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Enantioselective Synthesis of γ -Functionalized Cyclopentenones and δ -Functionalized Cycloheptenones Utilizing a Redox-Relay Heck Strategy

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Abstract

In this report, the desymmetrization of cyclic enones under relay Heck conditions with an array of aryl boronic acids, alkenyl triflates and indole derivatives is described. This method grants facile access to diverse γ -functionalized cyclopentenones and δ -functionalized cycloheptenones. Using this approach, a formal synthesis of (*S*)-baclofen was completed in high yield and excellent enantioselectivity.

Graphical Abstract

Keywords

Asymmetric Catalysis; C–C Coupling; Heck Reaction; Palladium

Optically active, γ -substituted cyclopentenones are important building blocks with applications in the pharmaceutical industry.^[1] To traditionally access these compounds, multiple synthetic steps are often required with a prevalence of ring-closing procedures. These include Ru-catalyzed ring-closing metathesis,^[1] enantioselective Nazarov cyclizations,^[2] Pauson-Khand reactions,^[3] and Au-catalyzed cycloisomerizations.^[4] We envisioned a complementary strategy to yield the desired functionalized cyclopentenone core directly from 3-cyclopentenone through enantioselective desymmetrization using a redox-relay

Heck reaction. If successful, products of type **3** are formed that would simplify the synthesis of enantiomerically enriched γ -substituted cyclopentenones.

Similar redox-relay Heck reactions have been extensively studied in our laboratory. These reactions differ from the traditional Heck reaction in that the unsaturation of the olefin is carried along a carbon chain via successive β -hydride eliminations and migratory insertions toward a redox acceptor, such as an alcohol, therefore resulting in the remote functionalization of an aldehyde or ketone (Scheme 1A).^[5] Our previous reports^[5] were heavily focused on the use of acyclic alkenyl substrates to access remotely functionalized carbonyl products (Scheme 1A). More recently, we have extended our efforts to the use of cyclic substrates, namely ene-lactams, to access conjugated lactam products (Scheme 1B).^[6] Inspired by this result, and the disclosures of Correia^[7] and others^[8] in the desymmetrization of cyclopentenones such as **A**, (Scheme 1C) we envisioned that the use of symmetric cyclic enones, such as cyclopentenone **1a**, would extend the synthetic utility of the redox-relay Heck reaction. A benefit of cyclic systems is that after migratory insertion has occurred to generate intermediate **B**, intermediate **C** is formed due to the *syn* nature of β -hydride elimination.^[9] Herein we disclose the successful Pd-catalyzed enantioselective desymmetrization of symmetric cyclic enones with arylboronic acids, alkenyl triflates, and indole derivatives to generate optically active γ -substituted cyclopentenones (**3**).

We began our studies by investigating previously reported arylation conditions used to functionalize di- and trisubstituted acyclic alkenols,^[5b, 5e] albeit without a copper additive.^[5f] When these optimized conditions were applied to cyclopentenone **1a** and phenyl boronic acid **2a**, we were fortunate to discover the arylated product **3a** was formed in 92% yield and 95:5 enantiomeric ratio (er), with only a detectable amount of diarylated product **4a** (Table 1, entry 1). Utilizing THF as solvent provided a similar yield, albeit in reduced enantioselectivity (entry 2). Longer reaction times (entry 3) and increasing the equivalents of boronic acid (entry 4) led to the amplified formation of **4a**. Switching to a more electron rich ligand (**L2**) produced the undesired diarylation compound **4a** as the major product (entry 5), and performing the reaction at 0 °C had little effect on the outcome of the reaction (entry 6).

Following these observations, we examined the scope of this transformation for a variety of arylboronic acids (Table 2). Electron withdrawing groups (4-chloro and 4-trifluoromethyl) were well tolerated producing products **3b** (79%) and **3c** (71%), both with excellent enantioselectivities. Electron donating groups such as 4-methoxy (**3d**), 4-methyl (**3e**), and 3-methoxy (**3f**) also provided the desired products in excellent yields and enantiomeric ratios. A methyl group at the *ortho* position was also tolerated delivering the corresponding product in 74% yield and 93:7 er (**3g**), indicating that the more sterically hindered arene had only a minor impact on the reaction outcome. Inclusion of additional electron withdrawing groups (**3h**) reduced the yield to 63%, likely due to a decreased rate of migratory insertion.^[10] Lastly, a benzodioxole (**3j**), naphthyl (**3k**), and indole (**3l**) were successfully incorporated delivering the corresponding products in excellent yields and enantioselectivities. It should be noted that the scope in terms of aryl boronic acid is similar to our original reports using acyclic alkenols.^[5b, 5e]

This Heck arylation was readily applied to the formal synthesis of biologically active compound baclofen, a muscle relaxer used in the treatment of multiple sclerosis (Scheme 2).^[11] This process is scalable to 1.0 mmol.

Next, we examined the scope of alkenyl triflates with cyclopentenone **1a** (Table 3) using similar reaction conditions in the absence of the terminal oxidant, O₂. A Pd⁰ precatalyst was required to initiate the oxidative addition of the alkenyl triflate.^[5g] We explored various alkenyl triflates that have historically been successful in the acyclic systems.^[5j, 5g] This includes the use of 6-membered endocyclic alkenyl triflates to cleanly generate products **6a** (86%) and **6b** (67%). Excellent enantioselectivity is observed with these coupling partners. A 5-membered endocyclic alkenyl triflate led to the formation of **6c** (97%) with a modest reduction of enantioselectivity. The use of a vinylogous lactone triflate provided product **6d** in 98% yield and a 92:8 er. Acyclic alkenyl triflates are also compatible with this transformation and gave products **6e** and **6f** in good yield and er.

Based on our success with cyclopentenone **1a**, we then examined whether the reaction would tolerate a larger ring. Cycloheptenone **1b** was a successful substrate for both arylation and alkenylation (Table 4). The use of phenyl boronic acid with cycloheptenone **1b** led to nearly complete consumption of **1b** to give **7a** in only four hours. As previously observed (Table 1, entry 3), longer reaction times led to the formation of the diarylation product analogous to **4a**. An electron poor boronic acid also performed well, generating **7b** in 91% yield and excellent er. The use of a vinylogous lactone triflate as the coupling partner produced the desired product **7c** in 71% yield in modest enantioselectivity while an acyclic alkenyl triflate yielded product **7d** in 56% and high enantioselectivity. Unfortunately, the use of unsymmetric cyclic alkenones (i.e., 3-cyclohexenone) results in poor site selectivity as a result of poor electronic bias between the alkene carbons in the migratory insertion event (not pictured).

Next, we postulated that other nucleophiles successfully used in related redox-relay Heck reactions may be compatible as these substrates were found to be relatively reactive. Pleasingly, alkenyl triflate **8a** provided **9a** in 87% yield with 90:10 er (Scheme 3). Additionally, a dehydrogenative Heck reaction using indole **8b** resulted in alkylation at the C3 position to yield **9c** (28% yield) in low er.^[6e] Using our recently reported aza-Wacker type conditions resulted in the desired product, albeit it was isolated as a racemate (see supporting information for details).^[12]

In summary, we have developed a method for the direct preparation of γ -functionalized cyclopentenones and δ -functionalized cycloheptenones from unsaturated cyclic enones. This strategy is compatible with both our previously reported arylation and alkenylation conditions. Regioselective alkylation of indole derivatives was also achieved in moderate yields.

Experimental Section

General Arylation Procedure:

To a 10 mL Schlenk flask was added $\text{Pd}(\text{CH}_3\text{CN})_2(\text{OTf})_2$ (10.6 mg, 0.1 equiv), ligand **L1** (6.5 mg, 0.12 equiv), 3 Å MS (60 mg), and DMF (2.0 mL). A three-way adapter fitted with a balloon of O_2 was then added to the Schlenk flask and evacuated via house vacuum and refilled with O_2 three times while stirring. The resulting mixture was stirred under an O_2 atmosphere for 15 min. The substrate **1** (0.20 mmol, 1.0 equiv) and arylboronic acid **2** (0.40 mmol, 2.0 equiv) was then added. The resulting mixture was stirred for another 24 h at 0 °C. The reaction progress was monitored by TLC, and upon complete consumption of **1**, the mixture was then transferred to a separatory funnel with EtOAc (30 mL) and partitioned with saturated brine (5 mL). The organic fraction was collected and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were then washed with brine (3 × 10 mL), dried over Na_2SO_4 , decanted, and concentrated under reduced pressure to give the crude product. The crude product was purified by chromatography on silica gel and afforded the desired product.

General Alkenylation Procedure:

Under nitrogen atmosphere, to a 2 mL vial equipped with a stir bar was added $\text{Pd}(\text{dba})_2$ (11.5 mg, 0.02 mmol, 0.1 equiv.), ligand (6.0 mg, 0.024 mmol, 0.12 equiv.), 3 Å molecular sieve (60 mg), and anhydrous DMF (2.0 mL). The resulting mixture was stirred for 10 min. Triflate **5** (1.0 equiv.) and substrate **1** (0.4 mmol, 2.0 equiv.) were then added. The resulting mixture was stirred for another 48 h at 0 °C. The reaction progress was monitored by TLC, and upon complete consumption of triflate **5**, the mixture was then transferred to a separatory funnel with EtOAc (30 mL) and partitioned with saturated brine (5 mL). The organic fraction was collected and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were then washed with brine (3 × 10 mL), dried over Na_2SO_4 , decanted, and concentrated under reduced pressure to give the crude product. The crude product was purified by chromatography on silica gel and afforded the desired product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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- [12]. *N*-alkylation was attempted with carbazole using the previously reported conditions (see reference 5k). The product was generated in 43% yield, but the product racemized upon workup. See supplementary information for more details.

A. Previous Work with Acyclic Alkenes **B. Recent Work with ene-lactams** **C. Precedent Set by Correia** **D. This Work** **◆ Key Questions**

- Enantioselective Insertion?
- Will the Product Undergo a Second Insertion?

Scheme 1.

- A.** Previous reports of redox-relay Heck reaction with acyclic alkenes, representative examples. **B.** Previous use of endocyclic alkenes. **C.** Desymmetrization reported by Correia. **D.** Proposed method to synthesize γ -functionalized cyclopentenones.

Scheme 2.

Formal synthesis of (*S*)-baclofen. Reaction conducted with **1a** (1.0 mmol), **2b** (2.0 mmol), and Pd(MeCN)₂(OTs)₂ in 10 mL DMF.

A. C2-alkylation

B. C3-alkylation

Scheme 3.

Regioselective alkylation of indole derivatives. **A.** Reaction conducted with **1a** (0.2 mmol) and **8a** (0.2 mmol) in DMF (2 mL). **B.** Reaction conducted with **1a** (0.2 mmol) and **8b** (1.0 mmol) in DMF (2 mL).

Table 1.

Optimization of Conditions

Entry	Ligand	1:2a	time (h)	3a:4a ^{a)}	Yield (%)	er
1	L1	1:2	24	>95:5	92	95:5
2 ^{b)}	L1	1:2	24	>95:5	94	87:13
3	L1	1:2	72	66:34	--	--
4	L1	1:3	72	28:72	--	--
5	L2	1:3	72	<5:95	85	90:10
6 ^{c)}	L1	1:2	24	>95:5	90	96:4

Reaction conducted with **1a** (0.2 mmol) and **2a** (0.4 mmol).

^{a)} The ratio of **3a:4a** was determined by ¹H NMR of the crude mixture.

^{b)} THF was used as solvent.

^{c)} Reaction performed at 0 °C.

Table 2.

Arylboronic Acid Scope

1a	2
3a:4a >95:5 90% yield 96:4 er	3b:4b >95:5 ^a 79% yield 96:4 er	3c:4c >95:5 ^a 71% yield 96:4 er
3d:4d >95:5 91% yield 93:7 er	3e:4e >95:5 77% yield 95:5 er	3f:4f >95:5 83% yield 96:4 er
3g:4g >95:5 74% yield 93:7 er	3h:4h >95:5 ^a 63% yield 93:7 er	3i:4i >95:5 82% yield 96:4 er
3j:4j >95:5 86% yield 96:4 er	3k:4k >95:5 ^a 87% yield 95:5 er	3l:4l >95:5 89% yield 93:7 er

Reaction conducted with **1a** (0.2 mmol) and **2** (0.4 mmol) in DMF (2 mL) at 0 °C. The ratio of **3:4** was determined by ¹H NMR of the crude mixture. Absolute stereochemistry determined to be (*R*) for **3a** by comparing optical rotation with literature value (See supplementary information), all others assigned by analogy.

^{a)} 0.3 mmol of **2** was used.

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Table 3.

Scope of Alkenyl Triflates

Reaction conducted with **1a** (0.4 mmol) and **5** (0.2 mmol) in DMF (2 mL). Absolute stereochemistry determined to be (*R*) for **3a** by comparing optical rotation to literature value (see supporting information), all others assigned by analogy.

^{a)} 20 mol % Pd(dba)₂ used.

Table 4.

7-Membered Enone Substrate Scope

Absolute stereochemistry determined to be (*R*) for **3a** by comparing optical rotation to literature value (see supporting information), all others assigned by analogy.

^{a)} Arylation reaction conducted with **1b** (0.2 mmol), **2** (0.3 mmol), Pd(MeCN)₂(OTf)₂ (10 mol %), Cu(OTf)₂ (3 mol %), **L1** (20 mol %), 3 Å MS, O₂ (balloon) and DMF.

^{b)} Reaction time was 4h.

^{c)} Alkenylation reaction conducted with **1b** (0.2 mmol), **5** (0.2 mmol), Pd(dba)₂ (10 mol %), **L3** (12 mol %), 3 Å MS, and DMF.