How to cite: *Angew. Chem. Int. Ed.* **2025**, *64*, e202425512
doi.org/10.1002/anie.202425512

C-H Activation

Palladium-Catalyzed Enantioselective C–H Arylations and Alkenylations of 2-Aminobiaryls with Atmospheric Air as the Sole Oxidant

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Abstract: Optically active 2-aminobiaryls are valuable chiral frameworks with broad applications in catalysis, synthetic chemistry, and materials science. Here, we present a simple and practical methodology for their asymmetric synthesis via enantioselective palladium catalyzed C–H arylations or alkenylations of racemic precursors. The methodology utilizes a kinetic resolution strategy, producing two highly valuable enantioenriched axially chiral molecules: the C–C coupling product and the unreacted starting material. Notably, we have established reaction conditions that enable the in situ regeneration of the active Pd(II) catalyst using atmospheric air as the sole oxidant. Finally, we showcase the synthetic utility of this approach by preparing several derivatives relevant to the field of asymmetric catalysis.

Axially chiral biaryl, and especially binaphthyl scaffolds, are privileged motifs of primary interest in material science and natural product synthesis, as well as in asymmetric catalysis.[1] Developing rapid, versatile and efficient methods for their assembly remains as a major goal in the field of asymmetric synthesis.[2] Conventional strategies to build these frameworks rely on enantioselective C–C couplings of purposely pre-functionalized aryl precursors, or in chiral resolutions of the products.[3]

In recent years, enantioselective transition-metal-catalyzed aryl C–H functionalizations have emerged as a direct and practical route for synthesizing axially chiral biaryls. However, their application to binaphthyl precursors has been rather limited.[4] These methods frequently require substrates that incorporate non-native metal-coordinating units that are challenging to remove after the C–H functionalization. Additionally, most reported reactions have been restricted to olefinations, significantly limiting the scope and diversity of the processes.[5]

Among axially chiral biaryls, derivatives with *ortho*-amino groups are particularly attractive due to their broad utility as ligands in organometallic catalysis (e.g., P, N-ligands, carbenes, nitrenes, NOBIN derivatives) and as organocatalysts (e.g., thioureas, Figure 1a). Despite this importance, asymmetric methods for the direct access to *ortho*-amino biaryls are very scarce. Indeed, progress in this endeavor has been essentially limited to the work of Shi and co-workers, who reported a Pd-catalyzed atroposelective olefination of biaryl and arylnaphthyl precursors using a chiral phosphoric acid ligand.[6a] The method is limited to

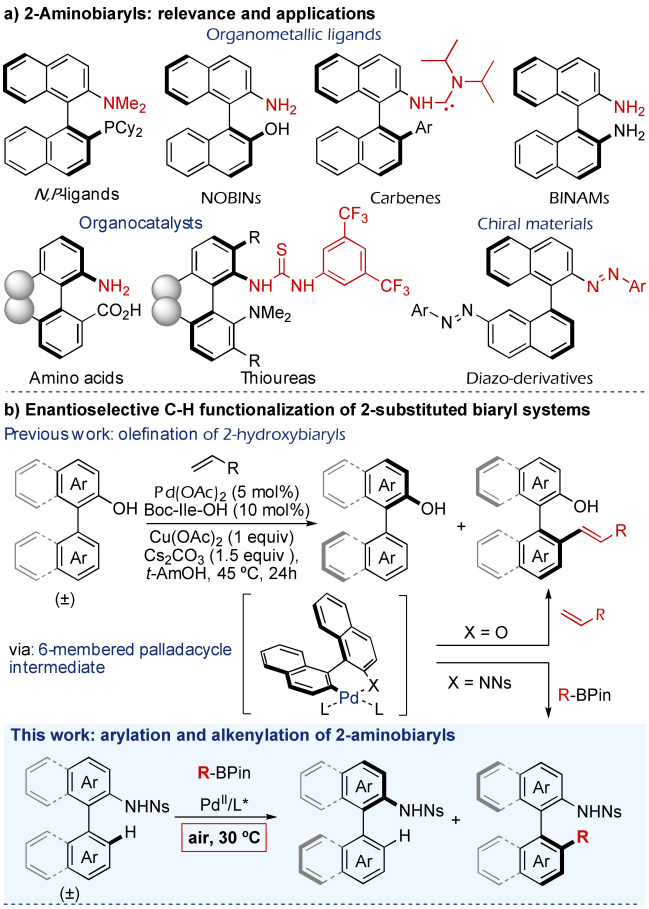

Figure 1. a) Some relevant chiral *ortho*-arylaniline scaffolds. b) Recent strategy for the enantioselective synthesis of 2-hydroxybiaryl products. This work: asymmetric resolution of *ortho*-aminobiaryls and related atropoisomeric precursors. BINAM = [1,1′-binaphthalene]-2,2′-diamine; NOBIN = 2′-amino-1,1′-binaphthalen-2-ol; Ns = 4-nitrobenzenesulfonyl (nosyl); Ar = aromatic

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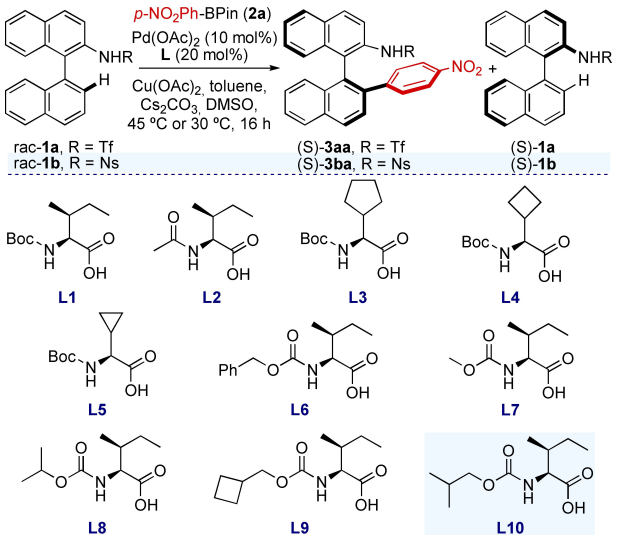
olefinations and does not address the asymmetric resolution of more appealing binaphthyl scaffolds. The Shi's group has also reported a cobalt-catalyzed desymmetrizing arylation, although it requires the installation and subsequent removal of metal-binding auxiliaries under harsh conditions.[6b] A palladium-based method reported by Yu's group produces *meta*- rather than *ortho*-arylated products, which limits its utility for obtaining chiral frameworks.[6c]

Building on our recent work in enantioselective olefination of 2-hydroxybiaryls using palladium catalysis (Figure 1b),[7] and in line with our ongoing work in asymmetric C–H functionalization reactions,[8] we present here a highly practical and versatile methodology for synthesizing optically active 2-substituted-2-aminobiaryls and binaphthyl products (Figure 1b). Our approach enables formal enantioselective cross-coupling reactions directly from simple racemic precursors. The methodology is also valid for Fujiwara-type olefinations. Notably, our optimization efforts revealed reaction conditions that eliminate the need for specific oxidants (e.g., Cu(II) salts), which allows to obtain excellent yields and enantioselectivities under exceptionally mild conditions. By conducting the reactions in open-air vessels with atmospheric air as the sole oxidant, this methodology establishes a new benchmark in sustainability and practicality for this type of asymmetric synthesis.

We first focused on the kinetic resolution of racemic trifluoromethylsulfonyl (triflyl: Tf) protected binaphthylaniline **1a**, that was synthetized in just one step from commercial sources. As coupling reagent, we used a pinacol phenylboronate owing to its stability and solubility properties. We started our screening by using *t*-amyl alcohol as solvent, a Boc-protected isoleucine as palladium ligand (**L1**), and stoichiometric copper acetate as oxidant. Although we were able to obtain the desired product, the efficiency of the reactions was modest, and the enantiomeric ratios (er) lower than 80:20. The addition of 15 equivalents of dimethylsulfoxide (DMSO) allowed to significantly increase the enantiomeric ratios in both the product (up to 87.5:12.5) and the recovered starting material (67.5:32.5). An extensive screening of solvents (see the Supporting Information for more details) revealed toluene as the best choice, which allowed to obtain the arylated product **3aa**, with up to 90.5:9.5 er (38% yield). The results are detailed in the Table 1 (entries 1–7).

Using the 4-nitrobenzenesulfonyl (nosyl: Ns) derivative **1b** we obtained similar results (88:12 er for the product **3ba**) under the above optimized conditions, but the reaction can be carried out at lower temperature (30 °C). Given that the nosyl is easier to remove than the triflyl group, we further optimized conditions using substrate **1b** (see Supporting Information for details).[9] The best results were obtained using the isobutoxylcarbonyl isoleucine ligand **L10**, which gave product **3ba** in 44% yield and 97:3 er, and the precursor **1b** in 47% yield and 92:8 er. Especially relevant was the finding that the reaction works without the copper salt additive, in an open-air vessel, leading to a near quantitative combined yield and excellent enantiomeric ratios (99:1 for the product and 95.5:4.5 for the starting material). This finding is remarkable, as the very few

Table 1: Optimization of conditions



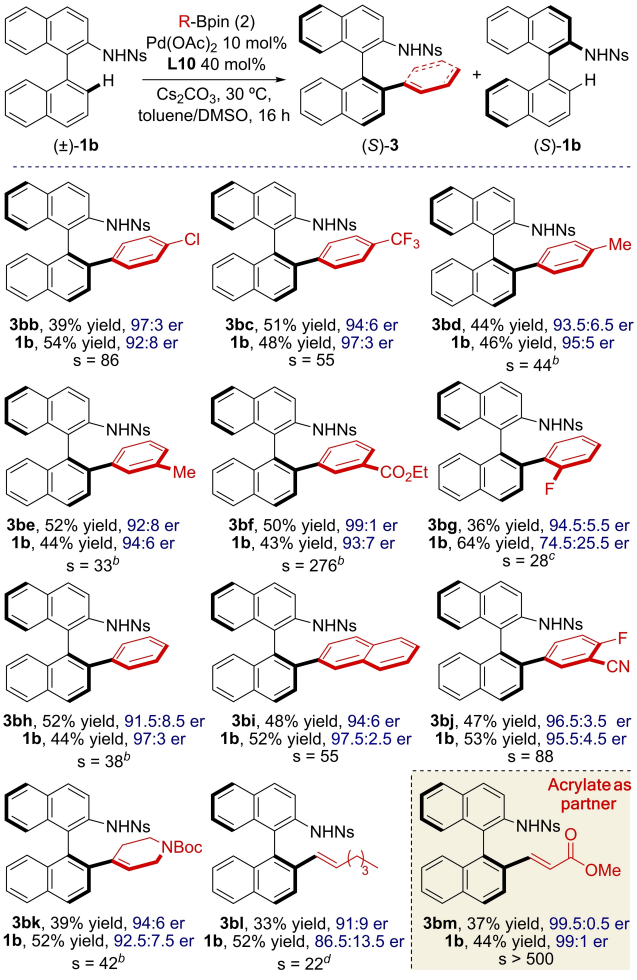
Entry	Deviation from the above conditions[a]	Yield (%)	er	er
	R = Tf	**3aa/1a**	**3aa**	**1a**
1[b]	*t*-AmylOH	30/61	77.5:22.5	61.5/38.5
2	*t*-AmylOH	35/64	87.5:12.5	67.5/32.5
3	THF	9/30	91:9	63.5/36.5
4	CH_3CN	-	-	-
5	HFIP	25/44	50:50	50:50
6	DCE	20/37	86:14	69:31
7	Toluene	38/50	90.5:9.5	85:15
	R = Ns	**3ba/1b**	**3ba**	**1b**
8	None (**L1**)	51/43	88:12	88.5:11.5
9	**L2**	32/58	57:43	55.5:44.5
10	**L3**	46/36	85.5:14.5	87:13
12	**L4**	47/42	88:12	89.5:10.5
11	**L5**	47/50	91:9	81.5:18.5
13	**L6**	51/30	89:11	97:3
14	**L7**	50/46	99:1	76.5:23.5
15	**L8**	32/48	93.5:6.5	77:23
16	**L9**	36/41	84.5:15.5	91:9
17	**L10**	44/40	92.5:7.5	93:7
18[c]	**L10**	44/47	97:3	92:8
19[c]	**L10**/no Cu^{+2}, open air	**48/52**	**99:1**	**95.5:4.5**
20	No ligand	23/72	-	-
21[c]	No DMSO	11/69	64:36	53:47

[a] Running conditions: *rac*-**1a** or rac-**1b** (0.1 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv), Cs_2CO_3 (1.5 equiv), DMSO (15 equiv), toluene (0.1 M), 45 °C when R = Tf, or 30 °C when R = Ns, 16 h. Isolated yields. [b] Without DMSO/0.25 equiv. $Cu(OAc)_2{\cdot}H_2O$. [c] 40 mol% of ligand.

reported examples that use air as a palladium(0) oxidant in C–H functionalizations typically require high temperatures, high pressures, or excess of acidic additives; and none of them entail the use of amino acid ligands.[10] A control experiment conducted in the absence of the ligand resulted in lower conversion (entry 20), confirming its accelerating role. Similarly, performing the reaction without DMSO led to even lower conversion, and an almost negligible enantiomeric ratio (entry 21). The nosyl group of **1b** can be easily removed by treatment with thiophenol and potassium carbonate, leading to the expected amino derivative whose

absolute configuration could be assigned by comparison with previously reported data.[11]

With the optimized conditions at hand, we studied the scope with respect to the boronic ester partner (Scheme 1). Pleasingly, the reaction is effective for aromatic boronic esters bearing different substituents in *para*, like chloride, trifluoromethyl or methyl. In all the cases we observed enantiomeric ratios up to 97:3 for the arylated products (**3bb**, **3bc** and **3bd**) and for the starting material (**1b**). Substituents in *meta* position such ester or methyl are also well tolerated providing similar results with enantiomeric ratios up to 99:1, and selectivities up to 276 for some products like **3bf**. Meanwhile *ortho*-substituted precursors present a lower reactivity probably because of steric reasons, although the fluorine substituted **3bg** was obtained with 94.5:5.5 er ratio. Unsubstituted phenylboronic and naphthylboronic esters also worked to give products **3bh** and **3bi** with up to 94:6 er. The disubstituted derivative **3bj** was also obtained with good yield and enantioselectivity.



Scheme 1. Scope of boronic esters. [a] Optimized conditions: *rac*-**1b** (0.1 mmol), **2** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **L10** (40 mol%), Cs_2CO_3 (1.5 equiv), toluene (0.1 M), DMSO (15 equiv), air, 30 °C, 16 h. [b] At 45 °C. [c] At 60 °C. [d] 1 equiv. $Cu(OAc)_2{\cdot}H_2O$. [e] Selectivity: (s) = ln[(1 − C)(1 − ee^{SM})]/ln[(1 − C)(1 + ee^{SM})]; ee = enantiomeric excess.

Importantly, the reaction also works with alkenylboronic esters, which allow to increase the range of products that can be formed. Therefore, products **3bk** and **3bl** were isolated with up to 94:6 er, and the starting precursors recovered with slightly lower enantiomeric ratios. Worth to note, the above optimized conditions were also effective for addition instead of cross coupling processes. Therefore, heating at 30 °C for 16 h the racemic compound **1b** with 1 equivalent of methyl acrylate, palladium acetate and ligand **L10** provides the product **3bm** (99.5:0.5 er), with the starting material recovered with 99:1 er, which represents a very high selectivity factor (>500).

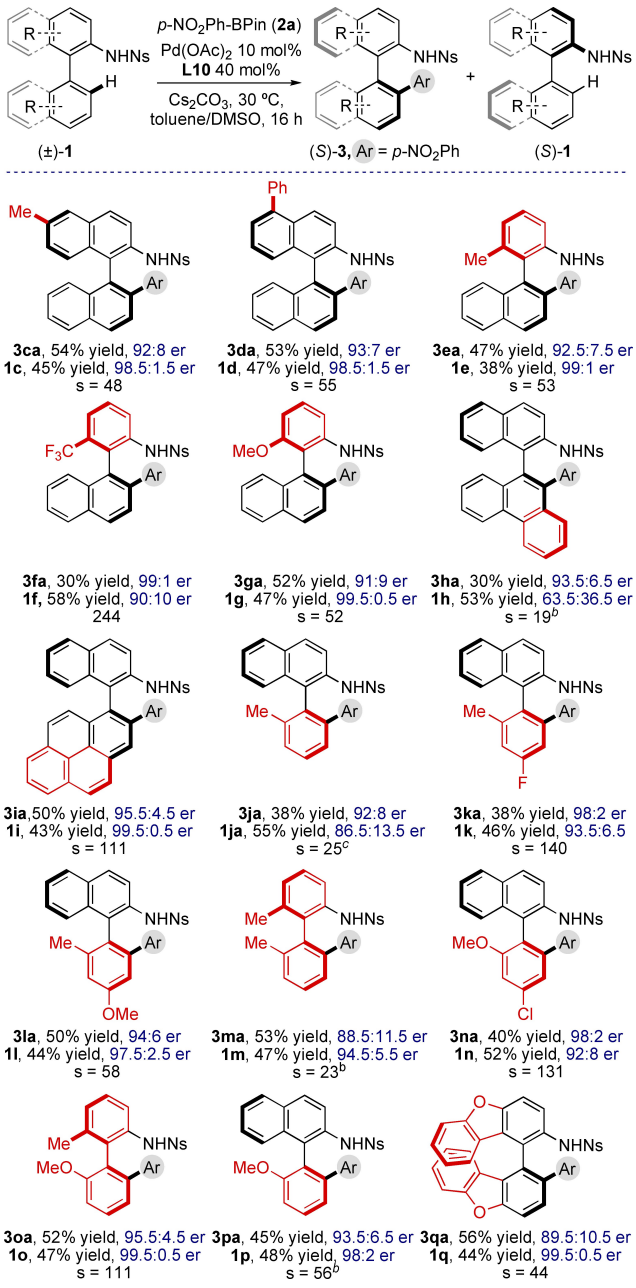
It is also possible to use as substrates 2-aminobinaphthyls equipped with different substituents (Scheme 2), and therefore, products like **3ca** and **3da** were formed with good yields and enantioselectivities. Not surprisingly, the reaction also works with other chiral biaryl precursors beyond binaphthyls. Indeed, anilide derivatives are excellent substrates, and products **3ea**, **3fa** and **3ga** were obtained with enantiomeric ratios up to 99:1, and selectivities up to 244.

Variations in the ring undergoing the functionalization are also well tolerated, such in the case of phenanthrene and pyrene precursors, that gave products **3ha** and **3ia** with up to 95.5:4.5 er for the products, and 99.5:0.5 for the recovered starting materials (combined yields up to 93%). Monophenyl units with substitution on the 6'-position also worked well under these conditions, as illustrated for example in the formation of products **3ja**-**3la**. Moreover, chiral biphenyl precursors also work effectively as shown for the methyl substituted product **3ma**. Substrates containing a 6'-methoxybenzene scaffold are of special interest, because the resulting products are NOBIN derivatives (**3na**-**3pa**), and can be formed with er up to 98:2, and selectivities up to 131. It is also worth to highlight the synthesis of helicene **3qa**, featuring a dibenzofuran moiety, obtained with 89.5:10.5 er and 99.5:0.5 er for the recovered starting material (**1q**). We made attempts of dynamic asymmetric resolution with **1p** by increasing the reaction temperature, but they were not successful (see the Supporting Information).

The enantioselective arylation protocol could be scaled up to grams without a detrimental effect in the reaction yield (Scheme 3A). For example, the chiral arylation of 2.5 g of **1b** provided 1.37 g of compound (*S*)-**3ba** and 1.36 g of (*S*)-**1b**, with exceptional enantiomeric ratios (98:2 for the product and 92.5:7.5 for the starting material). A sample of this material was effectively deprotected by treatment with thiophenol and potassium carbonate at 80 °C to give the free amine **4** (86% yield) without loss in the enantioselectivity. This amine is a highly valuable scaffold, and for instance it can be readily transformed in the isonitrile **5** which was used to form a chiral gold carbene **6**.[12] An X-Ray of the carbene complex allowed to further confirm the configuration of the products.[13]

Treatment of amine **4** with a phenyl isothiocyanate at room temperature yields the chiral thiourea **7** in a straightforward fashion, a product that looks appealing for asymmetric organocatalysis.[14]

On the other hand, products such the alkenyl derivative **3bl** also offer a significant manipulation potential because of



Scheme 2. Scope of 2-aminobiaryls. [a] Conditions: *rac*-**1** (0.1 mmol), **2a** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **L10** (40 mol%), Cs_2CO_3 (1.5 equiv), toluene (0.1 M), DMSO (15 equiv), air, 30 °C, 16 h. [b] At 45 °C. [c] 1 equiv. $Cu(OAc)_2 \cdot H_2O$.

the presence of the alkene handle. For instance, this substrate can be converted into the optically active δ-amino acid **8**, which presents axial chirality, by oxidative cleavage with potassium osmate and sodium periodate.[15] The products can also be easily converted into chiral ligands that are highly valuable in the field of asymmetric metal catalysis, like NOBIN and its derivatives. Therefore, NOBIN **10** was readily synthetized from **3oa** just by removing the protecting groups under standard conditions (Scheme 3B). Worth to note that the synthesis of similar biaryl NOBIN under traditional methodologies require many more steps.[16]

The embedded potential of the recovered chiral non-arylated products was also leveraged for the preparation of other valuable products, like the chiral azoderivative **12**, easily obtained from the deprotected amine **11** (Scheme 3C).[17] This latter compound has been already shown to be a useful substrate for the preparation of axially chiral products, including phosphines.[18]

From a mechanistic point of view, the arylation reaction may proceed by coordination of the acidic nitrogen to a Pd(II)-amino acid complex, followed by an asymmetric C–H activation through a concerted metalation-deprotonation (CMD) mechanism. Transmetallation and reductive elimination would give the product, and a Pd(0) complex than needs to be reoxidized to Pd(II) to start a new catalytic cycle (see the Supporting Information).

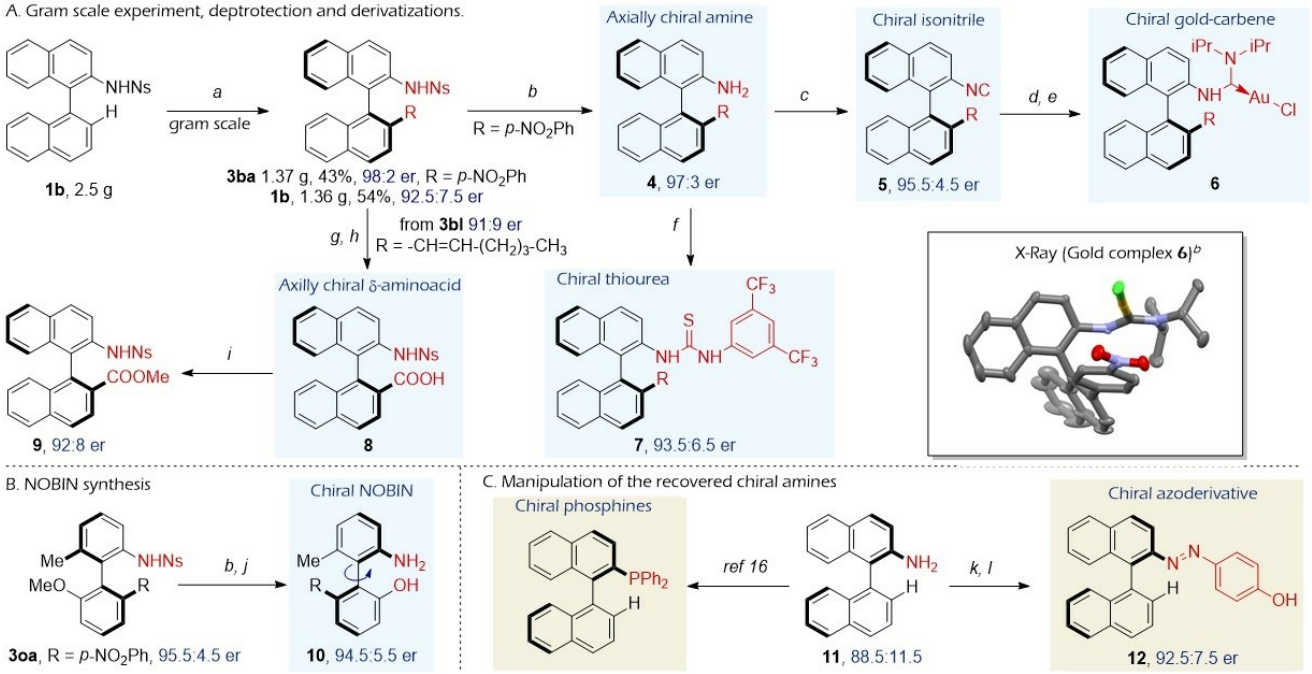
This oxidation is usually carried out by external additives, like $Cu(OAc)_2$, therefore we were surprised that our reaction could proceeded effectively just with the oxygen present in atmospheric air. To verify the role of this oxygen, we conducted control experiments under argon, and after careful removal of traces of air, using a racemic substrate and a racemic ligand. As expected, using 10 % of the Pd (II) source, we observed only a 11 % conversion, which contrasts with the 90 % yield of the arylated product obtained under the standard, open-air conditions (Scheme 4).

Consistent with the effective role of atmospheric air as oxidant, we found that the catalytic reaction can also be carried out using Pd(0) [$Pd(dba)_2$] instead of $Pd(OAc)_2$ as palladium source, yielding 81 % of the product. In contrast, under an argon atmosphere, no conversion was observed.

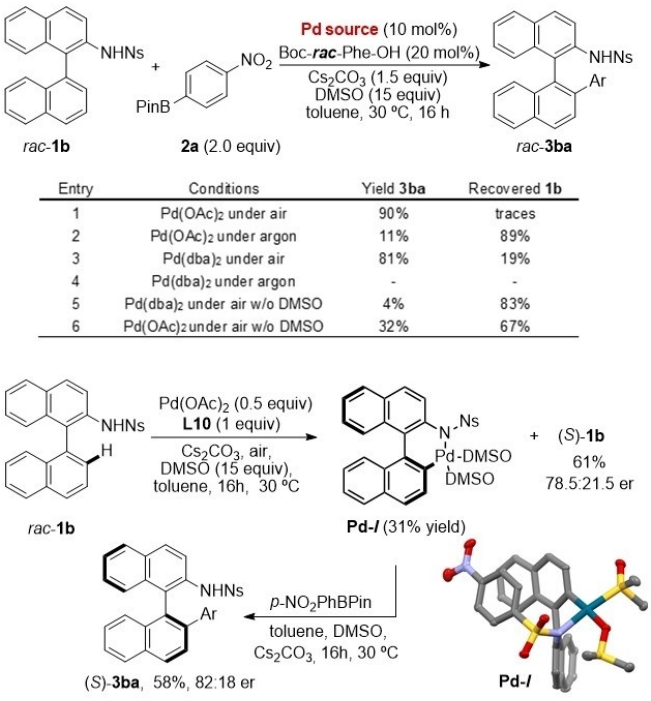
Notably, a control experiment using $Pd(dba)_2$ as the catalyst with toluene as the sole solvent, under air, resulted in only trace amounts of the product, suggesting that DMSO plays an essential role in the oxidation step. This effect is also evident in the standard catalytic reaction with $Pd(OAc)_2$, where the absence of DMSO produced a decrease in the yield of the product up to 32 %, compared to 90 % when using a toluene/DMSO mixture (Scheme 4). While the exact role of DMSO remains unclear, it may act as a ligand to prevent Pd(0) aggregation and/or increase the O_2 concentration in solution, thereby facilitating palladium reoxidation.[19]

In our efforts to identify reaction intermediates, we successfully isolated a palladacycle (**Pd-*I***) formed after the C–H activation step (Scheme 4). Notably, this complex features two coordinated DMSO molecules—one bound through oxygen and the other through sulfur.[20] The isolation of **Pd-*I*** suggests that DMSO plays a role beyond palladium oxidation, potentially stabilizing palladium intermediates. Upon treatment with a boronic ester and base, **Pd-*I*** was converted into the enantioenriched product **3ba**, demonstrating its viability as a reaction intermediate.

In conclusion, we have developed a mild and very practical kinetic resolution technology for the preparation of a great variety of optically active 2-amino-binaphthyl and biaryl derivatives that feature axial chirality, by means of a Pd-catalyzed enantioselective C–H arylation or alkenylation. The reaction is highly robust and chemoselective, and



Scheme 3. Gram-scale reaction and derivatizations of the products. [a] Conditions: a) Conditions Table 1. b) PhSH, K_2CO_3, CH_3CN/DMSO, 80 °C, 86% yield (for **4**), 66% yield (for **10**). c) $CHCl_3$, KOH, TEBAC, CH_2Cl_2, rt, 55% yield. TEBAC = Benzyltriethylammonium chloride. d) AuCl·DMS, CH_2Cl_2, rt, then: e) DIPA, CH_3CN, 60 °C, 42% yield (over two steps). DIPA = *N*-(Propan-2-yl)propan-2-amine. f) Arylisothiocyanate, THF, rt, 85% yield. g) $K_2OsO_4{\cdot}2H_2O$, $NaIO_4$, THF/H_2O, rt, 73% yield. h) $NaClO_2$, $NaH_2PO_4 2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O, rt, 60%. i) $SOCl_2$, CH_3OH, 60 °C, 76% yield. j) BBr_3, CH_2Cl_2, 0 °C to rt, 56% k) *t*-BuONO, HBF_4, EtOH, 0 °C to rt, 72% yield. l) Phenol, K_2CO_3, CH_3CN/H_2O, 0 °C to rt, 97% yield. [b] Hydrogens of the X-Ray removed for clarity.



Entry	Conditions	Yield **3ba**	Recovered **1b**
1	$Pd(OAc)_2$ under air	90%	traces
2	$Pd(OAc)_2$ under argon	11%	89%
3	$Pd(dba)_2$ under air	81%	19%
4	$Pd(dba)_2$ under argon	-	-
5	$Pd(dba)_2$ under air w/o DMSO	4%	83%
6	$Pd(OAc)_2$ under air w/o DMSO	32%	67%

Scheme 4. Control experiments under air and argon, using different Pd sources. Isolation of palladacyle. Hydrogen atoms of the X-Ray of **Pd-*I*** omitted for clarity.

can be performed in an open-air vessel, without the need of adding specific oxidants. Control experiments suggest that the toluene/DMSO solvent mixture is crucial for achieving such excellent results without the need for other oxidants or additives.

Importantly, the products formed using our technology present a great potential to divergently build different type of enantioenriched axially chiral derivatives that are not easily accessed using other methodologies. Indeed, we have already demonstrated that they can be readily converted into axially chiral gold carbenes, thioureas, NOBINs, or phosphines.

Acknowledgements

This work has received financial support from Spanish grants PID2022-137318OB–I00 and PID2022-136785NB–I00 funded by MCIN/AEI/10.13039/501100011033, Grant IHRC22-00009 funded by MCIN/ISCIII and the "European Union Next Generation EU/PRTR", and "ERDF A way of making Europe". We also thank the ORFEO – CINQA network (RED2022-134287-T), the Consellería de Cultura, Educación e Ordenación Universitaria (Grant ED431 C 2021/25 and Centro Singular de Investigación de Galicia accreditation 2023–2027, ED431G 2023/03) and the European Union (European Regional Development Fund-ERDF corresponding to the multiannual financial framework 2014–

2020). We thank the Spanish Government for the FPU fellowship to L.G. and Xunta de Galicia for the fellowship to P. L.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: C–H activation · palladium · atroposelective · arylation · 2-aminobiaryls

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Manuscript received: December 29, 2024
Accepted manuscript online: February 24, 2025
Version of record online: March 6, 2025