c]
1	**C1** (2.5)	2	r.t.	0	n.d.
2	**C2** (2.5)	2	r.t.	0	n.d.
3	**C3** (2.5)	2	r.t.	<10	19
4	**C4** (2.5)	2	r.t.	30	44
5	**C5** (2.5)	2	r.t.	40	53
6	**C5** (2.5)	1 $(PhBO)_3$	r.t.	20	43
7	**C5** (2.5)	2 ($K^+PhBF_3^-$)	r.t.	0	n.d.
8	**C5** (3)	5	r.t.	87	76
9	**C5** (3)	5	0 °C	60	79

[a] All reactions were performed in the presence of 0.5 mmol **2a**, 0.1 mmol **1a**, 2.5 or 3 mol% catalyst, 0.1 mmol K_3PO_4 in 0.5 mL of toluene at the stated temperature for 48 h. The structure of **3a** was determined via comparison of ^{1}H NMR and ^{13}C NMR spectra with known dossiers.[11]
[b] Isolated yield after column purification
[c] The ee were determined via HPLC using a chiral column, chirality of **3a** was determined via comparison of optical rotation values with known dossiers.[12]

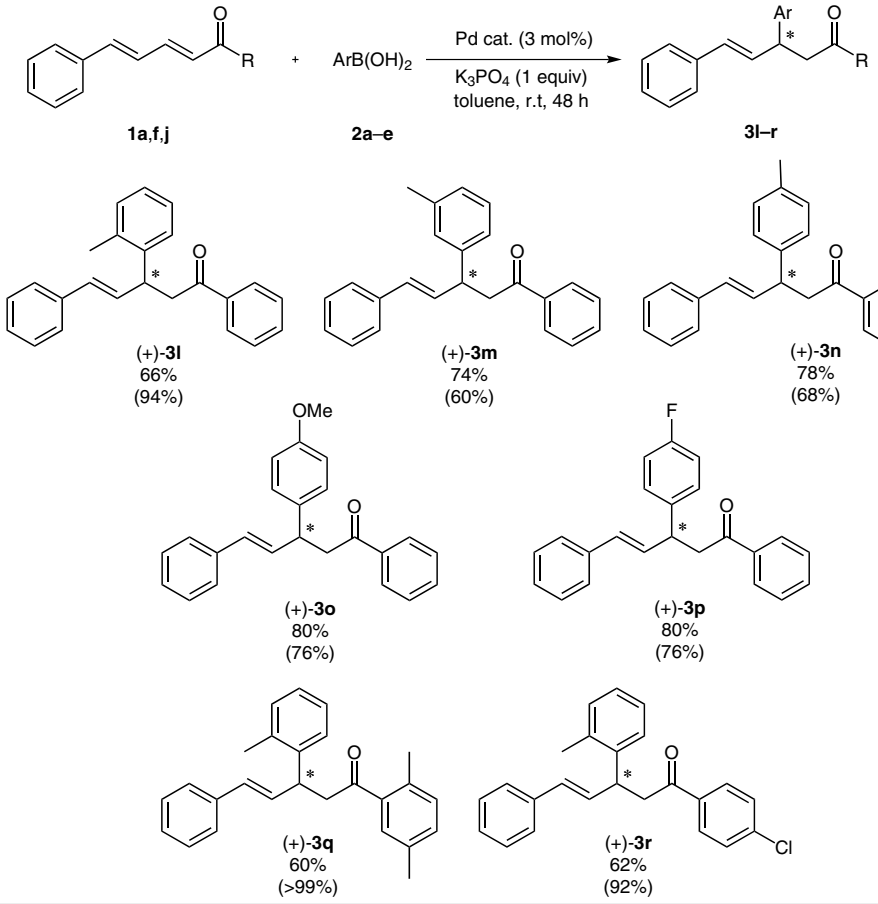
yields obtained were consistently high (90%), with fluorinated and brominated substrates providing 72% enantiomeric excess while the chlorinated derivative afforded 76% enantiomeric excess.

Subsequently, we studied the tolerance of this protocol to the use of other aryl boronic acids when used in conjunction with various linear dienones. Trace conversions were observed when bulky groups (1-naphthyl and 2-naphthyl boronic acids) were used. Tolyl boronic acids (Scheme 3, **3l**–**n**,**q**,**r**) in general gave comparatively low yields (60–66%) when the methyl substituent of the incoming aryl boronic acid moiety is aligned closer to the β carbon of the enone substrate. In other instances, the yields were appreciably higher (74–80%).

On the other hand, the enantiomeric excesses showed an opposite trend, with high enantiomeric excesses obtained (94–99%) when substituents on the aryl boronic acid moiety were in the 2-position while those where the substituents are in the 3- and 4-positions gave lower enantioselectivity values (60–76%). It was also noted that the addition of *o*-tolylboronic acids to conjugated enone substrates where the R group at the carbonyl carbon were substituted phenyls gave higher enantioselectivity values (Scheme 3, 3l vs. **3q** vs. **3r**).



Scheme 2 1,4-Addition of phenylboronic acid **2a** to polyconjugated enones **1a**–**k**. All reactions were performed in the presence of 0.5 mmol **2a**, 0.1 mmol **1a**–**k**, 3 mol% catalyst, 0.1 mmol K_3PO_4 in 0.5 mL of toluene at the stated temperature. Isolated yields are followed by enantiomeric excesses in brackets. The enantiomeric excess was determined by HPLC using a chiral column.



Scheme 3 1,4-Addition of functionalized boronic acids to **1a** All reactions were performed in the presence of 0.5 mmol **2a**, 0.1 mmol **1a–k**, 3 mol% catalyst, 0.1 mmol K_3PO_4 in 0.5 mL of toluene at the stated temperature. Isolated yields are followed by enantiomeric excesses in brackets. The enantiomeric excess was determined by HPLC using a chiral column.

In conclusion, we have developed a facile palladium(II)-catalyzed regioselective asymmetric 1,4-addition protocol for the reaction between arylboronic acids and linear α,β,γ,δ-unsaturated enones which can be conducted at room temperature using easily accessible and stable boronic acids. It needs to be noted that the previous reported method for the installation of aryl moieties on linear α,β,γ,δ-unsaturated enones required the use of Grignard reagents and had to be carried out at –70 °C. The ability of the current protocol to tolerate a wide range of substituted enone substrates as well as arylboronic acids makes it a versatile method which fills the lacunae that currently exists with regards to the lack of a regio- and enantioselective method for the introduction of aryl groups while allowing the use of cheap reagents under ambient conditions. Efforts in our laboratory are currently focused on further catalyst development and the application of this methodology to other asymmetric synthesis scenarios.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560513.

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(12) See Supporting Information.

(13) **Synthesis of Compound 3**

Arylboronic acid (0.5 mmol, 5 equiv) and α,β,γ,δ-unsaturated ketone (0.1 mmol, 1 equiv) were added to a solution of catalyst (0.015 mmol, 3 mol%) in toluene (0.5 mL). K_3PO_4 (0.1 mmol, 1 equiv) was subsequently added, and the solution left to stir for 48 h. The crude adduct was then purified via silica gel chromatography (*n*-hexanes–EtOAc = 10:1 or *n*-hexanes–CH_2Cl_2 = 1:1).

(*R*)-1,3,5-Triphenylpent-4-en-1-one (3a)

Light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.51 (m, 2 H, CH_2), 4.31 (m, 1 H, CHAr), 6.40 (m, 2 H), 7.18–7.56 (m, 13 H), 7.94 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.0, 44.6, 126.3, 126.7, 127.3, 127.8, 128.1, 128.5, 128.7, 128.7, 130.1, 132.7, 133.1, 137.2, 137.2, 143.4, 198.2. ESI-HRMS: *m/z* calcd for $C_{23}H_{21}O$ [M + H]$^+$: 313.1592; found: 313.1591. $[\alpha]_D$ 3.01 (*c* 0.7, $CHCl_3$). The er were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n*-hexanes–*i*-PrOH = 98:2, 0.5 mL/min, 254 nm: t_R (major) = 22.1 min; t_R (minor) = 25.3 min.

(+)-3,5-Diphenyl-1-(*p*-tolyl)pent-4-en-1-one (3e)

Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, ArMe), 3.46 (m, 2 H, CH_2), 4.29 (m, 1 H, CHAr), 6.39 (m, 2 H), 7.16–7.31 (m, 12 H), 7.84 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 44.0, 44.4, 126.3, 126.6, 127.2, 127.8, 127.9, 128.3, 128.5, 128.5, 128.7, 129.3, 130.0, 132.7, 134.7, 137.3, 143.4, 143.9, 197.8. ESI-HRMS: *m/z* calcd for $C_{24}H_{23}O$ [M + H]$^+$: 327.1749; found: 327.1744. $[\alpha]_D$ 0.8 (*c* 0.4, CH_2Cl_2). The er were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n*-hexanes–*i*-PrOH = 98:2, 0.5 mL/min, 280 nm: t_R (major) = 21.4 min; t_R (minor) = 23.2 min.

(+)-1,5-Diphenyl-3-(*p*-tolyl)pent-4-en-1-one (3n)

Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, ArMe), 3.47 (m, 2 H, CH_2), 4.26 (m, 1 H, CHAr), 6.38 (m, 2 H), 7.10–7.56 (m, 12 H), 7.94 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 43.7, 44.7, 126.2, 127.6, 128.1, 128.4, 128.6, 129.4, 132.8, 133.0, 136.2, 137.3, 140.3, 198.4. ESI-HRMS: *m/z* calcd for $C_{24}H_{23}O$ [M + H]$^+$: 327.1749; found: 327.1750. $[\alpha]_D$ 5.2 (*c* 0.2, CH_2Cl_2). The er was determined via HPLC using a chiral column (Daicel Chiralpak IC), *n*-hexanes–*i*-PrOH = 99:1, 0.5 mL/min, 210 nm: t_R (major) = 26.5 min (major); t_R (minor) = 29.9 min.