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# Oxidation−Reduction Condensation of Diazaphosphites for Carbon−Heteroatom Bond Formation Based on Mitsunobu Mechanism

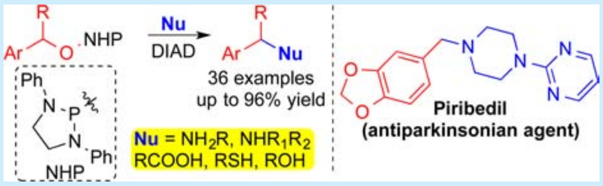
Hai Huang[†,‡] and Jun Yong Kang*[,†]

[†]Department of Chemistry and Biochemistry, University of Nevada Las Vegas, 4505 South Maryland Parkway, Las Vegas, Nevada 89154-4003, United States

[‡]Department of Applied Chemistry, College of Chemistry and Molecular Engineering, Nanjing Tech University, No. 30 Puzhu Road (S), Nanjing 211816, People's Republic of China

*Supporting Information*

**ABSTRACT:** An efficient oxidation−reduction condensation reaction of diazaphosphites with various nonacidic pronucleophiles in the presence of DIAD as a weak oxidant has been developed for carbon−heteroatom bond formation. This mild process affords structurally diverse tertiary amines, secondary amines, esters, ethers, and thioethers in moderate to excellent yields. The selective synthesis of secondary amines from primary amines has been achieved. Importantly, a practical application to the synthesis of antiparkinsonian agent piribedil has been demonstrated.



Because of its synthetic versatility and potential biological properties, benzylamine functionality has been extensively employed in various pharmaceutical products as a significant building block (Figure 1).[1] An impressive amount of pharmaceuticals containing a benzylamine moiety have been developed to improve human health conditions and cure diseases, for example, piribedil (**a**) ($D_2$ and $D_3$ receptor agonist),[2] rivastigmine (**b**) (antiparkinson agent),[3] muraglitazar (**c**) (peroxisome proliferator-activated receptor agonist),[4] and edonentan (**d**) (endothelin receptor antagonist).[5] Accordingly, many efforts have been devoted to the development of efficient methods for constructing benzylamines and their derivatives. Hydroamination of alkenes or alkynes,[6] benzylation of amines with benzyl halides,[7] reductive amination of benzaldehydes,[8] and *N*-benzylation of amines represent widely used protocols.[9] However, these precedent methods have several limitations such as the use of alkyl halide alkylating reagents, expensive transition-metal catalysts, and high reaction temperatures. Thus, the development of efficient and convenient strategies to introduce an amine group into target organic molecules under "mild and neutral" reaction conditions is highly desired, especially in drug discovery fields.

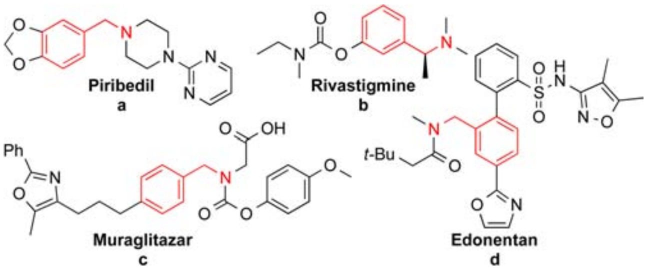


**Figure 1.** Benzylamine-containing biologically active and pharmaceutically important molecules.

Alternatively, the oxidation−reduction condensation reaction of alkoxydiphenylphosphines with acidic nucleophiles using quinones has emerged one of the most powerful synthetic tools for carbon−heteroatom bond formation in organic synthesis due to the mild and neutral reaction conditions[10] since its first report in 1963 by Mukaiyama.[11] This condensation reaction employs weak reductants and oxidants without the addition of acids or bases. Diverse nucleophiles including carboxylic acids,[12] thiols,[13] carbon nucleophiles,[14] phthalimide,[15] and others[16] have been successfully employed in this oxidation−reduction condensation of alkyl phosphinites. Despite a wide range of applicable acidic nucleophiles, biologically and pharmaceutically significant amine pronucleophiles such as piperazine, morpholine, and piperidine are rarely explored as potential nucleophiles in this oxidation−reduction condensation reaction due to the p$K_a$ restriction of pronucleophiles (p$K_a$ < 11).[17] While the Mitsunobu reaction is capable of forming C−O, C−N, C−S, C−X, and C−C bonds, it also faces this p$K_a$ restriction hurdle.[18] In addition, the Mitsunobu reaction generally suffers from generation of stoichiometric amounts of phosphine oxide and hydrazine byproducts, which leads to a laborious purification of the product from these byproducts. Diverse modified reagents and separation techniques are highly desired to achieve facilitated isolation of products in Mitsunobu-type reactions.[19] Therefore, we directed our attention to develop highly nucleophilic alkyl phosphinites **A** for oxidation−reduction condensation reaction using a weak oxidant of azo compound to afford *N*-alkylation of amines (Scheme 1). With the proposed reaction conditions, we

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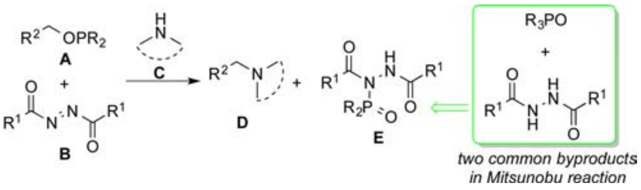
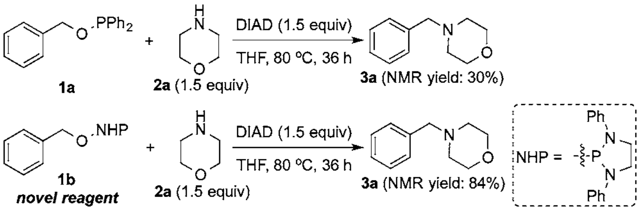
**Scheme 1. Design of Oxidation−Reduction Condensation Reaction Employing Alkyl Phosphinites and Azo Compounds**



hypothesized that the highly nucleophilic phosphinite **A** with azo compound **B** would generate a strongly basic hydrazo anion intermediate that can deprotonate nonacidic nucleophiles **C**. The resulting anionic nucleophile undergoes a substitution reaction with alkoxyphosphonium intermediates to afford alkylated amines **D** and phosphonohydrazines **E** as the sole byproducts, which also have been utilized as potential candidates for novel insecticides and for the synthesis of pharmaceutical compounds containing a P(=O)−N bond.[20] This synthetic transformation would avoid the phosphine oxide and hydrazine byproduct formation common in the traditional Mitsunobu reaction.

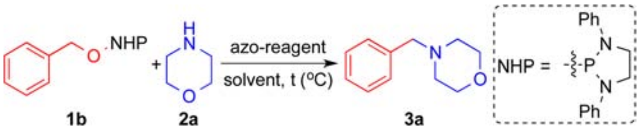
To test our hypothesis, we began with a control experiment employing (benzyloxy)diphenylphosphine **1a**, diisopropyl azodicarboxylate (DIAD) as a weak oxidant, and morpholine **2a** as an amine nucleophile, which provided **3a** with 30% NMR yield (Scheme 2). With this intriguing result as well as the unique properties of cyclic phosphonamide reagents,[21] a highly nucleophilic diazaphosphite **1b** was synthesized to evaluate the hypothesis. The reaction with diazaphosphite **1b** delivered the C−N bond product **3a** in 84% NMR yield under the same reaction conditions, which greatly inspired us to conduct further investigation on this transformation. Herein, we report an efficient oxidation−reduction condensation reaction of diazaphosphites for the synthesis of a variety of carbon−heteroatom (N, O, S) bonds by using DIAD as a weak oxidant.

**Scheme 2. Control Experiment for Evaluating Phosphinite and Diazaphosphite**



Next, we conducted an optimization study of the reaction conditions using the diazaphosphite **1b** as the model reagent (Table 1). First, we screened azo compounds, ADDP and DEAD, commonly used in Mitsunobu reaction. None of them showed a better cooperation with diazaphosphite **1b** than that of DIAD (entries 1−3). Second, the substrate ratio study revealed that a slight excess of morpholine (1.5 equiv) and DIAD (1.5 equiv) is required for maximum conversion (entries 4−6). Importantly, a control experiment in the absence of an azo compound showed no reaction (entry 7), which suggests that this transformation perhaps follows a Mitsunobu-type nucleophilic substitution reaction. Finally, a solvent screening study disclosed that halogenated solvents DCM and DCE are superior to other solvents, providing **3a** in 90% isolated yield (entries 8 and 9).

**Table 1. Optimization of the Reaction Conditions**[a]

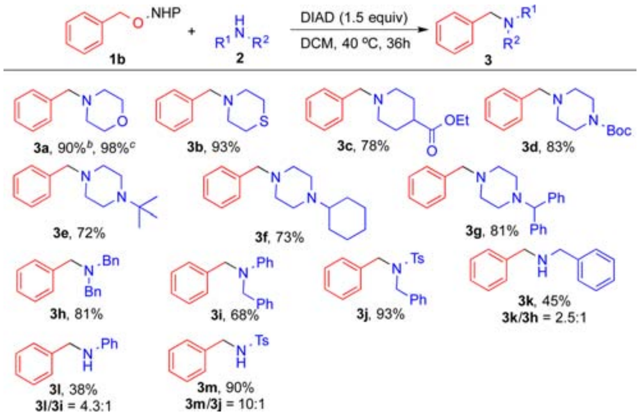


| entry | azo reagents | solvent | ratio of **1a**/**2a**/azo | temp (°C) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | ADDP | THF | 1/1.5/1.1 | 80 | 64 |
| 2 | DEAD | THF | 1/1.5/1.1 | 80 | 74 |
| 3 | DIAD | THF | 1/1.5/1.1 | 80 | 84 |
| 4 | DIAD | THF | 1/2.0/1.1 | 80 | 72 |
| 5 | DIAD | THF | 1/1.5/1.5 | 80 | 88 |
| 6 | DIAD | THF | 1/1.5/2.0 | 80 | 78 |
| 7 |  | THF | 1/1.5/0 | 80 | 0 |
| 8 | DIAD | DCM | 1/1.5/1.5 | 40 | 96(90[c]) |
| 9 | DIAD | DCE | 1/1.5/1.5 | 83 | 99(90[c]) |
| 10 | DIAD | $CHCl_3$ | 1/1.5/1.5 | 61 | 81 |
| 11 | DIAD | ether | 1/1.5/1.5 | 35 | 61 |
| 12 | DIAD | $CH_3CN$ | 1/1.5/1.5 | 81 | 93 |
| 13 | DIAD | ethanol | 1/1.5/1.5 | 78 | 60 |

[a]Reaction conditions: **1b** (0.1 mmol), **2a** (0.15 mmol), and DIAD (0.15 mmol) in solvent (0.5 mL) for 36 h. [b]Yield was determined by crude NMR using 1,3,5-trimethylbenzene as internal standard. [c]Isolated yield (%).

With the optimized reaction conditions established, we first explored the scope of this reaction by treating different amine nucleophiles (Scheme 3). Employing thiomorpholine instead of morpholine, the reaction also provided the corresponding product **3b** with 93% yield. Piperidine generated the desired product **3c** in 78% yield. In addition, piperazines with diverse *N*-substituted groups including Boc, *t*-Bu, cyclohexyl, and benzhydryl were well tolerated and provided the corresponding products **3d**−**g** in good to high yields. Furthermore, acyclic secondary amines, dibenzylamine and *N*-benzylaniline, were also suitable for this reaction to produce the corresponding products **3h** and **3i** in 81% and 68% yields, respectively. We also tested the reactivity of acidic sulfonamide nucleophile **2j** in this reaction, which smoothly furnished the desired product **3j**

**Scheme 3. Scope of Amines**[a]

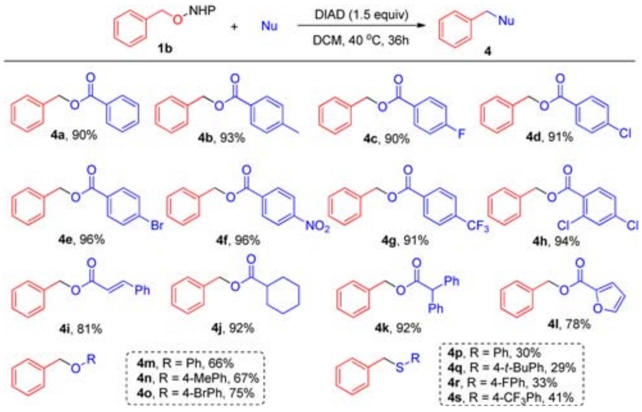


[a]Reaction conditions: **1b** (0.1 mmol), **2** (0.15 mmol), and DIAD (0.15 mmol) in DCM (0.5 mL) at 40 °C for 36 h. [b]Isolated yield (%). [c]Scale-up experiment with 1.0 mmol of **1b**.

in 93% yield. In order to develop an alternative route for the synthesis of secondary amines, we utilized primary amines as nucleophiles in this oxidation−reduction condensation system. Gratifyingly, secondary amine products **3k−m** were successfully isolated in 38%−90% yields with a 2.5:1−10:1 ratio of secondary amine to tertiary amine. Finally, it is noteworthy that a large-scale reaction (1.0 mmol) of **1b** with morpholine provided the corresponding product **3a** with excellent yield (98%).

We also explored the synthesis of diverse esters by employing benzoic acids as nucleophiles (Scheme 4). Benzoic acids with different substituents on a benzene ring provided the desired ester products **4a−h** in excellent yields. Cinnamic acid was also successful in producing the desired ester product **4i** in 81% yield. Aliphatic acids such as cyclohexanecarboxylic acid and 2,2-diphenylacetic acid also afforded the corresponding ester products **4j,k** in 92% yield. A heteroaromatic acid of furan-2-carboxylic acid also efficiently afforded the desired ester product **4l** in 78% yield. Substituted phenols turned out to be suitable substrates in this reaction to generate the corresponding ether products **4m−o** in 66−75% yields. Finally, efforts to achieve thioether synthesis demonstrated that the reaction tolerated a wide range of functional groups on benzene rings with an electron-donating group (*t*-Bu), a halogen (F), and an electron-withdrawing group ($CF_3$). The thioether products **4p−s** were produced in low yields due to the competing reaction of the disulfide formation.[22]

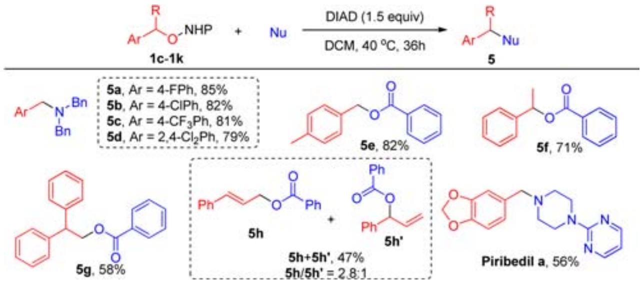
**Scheme 4. Scope of Acidic Nucleophiles**[a]



[a]Reaction conditions: **1b** (0.1 mmol), **Nu** (0.15 mmol), and DIAD (0.15 mmol) in DCM (0.5 mL) at 40 °C for 36 h. [b]Isolated yield (%).

Next, we studied the flexibility of this transformation with different diazaphosphites **1c−k** synthesized on the basis of the previous method (Scheme 5).[21k] Diazaphosphites **1c−g** with various substituents on a benzene ring were efficiently tolerated and provided the corresponding products **5a−e** in good yields. In order to test the steric influence of substituted diazaphosphites on this substitution reaction, α-methyl-substituted benzyloxy diazaphosphite **1h** was employed under the standard reaction conditions, and it afforded the desired product **5f** in 71% yield. A substitution product **5g** from 2,2-diphenylethoxy diazaphosphite **1i** was also isolated in moderate yield (58%). Cinnamyl diazaphosphite provided a mixture of α- and γ-substituted allyl esters **5h** and **5h′** in 47% yield with a ratio of 2.8:1. In addition, a known pharmaceutical, piribedil (**a**) (antiparkinsonian agent), was synthesized successfully with 56% yield.

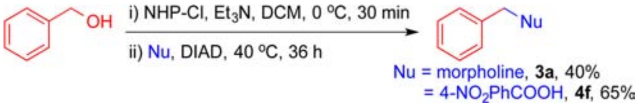
**Scheme 5. Scope of Diazaphosphites**[a]



[a]Reaction conditions: **1b** (0.1 mmol), **Nu** (0.15 mmol), and DIAD (0.15 mmol) in DCM (0.5 mL) at 40 °C for 36 h. [b]Isolated yield (%).

Further, we explored a one-pot synthesis strategy by employing benzyl alcohol as starting material (Scheme 6). This method involved an initial conversion of the alcohol with NHP-Cl to diazaphosphite **1b** in situ, followed by treatment with nucleophiles and DIAD. This one-pot synthesis from benzyl alcohol proved to be a practical procedure and provided the corresponding product in moderate yields. For example, when morpholine was employed, the corresponding product **3a** was isolated in 40% yield. 4-nitrobenzoic acid also provided the desired product **4f** with 65% yield.

**Scheme 6. One-Pot Synthesis from Benzyl Alcohol**



In summary, a new oxidation−reduction condensation reaction of diazaphosphites with nonacidic nucleophiles has been developed for various carbon−heteroatom bond formations. This transformation is the first example that demonstrated the utilization of nonacidic amines as pronucleophiles for the construction of variously substituted benzylamines via a "redox" condensation process. This methodology also features a convenient alternative route to esters, ethers, and thioethers with good to excellent yields. Further, it showcases the selective synthesis of secondary amines directly from primary amines. One-pot synthesis from benzyl alcohol for the carbon−heteroatom bond formation was also demonstrated with moderate yields. Finally, the application of this condensation reaction toward the synthesis of a known pharmaceutical, piribedil, was readily achieved.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03709.

Experimental details (PDF)
Spectral data for all new compounds (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: junyong.kang@unlv.edu.

**ORCID**

Jun Yong Kang: 0000-0002-9732-1454

## Notes

The authors declare no competing financial interest.

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