Cross-Coupling

Deutsche Ausgabe: DOI: 10.1002/ange.201607893
Internationale Ausgabe: DOI: 10.1002/anie.201607893

Ligand-Accelerated Direct C–H Arylation of BINOL: A Rapid One-Step Synthesis of Racemic 3,3′-Diaryl BINOLs

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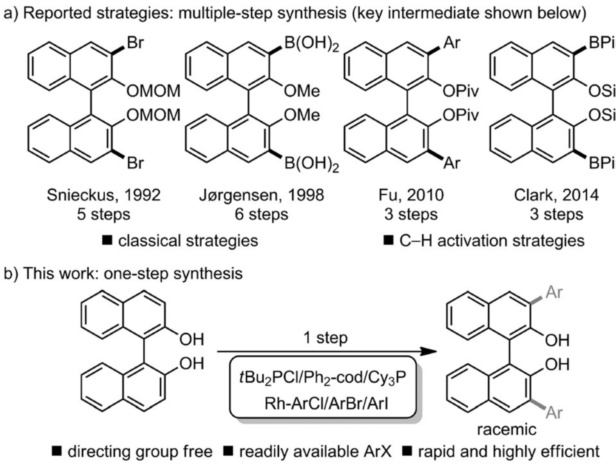
Abstract: *An ortho-selective rhodium-catalyzed direct C–H arylation of 1,1′-bi-2-naphthol (BINOL), to deliver the widely used but not easily available 3,3′-diaryl BINOL, has been developed. This highly efficient one-step synthetic approach is the shortest route to date and is greatly facilitated by the newly developed ligand system comprising* tBu_2PCl*,* Ph_2*-cod, and* $Cy_3P{\cdot}HBF_4$*. In addition, the same procedure can facilitate the challenging syntheses of 3-bulkyaryl BINOLs in good to excellent yields.*

3,3′-Diaryl BINOLs (BINOL = 1,1′-bi-2-naphthol) have been recognized as preferred backbones for a series of widely exploited BINOL-derived chiral ligands,[1] such as chiral phosphoric acids,[2] phosphoramides,[3] bis(sulfonyl)imides,[4] and ammonium salts.[5] Stimulated by the huge success of these privileged ligands in asymmetric catalysis over the past decades, much effort has been devoted to developing convenient methods to prepare 3,3′-diaryl BINOLs.[1,6] The classical strategies are multiple-step syntheses from readily available unsubstituted BINOL, involving a key Suzuki coupling reaction of either 3,3′-dihalide BINOL with aryl boronic acid (5 steps in Snieckus's protocol, Scheme 1 a)[7] or 3,3′-diboronic acid BINOL with aryl halide (6 steps in Jørgensen's protocol).[8] Despite many variations and improvements on them,[9] the frequently used procedures requiring not only the use of large amounts of sensitive alkyl lithium reagents, but also multistep reactions and long reaction time, are still extremely tedious and time consuming. Recently, great progress of transition metal catalyzed C–H functionalization[10] has evoked a new round of exploration on shorter routes to 3,3′-diaryl BINOLs. In 2010, Fu and co-workers developed an elegant three-step synthetic route to 3,3′-diaryl BINOL, and it involved a key pivalate group directed C–H arylation (Scheme 1 a).[11] Most recently, Clark and co-workers reported a promising streamlined three-step route to 3,3′-diaryl BINOLs and a preinstalled silyl group directed the C–H borylation reaction to provide the key intermediate 3,3′-boronate BINOL (Scheme 1 a).[12] Despite these remarkable achievements, the use of directing groups in such C–H activation strategies leads to extra reaction steps and stoichiometric amounts of waste from the installation and removal of directing groups. Therefore, a more straightforward approach involves avoiding the use of a preinstalled directing group to access 3,3′-diaryl BINOL and it remains an elusive challenge. Herein we report a rapid one-step route to 3,3′-diaryl BINOLs from readily available aryl halides and BINOL, a route wherein the newly developed ligand system of tBu_2PCl, Ph_2-cod, and $Cy_3P{\cdot}HBF_4$ greatly accelerate the direct C–H arylation reaction without requiring a preinstalled directing group (Scheme 1 b).



Scheme 1. Synthesis of 3,3′-diaryl BINOL. MOM = methoxymethyl, cod = 1,5-cyclooctadiene, Pin = pinacol, Piv = pivaloyl.

Direct *ortho*-selective C–H arylation of free phenol has always been a challenge because of the absence of preinstalled directing groups, as well as competitive reactions from either the oxygen atom or more electron-rich *para* position of phenol.[13] In 2003, a major breakthrough was achieved by Bedford and co-workers, who developed a rhodium-catalyzed *ortho*-arylation of substituted phenol with phosphinite as a cocatalyst.[14] We envisioned this protocol could be applied in the direct arylation of BINOL, but unfortunately, no reaction was observed at all under the reported optimal reaction conditions.

We reasoned that two possible unreactive catalytic species, phosphoramidite and bis(phosphinite) (Scheme 2), could be formed in the reaction from the interaction of BINOL, the P cocatalyst, and rhodium, and thus the central transition-metal rhodium would be prevented from approaching *ortho* C–H bonds. Actually, the substrate with a strong bidentate coordination to the catalyst, such as bipyridine, phenanthroline, and binap, remains a big challenge in the C–H activation field. Strong coordination could lead to either

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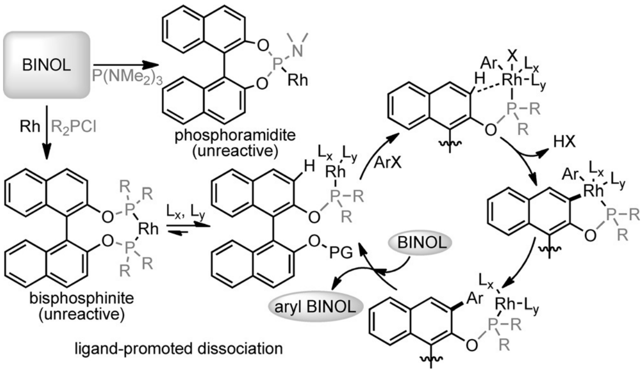
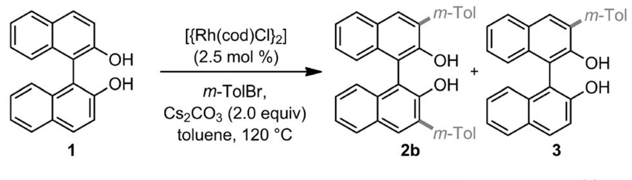
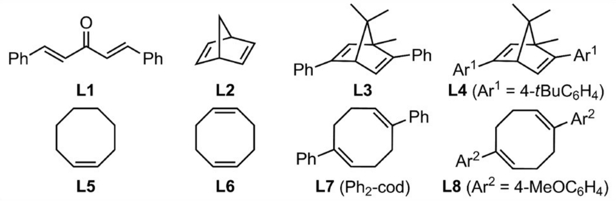
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607893.



Scheme 2. Proposed strategy. PG = protecting group.



Entry	P ligand (mol %)		Yield [%][a]	Yield [%][a]
1	Ph_2PCl (20)		0	0
2	iPr_2PCl (20)		0	0
3	Cy_2PCl (20)		0	0
4	tBu_2PCl (20)		11	21
5	tBu_2PCl (20)	**L1**	0	0
6	tBu_2PCl (20)	**L2**	trace	8
7	tBu_2PCl (20)	**L3**	12	23
8	tBu_2PCl (20)	**L4**	7	12
9	tBu_2PCl (20)	**L5**	9	18
10	tBu_2PCl (20)	**L6**	16	23
11	tBu_2PCl (20)	**L7**	35	26
12	tBu_2PCl (20)	**L8**	28	30
13	tBu_2PCl (30)	**L7**	39	38
14	tBu_2PCl (40)	**L7**	52	31
15	tBu_2PCl (50)	**L7**	80	12
16[b]	tBu_2PCl (50)	**L7**	96	4

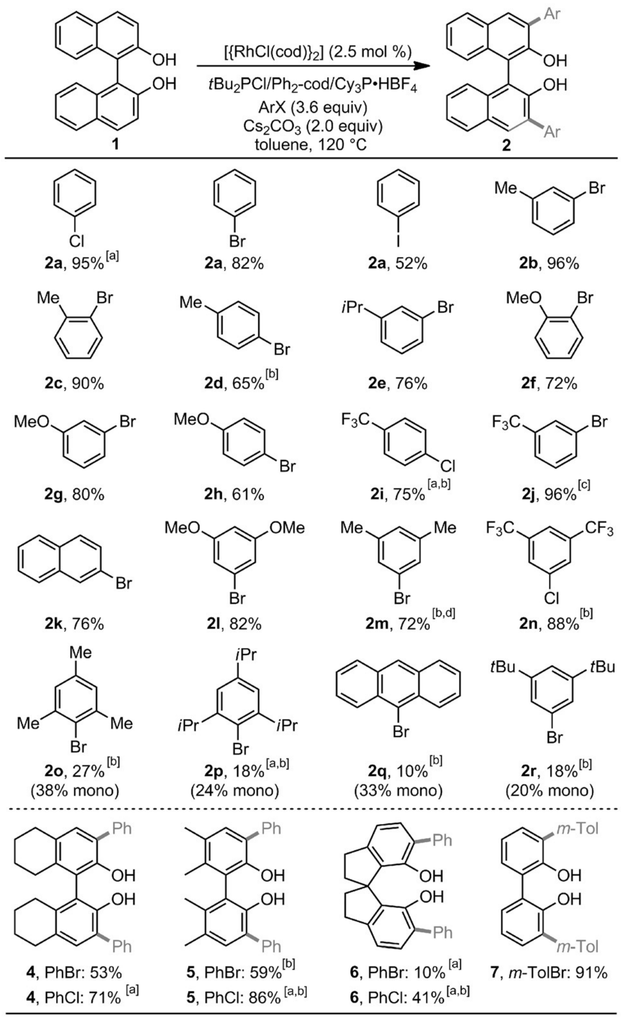


Scheme 3. Ligand effects. BINOL (0.2 mmol), m-TolBr (0.72 mmol), $[Rh(cod)Cl]_2$ (5 μmol), P ligand (0.04–0.1 mmol), diene (0.01 mmol), Cs_2CO_3 (0.4 mmol), toluene (2 mL), at 120 °C under N_2 for 24 h. [a] Yield of isolated product. [b] $Cy_3P\cdot HBF_4$ (5 μmol) added.

low turnover because of the difficult dissociation of catalyst from final products, or undesired reaction selectivity because of inaccessible proximity of the catalyst to expected C–H bonds. To develop a general strategy to facilitate the *ortho* arylation of free BINOL, herein we propose a ligand-promoted metal dissociation from a bidentate substrate. As shown in Scheme 2, bulky chlorodialkylphosphine cocatalysts are introduced first to weaken the coordination of bis(phosphinite) to rhodium, and then additional ligands (L_x/L_y/…) are added to further competitively coordinate to rhodium, thus obtaining a possible active catalytic species to enable the next C–H activation.

Based on this hypothesis, we first investigated some bulky chlorodialkylphosphine cocatalysts, and delightedly found that bulky tBu_2PCl was the sole cocatalyst which can promote the rhodium-catalyzed C–H arylation reaction of BINOL to deliver diaryl BINOL in 11 % yield and monoaryl BINOL in 21 % yield (Scheme 3, entries 1–4). Given the observation that $[\{Rh(PPh_3)_3Cl\}_2]$ instead of $[\{Rh(cod)Cl\}_2]$ only gave a trace amount of arylated product, we envisioned that an alkene ligand could play an important role in the reaction. So alkene ligands were selected as the first additional ligand to be examined. Among a range of screened diene ligands (entries 5–12), Ph_2-cod (**L7**; 5 mol %) provided the best result with up to 61 % total yield of diaryl and monoaryl BINOLs (entry 11). Considering two phenolic hydroxy groups embedded in one BINOL structure, we attempted to increase the loading of tBu_2PCl from 20 to 50 mol % (entries 13–15). Surprisingly, significant improvement of yield was observed with up to 80 % of diaryl and 12 % of monoaryl BINOL (entry 15), thus implying partial decomposition of tBu_2PCl could happen during the course of the reaction. For further improvement of the reaction, various phosphine ligands were then selected as the second additional ligand to be tested. The results showed that the addition of a catalytic amount of $Cy_3P\cdot HBF_4$ (2.5 mol %) as the best choice could furnish the corresponding arylated BINOLs in almost quantitative yield (96 % of diaryl and 4 % of monoaryl, entry 16).

With the above optimized reaction conditions in hand, we first explored a series of aryl halides to test the generality of the reaction (Scheme 4). Various phenyl halides, including PhCl, PhBr, and PhI, were all tolerant of these reaction conditions and provided **2a**. Among them, PhI afforded the lowest yield owing to the significant amounts of homocoupling product of PhI and multiarylated products. In the case of less reactive PhCl, a large excess of PhCl was needed to ensure a high yield. Accordingly, aryl bromides were then selected as ideal coupling partners for most of the coupling reactions. A wide range of aryl bromides bearing either electron-donating groups, like Me (**2b–d**), *i*Pr (**2e**), MeO (**2f–h**), or electron-withdrawing groups, like CF_3 (**2j**), proved to be suitable coupling partners for this reaction with good to excellent yields. In addition, sterically hindered aryl bromides, such as 2-naphthyl bromide (**2k**), and some disubstituted aryl bromides (**2l** and **2m**) were also compatible with this coupling process, and the yields varied from 58 to 88 %, albeit with a lower yield for bulky 3,5-$(Ph)_2C_6H_3Br$ (26 %). It is worth noting that aryl bromides containing strongly electron-withdrawing groups, like p-$CF_3C_6H_4Br$ and 3,5-$(CF_3)_2C_6H_3Br$, led to relatively low yields. In these cases, aryl chlorides would be better choices. For example, p-$CF_3C_6H_4Cl$ (**2i**) afforded 75 % yield, and likewise, as high as 88 % yield was obtained for 3,5-$(CF_3)_2C_6H_3Cl$ (**2n**). Notably, extremely bulky aryl bromides (**2o–r**), generally displaying very low reactivities in many coupling reactions, still gave impressive total yields for both the diaylated and monoarylated BINOLs. Next, we also examined other biphenols beyond simple BINOL under our coupling conditions. Biphenols with relatively flexible struc-

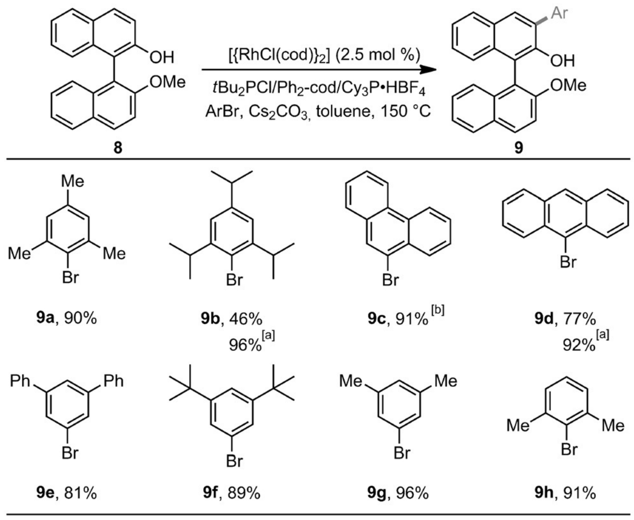


Scheme 4. Reaction scope. BINOL (0.2 mmol), ArBr (0.72 mmol), [{Rh(cod)Cl}$_2$] (5 μmol), tBu$_2$PCl (0.1 mmol), Ph$_2$-cod (0.01 mmol), Cy$_3$P·HBF$_4$ (5 μmol), Cs$_2$CO$_3$ (0.4 mmol), toluene (2 mL), at 120 °C under N$_2$ for 24 h. Yields for the isolated products are provided. [a] ArX (1 mL). [b] 150 °C. [c] ArBr (0.48 mmol). [d] ArBr (1.44 mmol).

tures were tolerated (**4**, **5** and **7**), with moderate to good yields for couplings with ArBr, and good yields for couplings with PhCl. In contrast, biphenol with a rigid structure, for example, spinol (**6**),[15] only provided 10 % yield for PhBr, and 41 % yield for PhCl, likely owing to the much more difficult dissociation of metal from rigid biphenol-derived bis(phosphinite).

To improve the reactivity of 3-bulkyaryl bromide in the present process, we attempted to protect one phenolic hydroxy group of BINOL with a methyl group, thus expecting the elimination of possible bidentate coordination of bis(phosphinite) could promote the reaction.

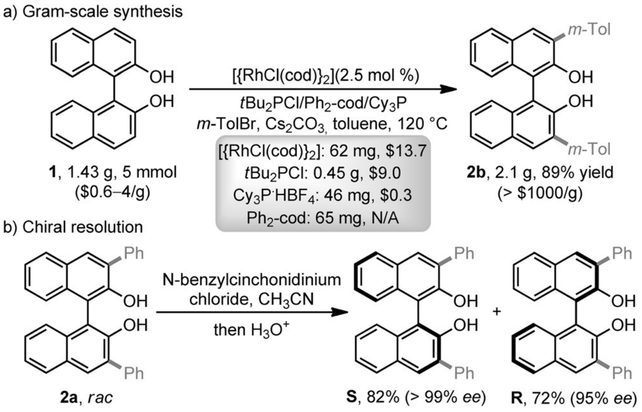
As shown in Scheme 5, treatment of protected BINOL with various bulky aryl bromides (**9a**–**h**) in the presence of tBu$_2$PCl, Ph$_2$-cod, and Cy$_3$P·HBF$_4$ provided the corresponding 3-bulkyaryl BINOLs with good to excellent yields (81–96 %). Impressively, the most sterically hindered aryl bromides, such as 2,4,6-(Me)$_3$C$_6$H$_2$Br (**9a**), 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$Br (**9b**), and 9-bromoanthracene (**9d**), afforded excellent yields. However



Scheme 5. 3-Bulkyaryl BINOL synthesis. BINOL (0.2 mmol), ArBr (0.72 mmol), [{Rh(cod)Cl}$_2$] (5 μmol), tBu$_2$PCl (0.04 mmol), Ph$_2$-cod (0.01 mmol), Cy$_3$P·HBF$_4$ (5 μmol), Cs$_2$CO$_3$ (0.4 mmol), toluene (2 mL), at 150 °C under N$_2$ for 24 h. Yields for the isolated products are provided. [a] tBu$_2$PCl (0.1 mmol) was used. [b] 1:1 mixed isomers.

neither Bedford's nor Inoue's optimal reaction conditions gave arylated products in the coupling reaction of the same monomethyl protected BINOL with 2,4,6-(Me)$_3$C$_6$H$_2$Br (**9a**),[14c,16] thus suggesting that the direct C−H arylation reaction was greatly accelerated by the newly discovered ligand system. Notably, treatment of 3-bulkyaryl BINOLs (**9**) with BBr$_3$ under mild reaction conditions produced deprotected 3-bulkyaryl BINOLs in high yields (see the Supporting Information). In fact, these unsymmetric 3-bulkyaryl BINOLs have already proven to be superior chiral ligands in some asymmetric reactions,[17] though their difficult syntheses, which generally require the use of extremely water- and air-sensitive organometallic coupling reagents, like organolithiums and Grignard reagents, greatly limited their wide applications. Thus the current coupling method provides a promising route to these bulkyaryl BINOLs.

To test the synthetic utility of current method, a gram-scale coupling reaction of simple BINOL with m-tolyl bromide was conducted under the optimal reaction conditions, and provided the target 3,3′-diaryl BINOL **2b** in 89 % yield (Scheme 6). This one-step synthesis of highly valuable 3,3′-diaryl BINOL (average of \$1000/gram) starting from inexpensive BINOL (\$0.6–4/gram) shows that the current method would be an attractive synthetic tool for 3,3′-diaryl BINOLs. A common limitation associated with unprotected BINOL coupling reactions is the potential racemization of chiral BINOLs and the corresponding products.[18] In our reactions, the racemizations of all BINOLs except for the rigid spinol **6** were observed to take place, even at 70 °C in the presence of Cs$_2$CO$_3$. However, considering that various chiral resolution techniques have been developed to date, the current approach combined with a subsequent chiral resolution would still be a pretty competitive protocol for the synthesis of chiral 3,3′-diaryl BINOL. To demonstrate the potential of our approach, we tested the chiral resolution of



Scheme 6. Gram-scale synthesis and chiral resolution.

2a using commercial *N*-benzylcinchonidinium chloride, based on the established technique,[19] and both the *S* enantiomer (99% *ee*) and *R* enantiomer (95% *ee*) can be readily accessed.

In summary, we have successfully developed a highly efficient rhodium-catalyzed one-step synthetic route to 3,3′-diaryl BINOLs from inexpensive BINOL and readily available aryl halides. To date, this highly selective arylation provides the most straightforward synthetic method for accessing 3,3′-diaryl BINOLs and 3-bulkyaryl BINOLs from simple BINOL. The newly developed ligand system proved to greatly accelerate this direct C–H arylation reaction. Further investigation of cheaper metals and other reaction types are under way in our laboratory.

Acknowledgments

We thank the National Natural Science Foundation of China (21402096, 21421062), Tianjin Applied Basic Research Project, and Cutting-edge Technology Research Plan (14JCYBJC41400) for financial support. We thank Prof. Qi-Lin Zhou in Nankai University and Dr. Pu-Cha Yan in Jiuzhou Pharmaceutical Co., Ltd. for the generous donation of spinols.

Keywords: arylation · biaryls · cross-coupling · ligand design · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 14116–14120
Angew. Chem. **2016**, *128*, 14322–14326

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Received: August 13, 2016
Revised: September 21, 2016