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Cu/Picolinamides-Catalyzed Coupling of (Hetero)aryl Halides with Secondary Phosphine Oxides and Phosphite

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dicated to Professor Christian Bruneau for his out-standing contribution to catalysis?

Keywords

Aryl phosphine oxides | Coupling | Aryl halides | Copper | Picolinamide

Main observation and conclusion

Some 4-hydroxy-picolinic acid derived amides were revealed as more efficient ligands for Cu-catalyzed coupling of (hetero)aryl halides with secondary phosphine oxides and phosphites. Only 3-5 mol% CuI and ligands were required to ensure coupling with a number of (hetero)aryl bromides and iodides complete at 120 °C in 10-20 h.

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Background and Originality Content

(Hetero)aryl phosphine oxides are important compounds that have been frequently used for assembling phosphine ligands. Direct coupling of (hetero)aryl halides with phosphine oxides represents one of the most convenient approaches for preparing these molecules.^[1-11] Since it was discovered in 1980 by Hirao group,^[2] Pd-catalyzed coupling of C(sp2) electrophiles with secondary phosphites and phosphine oxides has been intensively investigated and a great number of electrophiles such as aryl halides,^[3] trif Ites,^[4] boronic acids,^[5] and aryl sulfonates^[6] have been successively employed as the coupling partners. However, cost issue of alladium and requiring relatively high catalytic loadings (typically 5-10 mol%) limited its practical usage.^[1] Consequently much attention has been directed to development of alternative catalysts th less expensive transition metals in recent years.^[1] While Ni-catalyzed C-P coupling has made significant progress under the sistance of either ligands^[7] or light irradiation,^[8] Cu-catalyzed C-P bond formation has been less explored. Until now, J/ligand-catalyzed arylation of secondary phosphites or phosphine oxides is still limited to using aryl iodides and some special aryl bromides as substrates, even at higher catalytic loadings (>20 ol%).^[9,10] Accordingly, discovery of a more efficient Cu-based catalytic system for C-P coupling is of great interest.

Scheme 1 General methods for metal-catalyzed coupling of C(sp2) electrophiles with secondary phosphites or phosphine oxides



Results

In recent years, we have found that some oxalic diamides^[12,13] and N-heterocycle-embodied amides^[14] are more powerful ligands t at can be used to solve many existing problems in Cu-catalyzed arylation of nucleophiles. As an extension of this work, in this paper, we explored the possibility of using these ligands to promote -catalyzed coupling reaction of aryl bromides with secondary phosphine oxides. As indicated in Table 1, we selected the coun'ing of 2-bromo-6-methoxynaphthalene with diphenylphosphine oxide as the model reaction to seek suitable reaction conditions. Initially, three oxalic diamides L1-L3 that displayed excellent activity to promote Cu-catalyzed C-N or C-O bond formation were examined.^[13] It was found that under the catalysis of 10 mol% Cul and ligand, only L3 led to the formation of the desired product 3a in 8% yield after heating the reaction mixture in DMSO at 100 °C for 20 h (entries 1-3). Then we moved our attention to proline-derived amides that showed superior activity in Cu-catalyzed coupling of (hetero)aryl halides with sulfinic acid salts,^[14] and were pleased that the yields of 3a jumped to 21% and 40% when amides L4 and L5 were applied, respectively (entries 4 and 5). Further exploration revealed that 4-hydroxypicolinic acid derived amide L6 (4-hydroxy-N-(2-methylnaphthalen-1-yl)picolinamide, HMNPA) gave a better yield (entry 6). Changing the aniline part in this ligand seemed to have little influence to the reaction, as evident from that yields were slightly dropped in case of **L7** and **L8** as the ligands (compare entries 6-8). However, switching the acid part in this ligand dramatically decreased the reaction yields of **3a** (entries 9 and 10), indicating that subtle change in the pyridine ring of the ligands could alter the reaction course greatly.

Table 1 Cul-catalyzed coupling of 2-bromo-6-methoxy-naphthalene with diphenylphosphine oxide under the assistance of different ligands^a



entry	conditions	yield (%) ^b
1	10 mol% Cul, 10 mol% L1 , DMSO, 100 °C	0
2	10 mol% Cul, 10 mol% L2 , DMSO, 100 °C	0
3	10 mol% Cul, 10 mol% L3 , DMSO, 100 °C	8
4	10 mol% Cul, 10 mol% L4 , DMSO, 100 °C	21
5	10 mol% Cul, 10 mol% L5 , DMSO, 100 °C	40
6	10 mol% Cul, 10 mol% L6 , DMSO, 100 °C	74
7	10 mol% Cul, 10 mol% L7 , DMSO, 100 °C	65
8	10 mol% Cul, 10 mol% L8 , DMSO, 100 °C	69
9	10 mol% Cul, 10 mol% L9 , DMSO, 100 °C	36
10	10 mol% Cul, 10 mol% L10 , DMSO, 100 °C	11
11	10 mol% Cul, 10 mol% L6 , DMF, 100 °C	70
12	10 mol% Cul, 10 mol% L6 , <i>i</i> -PrOH, 100 °C	93
13	10 mol% Cul, 10 mol% L6 , <i>n</i> -BuOH, 100 °C	96
14	10 mol% Cul, 10 mol% L6 , <i>t</i> -BuOH, 100 °C	11
15	10 mol% Cul, 10 mol% L6 , MeCN, 100 °C	27
16	10 mol% Cul, 10 mol% L6 , dioxane, 100 °C	0
17	5 mol% Cul, 5 mol% L6 , <i>i</i> -PrOH, 100 °C	75
18	5 mol% Cul, 5 mol% L6 , <i>i</i> -PrOH, 120 °C	88

^aGeneral conditions: 1a (1.0 mmol), 2a (1.1 mmol), Cul (0.05-0.1 mmol), 20 h. ^bThe yield was determined by 1H NMR analysis of crude products using DMAc as the internal standard.

It is notable that 6-hydroxypicolinamide **L10** has showed excellent activity toward Cu-catalyzed coupling of heteroaryl primary amines with (hetero)aryl bromide.^[15] In our case, it was much less potent than 4-hydroxypicolinamide **L6**. With the amide **L6** as the ligand, we also checked the solvent effect, and found that while

DMF gave a similar result (entry 11), using *i*-PrOH or *n*-BuOH as the solvent significantly improved the yields (entries 12 and 13), and other solvents like *t*-BuOH, MeCN and dioxane led to low yields or no conversion (entries 14-16). Reducing the catalytic loading to 5 mol% caused incomplete conversion (entry 17). However, increasing the reaction temperature to 120 °C could solve this problem (entry 18). Based on these studies, we concluded the optimized reaction conditions are using 5 mol% Cul and **L6** as the catalytic system, *i*-PrOH as the solvent, and conducting the reaction at 120 °C.

scheme 2 Cul/HMNPA catalyzed coupling reaction of (hetero)aryl bromides with secondary phosphine oxides and diisopropyl phosphonate^a



^aGeneral conditions: 1 (1.0 mmol), 2 (1.1 mmol for secondary phosphine o ides, 1.5 mmol for diisopropyl phosphonate), Cul (0.05 mmol), L6 (0.05 mmol), K₂CO₃ (1.5 mmol), *i*-PrOH (1.0 mL), 120 °C, 20 h, isolated yield.
^bNa₂CO₃ as the base. ^cCul (0.1 mmol) and L6 (0.1 mmol) were used.

The established optimal reaction conditions were then examined with a series of (hetero)aryl bromides, secondary phosphine oxides and phosphites. As summarized in Scheme 1, coupling of diphenylphosphine oxide with aryl bromides with either electron-donating or electron-withdrawing groups at the *para*-position proceeded smoothly to provide **3b-3h** in 66-85% yields. Three *meta*-substituted aryl bromides also worked well, leading to the formation of **3i-3j** in 75-87% yields. However, *ortho*-substituted substrates are difficult ones under the present conditions, as evident from that **3l** was obtained in a low yield. After checked the coupling reaction with 5-bromo-benzo[*d*][1,3]dioxole (**3m**) and 2-bromonaphthalene (**3n**), we moved our attention to coupling with heteroaryl bromides, and were pleased that both electron-rich and electron-poor substrates were applicable, delivering the corresponding heteroaryl phosphine oxides **3o-3u**. Notably, coupling with 2-bromothiophene was rather sluggish, and incomplete conversion was seen even increasing the catalytic loading to 10 mol% (**3o**). When 2,6-dibromopyridine was utilized, double coupling occurred to furnish diphosphonate **3s**. Additionally, switching diphenylphosphine oxide to two other diarylphosphine oxides was possible, affording **3v-3y** in 62-80% yields. Furthermore, coupling with diisopropyl phosphonate was tested, and the desired coupling products **3z-3ae** were isolated, although the yields were relatively low because of slower conversion.

Scheme 3 Cul/L7-catalyzed coupling reaction of (hetero)aryl iodides with secondary phosphine oxides.^{*a*}



^{*a*}General conditions: **4** (2.0 mmol), 2 (2.3 mmol), Cul (0.06 mmol), **L7** (0.06 mmol), K_2CO_3 (3.0 mmol), *i*-PrOH (2.0 mL), 120 °C, 10 h, isolated yield. ^{*b*}Cul (0.12 mmol) and **L7** (0.12 mmol) were used.

In view of this encouraging result, we envisioned that further reducing the catalytic loadings would be possible if more reactive aryl iodides were employed as the coupling partners. As a result, we utilized 3 mol% CuI and ligands to examine the coupling reaction of 4-iodoanisole with diphenylphosphine oxide, and guickly discovered that the ligand L7 was slightly better than L6. In this case reaction completed after 10 h to provide 3b in 81% yield (Scheme 2). The other para- and meta-substituted aryl iodides tested also worked well, giving rise to 3c-3g, 3i and 3j in good to excellent yields. In case of 1-(3-iodophenyl)ethan-1-one (3j), increasing the catalytic loading to 6 mol% gave a better yield, implying that its reactivity was significantly lower than that of 3-iodoanisole. Pleasingly, coupling with two ortho-substituted aryl iodides was possible, providing 3af and 3ag in 93% and 59% yields, respectively. In addition, changing the coupling partners to 1-iodonaphthalene (3ah), 6-iodoquinazolines (3ai) and two other diarylphosphine oxides (3w and 3y) did not affect the catalytic efficiency.

The synthetic usage of the present catalytic system was demonstrated by preparing (*S*)-*t*-BuPHOX, a valuable ligand for several Pd-catalyzed reactions.^[10a,b] In an attempt to prepare this ligand in a more convenient and economical way, Stoltz and coworkers successively applied the copper-catalyzed C-P bond formation between bromide **5** (Scheme 3) and diphylphosphine oxide **2a**,^[10b] but higher catalytic loadings were required to ensure the complete conversion (>12.5 mol % Cul and >87.5 mol % *N*,*N*'-dimethylethylenediamine). With more efficient ligands in hand, we found that a similar result was observed using only 5 mol% Cul and **L7** in the coupling step, and the resultant coupling product **6** was reduced with Ph₂SiH₃ to afford (*S*)-*t*-BuPHOX in 70%

overall yield. Noteworthy is that the reaction conditions were essential for the coupling step. In our initial try by using standard conditions as outlined in Scheme 1, phosphonate 6 was isolated in a low yield, mainly because debromination of 5 occurred. Fortunately, switching the ligand from L6 to L7, and solvent from *i*-PrOH to *n*-BuOH greatly inhibit this side reaction.

Scheme 4 Synthesis of (*S*)-*t*-BuPHOX through CuI/**L7**-catalyzed arylation of diphylphosphine oxide



conclusions

In conclusion, we have revealed that some 4-hydroxy-picolinic acid derived amides are more efficient ligands for Cu-catalyzed coupling of (hetero)aryl halides with secondary phosphine oxides and phosphites, which allowed the coupling with a number of (hetero)aryl bromides and iodides complete at relatively low catalytic loadings. This method has been used for conveniently assembling (*S*)-*t*-BuPHOX, and may find more applications in pren ring other phosphine ligands and synthetically useful aryl phosphonates.^[16]

xperimental

General procedure for the Cu-catalyzed phosphorylation of aryl bromide. The (hetero)aryl bromide (1.0 mmol), phosphine xides (1.1 mmol) (or phosphites (1.5 mmol)), Cul (9.5 mg , 0.05 mmol), L6 (13.9 mg , 0.05 mmol) and K₂CO₃ (207.3 mg, 1.5 mmol) ₂CO₃ (159.0 mg, 1.5 mmol)) were placed into a Schlenk tube (10 mL) with a magnetic stir bar. The reaction vessel was evacua ed and backfilled with argon three times, then *i*-PrOH (1 mL) vas added under a positive argon pressure (Note: for liquid substrates, they were added after the tube was backfilled with argon). The reaction mixture was heated at 120 °C for 20 h under vigorous cirring. The cooled solution was diluted with ethyl acetate and washed with brine. The organic phase was dried over Na₂SO₄, c ncentrated in vacuo, and purified by silica gel flash chromatogaphy to afford the corresponding arylphosphine oxides or arylphosphonates.

General procedure for the Cu-catalyzed phosphorylation of aryl bromide. The (hetero)aryl iodides (2.0 mmol), phosphine oxides (2.2 mmol), Cul (11.4 mg, 0.06 mmol), L7 (15.5 mg, 0.06 n mol) and K_2CO_3 (414.6 mg, 3.0 mmol) were placed into a Schlenk tube (20 mL) with a magnetic stir bar. The reaction vessel was evacuated and backfilled with argon three times, then *i*-PrOH (2 mL) was added under a positive argon pressure (Note: for liquid substrates, they were added after the tube was backfilled with argon). The reaction mixture was heated at 120 °C for 10 h under vigorous stirring. The cooled solution was diluted with ethyl acetate and washed with brine. The organic phase was dried over Na₂SO₄, concentrated in vacuo, and purified by silica gel flash chromatography to afford the corresponding arylphosphine oxides.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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