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Pyridine–Hydrazone Ligands in Asymmetric Palladium-Catalyzed 1,4- and 1,6-Additions of Arylboronic Acids to Cyclic (Di)enones

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Abstract. Catalysts generated by combinations of $Pd(TFA)_2$ and enantiomerically pure pyridine-hydrazone ligands have been applied to the 1,4-addition of arylboronic acids to *β*-substituted cyclic enones, building all-carbon quaternary stereocenters in high yields and enantioselectivities (up to 93% ee). The developed methodology allows the efficient introduction of *ortho*-substituted aryl groups in *β*-position of cyclopentanone cores, giving scaffolds present in a broad range of biologically active natural products. These Pd(II)-complexes served also as catalysts in the 1,6-addition of arylboronic acids to cyclic dienones, affording complete regioselectivities, moderate yields and good enantioselectivities (up to 80% ee).

Keywords: Asymmetric Catalysis, Palladium, *N* Ligands, Arylboronic acids, Hydrazones

Introduction

The synthesis and practical evaluation of new chiral ligands are essential tasks for the continuous development of asymmetric metal catalysis.[1] In the last twenty years, there has been an increasing implementation of nitrogen-based ligands,[2] which offer an extraordinary structural variability and are in general stable and easy to handle compounds. In particular, bidentate *N*-(sp^2)-based ligands such as bipyridine (**I**),[3] bis-imine (**II**),[4] bis-oxazoline (**III**),[5] or pyridine-oxazoline (**IV**)[6] chiral ligands (Figure 1) have allowed a vast number of asymmetric reactions. Alternatively, hydrazones appear as a complementary family of chiral ligands which offer high thermal stability, compatibility with many reagents and distinct electronic, steric and conformational properties. The originally designed glyoxal bis-hydrazone **L1** afforded excellent results in Cu(II) catalyzed Diels-Alder cycloadditions[7] and Pd(0) catalyzed Suzuki-Miyaura cross-couplings.[8] In the original ligand design, C_2-symmetric dialkylamino groups were introduced at both ends to prevent the loss of suitable chiral environments around the metal by N–N bond rotations, and this design proved to be essential to reach high enantioselectivities.

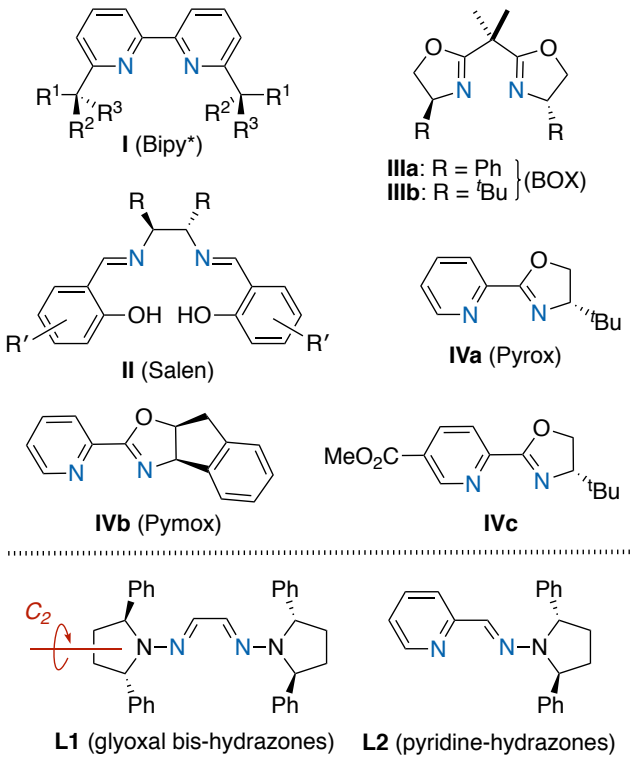
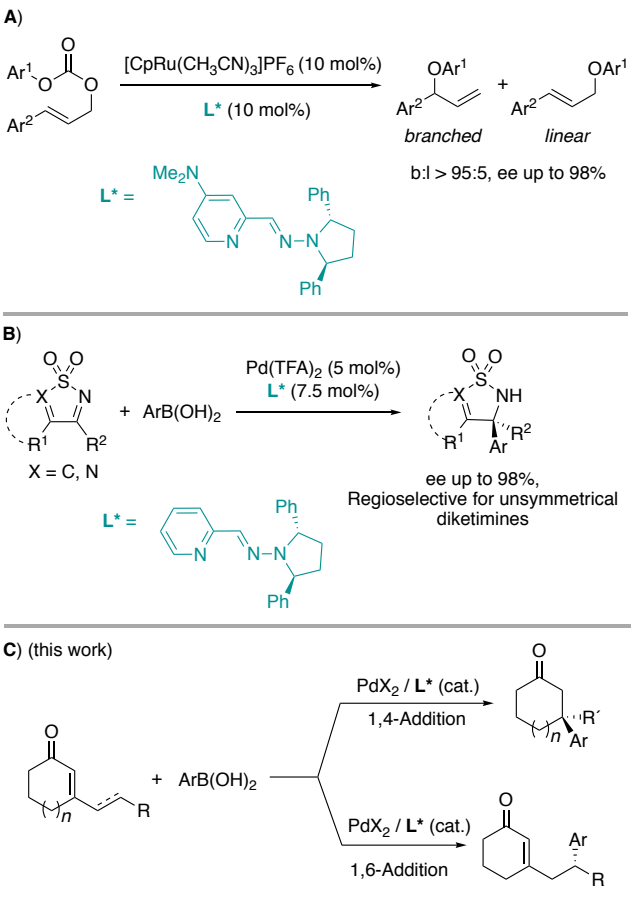


Figure 1. *N*-(sp^2)-based bidentate chiral ligands.

Additionally, the steric crowding around the metal center is modulated by the structure of the dialkylamino fragment, which in turn influences the electronic behaviour of C=N group [n→π (N-N=C) conjugation]. This key design was subsequently extended to phosphino-hydrazones[9] and pyridine-hydrazones[10] (**L2** and others). Pd(II) complexes of these bidentate ligands allowed to expand the scope of the Suzuki coupling to complementary families of electrophilic substrates. The latter pyridine-hydrazones, in combination with different metals, have proved to be also useful catalysts in processes such as Ru^{II}-catalyzed asymmetric decarboxylative allylic etherifications[11] or, in combination with $Pd(TFA)_2$, 1,2-addition of arylboronic acids to saccharin-derived cyclic ketimines (Scheme 1; A, B).[12] Remarkably, in both cases the pyridine–hydrazone ligand outperformed well-established pyridyl monooxazoline (pymox) ligands: in the first case the ligand provided substantially higher enantioselectivities while preventing racemizations and branched-to-linear isomerizations;[13] in the second, it was possible to perform unprecedented additions to diketimines,[14] reaching high yields and enantioselectivities, along with high regioselectivities for unsymmetrically substituted derivatives.

The asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl acceptors[15] is a well established method for the catalytic asymmetric formation of all-carbon quaternary stereocenters.[16]



Scheme 1. Pyridine-hydrazones in asymmetric catalysis

Pioneered by Hayashi and co–workers, different groups have described Rh-catalyzed asymmetric additions of arylboron reagents to β-substituted cyclic enones.[17] Alternatively, Pd(II) catalysts in combination with oxazoline-based ligands have also been used for the asymmetric 1,4-addition of aryl boronic acids to several Michael acceptors. In 2011, Stoltz and co-workers reported the addition of arylboronic acids to β-substituted cyclic enones catalyzed by $Pd(TFA)_2$/Pyrox (**IVa**).[18] This system efficiently generates benzylic[19] and bis-benzylic[20] quaternary sterocenters. Minaard and co-workers expanded this scope to lactones and other acceptors using $PdCl_2$/Box (**IIIa**) catalyst in combination with $AgSbF_6$ (20 mol%).[21] A more sophisticated catalytic system [$PdCl_2$/**IIIa** (4-8 mol%), $AgCF_3CO_2$ (10-20 mol%), NH_4PF_6 (10-20 mol%), H_2O (8 equiv.), 7 equiv. of cyclic enone] enabled reactions with *ortho*-substituted aryl boronic acids in good to excellent enantioselectivities, albeit in moderate yields.[22]

On the other hand, conjugate additions of arylboronic acids **1** to more challenging cyclic dienones, requires an efficient control of the regioselectivity (1,4- *vs* 1,6-addition) as an additional challenge. Iridium/diene complexes catalyze asymmetric 1,6-additions of aryl boroxines to cyclic and acyclic dienones.[23] Moreover, Rhodium/diene complexes catalyze asymmetric 1,6-addition of sodium tetraphenylborate to cyclic dienones.[24] To the best of our knowledge, however, the use of Pd-based catalysts in this context remains unexplored.

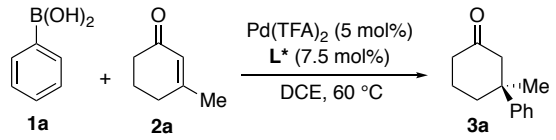
Encouraged by the efficiency of [$Pd(TFA)_2$/**L2**] catalyst in related contexts, we decided to explore the 1,4- and 1,6-additions of boronic acids to cyclic enones and dienones (Scheme 1, C); the collected results are discussed herein.

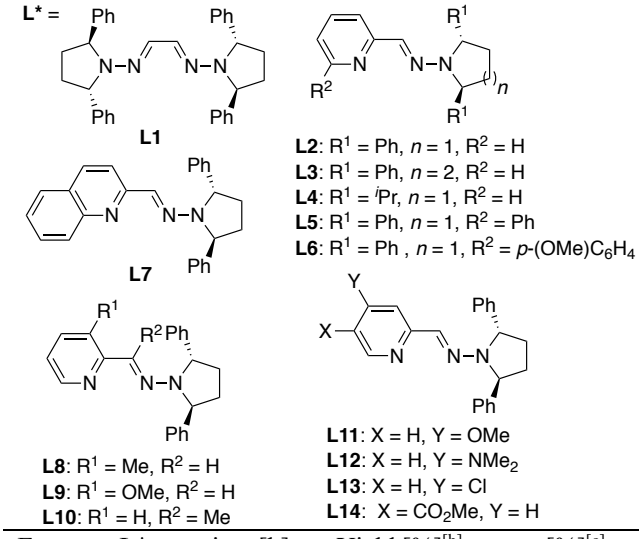
Results and Discussion

1,4-Addition of Aryl Boronic Acids to β-Substituted Cyclic Enones

The reaction between phenylboronic acid (**1a**) and 3-methyl-2-cyclohexenone (**2a**) was chosen as model system. Complexes prepared in situ from **L1**-**L14** (7.5 mol%) and different Pd(II) sources ($PdCl_2$, $Pd(OAc)_2$ and $Pd(TFA)_2$, 5 mol%) were initially evaluated in reactions performed at 60 °C in dichloroethane (DCE). $Pd(TFA)_2$ was identified as the best catalyst precursor (Table 1, entries 2-4). Its complex with glyoxal bishydrazone **L1** was totally inactive (entry 1), while pyridine-hydrazone ligand **L2** afforded a promising result (70% yield, 90% ee, entry 4), showing the need for a push-pull bidentate ligand containing a pyridine nitrogen. Subsequently, the influence by the hydrazone chiral unit was analyzed. (2*S*,6*S*)-2,6-Diphenylpiperidine derivative **L3** provided lower yield and enantioselectivity (42%, 40% ee, entry 5), a fact that has been repeatedly observed in related catalysts,[7],[8],[12] and that can be explained by the higher conformational flexibility of the piperidine

Table 1. Ligand screening.[a]





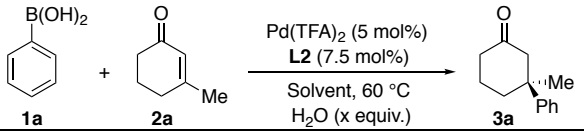
Entry	L*	time [h]	Yield [%][b]	ee [%][c]
1	**L1**	60	nr	--
2[d]	**L2**	60	nr	**--**
3[e]	**L2**	60	35	74
4	**L2**	**60**	**70**	**90**
5	**L3**	60	42	40
6	**L4**	60	8	18
7	**L5**	120	nr	--
8	**L6**	120	36	rac
9	**L7**	120	trace	rac
10	**L8**	60	57	80
11	**L9**	60	80	74
12	**L10**	60	trace	nd
13	**L11**	60	65	84
14	**L12**	60	46	64
15	**L13**	60	28	84
16	**L14**	60	54	90

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), **L** (7.5 mol%), $Pd(TFA)_2$ (5 mol%), DCE (1 mL), 60 °C. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. DCE = 1,2-Dichloroethane. [d] $PdCl_2$ (5 mol%). [e] $Pd(OAc)_2$ (5 mol%).

moiety and the weaker n→π conjugation. (2*S*,5*S*)-2,5-Diisopropylpyrrolidine derivative **L4** was also inadequate (entry 6). The (2*S*,5*S*)-2,5-diphenylpyrrolidine unit was consequently retained and the influence by substituents on the pyridine ring was next explored. The presence of aryl groups at C-6 (**L5**, **L6** or quinoline-derived **L7**) had a detrimental effect on the catalytic performance (entries 7-9). In the best case, $Pd(TFA)_2$/**L6** afforded **3a** in 36% yield after 120 h and as racemic mixture. Substitution at C-3 (**L8** and **L9**) had a moderate impact, yielding **3a** in lower 80% and 74% ee, respectively (entries 10 and 11). In contrast, substitution at the azomethine carbon in **L10** afforded only trace amounts of product **3a** after 60 h (entry 12). The influence of functional groups on the pyridine ring was also investigated. Unexpectedly, increasing the basicity of the pyridine N atom by introduction of electron-donating groups at C-4 (**L11** and **L12**) decreased reactivity and selectivity (entries 13 and 14). This can be tentatively explained assuming that the higher donor ability of the pyridine *N*-(sp^2) facilitates a hemilabile behaviour of the ligand, eventually facilitating dissociation of the hydrazone *N*-(sp^2) and hence giving **3a** with lower enantioselectivity [64% ee employing **L12** (4-NMe_2)]. On the contrary, introduction of electron-withdrawing groups at C-4 (**L13**) or at C-5 (**L14**) had no drastic influence in enantioselectivity, albeit **3a** was obtained in moderate to low yields (entries 15 and 16). A survey of different solvents was also performed (Table 2): THF as a coordinating solvent totally inhibited the catalytic activity (entry 2). In toluene, the reaction proceeded less efficiently than in DCE (entry 3) while MeOH or trifluoroethanol (TFE) afforded **3a** in lower yields and enantioselectivities (entries 4 and 5). In these polar protic solvents, reduction of Pd(II) to catalytically irrelevant Pd(0) species appeared as the main problem.

A further optimization of reaction temperature and concentration was performed to reduce side reactions such as homo-coupling, protodeboronation, and/or partial deactivation of the Pd(II) catalysts (entries 6-9). A poor yield was observed at 50 °C in DCE (entry 6), while running the reaction at 80 °C (entry 7) or higher concentration (entry 8) favored the formation of side-products. Finally, a modest improvement in

Table 2. Optimization of reaction conditions.[a]



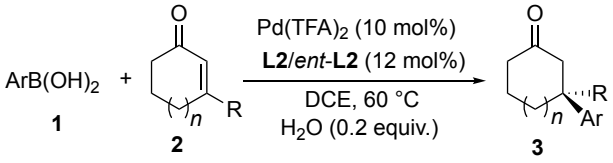
Entry	Solvent [M]	H_2O [equiv.]	*t* [h]	Yield [%][b]	ee [%][c]
1	DCE (0.25)	-	60	70	90
2	THF (0.25)	-	60	nr	--
3	Toluene (0.25)	-	60	38	83
4	MeOH (0.25)	-	60	16	74
5	TFE (0.25)	-	60	45	82
6[d]	DCE (0.25)	-	60	30	90
7[e]	DCE (0.25)	-	36	42	84
8	DCE (1)	-	36	30	90
9	DCE (0.5)	-	40	73	92
10[f]	DCE (0.5)	-	40	90	92
11[g]	DCE (0.5)	-	36	84	92
12[h]	DCE (0.5)	-	32	90	92
13[h]	DCE (0.5)	1.1	24	90	88
14[h]	**DCE** (0.5)	**0.2**	**24**	**94**	**91**

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), **L2** (7.5 mol%), $Pd(TFA)_2$ (5 mol%), solvent (M), 60 °C. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] 50 °C. [e] 80 °C. [f] Iterative addition of **1a** (0.125 mmol/10 h). [g] $Pd(TFA)_2$ (7.5 mol%), **L2** (9 mol%). [h] $Pd(TFA)_2$ (10 mol%), **L2** (12 mol%).

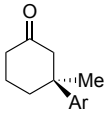
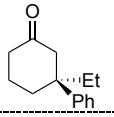
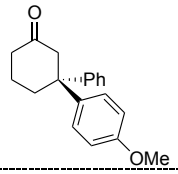
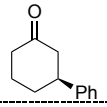
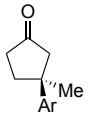
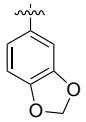
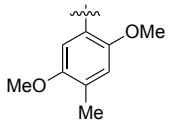
yield (73%) and enantioselectivity (92% ee) was observed at the optimal concentration (0.5M) at 60 °C (entry 9). An iterative addition of **1a**, avoiding high concentration of boronic acid, prevented bi-phenyl product formation and improved the yield up to 90% (entry 10). Additionally, a higher catalyst loading of $Pd(TFA)_2$ (7.5/10 mol%) led to appreciably shorter reaction times and good yields (entries 11 and 12). The presence of water had a strong impact in both reactivity and selectivity,[25] and was also the origin of some irreproducibility issues. Therefore, the remaining optimization was performed in dry DCE with controlled amounts of added water. Addition of stoichiometric quantities (up to 1.1-1.5 equivalents) led to faster (24 h) and cleaner reactions, giving **3a** in good yields albeit in slightly lower enantioselectivities (up to 88% ee, entry 13). 0.2 Equiv. was found to be the optimal amount, affording **3a** in 94% yield and 91% ee in only 24 h (entry 14).

The scope of the reaction was then explored by using different aryl boronic acids as nucleophiles (Table 3). In general, benzylic quaternary centers

Table 3. Substrate scope.[a]



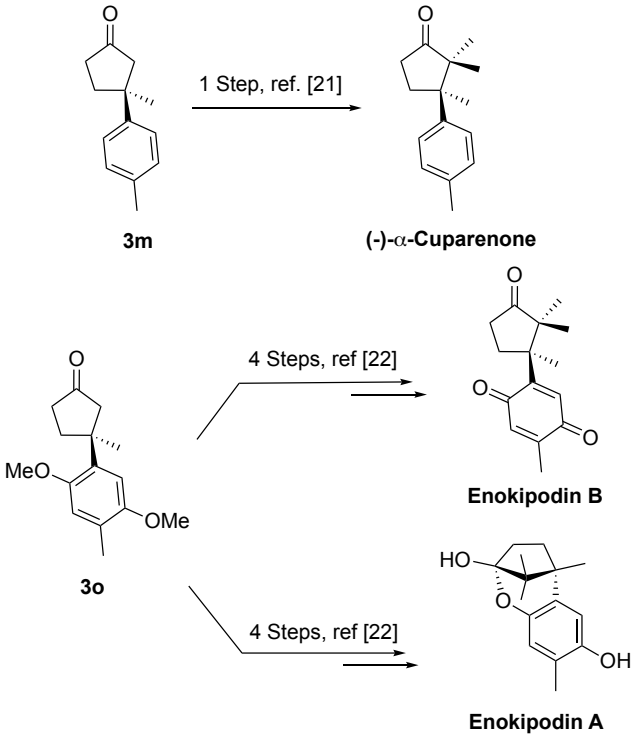
R = Me, n = 1 (**2a**)
R = Et, n =1 (**2b**)
R = Ph, n = 1 (**2c**)
R = H, n = 1 (**2d**)
R = Me, n = 0 (**2e**)

	Product	Ar, **3**	*t* [h]	Yield [%][b]	ee [%][c]
1		Ph, (*S*)-**3a**	24	94	91
2		Ph, (*R*)-**3a**	24	92	91
3		4-Me-C_6H_4, (*S*)-**3b**	48	93	91
4[d]		4-F-C_6H_4, (*S*)-**3c**	72	43	90
5[d]		4-Cl-C_6H_4, (*S*)-**3d**	72	77	90
6[d]		4-MeO-C_6H_4, (*S*)-**3e**	72	73	90
7[d]		4-CF_3O-C_6H_4, (*S*)-**3f**	72	65	90
8		3,5-$(Me)_2$-C_6H_3, (*S*)-**3g**	24	75	92
9[d]		(*S*)-**3h**	48	80	89
10		(*S*)-**3i**	72	--	--
11		(*S*)-**3j**	48	76	87
12[e]		Ph, (*S*)-**3k**	20	95	88
13		2-MeO-C_6H_4, (*S*)-**3l**	48	73	91
14		4-Me-C_6H_4, (*S*)-**3m**	48	97	88
15[d]		 , (*S*)-**3n**	60	65	86
16		 , (*S*)-**3o**	72	38	93
17[f]			72	54	90

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.25 mmol), **L2** (12 mol%), $Pd(TFA)_2$ (10 mol%), DCE (0.5 mL), H_2O (0.2 equiv.), 60 °C. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Iterative addition of **1** (0.125 mmol/18 h). [e] Reaction performed with $Pd(TFA)_2$ (7.5 mol%), **L2** (9 mol%). [f] Reaction performed with twofold excess of enone **2d**.

were generated in high enantioselectivities (88-92% ee). *p*-Substituted aryl boronic acids were well tolerated (entries 3-7), affording 3-aryl-3-methyl-cyclohexanones **3b-f** in variable yields depending on the substitution pattern. *p*-Tolyl boronic acid reacted slower (48 h) to give **3b** in 93% yield and 91% ee (entry 3). Arylboronic acids bearing halogens and ethers required longer reaction times (72 h) and iterative additions of **1** to achieve the optimal yields (43-77%, entries 4-7). An electron-rich di-substituted boron reagent leading to **3g** (75%, 92% ee) was also a suitable reaction partner (entry 8), while more challenging *ortho*-substituted boronic acids afforded products in lower yields. On the other hand, the uniformity of the enantioselectivities observed herein contrasts with the results reported with pyridine-oxazoline **IVa**: electron-rich nucleophiles often furnished products in lower enantioselectivities (Ar = 4-Me-C_6H_4, **3b** in 87% ee; Ar = 4-MeO-C_6H_4, **3e** in 69% ee).[18] Next, we explored the reactivity of cyclic enones with diverse *β*-substitutions and ring size. The reaction tolerated an ethyl substituent at the β carbon (entry 9), but a phenyl group at this position kills the reactivity (entry 10). Cyclohexenone (**2d**) gave (*S*)-**3j** in 76% yield and 87% ee (entry 11), together with 3-phenyl-cyclohex-2-enone (**2c**, heck-type product, 20%).[26] Finally, five-membered ring enone **2e**

afforded **3k** in 95% yield and 88% ee in a faster reaction (20 h, entry 12). The superior reactivity of this substrate allowed to reduce catalyst loading up to 7.5 mol% without practical deleterious effects and the introduction of *ortho*-substituted aryl groups, as shown for **3l** (entry 13), in good yield (73%) and enantioselectivity (91% ee).[27] A *meta-para* di-substituted boronic acid was also tolerated for the synthesis of **3n** in 65% yield and 86% ee (entry 15). Unfortunately, alkyl (isopropyl) and heteroaryl (2-furanyl and 2-thienyl) boronic acids were unsuccessfully tested with **2a** and **2e**. The methodology can be applied for the synthesis of advanced intermediates en route to several biologically active natural products (Scheme 2). Thus, **3m** [direct precursor of (−)-α-cuparenone] was obtained in an excellent 97% yield and 88% ee (Entry 14).[27] Additionally, the synthesis of **3o**, which is a key intermediate for the synthesis of enokipodin A and B, was accomplished in moderate yield (38%) but remarkable enantioselectivity (up to 93% ee, entry 16). The yield could be further improved to 54% by using a twofold excess of the enone **2e** with the same level of enantioselectivity (entry 17).[27] In order to evaluate the practical applicability of the developed methodology, the synthesis of (*S*)-**3a** (89%, 88% ee) was performed on a 1.5 mmol scale under slightly optimized reaction conditions [$Pd(OTf)_2$ (12 mol%), **L2** (14 mol%), H_2O (0.1 equiv.), iterative addition of **1a** (0.5 mmol/12 h), 48 h.]



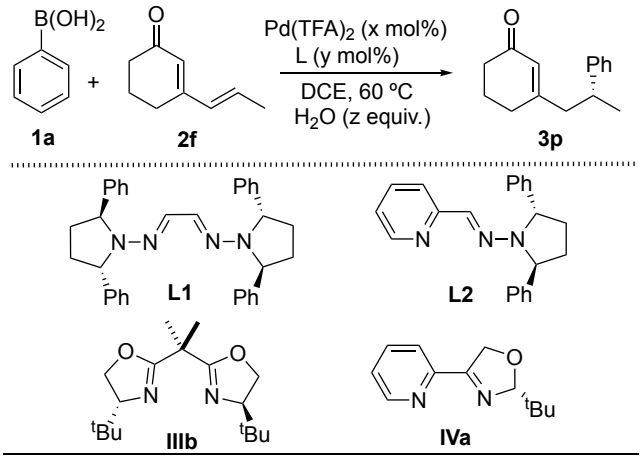
Scheme 2. Formal synthesis of (−)-α-cuparenone and enokipodin A and B

The absolute configuration of the newly created stereogenic center in products **3a-e**, **3h** and **3k-m** was determined to be *S* by chemical correlation (See ESI).

1,6-Addition of Aryl Boronic Acids to Cyclic Dienones

We initially analyzed the catalytic performance of several $Pd(TFA)_2$/**L*** complexes in the reaction between phenylboronic acid **1a** and cyclic dienone **2f** (Table 4). In contrast to the 1,4-addition pathway, the complex **L1**/$Pd(TFA)_2$ based on the bishydrazone ligand afforded a good conversion (71%) and perfect regioselectivity to **3p**, albeit with low enantioselectivity (entry 1). To our delight, the pyridine-hydrazone $Pd(TFA)_2$/**L2** system provided, also regioselectively, the 1,6-adduct **3p** with a higher enantioselectivity (62% ee), although the conversion remained moderate (45% after 60 h, entry 2). Different nitrogen ligands (bipyridines, bis-oxazolines and pyridine-oxazolines) were comparatively analyzed (See ESI), but lower conversions and enantioselectivities were obtained in all cases. As representative examples, bis-oxazoline **IIIb** furnished **3p** in 43% conversion (lower than **L1** and similar to **L2**) in racemic form (entry 3) while pyridine-oxazoline **IVa** provided **3p** in 49% ee, albeit in 20% conversion (entry 4). Structural variations of the pyridine-hydrazone ligand were also investigated but, as in the previous 1,4-addition case, none of the modified ligands proved to be superior than the basic **L2** (see ESI). Interestingly, none of these Pd-catalysts yielded 1,4- or heck-type side products. Alternative solvents, palladium salts and organoborane reagents (boroxines and borate salts) were also evaluated without any improvement. Increasing concentration up to 0.8M afforded **3p** with similar conversion and slightly better enantioselectivity in a shorter reaction time (entry 5). Iterative addition of arylboronic acid **1a** had a positive effect in the outcome of the reaction, affording **3p** in yet moderate conversion (52%) but a better 77% ee (entry 6). Then, the impact of water, as additive in this process, was also analyzed. Employing an excess (up to 6 equivalents) of water accelerated the reaction, improving conversion up to 75% in 24 h, although at the expenses of a lower enantioselectivity (entry 7). As in the 1,4-addition, a catalytic amount of water (0.2 equiv.) were found to be optimal, giving **3p** in 61% conversion after 48 h (entry 8) while keeping a reasonable level of asymmetric induction (78% ee). Upon these conditions and performing iterative additions of **1a** (0.06 mmol/12 h) during prolonged reaction times, conversions increased up to 71% and 90% for 72 and 96 h, respectively (entries 9,10).

Table 4. Optimization of reaction conditions.[a]

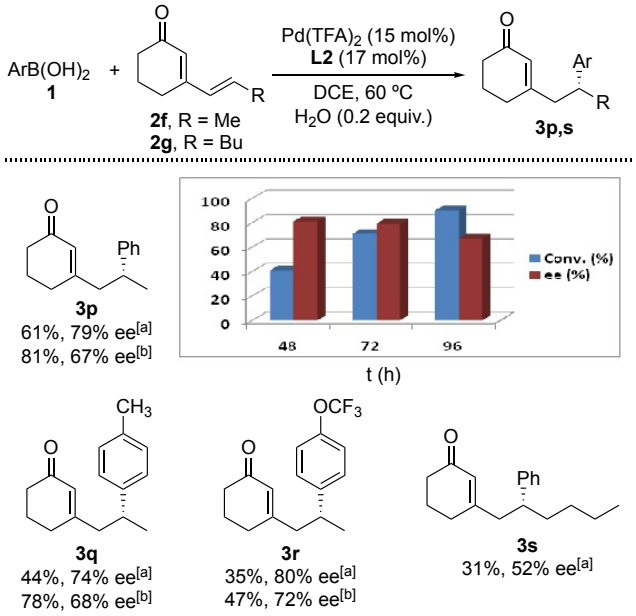


Entry	Ligand	H_2O [equiv.]	*t* (h)	Conv. [%][b]	ee [%][c]
1	**L1**	-	60	71	10
2	**L2**	-	60	45	62
3	**IIIb**	-	60	43	rac
4	**IVa**	-	60	20	49
5[d]	**L2**	-	36	44	67
6[d],[e]	**L2**	-	48	52	77
7[d]	**L2**	6.4	24	75	38
8[d],[e]	**L2**	0.2	48	61	78
9[d],[f]	**L2**	**0.2**	**72**	**71 (61)[g]**	**79**
10[d],[f]	**L2**	0.2	96	90 (81)[g]	67

[a] Reaction conditions: **1a** (0.5 mmol), **2f** (0.25 mmol), **L** (12 mol%), $Pd(TFA)_2$ (10 mol%), DCE (0.5 mL), 60 °C, 60 h. [b] Determined by ^{1}H-NMR of crude reaction mixtures. [c] Determined by chiral HPLC. [d] Reaction conditions: **1a** (0.5 mmol), **2f** (0.25 mmol), **L2** (17 mol%), $Pd(TFA)_2$ (15 mol%), DCE (0.3 mL), 60 °C. [e] Iterative addition of **1a** (0.125 mmol/12 h). [f] Iterative addition of **1a** (0.063 mmol/12 h). [g] In parenthesis, isolated yield after column chromatography.

However, a decrease of enantiomeric excess over reaction time was observed,[28] affording **3p** in 81% yield and 67% ee (entry 10). Alternatively, stopping the reaction after 72 h afforded **3p** in 61% yield and 79% ee, while some unreacted starting material was recovered (25%). With the optimal reaction conditions in hand, the method was extended to different boronic acids and dienones. (Scheme 3). *p*-Tolylboronic acid (**1b**) and [4-(trifluoromethoxy)phenyl] boronic acid (**1f**) exhibited similar reaction profiles than the model reagent **1a** (see ESI). Thus, reactions after 72 h allowed to obtain the corresponding adducts **3q** and **3r** in good enantioselectivities (74 and 80% ee) and modest yields. Alternatively, higher yields were obtained after 96 h, albeit lower enantioselectivities were observed (68 and 72% ee).

Finally, when dienone **2g** was used the addition of **1a** proceeded with a lower enantioselectivity (52% ee). The absolute configuration of **3s** was determined to be *R* by chemical correlation,[29] and those of **3p-r** were assigned by analogy assuming a uniform stereochemical pathway.



Scheme 3. 1,6-Addition to dienones. [a] Reaction time 72 h. [b] Reaction time 96 h.

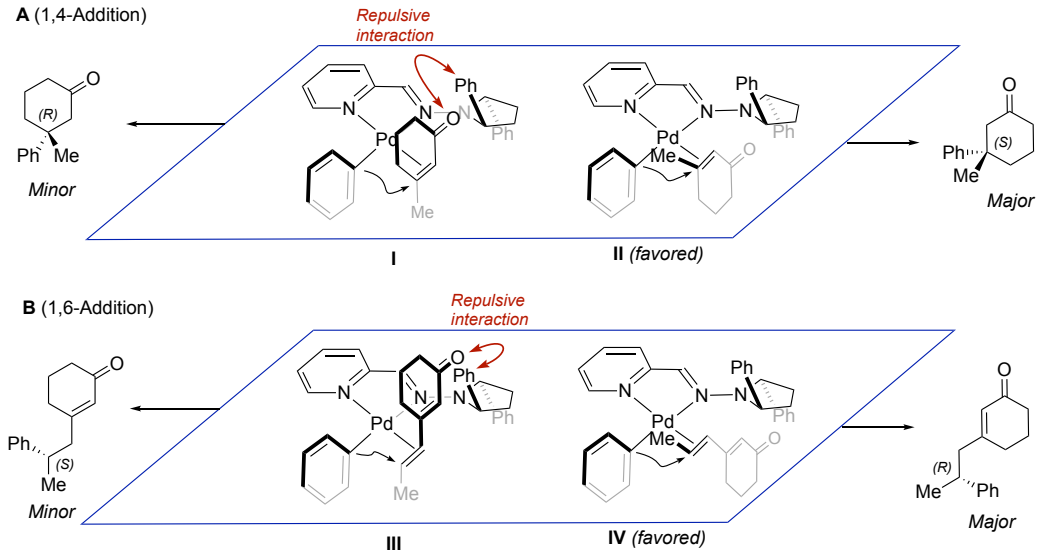
Proposed Intermediates and Stereochemical models

The proposed mechanism for Pd(II) catalyzed 1,4-addition of arylboronic acids to enones mediated by pyridine-oxazoline ligands[18],[19a] allowed to extrapolate a plausible catalytic cycle employing pyridine-hydrazone **L2**. The proposed intermediates **I**/**II** involved in the stereocontrolling step are depicted in Scheme 4A. In these intermediates, the aryl group from the boronic acid should be placed *trans* to the less basic hydrazone fragment after the transmetallation step, leaving the *cis* position available for the coordination of the cyclic enone. One of the two possible orientations of enone **2** (**I**) is clearly disfavoured due to a destabilizing steric interaction with the proximal phenyl group at position C(2') of the ligand. The alternative orientation (in **II**), however, lacks such interaction, guiding the stereoselective C-C bond formation to the experimentally observed major (*S*) enantiomer. Coordination of water to Pd is proposed to assist the re-generation of Pd(II)-OH catalyst (protonolysis step). For the 1,6-addition, and according with the stereochemical outcome, a consistent model with similar interactions is proposed. In Scheme 4B, only two intermediates **III**/**IV** out of other possibilities resulting from higher conformational flexibility of dienone, are depicted (See ESI), being **IV** favoured for the lack of repulsive steric interactions.

Conclusion

In summary, a $Pd(TFA)_2$/pyridine-hydrazone (**L2**) precatalyst provides fairly good yields and enantioselectivities in the 1,4-addition of arylboronic acids to *β*-substituted cyclic enones, generating all-

carbon quaternary stereocenters. The developed methodology allows the efficient synthesis of *β*-aryl-*β*'-methylcyclopentanones bearing *ortho*-substituted aryl groups, relevant precursors of biologically active molecules. The catalytic system was also tested employing more challenging cyclic dienones affording 1,6-addition products with complete, regioselectivities and moderate to good enantioselectivities. It was observed a positive effect of catalytic amounts of water, presumably assisting in the catalyst turnover, in both processes. The set of results presented herein show again that readily available pyridine-hydrazones constitute an interesting type of ligands, outperforming the well-stablished bis-oxazoline or pyridine-oxazoline families in some contexts.



Scheme 4. Proposed Intermediates and Stereochemical models.

Experimental Section

General Information

^{1}H NMR spectra were recorded at 300 MHz or 500 MHz; ^{13}C NMR spectra were recorded at 75.5 MHz or 126 MHz with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C respectively); ^{19}F NMR spectra were recorded at 471 MHz. Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminum backed plates (1.5 × 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F_{254}). Compounds were visualized by exposure to UV light or by dipping the plates in solutions of $KMnO_4$, anisaldehyde or phosphomolibdic acid stains followed by heating. Melting points were recorded in a metal block and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 MC polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC. Solvents were purified and dried by standard procedures. Dichloroethane was purchased from Across (99.5% Extra Dry, Over Molecular Sieves, <0.005% H_2O). Unless otherwise noted, commercially available reagents were used without further purification.

General Procedure for Pd(II)-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids 1 to Cyclic Enones 2a,d.

A test tube was charged with $Pd(TFA)_2$ (8.5 mg, 0.025 mmol), **L2** (9.8 mg, 0.03 mmol), arylboronic acid **1** (0.5 mmol), cyclic enone **2a,e** (0.25 mmol), DCE (0.5 mL) and H_2O (1 µL, 0.05 mmol). The mixture was stirred at 60 °C for the time specified for each substrate (tlc and ^{1}H-NMR monitoring). The solvent was removed at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/EtOAc). Enantiomeric excess (ee) was determined by HPLC analysis.

General Procedure for Pd(II)-Catalyzed Asymmetric 1,6-Addition of Arylboronic Acids 1 to Dienones 2f,g.

A test tube was charged with $Pd(TFA)_2$ (13 mg, 0.038 mmol), **L2** (13 mg, 0.04 mmol), arylboronic acid **1** (0.06 mmol), dienone **2f,g** (0.25 mmol), DCE (0.5 mL) and H_2O (1 µL, 0.05 mmol). Subsequently, addition of **1** (0.06 mmol/12 h) was performed. The mixture was stirred at 60 °C for 72/96 h [for each substrate, conversions (by ^{1}H-NMR) and ee's (HPLC) were monitored at different times (48, 72 and 96 h)]. The solvent was removed at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/EtOAc). Enantiomeric excess (ee) was determined by HPLC analysis.

Electronic supplementary information (ESI) contains: experimental procedures, additional optimizations, characterization data, NMR spectra for compounds, and HPLC traces

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[26] Chalcone and other acyclic enones afforded a complex mixture of addition (minor) and heck-type (major) products.

[27] In relevant cases, such as **3l**, **3m**, and **3o**, the catalyst based on **L2** clearly outperforms those based on oxazoline-based ligands: See ref. [21] and [22].

[28] A decrease of the enantiomeric excess over reaction time is proposed to be a consequence of hemilabile behavior of hydrazone fragment, leading to conversion by less-selective catalytic species. For a control experiment (see ESI).

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Pyridine–Hydrazone Ligands in Asymmetric Palladium-Catalyzed 1,4- and 1,6-Additions of Arylboronic Acids to Cyclic (Di)enones

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