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CoPc-catalyzed selective radical arylation of anilines with arylhydrazines for synthesis of 2-aminobiaryls†

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CoPc-catalyzed selective radical arylation of anilines with arylhydrazines to afford 2-aminobiaryls in moderate to good yields is described.

Biaryls have attracted considerable attention in chemical sciences because of their applications in organic synthesis, pharmaceuticals and materials.[1] A well-known method for synthesis of biaryls is the Gomberg–Bachmann reaction (first reported in 1924) using aryldiazonium salts by homolytic aromatic substitution.[2] Since then, many improvements in this reaction have been explored. Importantly, in the past few decades, transition-metal promoted or catalyzed cross-coupling reactions have been discovered, which provide powerful tools for synthesis of biaryls.[3] Along with the rapid progress in transition-metal catalyzed cross-couplings, catalyst controlled radical initiations and their subsequent reactions have gained increasing interest since the 1980s.[4] As radical reactions play a more important role in modern organic synthesis, the development and use of a highly efficient transition-metal catalyzed system has become a valuable field of research.[5]

Arylhydrazines are good radical precursors, as they are easily oxidized by air (O_2) and various other oxidants to yield aryldiazenes (aryldiimides). Aryldiazenes can decompose to generate aryl radicals, which can then be reacted with arenes to afford biaryls. The properties, reactivity and mechanisms of aryl radicals derived from arylhydrazines have been extensively investigated. However, until early 1980s arylhydrazines were not suitable substrates for synthesis of biaryls due to their poor reaction selectivities, low yields and non-catalytic processes.[6] In 1989 the Asensio group reported the reaction of arylhydrazines with alkenes promoted by excess copper(II) salts to afford the arylation products of alkenes.[7] Later, the Taniguchi group developed a $K_4[Fe(CN)_6]$-catalyzed reaction of arylhydrazines and alkenes to give oxyarylation products.[8] More recently, Jiao and co-workers disclosed that the reaction of arylhydrazines and alkenes could yield different products depending on the choice of catalyst.[9] Manganese(III) acetate has also been shown to promote the arylation of arenes, heteroarenes and C60 using arylhydrazines through a radical process to afford (hetero)biaryls and functionalized C60.[10–12] More recently, Heinrich and co-workers reported the reaction of arylhydrazines and anilines to afford 2-aminobiaryls in the presence of MnO_2.[13] 2-Aminobiaryls are key intermediates for synthesis of bestselling fungicides such as Boscalid, Xemium and Fontelis (Fig. 1).[14] Hence, developing new efficient catalytic and selective methods for the synthesis of 2-aminobiaryls is an important goal for both academia and industry.

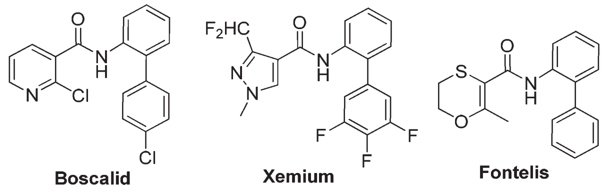

Fig. 1 Structure of fungicides **Boscalid**, **Xemium** and **Fontelis**.

In connection to our research on transition metal-catalyzed and/or promoted radical reactions,[15] this paper presents a novel CoPc-catalyzed,[16] regioselective radical arylation of anilines with arylhydrazines. The initial feasibility studies were performed using phenylhydrazine in benzene with a substoichiometric quantity of transition metal salts in air; consequently, CoPc was selected as the catalyst for further reaction exploration.

Initial feasibility studies were performed using phenylhydrazine in benzene with a substoichiometric quantity of transition metal salts in air (Table 1). Reactions were performed in the presence of different catalysts such as $CoCl_2$,

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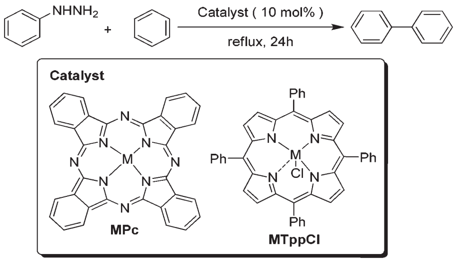
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00798k

Table 1 Catalyst screening[a]

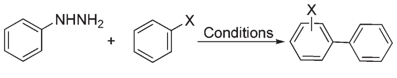


Entry	Catalyst	Yield[b] (%)
1	—	N.D.[c]
2	$CoCl_2$	8
3	$Co(OAc)_2$	10
4	$Co(acac)_3$	11
5	FePc	40
6	CoPc	43
7	CuPc	37
8	MnTppCl	20
9	FeTppCl	25
10	CoTppCl	28

[a] Reaction conditions: phenylhydrazine (1.0 mmol), benzene (5 mL) and catalyst (10 mol%) at reflux for 24 h in air. [b] Isolated yields. [c] The reaction was performed without a catalyst in air. N.D. means not detected.

$Co(OAc)_2$ and $Co(acac)_2$, the expected product biphenyl was obtained albeit in low yields (Table 1, entries 2–4). In the absence of a catalyst no desired product was observed (Table 1, entry 1). We then turned our attention to the use of phthalocyanine metal complexes MPc (M = Fe, Co, Cu), and to our delight, the reaction yields were greatly improved (Table 1, entries 5–7). Using CoPc as the catalyst delivered the desired product in the best yield (43%, Table 1, entry 6). Furthermore, utilization of the related tetraphenylporphyrin metal complexes MTppCl (M = Mn, Fe, Co) for the same reaction gave the products in 20–28% yields (Table 1, entries 8–10). Consequently, CoPc was selected as the catalyst for further reaction exploration. To understand the substrate scope, some substituted benzenes such as toluene, phenol, chlorobenzene and aniline were used for the reaction, the results indicated that aniline is a better substrate (Table 2, entry 4).

Table 2 Substrate screening[a]



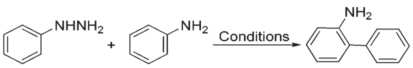
Entry	Solvent	*T* (°C)	Time (h)	Substrate (equiv.)	CoPc (mol%)	Yield[b] (%)
1	CH_3CN	80	24	Toluene (20)	10	Trace
2	CH_3CN	80	24	Phenol (20)	10	Trace
3	CH_3CN	80	24	Chlorobenzene (20)	10	Trace
4	CH_3CN	80	24	Aniline (20)	10	62[c]

[a] Using phenylhydrazine (1.0 mmol) and 10 mL CH_3CN as a solvent for all the reactions. [b] Isolated yield. [c] Mixture of 2-amino- and 4-aminobiphenyl (3 : 1), analyzed by GC.

With an initial promising result in hand, we applied these reaction conditions to the synthesis of 2-aminobiphenyl from phenylhydrazine and aniline. After screening the reaction solvent, temperature, time and catalyst loading (Table 3, entries 1–12), optimal reaction conditions were identified: the reaction of phenylhydrazine (1.0 equiv.) and aniline (10 equiv.) was carried out in the presence of CoPc (10 mol%) in CH_3CN at 80 °C for 24 h (Table 3, entry 9), which afforded 2-aminobiphenyl in 62% yield.

The optimal reaction conditions were then employed for the reaction of a variety of substituted anilines. Anilines with *para*-electron-withdrawing groups such as F, Cl, Br, NO_2 and CN were all tolerated, although a slight drop in yield was noted for **3c–f** (50–55%, Table 4, entries 2–6). In comparison, anilines with *para*-electron-donating groups such as CH_3, OH, OCH_3 and NH_2 showed a marked improvement in the reaction yield, producing the expected biaryl products in good yields (Table 4, entries 7–11). In most cases, the expected 2-aminobiaryls were generated as the sole products although somewhat surprisingly 4-cyanoaniline yielded a mixture of two isomeric products in a 1 : 1 ratio (Table 4, entry 6). To assess the effect of substitution pattern on the regioselectivity of the reaction, anilines with *ortho*- (CH_3, OH, NO_2) and *meta*- (OH and NO_2) substituents were subjected to the reaction conditions (Table 4, entries 12–16). The anilines bearing *ortho*- and *meta*-electron-donating substituents all gave biaryl products in good yields. Unfortunately, these reactions were not regioselective, generating isomeric mixtures (Table 4, entries 12, 13 and 15). In contrast, anilines with *ortho*- and *meta*-electron-withdrawing groups afforded single products **3l** (45%) and **3n** (57%), respectively (Table 4, entries 14 and 16). The results in Table 4 indicate that the phenyl radical generated from phenylhydrazine is electrophilic in nature, hence radical acceptors with high electron density are favored in the arylation reaction.

Table 3 Optimization of the reaction conditions[a]

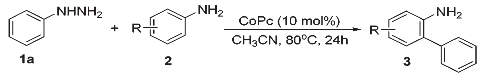


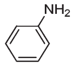
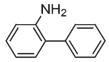
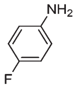
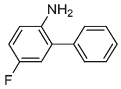
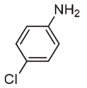
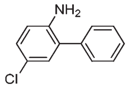
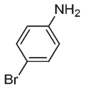
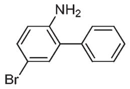
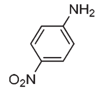
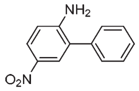
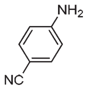
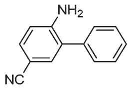
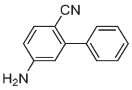
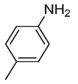
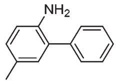
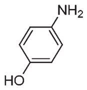
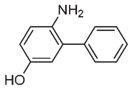
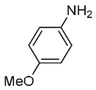
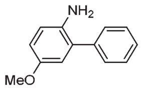
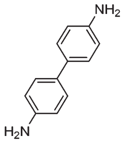
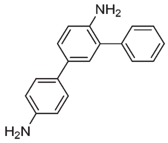
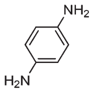
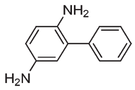
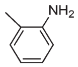
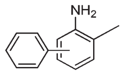
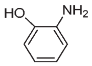
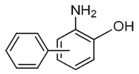
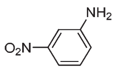
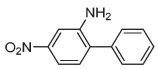
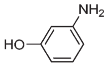
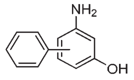
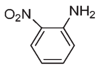
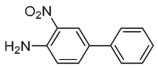
Entry	Solvent	*T* (°C)	Time (h)	Aniline (equiv.)	CoPc (mol%)	Yield[b] (%)
1	CH_3CN	80	24	20	10	62[c]
2	THF	80	24	20	10	50
3	DMSO	80	24	20	10	N.D.[d]
4	AcOH	80	24	20	10	N.D.[d]
5	DMF	80	24	20	10	N.D.[d]
6	CH_3NO_2	80	24	20	10	N.D.[d]
7	CH_3CN	25	24	20	10	20
8	CH_3CN	80	12	20	10	45
9	CH_3CN	80	24	10	10	62[e]
10	CH_3CN	80	24	5	10	38
11	CH_3CN	80	24	10	20	62
12	CH_3CN	80	24	20	5	48

[a] Using phenylhydrazine (1.0 mmol) and 10 mL solvent for all the reactions. [b] Isolated yield. [c] Mixture of 2-amino- and 4-aminobiphenyl (3 : 1), analyzed by GC. [d] Not detected. [e] No 4-aminobiphenyl was isolated.

Subsequently, the effect of substitution on arylhydrazines was probed (Table 5). In general, both the electron-donating group (CH_3) and the electron-withdrawing group (F, Cl and Br) at the *para*-position of the arylhydrazine afforded the expected products in good yields (Table 5, entries 1, 3, 4, 5, 11 and 12). However, 4-methoxyphenyl-hydrazine gave only a trace amount of the corresponding biaryl **3p** (Table 5, entry 2), the reason remained unknown. The reactions of *para*-methyl- and *meta*-methyl-phenylhydrazine with **2i** afforded the corresponding 2-aminobiaryl products in 76% and 70% yield, respectively (Table 5, entries 1 and 12). The *ortho*-methylphenyl-hydrazine on the other hand, led to only a trace amount of the expected product (Table 5, entry 10). It is likely that the *ortho*-substituent in this case has blocked the reaction of the *ortho*-methylphenyl radical with **2i**. In the cases where arylhydrazines

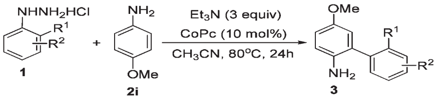
Table 4 Coupling reactions of phenylhydrazine (**1a**) with anilines (**2**)[a]

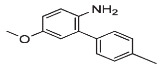
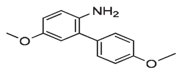
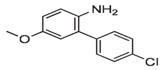
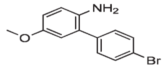
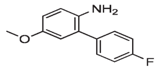
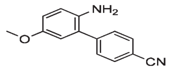
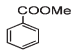
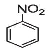
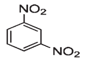
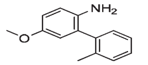
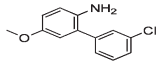
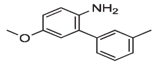
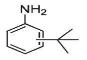


Entry	Aniline	Product	Yield[b] (%)
1			**3a** (62)
2			**3b** (61)
3			**3c** (55)
4			**3d** (53)
5			**3e** (50)
6		 	**3f** : **3f′** = 1 : 1 (50)
7			**3g** (70)
8			**3h** (74)
9			**3i** (77)
10			**3j** (79)
11			**3k** (73)
12			65[c]
13			70[c]
14			**3l** (45)
15			**3m** (70)[c]
16			**3n** (57)

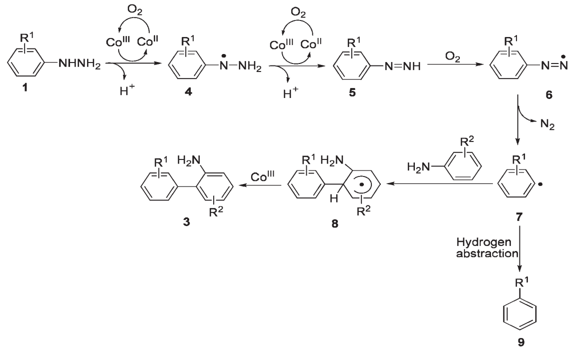
[a] Reaction conditions: **1a** (1.0 mmol), **2** (10 equiv.) and 10 mol% CoPc in CH_3CN (10 mL) at 80 °C for 24 h in air. [b] Isolated yields. [c] Total yield of the mixtures.

Table 5 Coupling reactions of arylhydrazines (**1**) with *p*-anisidine (**2i**)[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	H	4-Me		**3o** (76)
2	H	4-OMe		**3p** (trace)[c]
3	H	4-Cl		**31** (77)
4	H	4-Br		**3r** (78)
5	H	4-F		**3s** (80)
6	H	4-CN		**3t** (trace)[c]
7	H	4-COOMe		85
8	H	4-NO_2		90[d]
9	NO_2	4-NO_2		88
10	CH_3	H		**3u** (trace)[c]
11	H	3-Cl		**3v** (73)
12	H	3-Me		**3w** (73)
13				Trace[c]

[a] Reaction conditions: **1** (1.0 mmol), **2** (10 equiv.) and 10 mol% CoPc in CH_3CN (10 mL) at 80 °C for 24 h in air. [b] Isolated yield. [c] Analyzed by LC-MS. [d] 2-Nitrophenylhydrazine also gave nitrobenzene in 85% yield.



Scheme 1 Proposed mechanism.

bearing a strong electron-withdrawing group (CN, COOMe and NO_2), the aryl radical addition to 4-methoxyaniline (**2i**) did not proceed (Table 5, entries 6–9). Instead, the generated radical had abstracted a hydrogen to form the corresponding arene, the strong electron-withdrawing group may render the aryl radical too reactive to allow the desired process with aniline to proceed. Finally, an alkylhydrazine, *tert*-butylhydrazine hydrochloride, was applied to the reaction but only a trace amount of the expected product was detected (Table 5, entry 13), demonstrating that alkylhydrazines are not suitable precursors for alkyl radical in this process.

A plausible mechanism for the CoPc-catalyzed coupling of arylhydrazines and arylamines is proposed in Scheme 1. The arylhydrazines (**1**) can be oxidized by CoPc to form aryldiazenes (**5**) through consecutive oxidations *via* an intermediate arylhydrazyl radical (**4**). Aryldiazenes (**5**) are easily oxidized to the aryldiazenyl radicals (**6**) by O_2, followed by release of N_2 to generate aryl radicals (**7**). Aryl radicals can selectively add to the *ortho*-position of anilines to form a radical intermediate (**8**), allowing 2-aminobiaryls (**3**) to be formed by oxidation and rearomatization of **8**. On the other hand, radicals (**7**) with strong electron-withdrawing groups (shown to be ineffective substrates in this reaction) can abstract a hydrogen atom to produce arenes (**9**).[9,13]

Conclusions

In conclusion, a new CoPc-catalyzed method for synthesis of 2-aminobiaryls was developed for the reaction of arylhydrazines and anilines. The reaction proceeded under mild conditions in air to afford 2-aminobiaryls in up to 80% yield. As this reaction proceeds through a metal-catalyzed radical process utilizing oxygen as the terminal oxidant, there is no need to add oxidants and additives. A number of 2-aminobiaryls have been synthesized using the developed methodology, most with exquisite selectivity. 2-Aminobiaryls are key intermediates for the synthesis of fungicides, such as Boscalid, Xemium and Fontelis (Trade name), as well as building blocks for liquid crystals, organic electronic devices and conductors, dyes, ligands for metal catalysis and pharmaceuticals. This methodology provides a green and cost-effective method for the efficient preparation of 2-aminobiaryls.

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