Enantioselective transannular reactions by palladium-catalysed conjugate addition of aryl boronic acids

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Enantioselective Transannular Reactions by Palladium-Catalysed Conjugate Addition of Aryl Boronic Acids

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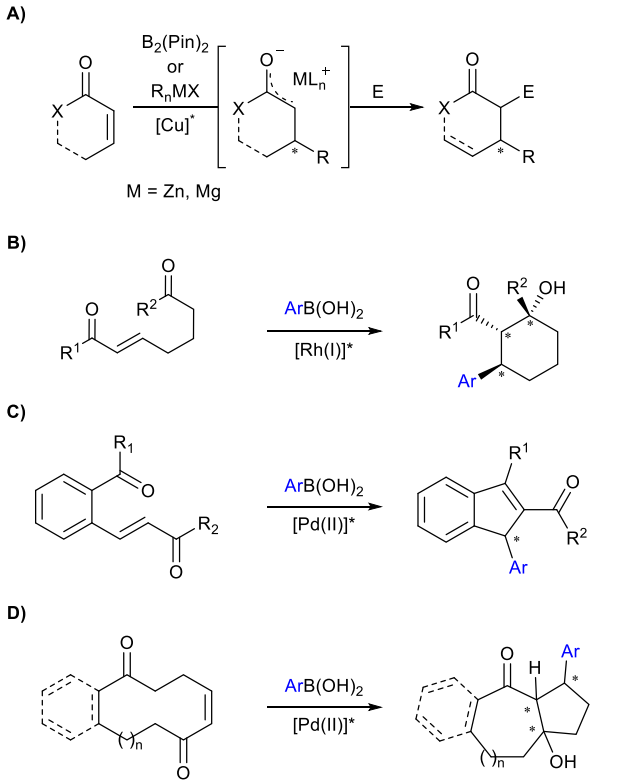
A palladium-catalyzed asymmeric conjugate addition of aryl boronic acids to medium-sized cycloalkenones followed by intramolecular aldol trapping is reported. The use of *in situ* formed [Pd/(QuinoxP*)] as the catalyst enables the synthesis of arylbicyclic scaffolds in good yields and with excellent stereocontrol (up to 7:1 dr, up to 99% ee). The reaction is applicable to a range of medium size ketoenone substrates and funcionalized aryl boronic acids, including heterocyclic compounds.

Transition metal-catalysed asymmetric tandem transformations with organometallic compounds represent useful strategies for the synthesis of complex targets in which, multiple bonds and stereocenters are sequentially formed, without the need to isolate reaction intermediates.[1] Among these strategies, the tandem annulation initiated by conjugate additions (CA) to Michael acceptors followed by electrophilic intramolecular trapping has proven extremely useful, with applications in the total synthesis of complex molecules and bioactive compounds.[2] While chiral copper complexes are generally used for the initial CA of hard organometallic nucleophiles[3] and diboron compounds[4] (Scheme 1A), rhodium catalysis arguably provides the most accommodating platform for the use of boronic acid nucleophiles.[5] A range of enantioselective Rh-catalyzed tandem conjugate arylation/electrophilic trapping sequence using arylboronic acids has been described, following the seminal inter- and intramolecular versions by Hayashi[6] and Krische, respectively[7] (Scheme 1B). In contrast, the use of palladium has been more limited, and one example of CA/aldol cascade sequence has been described by the group of Miyaura by for the synthesis of 1-aryl indenes (Scheme 1C).[8] Even so, Pd(II) catalysis has demonstrated to be an excellent alternative to Rh(I), for the addition of aryl boron reagents to electron-deficient olefins, showing higher turnover numbers for cyclic and acyclic enones and enals under much lower cost.[9]



Scheme 1. Metal-catalysed Conjugate addition/electrophilic trapping. A) Copper catalyzed CA/electrophilic trapping: Well established. B) Intramolecular rhodium-catalysed CA of arylboron compounds/enolate trapping. Seminal work. C) Palladium-catalysed CA of arylboron compounds for the synthesis of 1-aryl indenes. D) This work.

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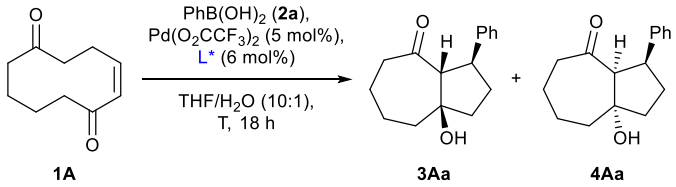
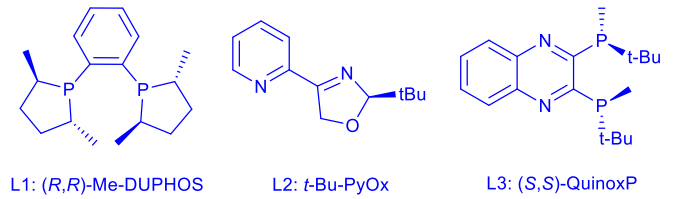
In fact, several palladium catalyst systems have been developed by the groups of Miyaura,[10] Stoltz,[11] Minnard,[12] Shi,[13] Pullarkat[14] and others, allowing for the synthesis of chiral linear-and five- to seven-membered (hetero)cycles, including pharmaceutically relevant molecules.

On the other hand, we have recently described a series of organocatalyzed-[15] and a copper-catalyzed[16] enantioselective transannular reactions of medium- and large sized cycloalkenones, that allows the synthesis of complex bicyclic scaffolds with high efficiency. We surmised if the palladium-based catalyst could be suitable to promote enantioselective transannular arylation process in these macrocycles through conjugate addition of arylboronic acids to an α,β-unsaturated ketone followed by intramolecular stereoselective aldol reaction of the resulting palladium enolate. Here we describe the implementation of this process that allows for the synthesis of complex (hetero)aryl bicyclic structures containing three contiguous stereocenters in good yields and diastereoselectivities, with excellent enantiocontrol (Scheme 1D).

To test the feasibility of the process, we selected the reaction between (*Z*)-cyclodec-2-ene-1,6-dione **1a** and phenylboronic acid **2a** as a model (Table 1).

Table 1. Screening of chiral ligands and optimization of the reaction.





Entry[a]	Ligand	T (°C)	Conv. (%)[b]	**3Aa**:**4Aa**	ee (%)[c],[d]
1	**L1**	50	>95	>20:1	61
2	**L2**	50	<5		
3	**L3**	50	58	6:1	93
4	**L3**	70	>95	7:1	96

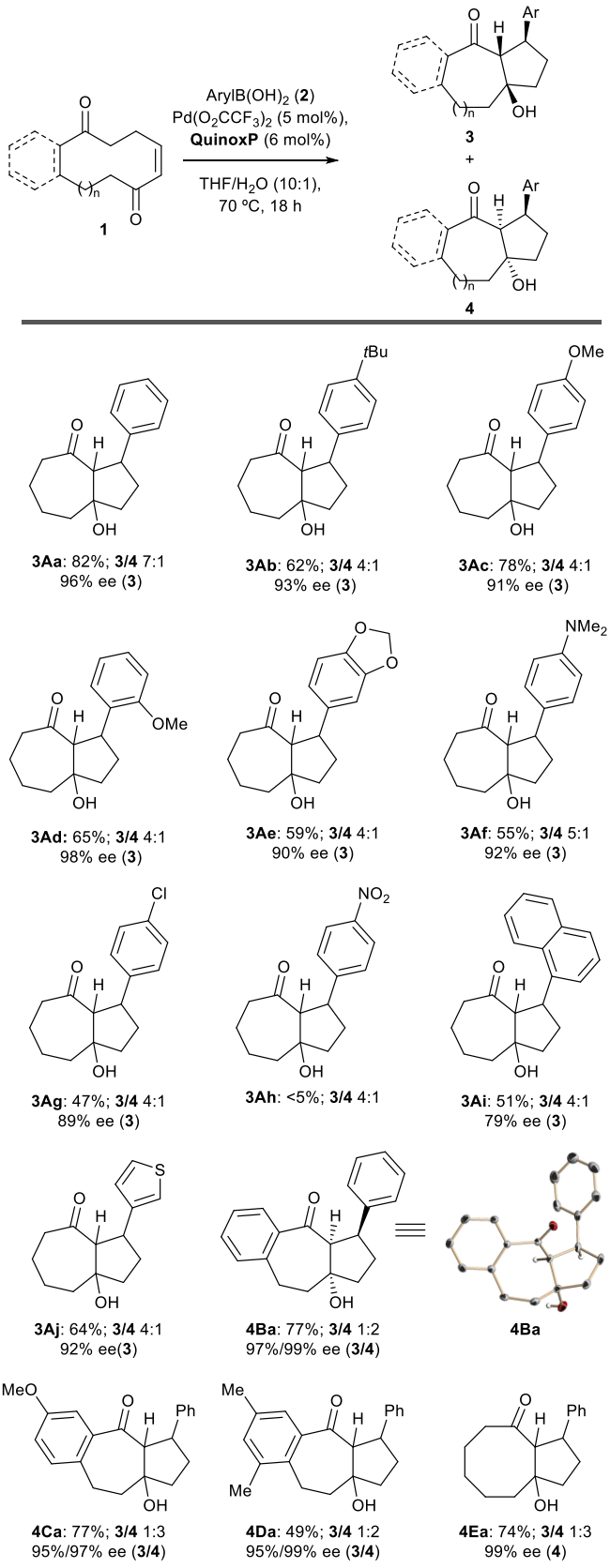
[a] Reactions performed on 0.1 mmol scale. [b] Estimated by ^{1}H-NMR spectroscopy. [c] Determined by HPLC on chiral stationary phase. [d] ee of **3Aa**.

Under previously described conditions[12a] for the enantioselective CA of arylboronic acids to electron-deficient alkenes, using 5 mol% of $Pd(O_2CCF_3)_2$ and 6 mol% (*R*,*R*)-Me-DUPHOS **L1** in THF/H_2O at 50 °C, the desired product **3Aa** was obtained as a single diastereomer, although in moderate conversion and enantioselectivity (entry 1). No improvements were observed using other *P*,*P* ligands such as BINAP derivatives (not shown), while the use of (*S*)-*t*-Bu-PyOx **L2**, which is the ligand of choice for the enantioselective CA of arylboronic acids to β-substituted cyclic enones,[11a] was unproductive (Table 1, entry 2). Gratifyingly, the use of QuinoxP* **L3** allowed the formation of desired phenyloctahydroazulenone as a 6:1 **3Aa**:**4Aa** mixture with high enantioselectivity although in moderate conversion (Table 1, entry 3). Finally, full conversion and higher levels of stereoselectivity could be achieved by increasing the temperature to 70 °C (Table 1, entry 4).

With the optimized reaction conditions in hand [5 mol% $Pd(O_2CCF_3)_2$/6 mol% QuinoxP*, as the catalyst, THF/H_2O 10:1, 70 °C], we next explored the scope of (hetero)arylboronic acids using macrocycle **1A** as electrophilic partner (Scheme 2). Phenylboronic acids with electrondonating (*p*-*t*Bu, *p*-MeO, *p*-MeO, NMe_2, etc.) or withdrawing substituents (*p*-Cl) afforded the desired bicyclo[5.3.0]decane scaffold (**3Aa**-**g**) in moderate to good yields and diasteroselectivities with high enantioselectivity for the major diastereomer (up to 98% ee, Scheme 2). The steric effect of substituents on the *ortho* position of the ring has a negligible effect on yield and enantioselectivity as demonstrated for the synthesis of **3Ad**. A diol protected as acetal was also tolerated, furnishing the bycylic aducts **3Ae** in 59% yield, 4:1 d.r. with high enantioselectivity (90% ee).. Surprisingly, the *p*-nitrophenylboronic acid was practically unreactive under the optimized reaction conditions (**3Ah**). Finally although a decrease in the enantioselectivity (79% ee) was observed when 1-naphthylboronic acid was used as arylating reagent (see adduct **3Ai**), heteroaromatic derived boronic acids offered good levels of enantioselectivity (see adduct **3Aj**).

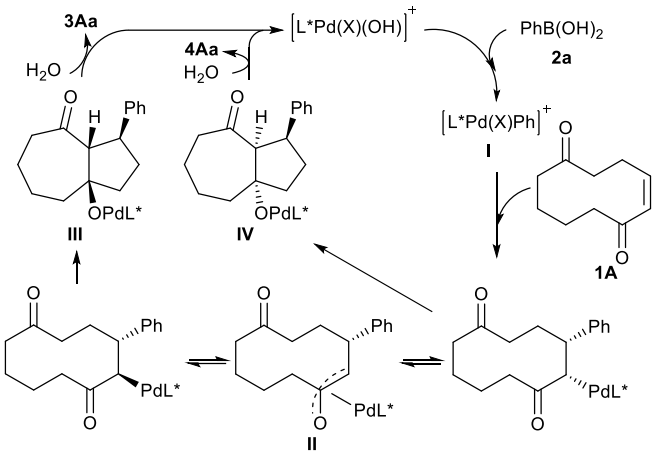
Substrates bearing fused aromatic systems with different substitution patterns were also suitable for this transformation, maintaining an excellent level of enantiocontrol (see, adducts **3Ba**-**3Da**). Importantly, the method could also be extended to the reaction of substrates with larger ring sizes. Thus, bicyclo[6.3.0]undecane scaffold was obtained in 74% yield, 1:3 d.r. and excellent enantioselectivity (93% ee). It should be noted that for compounds **1A** and **1B-E**, the major diastereomers present opposite configuration in the bridgehead carbons as shown the absolute configuration of products **3Ai** and **4Ba** determined by X-ray.[17]

In accordance with previous mechanistic studies[11c], a tentatively model to explain the stereochemical outcome of the reaction can be proposed. The hydroxo-palladium specie, (QuinoxP*)Pd(X)OH, undergoes transmetalation with an arylboronic acid (*e.g.* $PhB(OH)_2$) to yield cationic (QuinoxP*)PdArX (**i**) that after substrate coordination and enantioselectivity-determining *syn* insertion of the aryl moiety into the enone π system afford C-bound palladium enolate intermediate (**II**). The formation of the two observed diastereomers **3** and **4** can be explained by assuming isomerization of the Pd-enolate intermediate via oxa-π-allylpalladium species. Chelation of the oxygen atoms by palladium in a favourable cyclic transition state, in combination with a match effect with the ligand, may account for the high selectivity observed during the attack of the enolate to the ketone carbonyl. Finally, protonolysis of the resulting palladium alkoxide in **III** and **IV** yielded the final bicyclic product **3Aa**/**4Aa**, regenerating the catalytically active palladium species.



Scheme 2. Reaction scope. Isolated yields after column chromatography. **3/4** ratios were determined by ^{1}H NMR in the crude reaction mixtures. Major isomer is drawn in each case. Enantiomeric excesses were determined by HPLC on chiral stationary phase.

In conclusions, the palladium-catalysed conjugate addition of arylboronic acids to medium-sized cyloalkenones bearing an internal ketone electrophile can be used to trigger highly enantioselective transannular reactions, allowing for the synthesis of complex arylbicyclic scaffolds. Good yields and diasteromeric ratios and excellent enantioselectivities were observed for a range of substrates and arylboronic acids using [Pd/(QuinoxP*)] as the catalyst.



Scheme 3. Proposed mechanism for the stereochemical outcome of the reaction.

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Conflicts of interest

There are no conflicts to declare.

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