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Boron–Heck Reaction of Cyclic Enaminones: Regioselective Direct Arylation via Oxidative Palladium(II) Catalysis

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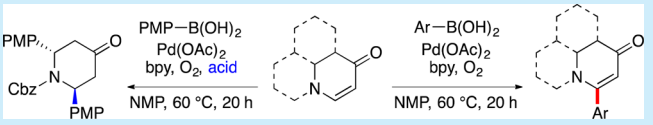
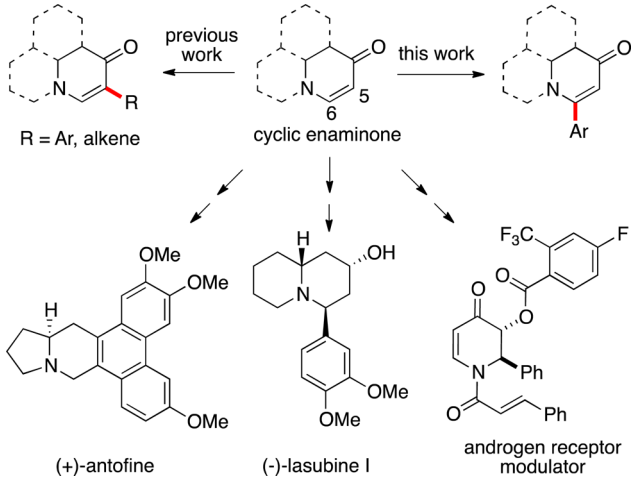
Supporting Information

ABSTRACT: An oxidative boron–Heck reaction of cyclic enaminones with arylboronic acids is reported. This protocol provides a regioselective arylation at the C6 position of cyclic enaminones. When an *N*-carbamylated cyclic enaminone was employed, a switch to a conjugate addition reaction occurred in the presence of acid.



Six-membered cyclic enaminones (2,3-dihydropyridin-4(1*H*)-ones) are versatile intermediates for the preparation of piperidine-containing molecules including indolizidines and quinolizidines alkaloids (Scheme 1).[1] These heterocyclic compounds are known to possess a variety of biological activities.[2] In our efforts to diversify cyclic enaminone scaffolds,[3] C5 arylation and olefination reactions have been developed and used to prepare biologically active compounds and natural products.[4] For alkylation/arylation reactions at the C6 position of cyclic enaminones, conjugate addition reactions can be employed to afford 4-piperidones.[5] C6 arylation with retention of the enaminone system has been achieved by cross-coupling of C6-halo derivatives[6] or organocuprate addition followed by oxidation.[7] A few cases of direct arylation involving a Heck-type reaction have been reported, but they are limited to intramolecular reactions.[8] Considering the utility of this scaffold, the development of an efficient Pd-mediated intermolecular C6 arylation would be a beneficial process.

Scheme 1. Utility of Cyclic Enaminones



Cyclic enaminones are considered to be challenging substrates for Heck-type reactions. Cyclic systems often generate a mixture of the Heck product and the conjugate addition product because the *syn* β-hydride elimination step needed for a Heck reaction is unfavorable.[9] In addition, electron-rich olefins are poor olefin donors for Heck-type reactions, and the scope of the substrates is limited to simple olefins and enamides.[10] Another challenge of a Heck reaction with the cyclic enaminone system is the competing electrophilic palladation (C5 functionalization)[3b−f] particularly with an electron-donating group at the nitrogen. In our previous research,[3f] a preference for C5 arylation was observed under the typical Jeffery conditions,[11] which was successfully used in intramolecular Heck reactions.[8b,d]

Recently, boron reagents have emerged as alternative halide surrogates in Heck-type reactions.[12] These oxidative boron–Heck reactions proved to be successful with a few cyclic systems.[12c,13] In parallel with our previous C5 arylation reaction with arylboronic acids,[3e] it was envisioned that an oxidative boron–Heck reaction could be employed to install an aryl group at the C6 position of cyclic enaminones by a slight modification of the C5 arylation conditions (Scheme 2). As shown in our previous studies,[3f] it is necessary to increase the electron density of the palladium catalyst to prevent C5 arylation. An electron-donating *N,N′*-bidentate ligand[14] was selected with the expectation that this would lead to a switch in the regioselectivity of the reaction. While the palladation is suppressed at the C5 position with an electron-enriched catalytic system, transmetalation will occur with an arylboronic acid to form the arylpalladium(II) complex, and then the insertion with the alkene should take place. Therefore, direct arylation at the C6-position could be accomplished. Herein, the direct C6 arylation using arylboronic acids under Pd(II) catalysis is described.

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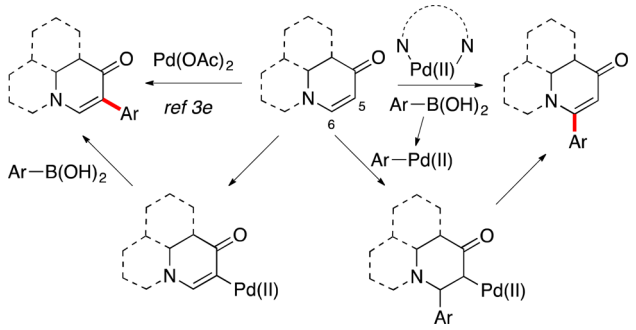
Scheme 2. Regioselective Arylation of Cyclic Enaminones

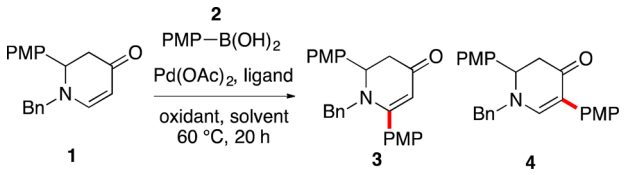


We initiated the optimization of the reaction using cyclic enaminone **1** and 4-methoxyphenylboronic acid (**2**) as model substrates (Table 1).[15] First, the reaction conditions without homocoupling. To address this issue, another equivalent of the arylboronic acid was added after 6 h (entry 14).

The scope of cyclic enaminones and arylboronic acids (Scheme 3) was investigated using the optimized reaction conditions. Electron-rich as well as electron-deficient arylboronic acids provided moderate to good yields (**3a**–**k**). However, 2-methoxyphenyl derivative **3l** was not observed, presumably due to steric hindrance. Other cyclic enaminones bearing *N*-phenyl (**3n**) or *N*-methyl (**3o** and **3p**) groups were suitable substrates for this reaction. Bicyclic enaminones with indolizidine and quinolizidine scaffolds also furnished the C6 arylated products **3q** and **3r** in good yields. While the Heck-type products were obtained exclusively with the substrates containing electron-donating groups at the nitrogen, the *N*-carbamylated cyclic enaminone produced the Heck product **5a** as well as conjugate addition product **5b**.

While investigating the factors for the conjugate addition reactions for a *N*-carbamylated cyclic enaminone, it was found that the addition of acid can switch the outcome (Table 2). As the acidity of the acid was increased, more conjugate addition product **5b** was formed while the yield of the Heck product **5a** decreased. A complete shift to the conjugate addition product **5b** was observed with 2 equiv of TFA (entry 7), albeit in lower yield than with 1 equiv. It is worth noting that the stereochemistry of **5b** was confirmed as *trans* by X-ray crystallography. Therefore, this protocol provides another route toward the synthesis of *trans*-2,6-disubstituted piper-

Table 1. Reaction Optimization[a]

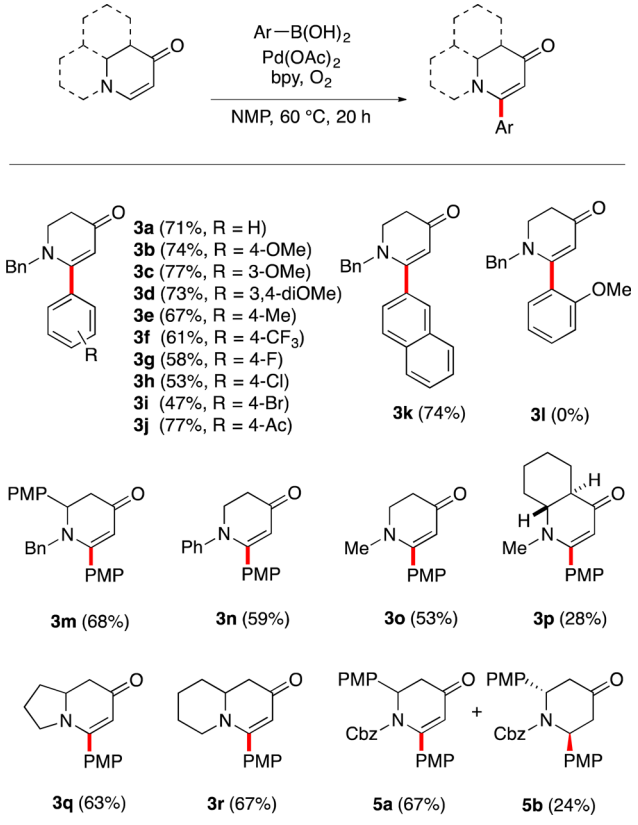


	solvent	ligand	oxidant	yield (3/4)[g] (%)
1[b]	DMF		$Cu(OAc)_2$	34 (1.8/1)
2	DMF	bpy	$Cu(CO_2CF_3)_2$	25 (1/12)
3	DMF	bpy	benzoquinone	46 (<1/20)
4	DMF	bpy	$PhCO_3tBu$	21 (>20/1)
5	DMF	bpy	O_2[f]	33 (>20/1)
6	DMSO	bpy	O_2[f]	4 (>20/1)
7	THF	bpy	O_2[f]	7 (>20/1)
8	DMA	bpy	O_2[f]	40 (>20/1)
9	NMP	bpy	O_2[f]	49 (>20/1)
10	NMP	1,10-phen	O_2[f]	39 (>20/1)
11	NMP	dmbpy	O_2[f]	47 (>20/1)
12[c]	NMP	bpy	O_2[f]	0
13[d]	NMP	bpy	O_2[f]	27 (>20/1)
14[e]	NMP	bpy	O_2[f]	68 (>20/1)

[a]Reaction conditions: **1** (0.2 M), **2** (2 equiv), $Pd(OAc)_2$ (10 mol %), ligand (11 mol %), oxidant (2 equiv). [b]Ag_2O (1 equiv). [c]Cs_2CO_3 (1 equiv). [d]AcOH (1 equiv). [e]Additional **2** (1 equiv) was added after 6 h. [f]Balloon pressure. [g]Yields and ratios were determined by ^1H NMR. PMP = *p*-methoxyphenyl, bpy = 2,2′-bipyridine, 1,10-phen = 1,10-phenanthroline, dmbpy = 4,4′-dimethyl-2,2′-bipyridine.

the ligand were investigated, and a mixture of C6 arylated **3** and C5 arylated **4** was observed (entry 1). The choice of oxidant was essential. It should be noted that C5-arylated derivative **4** was formed preferentially when a copper salt or benzoquinone was used as an oxidant (entries 2 and 3). The conditions with *tert*-butyl perbenzoate or oxygen provided Heck-type product **3** exclusively, although the yields were moderate (entries 4 and 5). The reaction was affected significantly by the solvent selection. Amide solvents such as DMF and NMP gave the best yields (entries 5–9). As expected, the use of a bidentate ligand is necessary to accomplish the regioselective reaction, and the use of 2,2′-bipyridine provided best results (entries 9–11). Furthermore, the addition of any acid or base additives did not improve the reaction efficiency (entries 12 and 13). Time-monitoring experiments revealed that the reaction decelerated after 6 h, resulting from the depletion of the arylboronic acid by

Scheme 3. Scope of the Reaction[a]



[a]Reaction conditions: cyclic enaminone (0.2 M), arylboronic acid (3 equiv), $Pd(OAc)_2$ (10 mol %), ligand (11 mol %), oxygen (balloon pressure).

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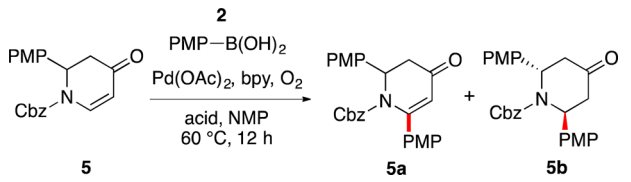
Table 2. Acid-Controlled Conjugate Addition of Cyclic Enaminones[a]



	acid (equiv)	yield (**5a**/**5b**)[c] (%)
1[b]		91 (2.8/1)[d]
2	AcOH (1.0)	86 (1/1.9)
3	AcOH (5.0)	87 (1/3.8)
4	AcOH (10.0)	82 (1/6.5)
5	TsOH·H_2O (1.0)	72 (1/6.2)
6	TFA (1.0)	88 (1/12)
7	TFA (2.0)	60 (<1/20)
8	HCO_2H (1.0)	87 (1/2.8)

[a]Reaction conditions: cyclic enaminone (0.2 M), arylboronic acid (2 equiv), $Pd(OAc)_2$ (10 mol %), ligand (11 mol %), oxygen (balloon pressure). [b]20 h. [c]Yields and ratios were determined by ^1H NMR. [d]Isolated yield.

idones, which have been previously prepared via conjugate addition using Grignard reagents.[5f,g]

A plausible mechanism is depicted in Figure 1. The electron-rich palladium ligand complex favors transmetalation with the

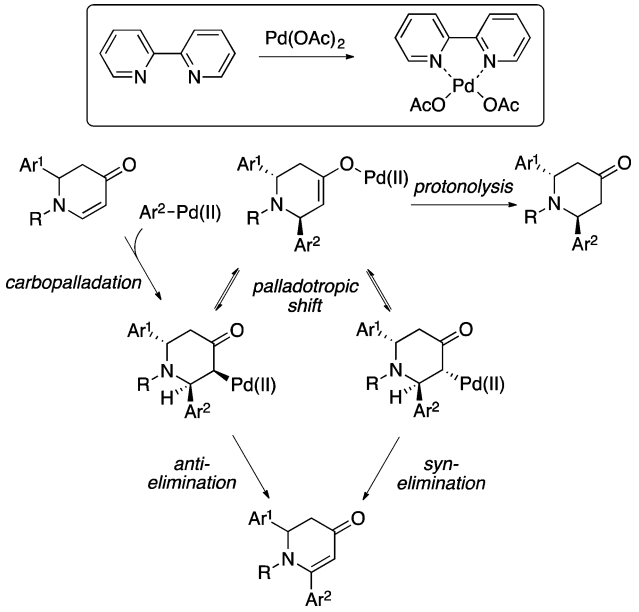
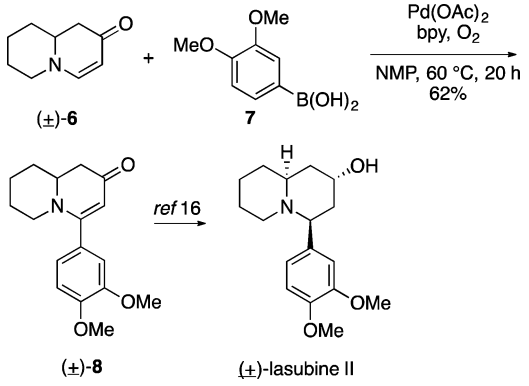


Figure 1. Proposed reaction mechanisms.

arylboronic acid rather than C5 palladation of the cyclic enaminone. Carbopalladation would take place trans to Ar^1, followed by a palladotropic shift to generate the palladium enolate.[12c,16] In the presence of acid, this intermediate would undergo protonolysis to furnish the conjugate addition product. The oxidative Heck product would be obtained via elimination reactions.

C6-arylated cyclic enaminones can serve as an intermediate in natural product synthesis. For example, lasubine II was obtained from compound **8** following the protocol developed by Rovis.[17] Reaction of 3,4-dimethoxyphenylboronic acid (**7**) with bicyclic enaminone **6** gave C6-arylated product **8** in 62% yield (Scheme 4). The analytical and spectral data of compound **8** are consistent with the literature report,[17] which establishes the formal synthesis of lasubine II.

Scheme 4. Formal Synthesis of Lasubine II



In summary, we have developed a C6 arylation protocol for 2,3-dihydropyridin-4(1*H*)-ones using the oxidative boron–Heck reaction that proceeds with excellent selectivity over C5 arylation and conjugate addition reactions.[18] This boron–Heck reaction provides a complementary protocol to previously developed arylations at the C6 position. Furthermore, an acid-controlled reactivity switch to a conjugate addition reaction was observed when the reaction was carried out with a *N*-carbamylated enaminone in the presence of a strong acid.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, ORTEP plot for **5b**, and copies of $^1H/^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for the full optimization experiments.

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(18) **General Procedure for the Synthesis of Compounds 3a−r and 5a−b (Table 2).** $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and 2,2′-bipyridine (3.4 mg, 0.022 mmol) in NMP (1.0 mL) were stirred for 30 min. To this solution were added the cyclic enaminone (0.20 mmol) and the arylboronic acid (0.40 mmol), and the reaction mixture was stirred under O_2 (balloon) at 60 °C. After the mixture was stirred for 6 h, another 1 equiv of the arylboronic acid (0.20 mmol) was added, and the mixture was stirred for an additional 14 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated. The crude mixture was diluted with EtOAc (5 mL), and the precipitate was filtered through Celite using EtOAc as the eluent. The filtrate was concentrated and purified by flash column chromatography on silica gel using hexanes and an increasing proportion of EtOAc as eluent.