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Direct Arylation under Catalysis of an Oxime-Derived Palladacycle: Search for a Phosphane-Free Method

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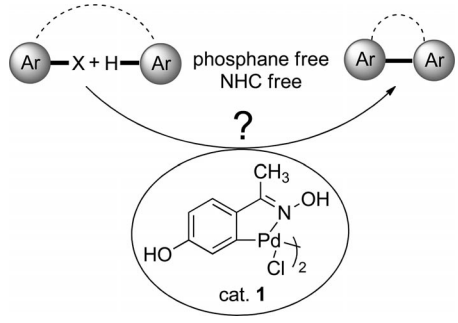
A phosphane-free method for the direct arylation of benzothiazole by employing oxime-derived palladacycle **1** as a catalyst was developed. The new catalyst system can be used for 2-arylations by using aryl bromides and iodides. In addition, this method is especially suitable for the intramolecular direct coupling of bromo- and iodoamides, as well as chloroamides, to achieve a rapid synthesis of benzo[*c*]phenanthridine alkaloids.

Introduction

Substituted biaryls are important building blocks for the syntheses of diverse natural products, medicinal agents, organic materials, crystals, and ligands.[1] Currently, among the vast number of methods available to form biaryl linkages, the direct arylation of arenes by catalytic C–H activation is widely chosen for aryl–aryl bond formation because of its atom economy and mild reaction conditions.[2] A variety of transition metals such as Fe,[3] Co,[4] Ni,[5] and Cu,[6] as well as noble metals such as Pd,[7] Rh,[8] Ru,[9] and Ir,[10] have been discovered to promote efficiently the direct coupling reaction. Palladium-catalyzed inter- or intramolecular direct coupling reactions in the presence of a phosphane ligand and base is undoubtedly among the most important and reliable methods.[11]

However, most phosphane ligands are air- and/or moisture-sensitive and toxic, which limits their large-scale application. Therefore, it is necessary to develop phosphane-free methods for direct arylation reactions. Ligand-free methods have been established in which Pd was combined with Ag[12] or Cu,[13] even without the assistance of a metal salt.[14] Despite the significant progress that has been achieved, an improvement in the efficiency and generality of a ligand-free procedure for arylation reactions is desirable. Nitrogen-based ligands such as N-heterocyclic carbenes[15] and phenanthrolines[16] have been used in place of phosphanes, and they have been show to promote direct arylation coupling reactions, but their synthetic complexity and high cost limit their widespread use. Over the past decades, owing to the their accessibility, thermal stability, and high catalytic activity, oxime-derived palladacycles have played a pivotal role in a wide variety of C–C coupling reactions, including Heck, Suzuki, Sonogashira, and Stille couplings.[17] In these C–C coupling reactions, intermediate Pd^0 species are proposed to be generated from oxime palladacycles, and the processes are thought to operate through a Pd^0–Pd^{II} mechanism, which leads us to consider oxime palladacycles as homogeneous phosphane-free catalysts in direct arylation couplings. Herein, we demonstrate the potential activity of oxime palladacycles to mediate inter- and intramolecular direct coupling reactions (Scheme 1).



Scheme 1. Direct arylation under catalysis of an oxime-derived palladacycle.

Results and Discussion

Initially, the direct arylation of benzothiazole with iodobenzene by using 4-hydroxyacetophenone oxime palladacycle **1** as the catalyst (Scheme 1)[18] was chosen as the model reaction. When Cs_2CO_3 was used as the base, no conversion was observed in the nonpolar solvent xylene (Table 1, Entry 1). Changing the solvent to *N*-methyl-2-pyrrolidone (NMP) or DMSO led to a trace amount of the desired product (Table 1, Entries 2 and 3). When the reaction was carried out in DMF or *N*,*N*-dimethylacetamide (DMA), product **4a** was obtained in 19 or 24% yield, respectively

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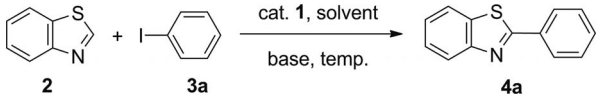
(Table 1, Entries 4 and 5). For further improvement, various inorganic and organic bases were tested in DMA for optimization. To out delight, replacing Cs_2CO_3 with Na_2CO_3 increased the yield of **4a** to 57% (Table 1, Entry 6). Notably, when K_2CO_3 was added as the base, the target product was obtained in 83% yield (Table 1, Entry 7). Moreover, a series of bases, such as K_3PO_4, AcOK, AcONa, *t*BuOK, NaOH, MeONa, and EtONa, were further investigated. However, no obvious improvements were observed (Table 1, Entries 8–14). Noteworthy is that when the tertiary amine Cy_2NMe or DBU was used as the base (Table 1, Entries 15 and 16), despite the fact that no conversion of benzothiazole was observed, an Ullmann-type coupling reaction of iodobenzene was found to occur. Specifically, when Cy_2NMe was used as the base, the yield of biphenyl increased up to 99%. After that, the reaction temperature was also examined. When the reaction was carried out at a lower (Table 1, Entry 17) or higher temperature (Table 1, Entry 18) than 140 °C, inferior conversion of **2** into **4a** was obtained. Aqueous conditions, under which palladacycle **1** has shown high activities in the Heck, Suzuki, and Hiyama reactions,[19] were then examined, but the yields sharply decreased when the reactions were performed in DMA/H_2O (Table 1, Entries 19 and 20). On the basis of further research, we found that a low catalyst loading was also unfavorable to the reactions (Table 1, Entries 21 and 22). Finally, we were pleased to note that the best yield for the direct arylation of benzothiazole with iodobenzene was obtained when the reaction time was extended to 24 h (90%; Table 1, Entry 23).

With acceptable conditions in hand, the scope of the direct arylation of benzothiazole with various aryl halides was examined. The results are present in Table 2. Generally, the yields of the reactions with aryl iodides (Table 2, Entries 1–7) were higher than those with aryl bromides (Table 2, Entries 8–11). It seems that aryl iodides with electron-donating (MeO, Me) or electron-withdrawing (Cl,

Table 1. Optimization of the arylation conditions.[a]

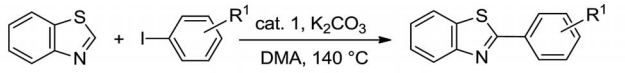


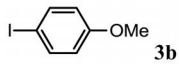
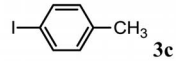
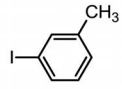
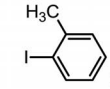
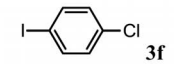
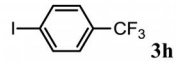
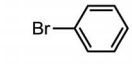
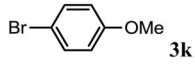
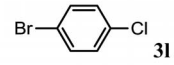
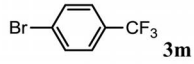
2 **3a** **4a**

Entry	Solvent	Base	*T* [°C]	Yield [%][b]
1	xylene	Cs_2CO_3	140	NR
2	NMP	Cs_2CO_3	140	trace
3	DMSO	Cs_2CO_3	140	trace
4	DMF	Cs_2CO_3	140	19
5	DMA	Cs_2CO_3	140	24
6	DMA	Na_2CO_3	140	57 (50)
7	DMA	K_2CO_3	140	83 (75)
8	DMA	K_3PO_4	140	34
9	DMA	AcOK	140	39
10	DMA	AcONa	140	25
11	DMA	*t*BuOK	140	NR[c]
12	DMA	NaOH	140	NR[c]
13	DMA	MeONa	140	NR[c]
14	DMA	EtONa	140	NR[c]
15	DMA	Cy_2NMe	140	0[d]
16	DMA	DBU	140	0[e]
17	DMA	K_2CO_3	120	44
18	DMA	K_2CO_3	160	54
19	DMA/H_2O	K_2CO_3	140	31[f]
20	DMA/H_2O	K_2CO_3	140	trace[g]
21	DMA	K_2CO_3	140	65[h]
22	DMA	K_2CO_3	140	26[i]
23	DMA	K_2CO_3	140	90 (80)[j]

[a] Conditions: benzothiazole (1 mmol), iodobenzene (1.5 mmol), **1** (5 mol-%), base (1.5 mmol), solvent (5 mL), 5 h. [b] HPLC yield; yield of the isolated product after column chromatography is given in parentheses. [c] Palladium black formed immediately when base was added to the system. [d] Isolated yield of biphenyl was up to 99%. [e] Isolated yield of biphenyl was 10%. [f] Reaction was carried out in DMA/H_2O (95:5). [g] Reaction was carried out in DMA/H_2O (80:20). [h] Catalyst loading was 3 mol-% with regard to benzothiazole. [i] Catalyst loading was 1 mol-% with regard to benzothiazole. [j] Yield was measured after 24 h.

Table 2. Scope for the direct arylation of benzothiazole with aryl halides.[a]



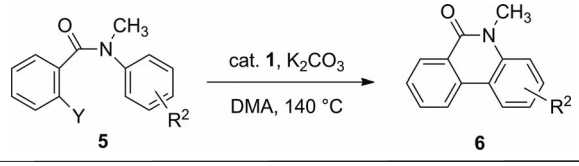
Entry	Aryl halide	Product	Yield [%][b]
1	 **3a**	**4a**	80
2	 **3b**	**4b**	75
3	 **3c**	**4c**	86
4	 **3d**	**4d**	85
5	 **3e**	**4e**	90
6	 **3f**	**4f**	72
7	 **3h**	**4h**	76
8	 **3j**	**4a**	30
9	 **3k**	**4b**	49
10	 **3l**	**4f**	65
11	 **3m**	**4h**	64

[a] Conditions: benzothiazole (1 mmol), aryl halide (1.5 mmol), cat. **1** (5 mol-%), K_2CO_3 (1.5 mmol), DMA (5 mL), 24 h. [b] Isolated yield after column chromatography.

CF_3) groups exhibit similar reactivities and generate the desired products in 72–90% yield (Table 2, Entries 1–7). To our surprise, aryl iodide **3e** with an *ortho* substituent afforded the desired product in excellent yield (Table 2, Entry 5) and higher than that obtained with an iodide containing a *meta* or *para* substituent (Table 2, Entries 3 and 4). As we observed, when aryl bromides were applied as substrates, the yields with electron-deficient iodides **3l** and **3m** (Table 2, Entries 10 and 11) were higher than those with electron-rich iodides **3j** and **3k** (Table 2, Entries 8 and 9).

In an effort to further explore the versatility of this method, we also tested the intramolecular direct coupling reaction with this new catalytic system. A series of haloamides with differing electronic and steric effects were examined. The results are summarized in Table 3. In general, iodoamides and bromoamides showed excellent reactivity. The yields obtained with iodoamides (88–97%; Table 3, Entries 1–7) were slightly higher than those obtained with bromoamides (75–93%; Table 3, Entries 8–14). Sterically hindered *ortho*-substituted haloamides **5d** and **5k** also participated in these coupling processes (Table 3, Entries 4 and 11) to give the corresponding products in comparable yields to those obtained with *para*-substituted substrates **5c** and **5j** (Table 3, Entries 3 and 10). To our delight, by employing our new system, the intramolecular direct coupling reactions proceeded even when relatively accessible and cheap chloroamides were used as substrates. The reaction of **5o** gave desired coupling product **6a** in 31% yield under the standard conditions (Table 3, Entry 15). By extending the reaction time to 72 h, **6a** could be isolated in 60% yield (Table 3, Entry 16). In addition, chloroamides containing electron-donating (MeO, Me) and electron-withdrawing (Cl) groups also afford the desired cyclization products (Table 3, Entries 17–19). In view of the above-mentioned facts, we affirm that the intramolecular direct coupling reaction of haloamides under catalysis of the oxime palladacycle provides rapid synthesis of benzo[*c*]phenanthridine alkaloids **6a**–**g**.

Table 3. Scope for the arylation of haloamides.[a]



5 **6**

Entry	R^2	Y	Amides	Product	Yield[%][b]
1	H	I	**5a**	**6a**	97
2	4-OMe	I	**5b**	**6b**	90
3	4-Me	I	**5c**	**6c**	95
4	2-Me	I	**5d**	**6d**	89
5	4-Cl	I	**5e**	**6e**	92
6	4-CF_3	I	**5f**	**6f**	89
7	4-NO_2	I	**5g**	**6g**	88
8	H	Br	**5h**	**6a**	93
9	4-OMe	Br	**5i**	**6b**	82
10	4-Me	Br	**5j**	**6c**	88
11	2-Me	Br	**5k**	**6d**	84
12	4-Cl	Br	**5l**	**6e**	89
13	4-CF_3	Br	**5m**	**6f**	85
14	4-NO_2	Br	**5n**	**6g**	75
15	H	Cl	**5o**	**6a**	31
16	H	Cl	**5o**	**6a**	60[c]
17	4-OMe	Cl	**5p**	**6b**	50[c]
18	4-Me	Cl	**5q**	**6c**	32[c]
19	4-Cl	Cl	**5r**	**6e**	18[c]

[a] Conditions: Amide **5** (1 mmol), cat. **1** (5 mol-%), K_2CO_3 (1.5 mmol), DMA (5 mL), 24 h. [b] Isolated yield after column chromatography. [c] Yield was measured after 72 h.

Conclusions

In summary, we have developed a phosphane-free method for the direct arylation coupling reaction by employing an oxime-derived palladacycle catalyst. The new catalyst system is applicable for the 2-arylation of benzothiazole by using aryl bromides and iodides. In addition, this method is especially suitable for the intramolecular direct coupling of bromo- and iodoamides, as well as chloroamides, to achieve the rapid synthesis of benzo[*c*]phenanthridine alkaloids.

Experimental Section

Representative Procedure for the 2-Arylation of Benzothiazole: Under an argon atmosphere at room temperature, a glass tube was charged with benzothiazole (**2**; 135.2 mg, 1.0 mmol), iodobenzene (306.0 mg, 1.5 mmol), cat. **1** (14.8 mg, 0.05 mmol), K_2CO_3 (276.5 mg, 1.5 mmol), and DMA (5 mL). The tube was heated at 140 °C for 24 h. After cooling to room temperature, the mixture was passed through a short pad of silica gel (EtOAc). The filtrate was concentrated, and the residue was purified by column chromatography to afford 2-phenylbenzothiazole (**4a**) as a white solid (169.0 mg, 80% yield). M.p. 86–87 °C. IR (KBr): $\tilde{\nu}$ = 1481, 1294, 976, 767, 733, 685, 624, 615 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.13–8.10 (m, 3 H), 7.93 (d, J = 7.8 Hz, 1 H), 7.53–7.50 (m, 4 H), 7.41 (t, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1, 154.1, 135.0, 133.6, 131.0, 129.1, 127.6, 126.4, 125.2, 123.2, 121.7 ppm. MS (ESI): m/z = 234 $[M + Na]^+$, 212 $[M + H]^+$.

Representative Procedure for the Synthesis of Benzo[*c*]phenanthridine Alkaloids: Under an argon atmosphere at room temperature, a glass tube was charged with amide **5a** (337.2 mg, 1.0 mmol), cat. **1** (14.8 mg, 0.05 mmol), K_2CO_3 (276.5 mg, 1.5 mmol), and DMA (5 mL). The tube was heated at 140 °C for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc and then wash with brine. The organic layer was dried with $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography to afford 5-methylphenanthridin-6(5*H*)-one (**6a**) as a white solid (202.9 mg, 97% yield). M.p. 107–108 °C. IR (KBr): $\tilde{\nu}$ = 1648 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, J = 8.0 Hz,1 H), 8.30–8.28 (m, 2 H), 7.77 (t, J = 7.6 Hz, 1 H), 7.61–7.56 (m, 2 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.34 (t, J = 7.7 Hz, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.6, 138.0, 133.5, 132.4, 129.5, 128.9, 127.9, 125.6, 123.2, 122.4, 121.6, 119.3, 115.0, 30.0 ppm. MS (ESI): m/z = 232 $[M + Na]^+$, 210 $[M + H]^+$.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^1H and ^{13}C NMR data.

Acknowledgments

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