1,2-Additions

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Exogenous-Base-Free Palladacycle-Catalyzed Highly Enantioselective Arylation of Imines with Arylboroxines**

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Abstract: *Enantiomerically pure benzylic amines are important for the development of new drugs. A readily accessible planar-chiral ferrocene-derived palladacycle is shown to be a highly efficient catalyst for the formation of N-substituted benzylic stereocenters; this catalyst accelerates the 1,2-addition of arylboroxines to aromatic and aliphatic imines with exceptional levels of enantioselectivity. Using aldimines an exogenous base was not necessary for the activation of the boroxines, when acetate was used as an anionic ligand. Common problems such as aryl–aryl homocouplings and imine hydrolysis were fully overcome, the latter even in the absence of molecular sieves.*

Chiral α-branched benzylic amines constitute an important structural motif in active pharmaceutical ingredients (APIs) like Cetirizine[1] and Sertraline (both from Pfizer, Figure 1).[2] Driven by the application of enantiopure benzylic amines as APIs, the arylation of aldimines has been established as an attractive strategy to set up N-substituted benzylic stereocenters. Various types of arylmetal species including zinc,[3] titanium,[4] and tin[5] reagents have been successfully employed. The use of arylboronic acid derivatives has also been intensively studied owing to the stability of these reagents, their compatibility with a large number of functional groups, their straightforward preparation, commercial availability, and relatively low cost.[6] Rhodium complexes have emerged as the most versatile catalysts for the asymmetric arylation of aldimines by arylboronic acids.[6,7] In addition, several reports have described the use of palladium(II) catalysts for this transformation.[8,9] In general, the Pd^{II}-catalyzed additions of arylboronic acids to aldimines are plagued by a competing imine hydrolysis and require the use of molecular sieves to achieve acceptable yields.[8a,b,f] So far the catalytic proficiency of Pd catalysts has not been comparable to that of the best Rh catalysts in terms of enantioselectivity and activity.[8] Pd catalysts with a comparable efficiency would provide an attractive alternative, as Rh is more expensive than Pd.[10]

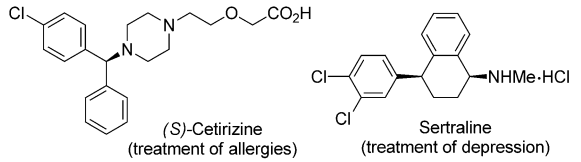

Figure 1. Examples for approved chiral benzylic amine drugs.

Herein, we report that a readily available planar-chiral ferrocene imidazoline palladacycle (FIP) previously developed by our group[11a,b] has been identified as an attractive Pd catalyst for the arylation of imines with arylboroxines, providing a variety of benzylic amines in almost enantiomerically pure form. Important for the high performance is the use of acetate as anionic ligand, which makes it possible to run the reaction without stoichiometric amounts of an exogenous base, which is often required to promote the transmetalation of the aryl residue from boron to palladium.[12]

To our knowledge, all Pd complexes previously described as catalysts in enantioselective arylations of imines using arylboronic acid derivatives made use of neutral bidentate ligands coordinating to a Pd^{II} center.[8,9] Besides imine hydrolysis as a general problem, the undesired formation of bisaryl homocoupling products (Ar–Ar) has been frequently reported, which is explained by the formation of neutral bisaryl–Pd^{II} intermediates[8] and subsequent reductive elimination. Pd^0 is thus formed and this corresponds to the loss of active catalyst. The use of palladacycle catalysts instead, in which Pd^{II} is coordinated by a monoanionic C,N-ligand,[13] might impede the formation of an undesired bisaryl–Pd^{II} intermediate, as a second transmetalation should be less favorable due to the formation of an anionic Pd center.

C,N-Palladacycles offer the additional advantage that the position of different ligands can often be controlled since neutral ligands (substrates) prefer the position *trans* to the N-donor, whereas anionic ligands bind *trans* to the C-donor.[13] Using a planar-chiral palladacycle we expected that this preference might contribute to high enantioselectivity.[14] To prove these hypotheses the addition of Ph-$B(OH)_2$ (**2a**) to *N*-tosylimine **1a** was studied (Table 1). Product **4a** has previously been shown to be a valuable precursor of Cetirizine.[7g]

Metallocene-derived imidazoline palladacycles have been reported by our research group to be efficient catalysts for various types of catalytic reactions.[11,15,16] With [{FIP-Cl}$_2$] (6 mol%)—activated by AgOTf (12 mol%) through removal of the Cl bridges to facilitate substrate coordination[11]—product **4a** was formed in almost enantiomerically pure form (Table 1, entry 1). This initial reaction was performed at 20 °C in toluene in the presence of activated 4 Å molecular sieves

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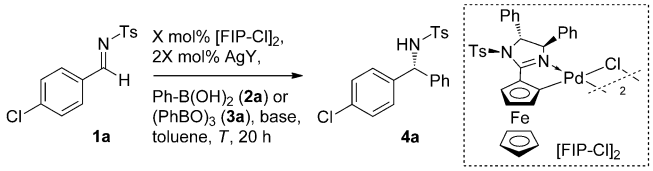
Table 1: Development of the title reaction.



No.	X	Y	**2a** or **3a** (equiv)	Base[a]	Additive	*T* [°C]	Yield **4a** [%][b]	Hydrolysis [%][b]	*ee* **4a** [%][c]
1	6	OTf	**2a** (2)	KF	4 Å MS	20	92	3	>99
2	1	OTf	**2a** (2)	KF	4 Å MS	20	74	13	>99
3	1	–	**2a/3a** (2)	KF	4 Å MS	20	<1–92	<1–7	>99
4	1	OAc	**3a** (1)	NaOAc	–	20	25	<1	>99
5	1	OAc	**3a** (1)	–	–	20	2	<1	n.d.
6	1	OAc	**3a** (1)	–	–	70	99	<1	>99
7[d]	**1**	**OAc**	**3a (1)**	**–**	**–**	**65**	**99**	**<1**	**>99**

[a] 1 equiv was used. [b] Determined by ^{1}H NMR analysis of the crude product using mesitylene as internal standard. [c] Determined by HPLC. [d] The reaction was performed in chlorobenzene as solvent. OTf = F_3CSO_3.

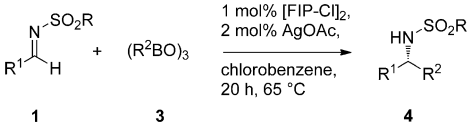
(MS) and with KF as a stoichiometric base.[17] With a precatalyst loading of 1 mol% hydrolysis was not fully suppressed (Table 1, entry 2). This problem seemed to be solved initially by the direct use of $[FIP\text{-}Cl]_2$ (1 mol%), that is, without catalyst activation by a silver salt. Using boronic acid **2a** the product was formed in high yield and in nearly enantiopure form (Table 1, entry 3).

However, we noticed that the reactivity strongly depended on the purity of the boronic acid. Analysis of different new batches of **2a** from different commercial suppliers revealed that **2a** is very often contaminated by large quantities of the corresponding boroxine. Sometimes commercial batches labeled as boronic acid **2a** were in fact mainly boroxine **3a** and resulted in no product under the conditions of Table 1, entry 3, while in general yields decreased with increasing proportion of **3a**.[18] The use of pure **3a** gave no reaction at all, even when the catalyst loading was increased to 6 mol%. Still, the development of a method making use of arylboroxines appeared to be more desirable in order to avoid reproducibility problems caused by the varying composition of commercial boronic acids.

As **3a** was found to be significantly less reactive than **2a**, the transmetalation was expected to be less efficient with the former. We were speculating that it might be facilitated by an anionic ligand at the Pd center which would offer sufficient Lewis basicity for additional coordination to the boroxine (similar to the "oxo–palladium pathway").[17,19] Promising results were obtained with acetate as ligand.[20] At 20 °C in the presence of stoichiometric NaOAc some reactivity was noticed towards **4a** which was formed in nearly enantiomerically pure form (Table 1, entry 4). In the absence of NaOAc this reactivity disappeared (Table 1, entry 5); however, **4a** could be obtained in quantitative yield at higher temperatures (Table 1, entry 6). A survey of different silver salts for chloride removal showed that the nature of the anionic ligand is crucial for the observed reactivity. With less Lewis basic anions like triflate and trifluoroacetate, little or no product was formed (not shown). The use of chlorobenzene as solvent led to slightly improved reactivity. Under otherwise identical conditions the product was formed in nearly quantitative yield and with >99% *ee* at 65 °C (Table 1, entry 7).[21]

We then applied these optimized conditions to the reactions of other imine and boroxine substrates (Table 2). In general, imine hydrolysis was largely avoided in all 21 examples, while products were usually formed in good to excellent yields. In most examples the products were nearly enantiomerically pure with *ee* values exceeding 99%. Exceptions were found for only entries 11 and 20 (both 99% *ee*) and 17 (98% *ee*). *Ortho*, *meta*, and *para* substituents on the aromatic residues R^1 and R^2 of the imine and the boroxine substrates, respectively, were accommodated under the reaction conditions. The efficiency when an *ortho* residue is present on the boroxine is of particular note (Table 2, entry 7), as these substrates are usually quite challenging. Electronic effects caused by substituents on R^1 did not significantly affect the product yields. Both σ-donors (Table 2, entry 15) and σ-acceptors (entries 1–10) as well as π-donors (entry 13) and π-acceptors (entry 14) were all well tolerated on the aromatic rings. In addition, good to high yields were obtained for

Table 2: Application of the optimized reaction conditions to various substrates.



No.	**4**	R^1	R^2	SO_2R	Yield [%][a]	*ee* [%][b]
1	**4a**	4-ClC_6H_4	Ph	Ts	99	>99
2	**4b**	4-ClC_6H_4	4-$MeOC_6H_4$	Ts	84	>99
3	**4c**	4-ClC_6H_4	4-PhC_6H_4	Ts	98	>99
4	**4d**	4-ClC_6H_4	3,4-$F_2C_6H_4$	Ts	70[c,d]	>99
5	**4e**	4-ClC_6H_4	4-$MeO_2CC_6H_4$	Ts	50[d]	>99
6	**4f**	4-ClC_6H_4	3-$MeOC_6H_4$	Ts	95	>99
7	**4g**	4-ClC_6H_4	2-$MeOC_6H_4$	Ts	96	>99
8	**4h**	3-ClC_6H_4	4-$MeOC_6H_4$	Ts	99	>99
9	**4i**	2-ClC_6H_4	Ph	Ts	91	>99
10	**4j**	2-ClC_6H_4	4-PhC_6H_4	Ts	85	>99
11	**4k**	Ph	4-$MeOC_6H_4$	Ts	98	99
12	**4l**	Ph	4-PhC_6H_4	Ts	99	>99
13	*ent*-**4k**	4-$MeOC_6H_4$	Ph	Ts	86	>99
14	**4m**	4-$O_2NC_6H_4$	4-PhC_6H_4	Ts	85	>99
15	**4n**	4-MeC_6H_4	Ph	Ts	96	>99
16	**4o**	2-naphthyl	Ph	Ts	91	>99
17	**4p**	thiophen-2-yl	Ph	Ts	55[c,d]	98
18	**4q**	Cy	Ph	Ts	95[c,d]	>99
19	**4r**	*i*Pr	Ph	Ts	92[c,d]	>99
20	**4s**	$Ph(CH_2)_2$	Ph	Ts	32[d,e]	99
21	**4a′**	4-ClC_6H_4	Ph	*p*Ns	91[d]	>99

[a] Yield of isolated product. [b] Determined by HPLC. [c] Reaction temperature: 80 °C. [d] 2 mol% of $[FIP\text{-}Cl]_2$. [e] Determined by ^{1}H NMR analysis using an internal standard (*p*Ts = 4-$MeC_6H_4SO_2$, *p*Ns = 4-$O_2NC_6H_4SO_2$).

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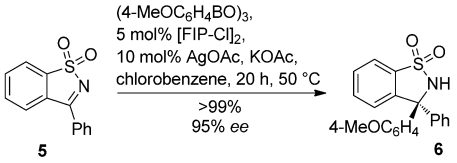
imines in which R^1 is either a polycyclic aromatic hydrocarbon (Table 2, entry 16), an electron-rich heterocycle (entry 17), or an α-branched alkyl residue (entries 18 and 19). Imines with an α-unbranched alkyl residue, which are challenging due to the imine/enamine equilibrium, also react with high enantioselectivity, but side reactions were noticed and the product decomposed during its purification (Table 2, entry 20). Gratifyingly, the title reaction is also applicable to imines with other N-sulfonyl residues besides tosyl. This is shown in Table 2, entry 21 for a *para*-nosyl residue, which is well known as a very versatile N-protecting group that is readily removable under mild reaction conditions.[22]

Also the boroxine residues R^2 can be equipped with functional groups displaying electron-withdrawing or -donating effects. Still relatively good reactivity was found, for example, with a less nucleophilic boroxine carrying two fluorine atoms on R^2, albeit a higher temperature and catalyst loading were required to obtain a useful yield of **4d** (Table 2, entry 4). A useful yield was also obtained for the difficult case of a boroxine carrying ester moieties as π-acceptors (Table 2, entry 5).

Entries 11 and 13 in Table 2 demonstrate that both possible product enantiomers are accessible on demand in almost enantiomerically pure form with an identical catalyst batch by simply switching the imine's and boroxine's substitution patterns. The absolute configurations of products **4a** and **4k** were unambiguously determined by X-ray crystal structure analysis.[23]

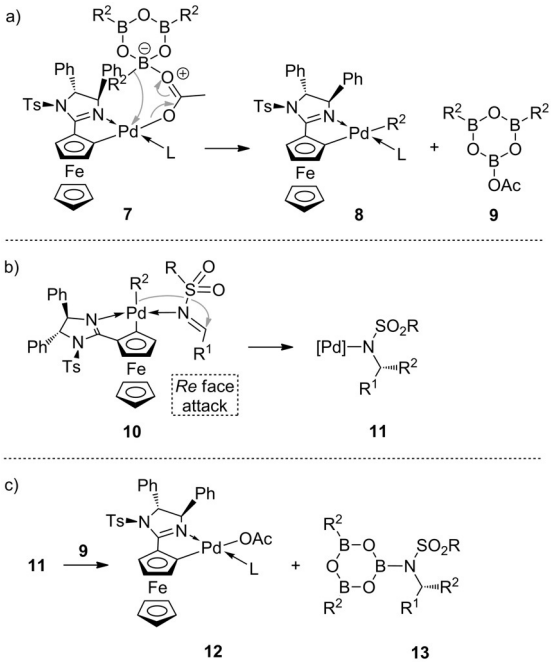
Preliminary studies have shown that the formation of *N*-substituted quaternary stereocenters[9] is also possible with high yield and enantioselectivity using our palladacycle catalyst [Eq. (1)].[24] Starting from ketimine **5**, a base (here KOAc, 2 equiv) was necessary though for high efficiency in terms of reactivity and enantioselectivity which are otherwise moderate.



(1)

Our current understanding of the title reaction is illustrated in Scheme 1. We propose that a Pd^{II}-bound acetate ligand activates the boroxine by an additional coordination to give intermediate **7** thus enabling a shift of R^2 (Scheme 1a). In this scenario the acetate would be trapped by a boron atom to give **9** (the other R^2 groups in **9** might also be replaced then).

The stereochemical outcome of the addition reaction is explained by the working model **10** (Scheme 1b). Based on the typical coordination behavior of C,N-palladacycles,[11e] we assume that neutral imines preferably coordinate *trans* to the N donor, whereas the anionic residue R^2 adopts the *cis* position. The very efficient face differentiation of the imine is expected to be supported by a reactive conformation in which the sulfonyl moiety of the imine points away from the ferrocenyl core to minimize repulsive steric interactions.[25] Product decomplexation should be possible by reaction of **11** with **9** and would be accompanied by acetate transfer to the Pd^{II} center, thus regenerating catalyst **12** (Scheme 1c).



Scheme 1. Possible explanations of the catalytic key steps: a) acetate-promoted transmetalation of R^2 from boroxines to Pd^{II}; b) working model to rationalize the stereochemical outcome of the 1,2-addition reaction; c) product decomplexation and regeneration of a Pd–OAc moiety.

Mechanistic support for the acetate-promoted transmetalation was obtained by ESI-HRMS examination of a solution in which activated catalyst (2 mol%) and boroxine **3a** were stirred for 1 h in chlorobenzene at 65 °C in the absence of an exogenous base. As dominant Pd-containing species the Pd–Ph adduct **8** was detected (R^2 = Ph, no ligand L present, mass found: $m/z = 742.0552$; calculated: $m/z = 742.0579$). In contrast, in the presence of additional imine **1a** (1 equiv) complex **8** was not detectable under otherwise identical conditions, but a species with a mass that would fit to either **10** or **11** (mass found: $m/z = 1060.0725$; calculated: $m/z = 1060.0745$).

In conclusion, we report a highly enantioselective asymmetric arylation of *N*-sulfonylimines catalyzed by a readily available planar-chiral palladacycle (prepared in three steps starting from $FcCONH_2$[11a,b]). Arylboroxines were initially found to be unreactive. High efficiency could be achieved by use of acetate as an anionic ligand for the catalytically active Pd^{II} center. The latter should facilitate the transmetalation step and an exogenous stoichiometric base could thus be avoided allowing for mild reaction conditions. In addition, imine hydrolysis could be fully suppressed even in the absence of molecular sieves, which is necessary for other Pd catalysts, while aryl–aryl homocouplings are avoided probably as a result of the anionic nature of the C,N-ligand.

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