



Cobalt-catalyzed oxidative arylmethylation of phosphorylamides

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ABSTRACT

A cobalt-catalyzed strategy for *N*-arylmethylation of phosphorylamides was herein achieved with the assistance of azodiisobutyronitrile as the radical initiator and di-*tert*-butyl peroxide as the oxidant. Both methylenes and diaryl methanes were compatible under the oxidative conditions, expressing broad substrate scope (51 examples) and high efficiency (up to 87% yield).

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1. Introduction

Phosphorylamides [1], which possess -P(O)-N- unit, have been appealing research topic not only because of their unique architecture, but also for the extraordinary pharmaceutical and material properties [2]. Additionally, -P(O)-N-backboned molecules have been elaborately designed for asymmetric syntheses [3], and some biologically active heterocycles have been successfully prepared from the principal intermediates [4]. However, novel methodologies are still highly demanded in the light of diversification requirement which was driven by the nature of screening process. Despite the rapid growth have been witnessed in the field [1–9], the direct modifications of the NH₂ group on the phosphorylamides remained underexploited due to the facile cleavage of P–N bonds [10] and superior stability of their N–H bonds relative to other amides [11], which means the direct *N*-functionalization of the amides has remained a great challenge. Benzylation attracted our attention due to a recent description of a benzylated compound

that can function as a flame retardant (BA-DOPO, Scheme 1) [6b,6c].

Traditional means of benzylic functionalization involving pre-activated substrates suffer from requiring harsh conditions and tedious steps and generating halogenated waste [6,7] among other issues. However, benzylic C–H bonds, which are highly reactive [12], have been directly oxidized to construct different C(sp³)-N bonds because direct functionalization is more environmentally friendly and atom/step economical. Amines [13], amides [14], sulfonamides [14c,15], and sulfoximines [16] can be readily benzylated by straightforward procedures. Based on the previous successfully established arylation [8], methylation (alkylation) [9] of phosphorylamides, we wish to describe our durative studies on benzylation of the same substrates by (di)arylmethanes. Beyond our expectations, simple transferring the conditions of methylation (alkylation) for arylmethylation gave benzylated product in trace amount. Therefore, cobalt catalysts, which were considered cheaper and more environmentally benign, were turned to for the arrival of the useful transformation. Additionally, the oxidative methodology possessed the advantages including high substrate generality and P–N bond reservation under the oxidative conditions.

2. Results and discussions

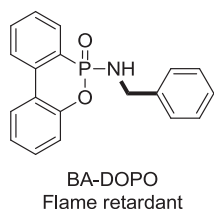
Firstly, the conditions for the reaction between diphenyl

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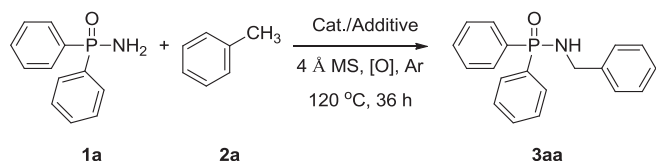
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Scheme 1. Useful *N*-benzyl phosphorylamide.

phosphinamide (**1a**) and toluene (**2a**) were optimized, as shown in Table 1. Under the standard methylation/alkylation conditions, the combination of CuI/1,10-phenanthroline was capable to make the arylmethylation reaction happen in the presence of DCP (dicumyl peroxide) with low efficiency, and **3aa** was detected in trace amount after 36 h at 120 °C (entry 1). Other copper catalysts, such as CuCl and CuBr did not make the reaction occur in the presence of 1,10-phenanthroline under the oxidative conditions (entries 2 and 3). Palladium catalysts, which were exemplified by PdCl₂ and Pd(OAc)₂, failed to offer positive effect to the transformation, and no reaction was detected (entries 4 and 5), either did AgOAc (entry 6). Gratifyingly, iron catalysts in general gave positive performance in the system. Employment of FeCl₂, FeBr₂, FeBr₃ rendered the benzylation of phosphorylamide **1a** take place smoothly, forming the desired product **3aa** in yields from 25% to 28% (entries 7–9). The best performance of the arylmethylation protocol was obtained with the assistance of cobalt-catalysts. And

Table 1
Optimization of the reaction conditions.^a



Entry	Cat.	Additive	[O]	Yield ^b
1	CuI	Phen ^c	DCP	trace
2	CuCl	Phen	DCP	n.d. ^d
3	CuBr	Phen	DCP	n.d.
4	PdCl ₂	Phen	DCP	n.d.
5	Pd(OAc) ₂	Phen	DCP	n.d.
6	AgOAc	Phen	DCP	n.d.
7	FeCl ₂	Phen	DCP	20%
8	FeCl ₃	Phen	DCP	25%
9	FeBr ₃	Phen	DCP	28%
10	CoCl ₂	Phen	DCP	38%
11	CoBr ₂	Phen	DCP	42%
12	NiCl ₂	Phen	DCP	n.d.
13	NiBr ₂	Phen	DCP	n.d.
14	CoBr ₂	TMEDA	DCP	35%
15	CoBr ₂	DMEDA	DCP	32%
16	CoBr ₂	AIBN	DCP	68%
17	CoBr ₂	AIBN	DTBP	82%
18	CoBr ₂	AIBN	TBHP	72%
19	CoBr ₂	AIBN	DTBP	78% ^e
20	—	AIBN	DTBP	n.d.
21	CoBr ₂	AIBN	DTBP	42% ^f

^a Reactions conditions: **1a** (0.3 mmol), **2a** (3.0 mL, ca. 30 mmol), cat. (10 mol%), 4 Å molecular sieves (MS, powdered, 200 wt%), additive (0.2 equiv.), [O] (2.0 equiv.) at 120 °C under argon (1 atm) in a sealed tube for 36 h.

^b Isolated yields.

^c For 1,10-phenanthroline.

^d For not detected.

^e At 140 °C.

^f No 4 Å MS added.

CoBr₂ offered superior effect to CoCl₂ did for higher 42% of **3aa** was isolated in the CoBr₂-mediated system (entries 10 and 11). Disappointingly, NiCl₂ and NiBr₂ failed to provide positive effect to the strategy and no reaction was checked at 120 °C for 36 h (entries 12 and 13). Successive screening on the additives was also conducted. And diamine ligands, for example, tetramethylethylenediamine (TMEDA) and *N,N'*-dimethylethylenediamine (DMEDA) afforded the similar effect to 1,10-phenanthroline did, and 35% and 32% of **3aa** was isolated, respectively (entries 14 and 15). Beyond our expectations, participation of AIBN (azodiisobutyronitrile), which was regarded as the radical initiator generally, dramatically increased the yield of **3aa** up to 68% (entry 16). And replacement of DTBP (di-*tert*-butyl peroxide) with DCP led to higher efficiency of the transformation, and 82% of **3aa** was separated successfully (entry 17). However, TBHP (*tert*-butyl hydroperoxide) gave inferior effect to that DTBP did (entry 18). Elevated temperature (140 °C) did not provide positive effect to the protocol and decreased yield of **3aa** was observed (entry 19). No doubt, no reaction was detected without an addition of the cobalt catalyst to the system (entry 20). Moreover, decreased efficiency of the transformation (42% yield of **3aa**) was observed if the reaction was conducted without addition of 4 Å MS, probably due to the absorption of the H₂O, which was generated in situ under the oxidative conditions (entry 21).

Following the successful establishment of the optimal conditions, the substrate scope and limitations of the phosphonamides were evaluated in the CoBr₂-catalyzed systems (Table 2).

Alkoxy substituted phosphonamides, such as *P*-methoxy-, *P*-ethoxy-, *P*-isopropoxy- and *P*-*n*-butoxy-*P*-phenyl phosphonamides (**1b** – **1e**) coupled efficiently with **2a** in the Co-catalyzed system, and they provided the corresponding *N*-benzyl amides **3ba** – **3ea** in 70%–76% yields. Additionally, *P*-cyclohexyloxy-*P*-phenyl phosphonamide (**1f**) provided **3fa** in 79% yield. In a similar fashion, *P*-methoxyethoxy-*P*-phenyl phosphonamide (**1g**) and *P*-chloropropoxy-*P*-phenyl phosphonamide (**1h**) readily coupled with **2a** and furnished **3ga** and **3ha** in 66% and 69% yields, respectively. (Un)substituted benzyloxy-decorated phosphonamides were also well tolerated in the system. For instance, *P*-benzyloxy-, *P*-(2-fluorobenzyloxy)-, *P*-(4-chlorobenzyloxy)- and *P*-(4-bromobenzyloxy)-*P*-phenyl phosphonamides (**1i** – **1l**) were smoothly benzyloxy-decorated to afford corresponding products in **3ia** – **3la** in yields of 76%–80%. Similarly, the flame retardant BA-DOPO (**3ma**) was also provided in 68% yield by the oxidative protocol.

Furthermore, the scope of methylarenes in the oxidative system was also examined. To our satisfaction, 2-methyltoluene (**2b**), 3-methyltoluene (**2c**), 4-methyltoluene (**2d**) and mesitylene (**2e**) smoothly underwent the phosphorylamidation reaction and provided **3ab** – **3ae** in yields from 82% to 87%. In addition, varying the methyl groups on the methylarenes did not affect the efficiency of the reaction. *p*-*tert*-Butyltoluene (**2f**) and *p*-methoxytoluene (**2g**) were also tolerated, and **3af** and **3ag** were isolated in 80% and 70% yields, respectively. Halogenated toluenes could also serve as benzylating agents for 4-fluoro-, 2-chloro-, 3-chloro-, 4-chloro-, and 4-bromotoluenes (**2h** – **2l**), which easily coupled with **1a** to give **3ah** – **3al** in 72%–87% yields. *p*-Trifluoromethyltoluene (**2m**) and *p*-methylbenzoic methyl ester (**2n**) underwent amidation, and **3am** and **3an** were obtained in moderate yields. Polyarenes 1-methylnaphthalene (**2o**) and 2-methylnaphthalene (**2p**) provided **3ao** and **3ap** in 67% and 62% yields, respectively. However, electron-deficient methylarenes and methylheteroarenes, like 4-nitrotoluene (**2q**), *p*-tolunitrile (**2r**), 2-methylfuran (**2s**) and 2-methylpyridine (**2t**), failed to couple with **1a** under the oxidative reaction conditions. Contrary to our expectations, phosphorylamidation occurred at the benzylic position of ethylbenzene (**2u**) and afforded **3au** in 62% yield.

Encouraged by the broad substrate scope and high efficiency of

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