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Dynamic Kinetic Cross-Coupling Strategy for the Asymmetric Synthesis of Axially Chiral Heterobiaryls

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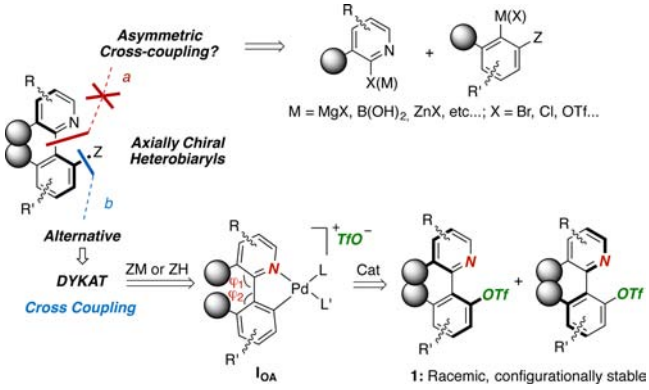
Supporting Information

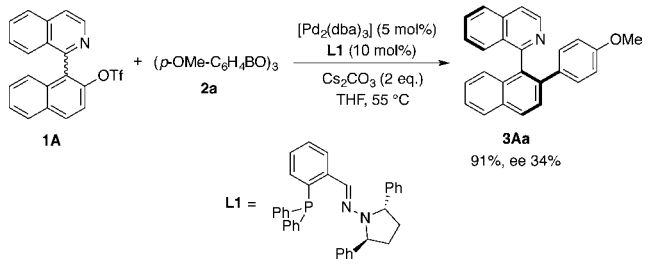
ABSTRACT: A dynamic kinetic asymmetric transformation (DYKAT) technique has been designed for the synthesis of 2′-substituted 2-aryl pyridines/isoquinolines and related heterobiaryls. In this way, the Pd(0)-catalyzed coupling of racemic 2-triflates with aryl boroxines using a TADDOL-derived phosphoramidite as the ligand provides the corresponding coupling products with good to excellent enantioselectivities. Structural studies support that the formation of configurationally labile oxidative addition palladacycles is the key for the success of the methodology.

In the field of asymmetric C(sp^2)−C(sp^2) cross-couplings, the synthesis of heterobiaryls (e.g., 2-aryl pyridines or analogues) remains as a challenging, yet unsolved, problem. While significant advances have been recently recorded in asymmetric cross-couplings for the synthesis of different axially chiral biaryls,[1] the introduction of heterocyclic coupling partners raises the level of difficulty due to the problems associated with the coordination ability of the substrate, their reduced stability and/or reactivity, and the poorer configurational stability of the products[2] (Scheme 1, path a). Consequently, there is only one recent example of such couplings, but a disappointing 20% ee was reached in an isolated case.[3] Alternatively, asymmetric coupling via CH activation of C(3)−H in thiophenes[4] and direct Rh-catalyzed CH activation/ethylene coupling of 2-aryl pyridines[5] have also been reported, although with modest enantioselectivities. To date, highly enantioselective catalytic synthesis of 2-aryl pyridines is limited to [2 + 2 + 2] cyclotrimerizations.[6] Therefore, we decided to explore a retrosynthetic alternative consisting of making the C(2′)−Z bond (path b) instead of the direct (asymmetric) coupling of the C(1)−C(1′) bond. According to this idea, readily available and configurationally stable racemic triflates **1** were chosen as the starting materials. The strategy relies on the assumption that the oxidative addition of the Pd(0) catalysts should afford cationic palladacyclic intermediates $\mathbf{I_{OA}}$ incorporating the basic pyridine N atom as a ligand, a process particularly favored a priori for noncoordinating triflate counteranions. As a working hypothesis, we assume that the configurational stability of the stereogenic axis in these structures is compromised as a consequence of the widening of the concerned angles φ_1 and φ_2, and in this scenario, a dynamic kinetic asymmetric transformation (DYKAT) protocol was envisaged as a valuable tool for the synthesis of enantioenriched coupling products. The Suzuki coupling of *p*-anisyl boroxine **2a** with readily available 1-(isoquinolin-1-yl)naphthalen-2-yl triflate **1A** was chosen as a model reaction (Scheme 2). After a screening with a number of available chiral bidentate ligands, previously reported phosphino hydrazone **L1**[7] combined with [Pd_2(dba)$_3$] (1:1 Pd/ligand, 10 mol %) led to a clean and complete conversion to afford the expected coupling product **3Aa** with a 34% ee. Though not of much practical interest from a synthetic point of view, this result constitutes a validation of the starting hypothesis.[8] Additional evidence was collected from a structural study of the isolated oxidative addition intermediate for this

Scheme 1. Retrosynthetic Analysis for Chiral Heterobiaryls



Scheme 2. Model Reaction



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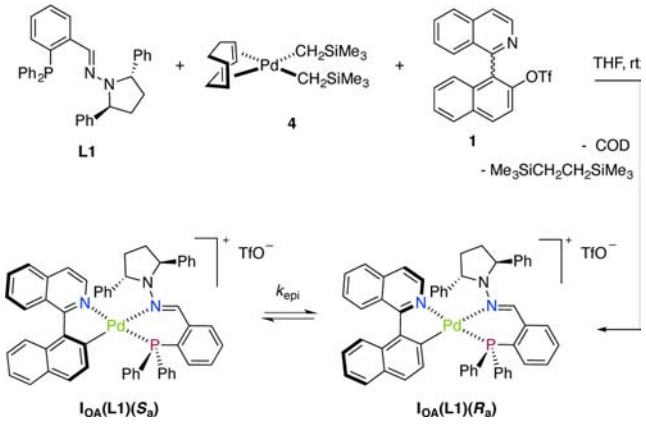
particular ligand. The reaction of 1 equiv of ligand **L1** with 1 equiv of **1A** in the presence of $[Pd(cod)(CH_2SiMe_3)_2]$ **4**[9] (Scheme 3) was performed to afford the expected complex

Scheme 3. Synthesis of the Oxidative Addition Intermediate



$\mathbf{I_{OA}}$[10] in 65% yield as a 2.7:1 mixture of two compounds (^{31}P NMR: δ 35.1 and 30.9 ppm), initially assigned to be the diastereomeric atropisomers $\mathbf{I_{OA}(L1)}(S_a)$ and $\mathbf{I_{OA}(L1)}(R_a)$.

However, variable-temperature ^{31}P NMR experiments in $CDCl_3$ revealed no dynamic behavior, and a high barrier for the interconversion of both species makes this assignment inconsistent with the experimentally observed dynamic kinetic asymmetric coupling. As *cis*–*trans* mixtures were also ruled out for the strong *trans* influence effected by the aryl ligand,[11] we concluded that the observed isomers should correspond to configurationally stable conformations $\mathbf{I_{OA}(L1)}^{Pd}$ and $\mathbf{I_{OA}(L1)}_{Pd}$, resulting from the two possible relative arrangements of the ligand plane and the Pd coordination plane. Thus, the Pd atom could be placed below or above the ligand plane as depicted in Figure 1. Although previous structural studies[7]

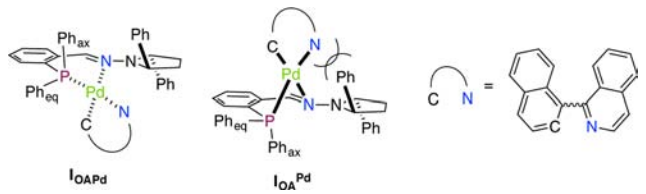


Figure 1. Diastereomeric intermediates $\mathbf{I_{OA}(L1)}_{Pd}$ and $\mathbf{I_{OA}(L1)}^{Pd}$.

performed with these types of complexes suggested that a considerable steric repulsion would arise from the Ph–N(CH) contact in the latter, the lack of alternatives made us reconsider this possibility. Fortunately, crystallization from CH_2Cl_2/THF afforded good quality crystals of the major isomer (^{31}P NMR: δ 35.1 ppm), suitable for X-ray diffraction analysis (Figure 2). According to the initial hypothesis, a cationic complex with a core five-membered palladacycle was formed, with the angles φ_1 [C(47)–C(46)–C(37)] and φ_2 [C(46)–C(37)–C(38)] significantly widened (127.0 and 123.6°, respectively) with respect to the ideal 120° value. Note, the complex exhibits the configuration $\mathbf{I_{OA}(L1)}^{Pd}$ considered a priori as disfavored, with an angle between the ligand plane [defined as fitting through P–C(3)–C(2)–C(1)–N(1)] and the coordination plane [defined as fitting through P–N(1)–Pd–N(2)–C(36)] of 117.0°. As shown in Figure 2, the predicted repulsive interaction between the 2-phenyl group of the pyrrolidine and the isoquinoline moiety is relaxed due to a severe distortion of the square planar geometry at the palladium center. Thus, the torsion angle of 28.3° between the P–Pd–N(1) and the C(36)–Pd–N(3) (see distortion perspective in Figure 2) planes results in a nearly coplanar arrangement of the latter with the 2-phenyl group in the pyrrolidine moiety [distance of *ortho* carbons: 3.08 Å for C(35) and 3.06 Å for C(31)]. Interestingly, when this compound (or the original mixture of isomers) was dissolved in THF-d_8, a different 7:1 isomer ratio was observed in the ^{31}P NMR spectrum. This result suggests that a interconversion of both diastereomers takes place in this solvent, presumably via a temporary dissociation of the hydrazone sp^2 nitrogen.[12]

Considering that the presence of this additional isomerism in the OA intermediates and/or the potential hemilability of bidentate ligands might have a detrimental effect on enantioselectivity, the alternative use of *monodentate* ligands was suggested to address both issues. Moreover, a higher flexibility in the coordination geometry of the corresponding $\mathbf{I_{OA}}$ intermediates could possibly make the interconversion of atropisomers even easier. Consequently, a second screening with monodentate chiral ligands was performed in the same model reaction, leading to the identification of TADDOL-derived phosphoramidite **L2** as the best alternative, affording the product **3Aa** in 64% isolated yield and 64% ee using in this case $Pd(dba)_2$/ligand (1:1, 5 mol %) under the previously used conditions (Table 1, entry 1). A further optimization led to an improved 76% yield and 84% ee for the reaction carried out in dioxane (entry 2). The use of boroxine **2a** as the reagent proved to be essential, as both the reactivity and the

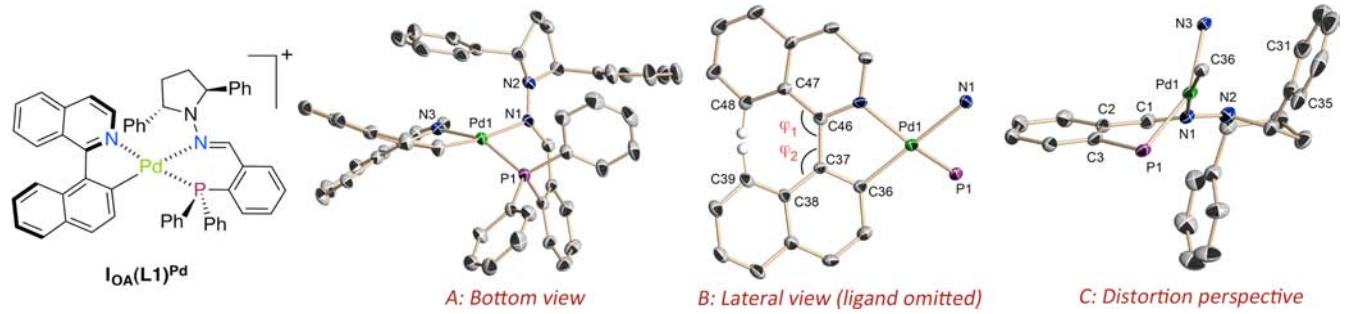


Figure 2. X-ray structure of the cationic $\mathbf{I_{OA}(L1)}^{Pd}$ intermediate. (A) Bottom view (OTf counteranion and H atoms omitted). (B) Lateral view (OTf counteranion, H atoms except H(39) and H(48) and chiral ligand omitted. (C) Perspective of coordination plane (isoquinoline and naphthyl groups, H atoms, and P-phenyl groups omitted).

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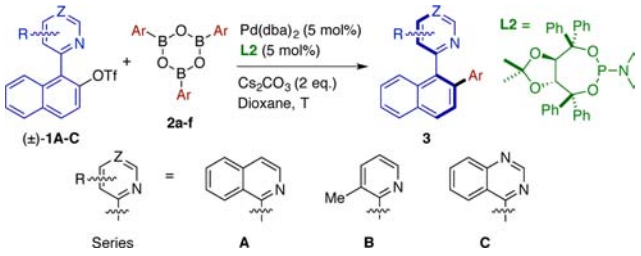
Table 1. Dynamic Kinetic Suzuki–Miyaura Couplings

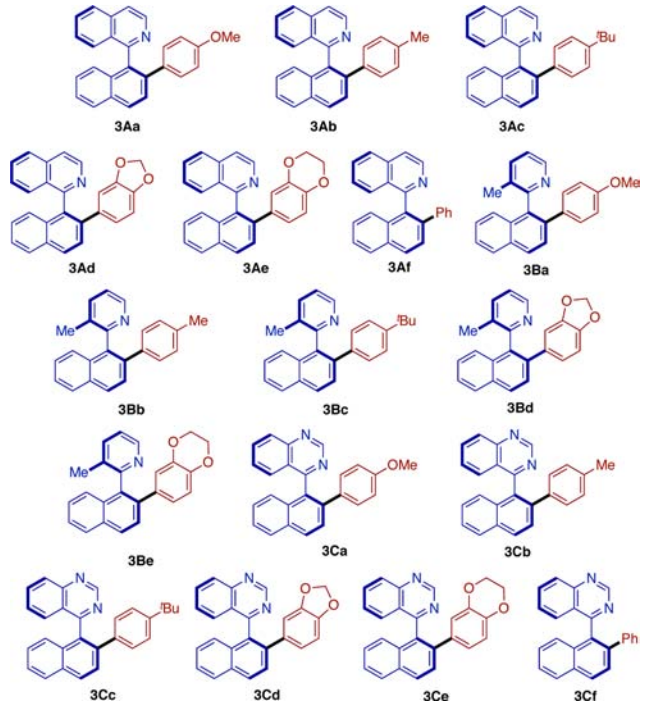


entry	1	2	T (°C)	t (h)	3	yield (%)[b]	ee (%)[c]
1[d]	**1A**	**2a**	55	24	**3Aa**	64	64
2	**1A**	**2a**	55	8	**3Aa**	76	84
3[e]	**1A**	**2a′**	55	8	**3Aa**	42	38
4	**1A′**	**2a**	55	24	**3Aa**	78	40
5	**1A**	**2a**	40	48	**3Aa**	87	90
6	**1A**	**2b**	40	48	**3Ab**	87	80
7	**1A**	**2c**	40	48	**3Ac**	66	82
8	**1A**	**2d**	40	48	**3Ad**	77	80
9	**1A**	**2e**	40	48	**3Ae**	79	90[f]
10	**1A**	**2f**	40	48	**3Af**	52	59
11	**1B**	**2a**	40	48	**3Ba**	86	90
12	**1B**	**2b**	40	48	**3Bb**	88	92
13	**1B**	**2c**	40	48	**3Bc**	82	84
14	**1B**	**2d**	40	48	**3Bd**	96	80
15	**1B**	**2e**	40	48	**3Be**	76	93
16	**1C**	**2a**	25	66	**3Ca**	95	90
17[g]	**1C**	**2b**	25	72	**3Cb**	96	90
18[g]	**1C**	**2c**	25	72	**3Cc**	84	87
19[g]	**1C**	**2d**	25	72	**3Cd**	98	88
20[g]	**1C**	**2e**	25	72	**3Ce**	97	86
21	**1C**	**2f**	25	72	**3Cf**	98	65

[a]Performed at 0.15 mmol scale. [b]Isolated yield. [c]Determined by HPLC on chiral stationary phases. [d]Performed in THF. [e]Performed with *p*-anisylboronic acid. [f]98% ee obtained after crystallization. [g]Performed with a 7.5 mol % catalyst loading.

enantioselectivity dropped when anisylboronic acid **2a′** was used instead (entry 3). On the other hand, the coupling performed with 1-(2-bromonaphthalen-1-yl)isoquinoline **1A′** and **2a** under identical conditions proceeded also as a DYKAT process, but the enantioselectivity significantly dropped (entry 4), highlighting the importance of the noncoordinating counteranion (triflate vs bromide) generated upon oxidative addition. In a control experiment, the model reaction was stopped at ∼50% conversion, leading to the product **3Aa** in 88% ee, and the unreacted triflate had a 68% ee, thereby ruling out a mechanism relying on a fast racemization of **1A** (dynamic kinetic resolution). Moreover, both *R*- and *S*-enantiomers of **1A** were separated, and their reactions with **2a** performed at 55 °C afforded the same major enantiomer (*S*)-**3Aa** in 82 and 84% ee, respectively, strongly supporting the occurrence of a common intermediate. Finally, the good reactivity observed in dioxane allowed us to carry out reactions at 40 °C to obtain the product in excellent yield and an improved 90% ee (entry 5). With the validated strategy and a selective catalyst in hand, further efforts were directed to explore the scope of the methodology. To this aim, several combinations of heterobiaryl triflates **1A–C** with arylboroxines **2a–f** were made to react in the presence of $Pd(dba)_2$ and **L2** to afford products **3** in good to excellent yields and high enantiomeric excesses (Table 1 and Chart 1).[13]

Chart 1. Structures of Products 3



The absolute (S_a) configuration of the product **3Ae** was assigned after X-ray diffraction analysis (Figure 3), and those of other products **3** were assigned by analogy.

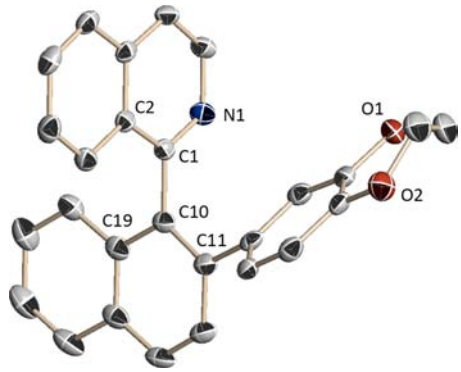


Figure 3. X-ray structure of (S_a)-**3Ae**. H atoms are omitted for clarity.

Concluding, the deracemization of configurationally stable 2-aryl pyridines and analogues has been efficiently achieved by applying a dynamic kinetic asymmetric cross-coupling strategy. The use of TADDOL-derived phosphoramidite **L2** as the ligand allowed the isolation of coupling products in good yields and high enantioselectivities. Further applications based on this strategy will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds, crystallographic data for $\mathbf{I}_{OA}(\mathbf{L1})^{Pd}$ and **3Ae**, and HPLC traces for compounds **3**. 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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(8) Interestingly, the introduction of a phenyl group at position 3 of the isoquinoline ring (substrate **1D**; see Supporting Information for details) results in a complete loss of selectivity, suggesting that the steric hindrance at the N atom inhibits the formation of the cationic palladacycle and, therefore, the required isomerization at this stage.

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(13) As a limitation, poor reactivities and enantioselectivities were observed for reactions performed with electron-deficient aryl boroxines.