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Enantioselective, Palladium-Catalyzed Conjugate Additions of Arylboronic Acids to Form Bis-benzylic Quaternary Stereocenters

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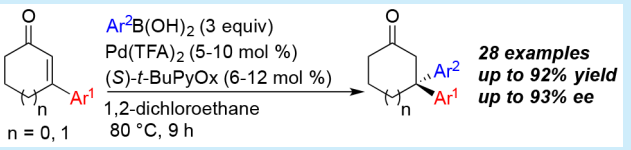
Supporting Information

ABSTRACT: We report enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β-aryl, β,β-disubstituted enones to generate ketones containing bis-benzylic quaternary stereocenters. A catalyst generated from palladium trifluoroacetate and (*S*)-4-*tert*-butyl-2-(2-pyridyl)oxazoline ligand ((*S*)-*t*-BuPyOx) promotes conjugate additions of a wide range of arylboronic acids to a variety of β-aryl, β,β-disubstituted enones. Iterative addition of the arylboronic acid to minimize undesired protodeboronation pathways leads to efficient formation of the corresponding ketones containing bis-benzylic quaternary stereocenters in up to 92% yield and up to 93% enantioselectivity.



Compounds containing bis-benzylic quaternary centers are present in an array of biologically active compounds[1] (Figure 1) and are a structural motif found in the cardo class of polymers.[2] Enantioselective, transition metal-catalyzed conjugate addition reactions of organometallic nucleophiles to β,β-disubstituted enones are a powerful approach to form quaternary stereocenters.[3] Despite recent advances in enantioselective, transition metal-catalyzed conjugate additions of organometallic nucleophiles, asymmetric additions to β-aryl β,β-disubstituted enones to form bis-benzylic quaternary stereocenters remain challenging.

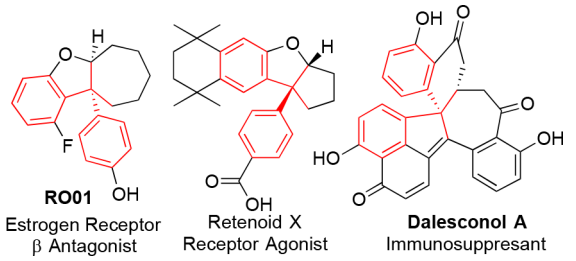
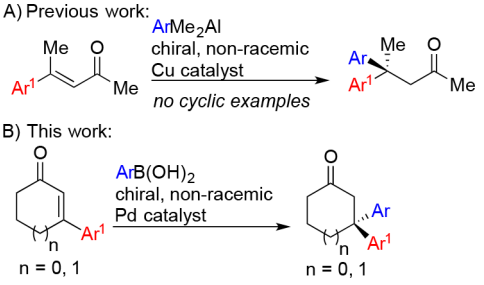


Figure 1. Biologically active compounds containing bis-benzylic quaternary centers.

Over the past decades, enantioselective conjugate additions of arylzinc,[4] arylaluminum,[5] arylmagnesium,[6] and arylboron[7] nucleophiles to β,β-disubstituted enones in the presence of chiral copper, rhodium, and palladium catalysts have been developed as practical methods to synthesize compounds containing benzylic quaternary stereocenters. In particular, Stoltz and co-workers developed enantioselective conjugate additions of arylboronic acids to a variety of β-substituted cyclic enones to form quaternary stereocenters in the presence of Pd(II) complexes of a chiral, nonracemic pyridine-oxazoline ligand ((*S*)-*t*-BuPyOx).[7d,f,h−k] However, examples of enantioselective, transition metal-catalyzed conjugate additions of aryl organometallic nucleophiles to β-aryl β,β-disubstituted enones to generate compounds containing bis-benzylic quaternary stereocenters are limited to copper-catalyzed additions to acyclic electrophiles.

In 2013, Hoveyda and co-workers reported copper-catalyzed conjugate additions of arylaluminum compounds to β-aryl β,β-disubstituted acyclic enones to form acyclic ketones containing bis-benzylic quaternary stereocenters with good-to-excellent enantioselectivity (Scheme 1A).[5c] In this report, however, there are no examples of additions of arylaluminum nucleophiles to β-aryl β,β-disubstituted cyclic enones. In addition, these copper-catalyzed conjugate addition reactions use air and moisture sensitive arylaluminum nucleophiles and have low functional group compatibility.

Scheme 1. Enantioselective, Conjugate Additions of Aryl Nucleophiles to β-Aryl β,β-Disubstituted Enones



We recently reported palladium-catalyzed conjugate additions of bench stable and commercially available arylboronic acids to β,β-disubstituted enones in aqueous media to form an array of ketones with bis-benzylic quaternary centers in moderate-to-high yields (54−74%).[8,9] However, efforts from our group and others

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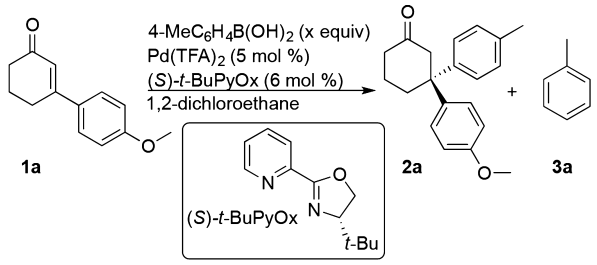
to develop enantioselective variants of these reactions have been limited by modest enantioselectivity in aqueous media, poor reactivity in organic solvents,[7i] and competing decomposition of the arylboronic acid nucleophile. We now report catalytic, enantioselective additions of arylboronic acids to β-aryl β,β-disubstituted cyclic enones that occur in up to 92% yield with high enantioselectivity and minimize undesired pathways for nucleophile decomposition (Scheme 1B).

Early efforts to identify an enantioselective catalyst for conjugate addition of phenylboronic acid to 3-(4-methoxyphenyl)-cyclohexen-2-one in aqueous reaction media led to modest yields of the corresponding ketone product and relatively low enantioselectivity (see Table S1 in the Supporting Information). After an initial evaluation of palladium(II) catalysts generated from chiral, nonracemic pyridine-oxazoline and bisoxazoline ligands, we identified reactions conducted in 1,2-dichloroethane and a catalyst generated *in situ* from palladium trifluoroacetate ($Pd(TFA)_2$) and (*S*)-*t*-BuPyOx[7k] as leads for further reaction optimization.[7d,f,h–k]

We then selected the addition of 4-tolylboronic acid to 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** in the presence of 5 mol % of the catalyst generated from $Pd(TFA)_2$ and (*S*)-*t*-BuPyOx as a model reaction (Table 1) that would facilitate straightforward analysis of reaction products and byproducts. The addition of 4 equiv of 4-tolyboronic acid to **1a** at 90 °C formed 3-(4-methoxyphenyl)-3-(4-tolyl)cyclohexanone **2a** in 46% yield with 89% ee (entry 1). Palladium-catalyzed conjugate additions of arylboronic acids are often plagued by protodeboronation reactions that can occur through multiple pathways[7g,10] and have hindered the development of conjugate additions to form bis-benzylic quaternary stereocenters. The addition of 4 equiv of 4-tolylboronic acid to **1a** led to protodeboronation of 43% of the total tolylboronic acid, formation of 2% of the homocoupling byproduct 4,4′-dimethyl-1,1′-biphenyl, and oxidation of **1a** to form 4% 3-(4-methoxyphenyl)phenol. When the model reaction was conducted with 1 equiv of 4-tolylboronic acid, the reaction generated **2a** in 45% yield and 89% ee. The formation of 25% toluene through protodeboronation and small amounts (<5%) of 4,4′-dimethyl-1,1′-biphenyl and 3-(4-methoxyphenyl)-phenol were also observed.

Table 1. Identification of Reaction Conditions[a]



entry	temp (°C)	*x*	yield **2a** (%)[b]	yield **3a** (%)[c]	ee (%)[d]
1[e]	90	4	46	43	89
2	90	1	45	25	89
3	80	1	42	10	89
4	60	1	42	9	91
5	40	1	24	6	94
6[f]	60	1	49	10	91
7[f,g]	60	1	55	12	92
8[g,h]	60	2	70	11	91
9[g,h]	60	3	82	14	91
10[g,i]	60	3	64	9	91
11[g,i]	80	3	83	21	89
12[g,i,j]	80	3	80	nd[k]	87

[a]Reaction conditions: **1a** (1.0 equiv), 4-tolylboronic acid (*x* equiv) $Pd(TFA)_2$ (5 mol %), (*S*)-*t*-BuPyOx (6 mol %), 1,2-dichloroethane (0.5 M), 3 h. [b]Isolated yields. [c]GC yield, calculated based on the total number of equiv of 4-tolylboronic acid. [d]Determined by chiral HPLC analysis. [e]Reaction time = 24 h. [f]Reaction time = 6 h. [g][**1a**] = 2 M. [h]Addition of 4-tolylboronic at 6 h intervals. [i]Addition of 4-tolylboronic at 3 h intervals. [j]Reaction run in the presence of 10 mol % 2,6-di-*tert*-butylpyridine. [k]nd = not determined.

The absolute configuration of ketone **2a** was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone. The absolute configuration was determined to be 3*S* by X-ray crystallographic analysis (see the SI for details).

We next studied the impact of reaction temperature on the relative rate of protodeboronation to conjugate addition (Table 1, entries 2–5). The amount of toluene generated decreases with lower reaction temperature. The best ratios of ketone **2a**/toluene **3a** (4.2–4.7:1) are observed at 60–80 °C, and the reactions generate **2a** in 42% yield and 89–91% ee (entries 3–4). Increasing the reaction time (entry 6) and the reaction concentration (entry 7) led to modest improvement in the yield of **2a** without increasing the rate of protodeboronation. To increase the yield of **2a**, we adopted an iterative addition strategy to maintain low concentrations of tolylboronic acid and hence a low rate of protodeboronation (entries 8–11). These reactions were conducted by starting the reaction with 1 equiv of 4-tolylboronic acid and adding additional equivalent(s) at 3 or 6 h intervals. This approach to arylboronic acid addition led to significantly higher yields of ketone **2a** (64–83%) and high enantioselectivities without a dramatic increase in the rate of protodeboronation. The model reaction occurs to form **2a** with similar yields and enantioselectivities in the presence and absence of 2,6-di-*tert*-butylpyridine (compare entries 11 and 12) suggesting that residual TFA is not required for product formation. We chose to evaluate the scope of the conjugate addition reaction using the conditions in entry 11 as a practical combination of reactivity, enantioselectivity, and relative rates of productive versus unproductive reaction pathways.

Studies to establish the scope of additions of a variety of arylboronic acids to 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** are summarized in Scheme 2. Additions of electronically diverse, para- and meta-substituted arylboronic acids occurred to generate the corresponding ketone products **2a–2k** in 18–92% yields with 82–91% enantioselectivities. Additions of para-substituted electron-rich, electron-neutral, and halogenated arylboronic acids to **1a** formed ketones **2a–2e** in moderate-to-high yields (49–92%) with high enantioselectivities (82–91% ee). However, the addition of electron-deficient arylboronic acids, which are less nucleophilic, generated **2f** and **2g** in 39% and 38% yields. Additions of electron-rich meta-substituted arylboronic acids to **1a** formed **2h** and **2i** in 60% and 88% yield with 90% ee. In contrast, additions of meta- and ortho-halogenated arylboronic acids generate ketones **2j–2l** in low yields but with good enantioselectivities (81–84% ee).

These reactions also encompass additions of a variety of di- and trisubstituted arylboronic acids. The corresponding ketone products **2m–2q** are generated in moderate-to-good yields (36–67%) with good-to-high enantioselectivities (78–90%). However, additions of 2-methoxyphenylboronic acid, 3-furylboronic acid, and 6-indolylboronic acid, which are more susceptible to protodeboronation,[10a,11] were unsuccessful.

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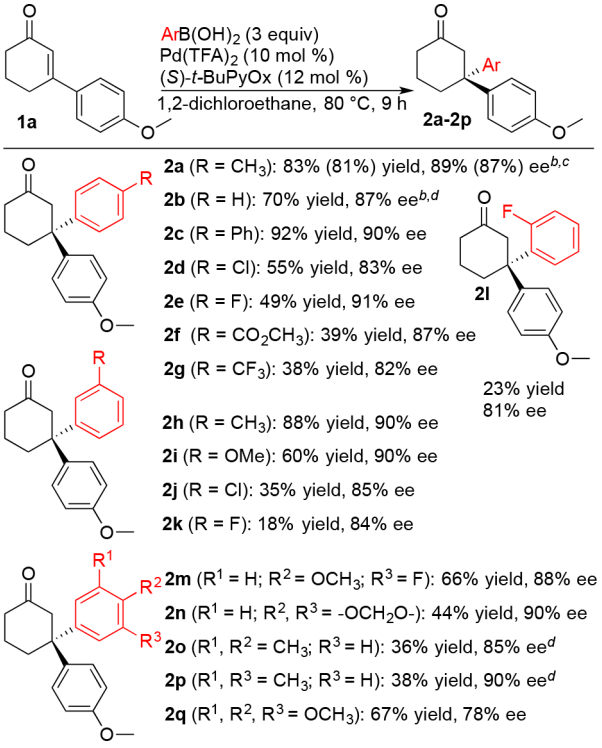
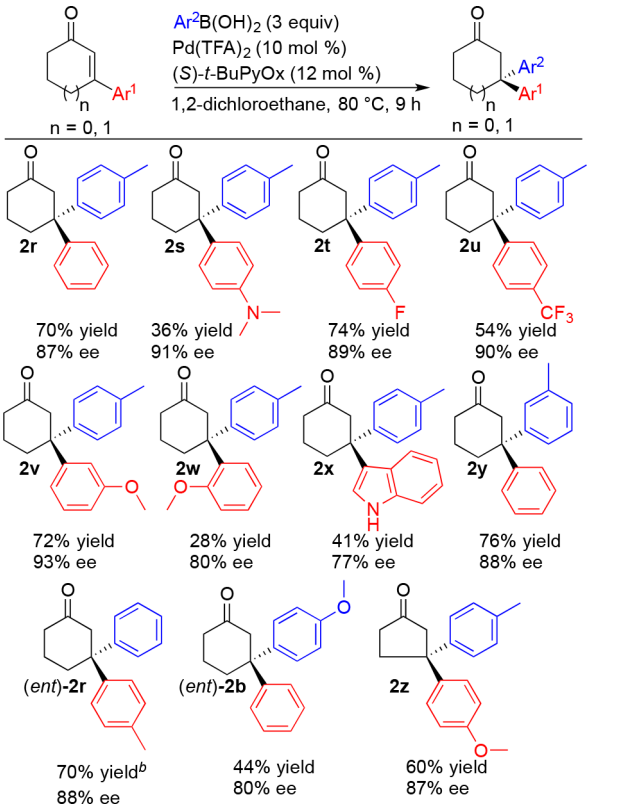
Scheme 2. Enantioselective, Pd-Catalyzed Conjugate Additions of Arylboronic Acids to 1a[a]



[a]Reaction conditions: **1a** (1.0 equiv), arylboronic acid (3.0 equiv), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), 1,2-dichloroethane (2 M). [b]Reaction run in the presence of 5 mol % of the palladium catalyst. [c]Values in parentheses are for a 1.00 mmol scale experiment in the presence of 5 equiv of water. [d]Reaction performed in the presence of 5 equiv of water.

Scheme 3. Enantioselective Pd-Catalyzed Conjugate Additions of Arylboronic Acids to *β*-Aryl *β*,*β*-Disubstituted Enones[a]



[a]Reaction conditions: 3-arylcyclohex-2-enone (1.0 equiv), arylboronic acid (3.0 equiv), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), 1,2-dichloroethane (2 M). [b]Reaction performed in the presence of 5 equiv of water.

To further expand the scope of these reactions, we studied additions of arylboronic acids to a variety of *β*-aryl *β*,*β*-disubstituted enones. These results are summarized in Scheme 3. Additions of 4-tolylboronic acid to 3-arylcyclohex-2-enones containing electron-neutral, halogenated, electron-deficient, and electron-rich aryl groups generated **2r**−**2v** in moderate-to-good yields (36−74%) with high enantioselectivities (87−93%). The additions of 4-tolylboronic acid to *β*,*β*-disubstituted enones containing either an ortho-substituted aryl unit or a heteroarene enables the formation of ketones **2w** and **2x**, products that cannot be formed by addition of the corresponding ortho-substituted arylboronic acid or heteroarylboronic acid. To demonstrate the addition of meta-substituted arylboronic acids to an additional enone, we conducted the reaction of 3-methylphenylboronic acid with 3-phenylcyclohex-2-enone to generate **2y** in 76% yield with 88% ee. The addition of phenylboronic acid to 3-(4-methylphenyl)cyclohex-2-enone and 4-methoxyphenylboronic acid to 3-phenylcyclohex-2-enone generated (*ent*)-**2r** and (*ent*)-**2b** in 40−77% yield and 80−88% ee. We also studied the addition of 4-tolylboronic acid to cyclic enones with different ring sizes and to an acyclic enone. Addition of 4-tolylboronic acid to 3-(4-methoxyphenyl)cyclopent-2-enone generated **2z** in 60% yield and 91% ee. However, addition of 4-tolylboronic acid to 3-phenylcyclohept-2-enone and (*E*)-4-phenylpent-3-en-2-one generated the corresponding ketone products in less than 15% yield.

In summary, we have developed the first examples of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to *β*-aryl *β*,*β*-disubstituted cyclic enones. A catalyst generated *in situ* from $Pd(TFA)_2$ and (*S*)-*t*-BuPyOx catalyzes enantioselective conjugate additions of electronically and structurally diverse arylboronic acids to a variety of *β*-aryl *β*,*β*-disubstituted enones. These reactions generate cyclic ketone products containing bis-benzylic quaternary carbon stereocenters in up to 92% yield and up to 93% ee by iterative addition of the arylboronic acid nucleophile to minimize protodeboronation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01825.

Experimental procedures, characterization data, NMR spectra, and HPLC traces for new compounds (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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