Communication

Synthesis of IAN-type N,N-ligands via Dynamic Kinetic Asymmetric Buchwald–Hartwig Amination

Pedro Ramírez-López, Abel Ros, Antonio Romero-Arenas, Javier Iglesias-Sigüenza, Rosario Fernandez, and José M. Lassaletta

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b07972 • Publication Date (Web): 05 Sep 2016

Synthesis of IAN-type N,N-Ligands via Dynamic Kinetic Asymmetric Buchwald–Hartwig Amination

Pedro Ramírez-López,[§,Σ] Abel Ros,[§,Σ] Antonio Romero-Arenas,[§] Javier Iglesias-Sigüenza,[∫] Rosario Fernández,*[,∫] José M. Lassaletta*[,§]

[§]Instituto Investigaciones Químicas (CSIC-US), C/ Américo Vespucio, 49, 41092 Sevilla, Spain.

[∫]Departamento de Química Orgánica, C/ Prof. García González, 1, 41012 Sevilla, Spain

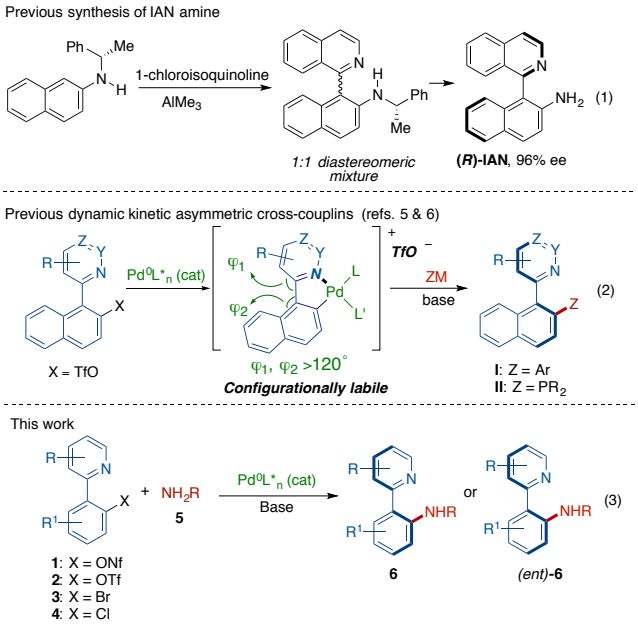
Supporting Information Placeholder

ABSTRACT: The Pd^0–catalyzed coupling of racemic heterobiaryl bromides, triflates or nonaflates with aryl/alkyl primary amines using QUINAP as the ligand provides the corresponding axially chiral heterobiaryl amines with excellent yields and enantioselectivities. Reactivity and structural studies of neutral and cationic oxidative addition intermediates support a dynamic kinetic asymmetric amination mechanism based on the labilization of the stereogenic axis in the latter, and suggest that coordination of the amine to the Pd center is the stereodetermining step.

In recent years, significant advances have been achieved in the field of asymmetric cross–coupling, in particular for the synthesis of axially chiral biaryls.[1] In sharp contrast, the direct asymmetric heteroaryl-aryl cross–coupling remains as an unmet challenge,[2] limiting the access to functionalized heterobiaryls with appealing structures for their use as ligands in asymmetric catalysis. As a remarkable example, the use *I*soquinoline-*A*mino *N*aphthalene (IAN) and related derivatives, which can be seen as N(sp^2),N(sp^3) analogues of QUINAP, have been scarcely investigated.[3] A plausible explanation is the poor availability: there are no commercially available representatives and their synthesis still requires chromatographic separation of diastereomeric mixtures (Scheme 1, eq. 1),[4] while the lack of a general and practical method of synthesis has also limited the structural diversity of known ligands of this type. Recently, we have reported a novel strategy for the synthesis of functionalized heterobiaryls based on dynamic kinetic asymmetric C–C[5] and C–P[6] bond formations starting from heterobiaryl triflates to ensure the formations of cationic oxidative addition intermediates (Scheme 1, eq. 2). Stimulated by the growing potential of related axially chiral heterobidentate ligands,[7] we decided to focus on the development of dynamic kinetic Buchwald-Hartwig (DYKAT: *Dy*namic *K*inetic *A*symmetric *T*ransformation) amination of heterobiaryl electrophiles for the asymmetric synthesis of axially chiral IAN-type diamines (Scheme 1, eq. 3).

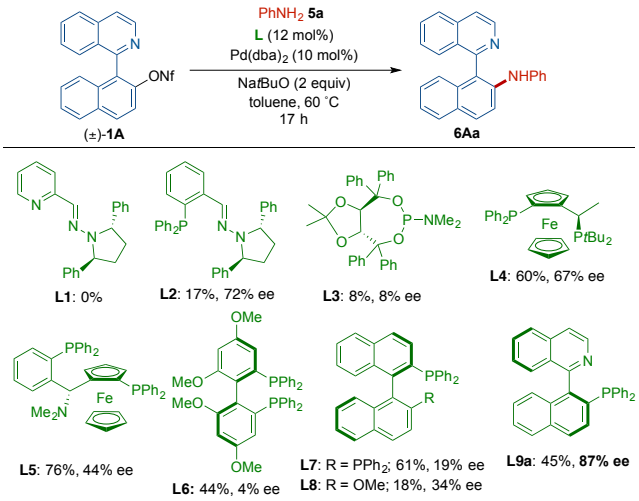
The unprecedented asymmetric amination of heterobiaryls is a particularly challenging goal due to the specific conditions required. First, a strong base is generally needed to achieve good reactivities, so that compatibility issues might arise with the heterobiaryl triflates used in previous DYKAT processes. Second, the racemization barriers for IAN amines are significantly lower than those of arylated products **I** or QUINAP-type products **II**,[8] making necessary to work under exceptionally mild conditions.[9] In order to minimize the hydrolysis of the starting material, we started using the coupling between nonaflate (±)-**1A**[10] and aniline **5a** as a model reaction for the synthesis of IAN **6Aa**, using NaO*t*Bu as the base, dry toluene as the solvent at 60 °C and 10 mol% $Pd(dba)_2$/12 mol% ligand as the catalyst system (Scheme 2).

Scheme 1. Synthetic approaches to IAN amines



Ligands that showed a good performance in related processes were selected for a preliminary screening: hydrazone–based ligands **L1**-**L2**, which provided good to excellent enantioselectivities in asymmetric Suzuki-Miyaura reactions,[11] and TADDOL-derived phosphoramidites **L3,** which exhibited an excellent behavior in dynamic kinetic Suzuki-Miyaura couplings,[5] showed a poor activity and only in the case of ligand **L2** a relatively high enantiomeric excess (72% ee) was observed. Similarly, ferrocene–based ligands **L4**-**L5**, previously used in C–P coupling reactions,[6] or

Scheme 2. Ligand Screening.[a]

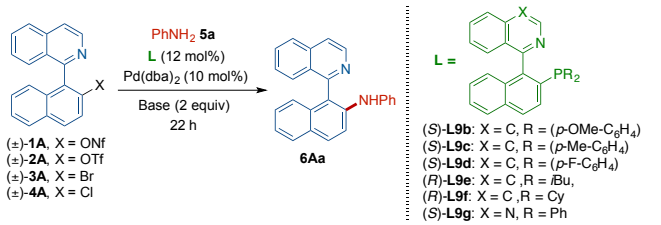


[a] Reactions conditions: 0.1 mmol **1A** in toluene (2 mL), 2 equiv. of **5a**, 2 equiv. of NaO*t*Bu. Ee's were determined by chiral HPLC analysis. See the Supporting Information for a more comprehensive screening.

commercially available axially chiral P,P and P,O-ligands such as **L6-L8** afforded moderate yields (18-76%) and variable enantioselectivities (4-67% ee). Taking into account the poor results provided by the atropo P,N-ligand QUINAP **L9a** in dynamic kinetic C–P bond formation,[6a] it was rather surprising to see the high level of enantioselectivity (87% ee) observed in this case, although partial hydrolysis of the starting (±)-**1A** resulted in an unsatisfactory 45% yield. This undesired hydrolysis, however, could be avoided in two ways. First, it was possible to use a less nucleophilic base such as Cs_2CO_3, and the desired diamine (*R*)-**6Aa** was obtained in near quantitative yields while maintaining the level of enantioselectivity (Table 1, entry 1). At 50 °C, these mild conditions could also be applied to the amination of triflate (±)-**2A** with a slightly lower yield (entry 2). Second, we speculated whether 1-(2-bromonaphthalen-1-yl)isoquinoline (±)-**3A** could also be a suitable substrate in this reaction. Although this material afforded disappointing results in dynamic kinetic asymmetric Suzuki coupling,[5] the reaction of (±)-**3A** with aniline **5a** using NaO*t*Bu as the base under the above conditions afforded the desired product (*R*)-**6Aa** in 95% yield with 89% ee in a shorter reaction time (17h, entry 3). The reactions of (±)-**1A,** (±)-**3A** and even chloride (±)-**4A** could also be performed at 50 °C, leading to slightly better enantioselectivities (entries 4-6). Other QUINAP and QUINAZOLINAP-type ligands **L9b-g** containing modified diaryl and dialkyl phosphino groups[6a] were also tested in the model reaction but, unfortunately, none of them led to improved enantioselectivities (entries 7-12). Racemization studies performed with a toluene solution of **6Aa** at 60, 80 and 100 °C showed that, after 48h, the product is configurationally stable at 60 °C, but slowly racemizes at 80 °C and above.

With the optimized conditions (entry 5) at hand, the scope of the methodology was explored using different bromides (±)-**3A-C** and amines **5a-m** (Table 2). The reaction of bromide (±)-**3A** (Series A) and arylamines **5a-c** and **5g-h** worked well at 50 °C, affording the coupling products **6Aa-c** and **6Ag-h** with excellent yields and 90-96% ee in acceptable reaction times (~25 hours). Sterically hindered and electron-poor amines **5d-f** and **5h-j** required longer reaction times (30–48 h), and a higher reaction

Table 1. Optimization.[a]



	Substrate	Base	T (°C)	L	Yld. (%)	ee[b]
1	(±)-**1A**	Cs_2CO_3	60	(*S*)-**L9a**	99	88
2[c]	(±)-**2A**	Cs_2CO_3	50	(*S*)-**L9a**	81	92
3[d]	(±)-**3A**	NaO*t*Bu	60	(*S*)-**L9a**	95	89
4	(±)-**1A**	Cs_2CO_3	50	(*S*)-**L9a**	84	90
5	(±)-**3A**	NaO*t*Bu	50	(*S*)-**L9a**	**90**	**91**
6	(±)-**4A**	NaO*t*Bu	50	(*S*)-**L9a**	92	89
7	(±)-**3A**	NaO*t*Bu	60	(*S*)-**L9b**[f]	99	84
8	(±)-**3A**	NaO*t*Bu	60	(*S*)-**L9c**[g]	98	77
9	(±)-**3A**	NaO*t*Bu	60	(*S*)-**L9d**	98	61
10	(±)-**3A**	NaO*t*Bu	60	(*R*)-**L9e**	26	50
11	(±)-**3A**	NaO*t*Bu	60	(*R*)-**L9f**	77	68
12	(±)-**3A**	NaO*t*Bu	60	(*S*)-**L9g**[h]	78	20

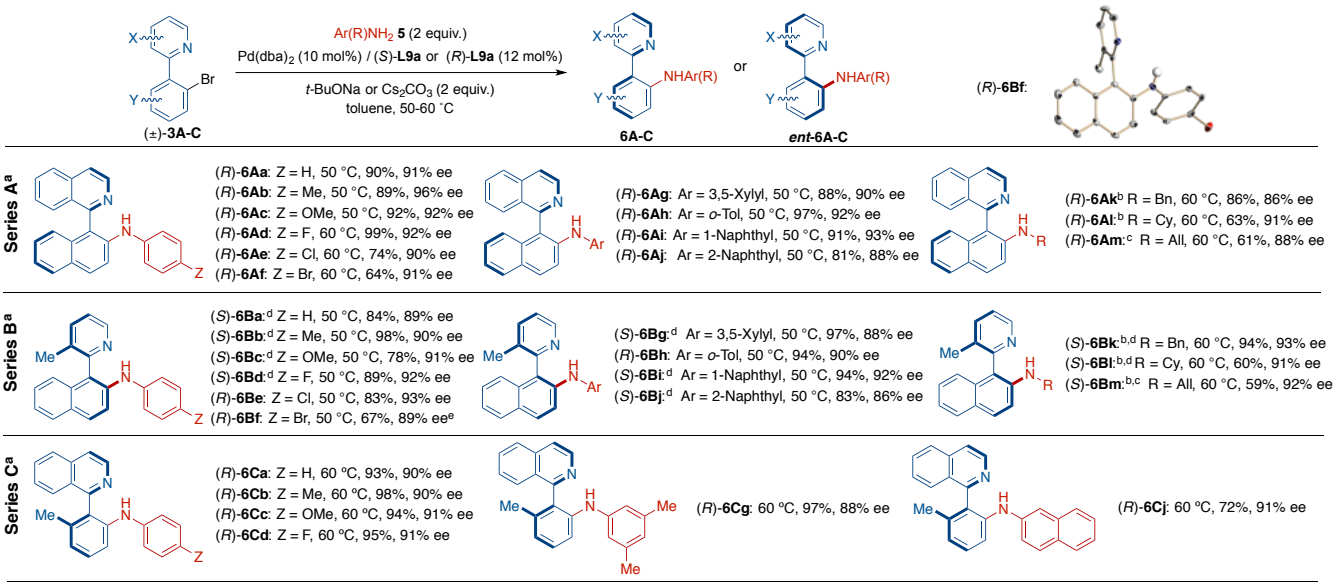
[a] Reactions conditions: 0.1 mmol scale in toluene (2 mL), 2 equiv. of **5a**, 2 equiv. of base. [b] Determined by chiral HPLC analysis. [c] *t*: 48 h. [d] *t*: 17h. [f] 98% ee. [g] 96% ee. [h] 99% ee.

temperature of 60 °C was also needed for the latter, but in all cases the corresponding products **6** were obtained in good yields and enantioselectivities (88-93% ee). Interestingly, *p*-chloro- and *p*-bromo-anilines **5e** and **5f** are suitable substrates, highlighting the higher relative reactivity of the heterobiaryl bromide, which can be attributed to the directing effect by the isoquinoline N atom. Aliphatic amines **5k-m** could also be coupled using 4-10 equiv. of amine and 4 equiv. of NaO*t*Bu to give the desired products (*R*)-**6Ak-m** in good to excellent yields (61-86%) and 86-91% ee after 72 hours at 60 °C. Bromide (±)-**3B** showed similar reactivity patterns and the desired diamines **6Ba-m** were obtained in good to excellent yields and 86-93% ee. Finally, bromide (±)-**3C** was also used in atroposelective amination with anilines **5a-d,g,j** to afford **C**-series products. A higher reaction temperature (60 °C) and longer reaction time (45 h) were in general required, but good yields (72-98%) and enantioselectivities (88-91% ee) were also achieved. As a limitation, poor reactivity was observed when secondary amines were used as reagents.

Compounds (*R*)-**6Bf** and (*R*)-**6Bl** were obtained in enantiopure form (>99% ee) after crystallization. Additionally, X-ray analysis of the former was used to assign the absolute R_a configuration. Similarly, X-ray analysis of the cationic complex $\{Cu(I)[(R)\text{-}\mathbf{6Aa}]_2\}^+PF_6^-$ was used to confirm the absolute *R* configuration of (*R*)-**6Aa**. The absolute configuration of other products **6A-C** was assigned by analogy assuming a uniform reaction pathway.

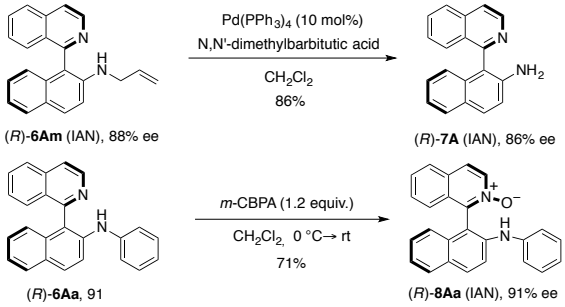
The free IAN amine (*R*)-**7** could be obtained after Pd-catalyzed deprotection of allylamine (*R*)-**6Am** using *N*,*N*'-dimethylbarbituric

Table 2. Dynamic Kinetic Asymmetric C-N Couplings: Scope.[a]

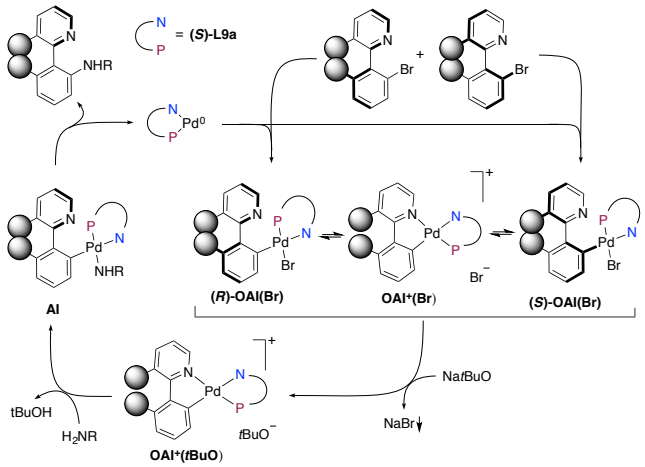


[a] Reaction conditions: 0.1 mmol scale in toluene (2 mL), 2 equiv. of **5**, 2 equiv. of NaO*t*Bu, *t*: 22-48h (see Supporting Information). [b] 4 equiv. of NaO*t*Bu and 4 equiv. of **5** were used. [c] 4 equiv. of NaO*t*Bu and 10 equiv. of **5** were used. [d] (*R*)-**L9a** was used. [e] >99% ee after crystallization.

Scheme 3. Representative transformations.

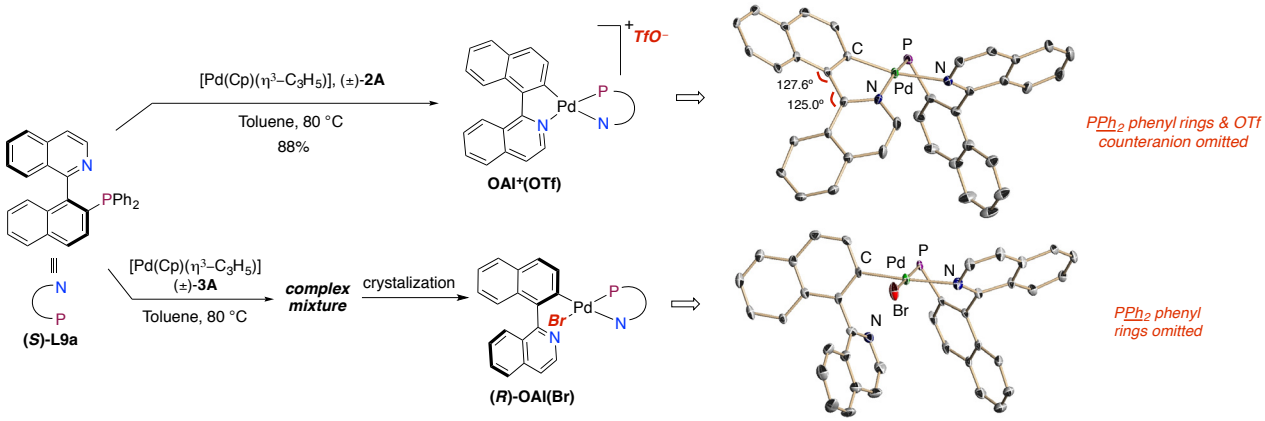


Scheme 4. Proposed amination mechanism.



acid as the reagent[12] (Scheme 3). Additionally, products **6** are direct precursors of axially chiral N-oxides[7b] by virtue of the selective N(sp^2) oxidation performed with *m*-CPBA, as illustrated with the synthesis of (*R*)-**8**. Compared to the previously developed Suzuki coupling,[5] the better performance of (±)-**3A** can be explained for the different reaction conditions applied in this case. According to the mechanism depicted in Scheme 4, the base is believed to play a dual role, behaving also as an efficient bromide scavenger thanks to the low solubility of NaBr in toluene. In order to provide some support for this hypothesis, we tackled the isolation of the oxidative addition intermediates from heterobiaryl triflate (±)-**2A** and bromide (±)-**3A**. The equimolar reaction of the former with (*S*)-**L9a** and [Pd(Cp)(allyl)] afforded the cationic OA intermediate **OAI$^+$(OTf)** in 88% yield after crystallization (Scheme 5). The single–crystal X-ray diffraction analysis of this complex showed the expected five-membered, cationic palladacycle structure and confirmed that the angles φ_1 [C(39)-C(40)-C(41)] and φ_2 [C(40)-C(41)-C(42)] are significantly wider (127.6° and 125.0°, respectively) than the ideal value of 120°. The structure reveals also a severe distortion of the square planar geometry at the Pd^{II} center (torsion angle of 23.1° between the P-Pd-N(1) and the C(50)-Pd-N(2) planes), with a Pd-N(1) bond longer than the Pd-N(2) one (2.141 Å and 2.098 Å, respectively), as a consequence of the stronger *trans* influence by the aryl ligand. This complex was treated with aniline (20 equiv.) and Cs_2CO_3 (20 equiv.) to afford (*R*)-**6Aa** after 7 h at 50 °C in 57% yield and 74% ee.[13] Although an apparent (S_a) configuration is observed, we assume that the aforesaid widening of angles φ_1 and φ_2 results in a rapid interconversion of atropoisomers.[14] In the same way, equimolar amounts of (*S*)-**L9a**, bromide (±)-**3A**, and [Pd(Cp)(allyl)] were made to react overnight at 80 °C in toluene; ^{1}H-NMR and ^{31}P NMR analysis of the crude reaction mixture revealed a complex mixture[15] in which signals assigned to the cationic OA intermediate **OAI$^+$(Br)** were identified. Stoichiometric reaction of this mixture with aniline quantitatively afforded the product (*R*)-**6Aa** with 87% ee. Additionally, crystals of the neutral intermediate **(*R*)-OAI(Br)** suitable for X-ray diffraction analysis could be obtained from this mixture. In this complex, the bromine atom remains attached to the Pd center [Pd-Br bond length 2.491 Å] and the isoquinoline and 2-naphthyl rings are placed in a near perpendicular arrangement. It is assumed that the reaction of this mixture with the base results in a Br$^-$ to *t*BuO$^-$ ligand exchange facilitated by the low solubility of NaBr in toluene. Arguably, the poorer coordinating ability and

Scheme 5. Synthesis and and X-ray structures of oxidative addition intermediates **IOA⁺(OTf)** and **(*S*)-IOA(Br)**.



bigger size of the counteranion favors the formation of the cationic intermediate **OAI⁺(*t*BuO)**, from which the coordination of the amine **5** generates the amination intermediate **AI** in the enantioselectivity determining step. It is worth noting that the structure of the proposed **OAI⁺(*t*BuO)** intermediate should closely mimic that of the isolated complex **IOA⁺(OTf)**, accounting for the similar stereochemical result through both intermediates.

In summary, we have developed a new and efficient procedure for the asymmetric synthesis of IAN-type N,N-ligands based on a dynamic kinetic asymmetric Buchwald-Hartwig amination of racemic heterobiaryl electrophiles. The use of QUINAP as the ligand allowed the isolation of the products in high yields and good to excellent enantioselectivities. The isolation of cationic and neutral oxidative addition intermediates supports a mechanism based in the labilization of the stereogenic axis in the former.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for new compounds, crystallographic data for (*R*)-**6Bf**, **OAI⁺(OTf)** and **(*S*)-OAI(Br)**, and HPLC traces for compounds **6**, **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

ffernan@us.es, jmlassa@iiq.csic.es

Author Contribution

[Σ]P. R.-L. and A. R. contributed equally to this work.

ACKNOWLEDGMENT

We thank the Ministerio de Ciencia e Innovación (Grants CTQ2013-48164-C2-1-P and CTQ2013-48164-C2-2-P, contract RYC-2013-12585 for A.R.), European FEDER Funds, and Junta de Andalucía (Grant 2012/FQM 10787) for financial support.

REFERENCES

(1) Recent reviews: (a) Zhang, D.; Wang, Q. *Coord. Chem. Rev.*, **2015**, *286*, 1. (b) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. *Chem. Soc. Rev.* **2015**, *44*, 3418. (c) Pauline, L.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. *Coord. Chem. Rev.* **2016**, *308*, 131.

(2) Mosquera, A.; Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A., *Eur. J. Org. Chem.* **2013**, 2555.

(3) (a) Cortright, S. B.; Huffman, J. C.; Yoder, R. A.; Coalter, J. N.; Johnston, J. N. *Organometallics* **2004**, *23*, 2238. (b) Cortright, S. B.; Johnston, J. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 345.

(4) Luesse, S. B.; Counceller, C. M.; Wilt, J. C.; Perkins, B. R.; Johnston, J. N. *Org. Lett.*, **2008**, *10*, 2445.

(5) Ros, A.; Estepa, B.; Ramírez-López, P.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.*, **2013**, *135*, 15730.

(6) (a) Ramírez-López, P.; Ros, A.; Estepa, B.; Fernández, R.; Fiser, B.; Gómez-Bengoa, E.; Lassaletta, J. M. *ACS Catal.* **2016**, *6*, 3955. See also: (b) Bhat, V.; Wang, S.; Stoltz, B. M.; Virgil, S. C. *J. Am. Chem. Soc.*, **2013**, *135*, 16829.

(7) (a) Fernández, E.; Guiry, P. J.; Connole, K. P. T.; Brown, J. M. *J. Org. Chem.* **2014**, *79*, 5391. and references cited therein; (b) Malkov, A. V.; Ramírez-López, P.; Biedermannová, L.; Rulíšek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kočovský. P. *J. Am. Chem. Soc.* **2008**, *130*, 5341; (d) Tanaka, S.; Seki, T.; Kitamura, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8948; (e) Francos, J.; Grande-Carmona, F.; Faustino, H.; Iglesias-Sigüenza, J.; Díez, E.; Alonso, I.; Fernández, R.; Lassaletta, J. M.; López, F.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 14322. (f) Liu, Y. E.; Lu, Z.; Li, B.; Tian, J.; Liu, F.; Zhao, J.; Hou, C.; Li, Y.; Niu, L.; Zhao, B. *J. Am. Chem. Soc.* **2016**, DOI: 10.1021/jacs.6b03930.

(8) Cortright, S. B.; Yoder, R. A.; Johnston, J. N. *Heterocycles* **2004**, *62*, 223.

(9) Paradies, J. In *Metal-Catalyzed Cross- Coupling Reactions and More*; de Meijere, A., Brase, S., Oestreich, M., Eds.; Wiley: Weinheim, 2014; Ch 13, pp 995-1060.

(10) Nonaflates (nonafluorobutanesulfonates) have been used as an alternative to triflates due to their higher stability and similar reactivity: Högermeier, J.; Reissig H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747.

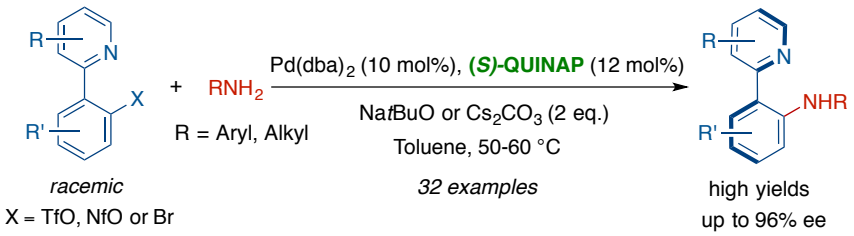
(11) (a) Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 4740. (b) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M.; *J. Am. Chem. Soc.* **2008**, *130*, 15798.

(12) Garro-Helion, F.; Merzouk, A.; Guibé; F. *J. Org. Chem.* **1993**, *58*, 6109. Deallylation with polymethylhydrosiloxane/$ZnCl_2$/$Pd(PPh_3)_4$ (Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Tetrahedron* **2001**, *57*, 3435) or $PhSO_2Na$/CSA/$Pd(PPh_3)_4$ (Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932) afforded the product in racemic form, while catalytic hydrogenation (H_2, Pd/C) was uneffective.

(13) In spite of the evident strain in the structure of **OAI⁺(OTf)**, no reaction with aniline **5a** (20 equiv.) was observed in the absence of Cs_2CO_3, even after heating at 70 °C overnight.

(14) Variable temperature ^{1}H NMR (25 °C→ −78 °C) spectrometry did not show a dynamic behavior, indicating that the barrier for the interconversion of atropoisomers is very low (see Supporting Information).

(15) We assume that the C(2)–Pd bond in neutral intermediates **OAI(Br)** is a configurationally stable stereogenic axis and, therefore, four possible isomers can be formulated.



racemic
X = TfO, NfO or Br

32 examples

high yields
up to 96% ee