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# Catalytic Cyclization Reactions of Huisgen Zwitterion with α-Ketoesters by in Situ Chemoselective Phosphine Oxide Reduction

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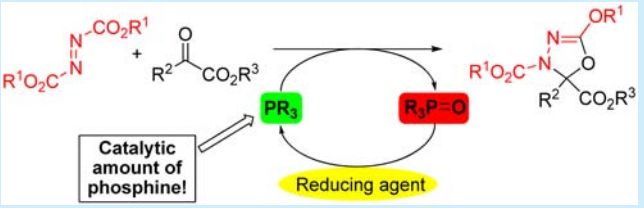
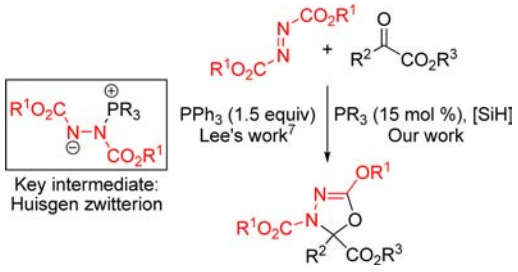
Supporting Information

**ABSTRACT:** The first examples of catalytic cyclization reactions between the Huisgen zwitterion and α-ketoester derivatives are reported. The use of phenylsilane with a substoichiometric amount of bis(*p*-nitrophenyl)phosphate/diisopropylethylamine proved to be crucial for the in situ reduction of the phosphine oxide formed during the reaction. The optimized protocol is applied to alkyl or aryl ketoesters, furnishing either the corresponding cycloadducts or the hydrazone derivatives, depending on the substitution patterns of the substrates, in moderate to good yields (up to 80% yield, 18 examples).




Tertiary phosphines have been widely used in organic chemistry as stoichiometric promoters in numerous reactions.[1] However, the concomitant formation of at least 1 equiv of phosphine oxide reduces the atom economy of these processes. The in situ regeneration of the phosphine represents an ideal way to make these processes catalytic. This strategy aimed at reducing waste[2] and improving atom efficiency has already been successfully applied to the Wittig,[3] Staudinger,[4] and Appel[5] reactions, among others.[6] Herein, we describe a catalytic version of the phosphine-promoted cyclization of diazodicarboxylate with α-ketoesters (Scheme 1).[7] To the best of our knowledge, this work presents the first example of catalytic cyclization reaction involving Huisgen betaine.

**Scheme 1. Stoichiometric Cyclization Reaction and Proposed Work**




The addition of triphenylphosphine to diazenedicarboxylate derivatives to generate the corresponding zwitterion was first observed by Cookson and Locke in 1963,[8] but the correct structure of the adduct was assigned in 1969 by Huisgen.[9] The so-called "Huisgen zwitterion" was found to be the key intermediate of Mitsunobu reactions.[10] It was also demonstrated that this betaine could react with carbonyl compounds,[11] imines,[12] allenes,[13] alkenes,[14] or 2-acylaziridines,[15] giving access to an impressive molecular diversity. If this zwitterion constitutes a potentially useful "three atom synthon" for [3 + 2] annulation reactions, such reactions require the use of at least a stoichiometric amount of phosphine, which is oxidized during the process. We envisioned that the use of an appropriate reduction system would allow the use of substoichiometric amount of phosphine.

The reducing agent has to be chosen very carefully, since it must be compatible with the other chemical functionalities present in the substrates, reaction intermediates, and products.[16] Among the methods for the reduction of phosphine oxide based on metallic species or electroreduction, silanes[17] appeared to us as the more practical and eco-friendly reducing agents. Furthermore, silanes are known to allow chemoselective reduction of phosphine oxides in the presence of aldehydes, ketones, esters, or cyano derivatives.[18] We turned our attention most particularly to the very efficient and chemoselective metal-free reduction of phosphine oxide to phosphine, developed by Beller in 2012,[19a] using diethoxymethylsilane as reducing agent, in the presence of a phosphoric acid bis ester.

We initially examined the effect of phosphine, silane, additives, solvent, and temperature in the catalytic cyclization of diisopropyl azodicarboxylate (DIAD) **1a** with ethyl 2-oxo-4-phenylbutanoate **2a** (Table 1).

We started the optimization of the catalytic reaction by screening different phosphine oxides at 15 mol % loading (Table 1, entries 1−5). With acyclic phosphines such as triphenylphosphine oxide or tributylphosphine oxide, encouraging yields were obtained (entries 1 and 2). As already observed,[20] better yields were obtained with five-membered cyclic phosphines than with acyclic phosphines, indicating that

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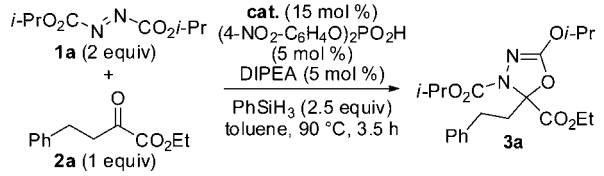
**Table 1. Optimization of the Catalytic Reaction between DIAD and Ethyl 2-Oxo-4-phenylbutanoate**




| entry | cat. | $(ArO)_2PO_2H$ | DIPEA | yield **3a** (%)[a] |
|---|---|---|---|---|
| 1 | $Ph_3PO$ | ✓ | ✓ | 25 |
| 2 | $Bu_3PO$ | ✓ | ✓ | 42 |
| 3 | **4** | ✓ | ✓ | 41 |
| 4 | **5** | ✓ | ✓ | 51 |
| 5 | **6** | ✓ | ✓ | 75 |
| 6[b] | **6** | ✓ | ✓ | 55 |
| 7 | **6** | ✗ | ✗ | 8 |
| 8 | **6** | ✗ | ✓ | 29 |
| 9 | **6** | ✓ | ✗ | 23 |
| 10 | **7** | ✓ | ✓ | 85 (80) |

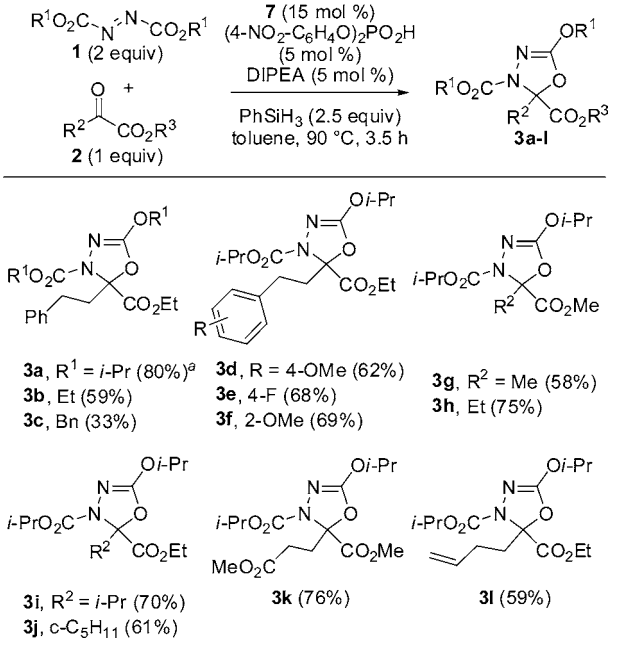
cat. = **4** **5** **6** **7**

[a]Yields determined by $^1$H NMR with trimethoxybenzene as internal standard (yield of isolated compound). [b]10 mol % of catalyst **6** was used.

the rate of reduction of phosphine oxide is crucial. We used phenylphosphane and phenylphospholene oxide derivatives **4** and **5** and obtained the desired compound in 41−51% yields (entries 3 and 4). The best yield was obtained using phenyl dibenzophosphole oxide **6**[21] as catalyst (75% yield, entry 5). Decreasing the catalytic loading to 10 mol % gave a lower yield (entry 6). The additions of both substoichiometric amounts of bis(4-nitrophenyl)phosphate and a tertiary amine such as diisopropylethylamine (DIPEA), in the presence of phosphine and phenylsilane were necessary to obtain good conversion rate (entries 7−9). Without phosphoric acid derivative and base, only 8% yield was obtained (entry 7). If the reaction occurred without acid or base, poor yields of 23−29% were observed (entries 8 and 9). The addition of either 1 equiv of bis(nitrophenyl)phosphate/DIPEA in 1/1 ratio or a preformed phosphate salt $[(ArO)_2PO_2HN\text{-}i\text{-}Pr_2Et]$ gave the product **3a** in comparable yields. Thus, the phosphate was necessary for the phosphine oxide reduction, and the tertiary amine base seems to play a major role by avoiding the protonation of the Huisgen zwitterion. The use of $4\text{-}NO_2C_6H_4CO_2H$[3b] instead of $(4\text{-}NO_2C_6H_4O)_2PO_2H$ as acidic additive did not improve the yield of the reaction. A wide range of silanes was surveyed, including diphenylsilane, diethoxymethylsilane, or TMDS (tetramethyldisiloxane), without improvement in the formation of the cyclization product. Finally, the use of air-stable phenyl dibenzophosphole **7** gave the desired product **3a** in 80% isolated yield (entry 10).[22]

Having established the optimized conditions for the catalytic reaction involving the Huisgen zwitterion with $\alpha$-ketoester derivatives, we surveyed the substrate scope of the reaction (Scheme 2). Ethyl 2-oxo-4-phenylbutanoate **2a**, in the presence of both diisopropyl, diethyl, or dibenzyl azodicarboxylate **1**, gave the corresponding products **3a−c** in 33−80% isolated yields. In the following experiments, the use of DIAD with variously substituted 2-alkyl ketoesters furnished the desired highly functionalized 2,3-dihydro-1,3,4-oxadiazole derivatives

**Scheme 2. Scope of the Catalytic Cyclization Reaction**




[a]Yields of isolated compounds.

**3d−l** in good yields (58−76%). As shown in Scheme 2, the catalytic cyclization reaction proceeded smoothly with products **3d−f**, substituted with electron-withdrawing or electron-donating groups at *para*- or *ortho*-position of the benzene ring. More sterically demanding groups such as isopropyl or cyclopentyl gave compounds **3i,j** in good yields (61−70%). The use of substrates containing ester or olefin functions afforded the products **3k,l** in 59−76% yields, demonstrating the high chemoselectivity of the reduction of phosphine oxide **6** to the trivalent phosphine **7**.

We then explored the possibility of applying the catalytic approach to the cyclization of 2-oxo-2-arylacetates (Table 2). In this case, after 5 h in toluene at 90 °C, we did not observe the formation of cycloadduct **3**, but the *N*,*N*-dicarboxylate hydrazones **9a−d** appeared in moderate to good yields (entries 1−4). The formation of these hydrazone derivatives has been already observed by Shi, with the use of acyl cyanide and aryl trifluoroethanone.[11f] Here, the electronic properties of substrates played an important role in the reaction outcome. A poor yield of 36% was obtained with the methoxy-substituted substrate (entry 3), whereas we observed an increase of the catalytic activity with the use of electron-withdrawing groups (R′ = CN, 66% yield, entry 4). *N*-Methylisatin reacted similarly with the Huisgen betaines, giving hydrazones **9e,f** in 52−64% yields (entries 5 and 6).

Concerning the reaction mechanisms (Scheme 3), we can postulate that after the addition of the phosphine to the diazene substrate **1** the corresponding betaine adds on the carbonyl of the ketone **2** to form the five-membered intermediate **A**. At this stage, divergent pathways could be proposed, depending of the substitution pattern of the substrate. In the case of alkyl ketoesters, the cyclized products **3** are obtained after an intramolecular nucleophilic substitution process of the intermediate **B**, with concomitant release of phosphine oxide. With the use of aryl ketoesters, the intermediate could rearrange to *N*,*N*-dicarboxylate hydrazones **9** via migration of the carboethoxy group.[11f]



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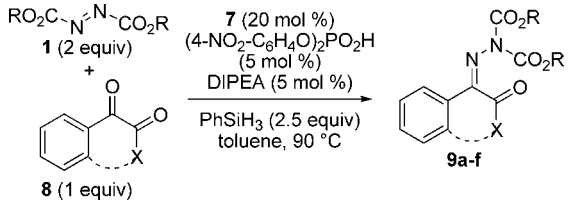
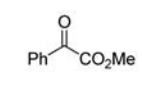
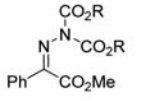
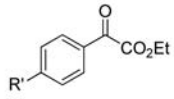
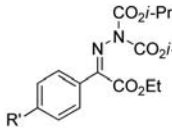
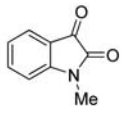
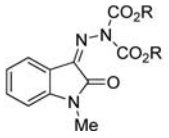
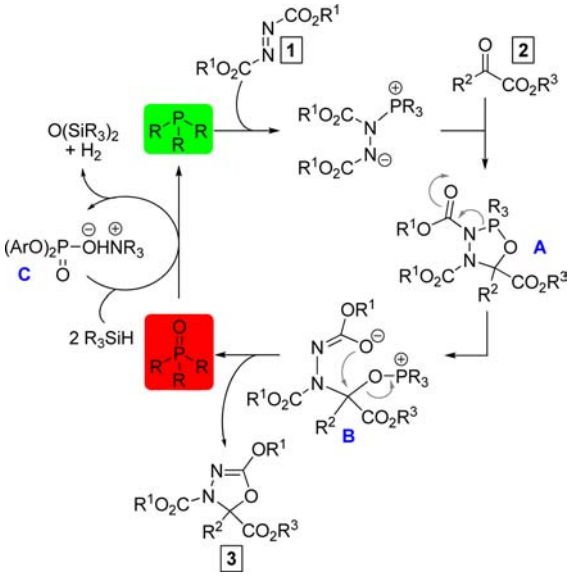
**Table 2. Use of 2-Oxo-2-arylacetate and *N*-Methylisatin Substrates**




| entry | R | substrate **1** | product **9a-e** | yield (%)[a] |
|---|---|---|---|---|
| 1 | *i*-Pr |  |  | **9a**, 64 |
| 2 | Et | | | **9b**, 54 |
| 3 | *i*-Pr |  |  | R' = OMe **9c**, 36 |
| 4 | *i*-Pr | | | R' = CN **9d**, 66 |
| 5 | *i*-Pr |  |  | **9e**, 64 |
| 6 | Et | | | **9f**, 52 |

[a]Yields of isolated compounds.

**Scheme 3. Proposed Mechanism for the Cyclization Reaction and the Reduction of Phosphine Oxide**




Concerning the mechanism of reduction of the phosphine oxide to phosphine with the reductive system silane/phosphate/amine, and inspired by the work of Beller,[19a] the mechanism could be proposed as follows (Scheme 3). The phosphate−amine salt **C** reacts with phenysilane to form a phosphasilane intermediate. The latter could act as a bifunctional catalyst, which activates both the silane and the phosphine oxide. After reduction of the phosphine oxide to trivalent phosphine, the formation of disiloxane $[O(SiR_3)_2]$ was observed, with the regeneration of phosphate salt **C**. This mechanism could explain why the use of at least 2 equiv of silane is necessary.

This work presents the first catalytic cyclization reactions between the Huisgen zwitterion and carbonyl substrates by in situ recycling of the phosphine oxide. This proves the feasibility of such a process, and these results will allow us to envisage an extension in other phosphine-promoted reactions. We are currently investigating the catalytic reaction of the Huisgen zwitterion with allenes, imines, and olefins, specifically working to develop asymmetric variants of these reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(21) For the use of phenyl dibenzophosphole in the catalytic Appel reaction, see ref 5a. In the reaction conditions of Table 1, entry 5, when the reaction is run without phosphine or phosphine oxide, no reaction occurred.
(22) The practicability of the protocol was further demonstrated by a 1-mmol-scale synthesis of product **3a**. The desired product was obtained in 79% isolated yield (310 mg). After purification on silica gel, recovery of the phosphine **7** was possible.



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