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Letter

Phosphine-Catalyzed Dearomative [3 + 2] Cycloaddition of Benzoxazoles with a Cyclopropenone

Xingben Wang, Congjun Yu, Iuliana L. Atodiresei, and Frederic W. Patureau*

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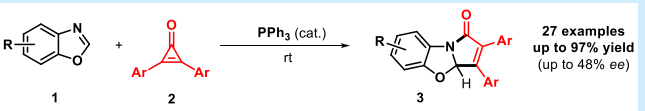
ABSTRACT: The triphenylphosphine-catalyzed dearomative [3 + 2] cycloaddition of benzoxazoles with 1,2-diphenylcyclopropenone is herein described. The reaction scope, mechanism, and possible future applications of this rare organocatalyzed cycloaddition are herein discussed.



"[···] The cyclopropenone system must have strong resonance stabilization indeed to compensate for its high angle strain." So did Breslow and his team express their surprise at the unexpected relative stability of 1,2-diphenylcyclopropenone (1959).[1]

The activation of C−C bonds is a powerful concept for the reorganization or coupling of organic scaffolds, yet it is a relatively challenging process to achieve in the context of synthetic methodology because of their inherent stability.[2] In order to enable such methods, one can use C−C-strained, often cyclic, building blocks that are consequently spring loaded for C−C bond activation.[3] In this context, 1,2-diphenylcyclopropenone, a particularly strained cyclic substance known since the late 1950s,[1] is currently witnessing a spectacular rebirth in the context of synthetic method developments that rely on C−C bond activation. Even though its highly strained structure makes it an ideal building block for C−C bond activation, it usually still requires a precious metal salt as catalyst.[4−7] Because 1,2-diphenylcyclopropenone is a particularly versatile building block for organic coupling reactions, yielding both open and (poly)cyclic complex skeletons (Scheme 1, eqs 1−4), its activation with more trivial and less onerous (organo)catalysts would constitute an important objective for rendering such methods sustainable and practical.[8] We propose herein such a method with the simple triphenylphosphine-catalyzed[9] dearomative [3 + 2] cycloaddition of benzoxazoles with 1,2-diphenylcyclopropenone.

Prescher and co-workers recently utilized a triphenylphosphine organocatalyst in order to elegantly ring open 1,2-diphenylcyclopropenone with amines (Scheme 1, eq 4).[8] We therefore reasoned that other highly important coupling partners, such as benzoxazoles, might intercept the cyclopropenone ring opening under simple phosphine catalysis, leading to unprecedented fused poly-heterocyclic rings.

We commenced our study by engaging 1,2-diphenylcyclopropenone **2a** in the presence of an excess of test substrate benzoxazole **1a** and triphenylphosphine (PPh_3, 12.5 mol %, 1:8 ratio) in chloroform at 25 °C for 15 h. This afforded a new dearomatized polycyclic substance **3aa** in impressive 96% isolated yield (Table 1, entry 1). This particular scaffold, a benzopyrrolo-oxazolone, is relevant, as similar structures are found at the core of several bioactive substances of interest (Scheme 1).[10] Its direct synthesis from trivial building blocks such as presented here would therefore represent a significant advancement for the field. No conversion was observed in the absence of the PPh_3 catalyst (Table 1, entry 2) nor with bulkier phosphines such as BINAP (Table 1, entry 3). This is an important result because PPh_3 is by far the cheapest triarylphosphine available. No other solvents performed any better than chloroform (entries 4−7), nor any other relative ratio between the coupling partners (entries 8−10).

With these simple reaction conditions in hand, we then investigated the reaction scope with various benzoxazoles (Scheme 2). First, we tested C5-substituted benzoxazole substrates. Electron-neutral (**3ba**) and electron-donating (**3aa**, **3fa**, **3ga**, **3ha**) functional groups afforded the corresponding benzopyrrolo-oxazolone coupling products in excellent yields (88−97%). Although electron-withdrawing substituents performed somewhat less well at 25 °C (**3ca**−**3ea**), increasing the reaction temperature to 70 °C afforded promising yields (56−60%). Next, C6-substitution was also explored (**3ja**−**3ma**), as well as C7 (**3pa**, **3qa**) with promising to excellent yields. Di- and trisubstituted benzoxazole structures (**3na**, **3oa**, **3ra**−**3ua**) as well as bulky C4-substitutents were likewise well tolerated (**3ga**, **3ha**), with 97 and 96% yields, respectively. Interestingly, even fused or alternatively tethered *di*benzoxazole substrates were found applicable, yielding the corresponding single coupling cycloaddition products (**3va**−**3za**) in 22−60% yields. Moreover, the

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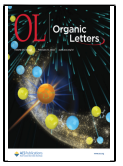

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Scheme 1. Selected Couplings with Cyclopropenones

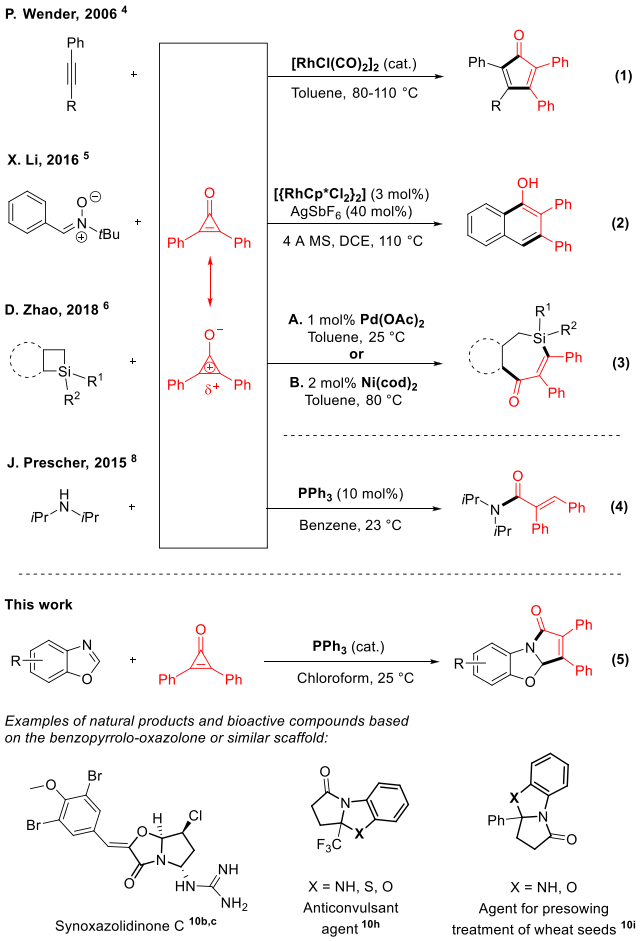
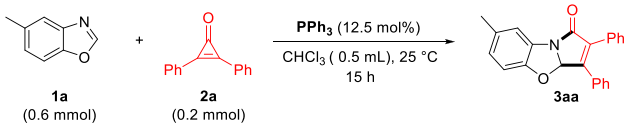


Table 1. Optimization Table[a]



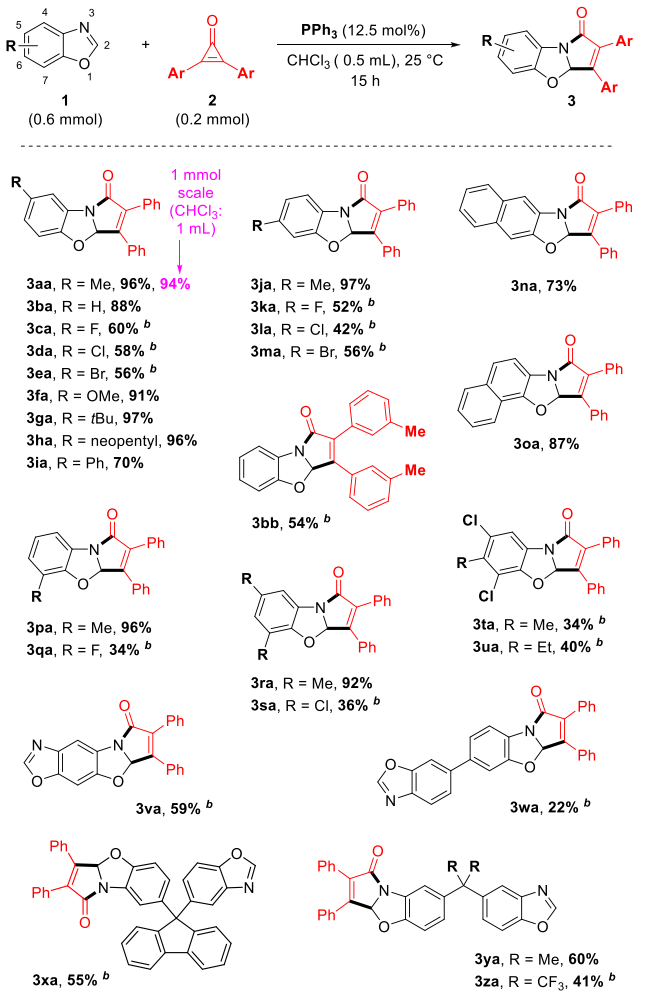
entry	variations from standard conditions[a]	yield (%)[b] of **3aa**
1	**none**	**97 (96)**[c]
2	without PPh_3	NR
3	BINAP instead of PPh_3	NR
4	toluene instead of $CHCl_3$	60
5	DCM instead of $CHCl_3$	78
6	EtOAc instead of $CHCl_3$	64
7	$CDCl_3$ instead of $CHCl_3$	93
8	1 equiv of **1a**	46
9	2 equiv of **1a**	82
10	0.2 mmol **1a** and 2 equiv of **2a**	20

[a]Unless otherwise noted, the standard reaction conditions were as follows: **1a** (0.6 mmol), **2a** (0.2 mmol), solvent (0.5 mL). [b]The yield was determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield.

1,2-diphenylcyclopropen-3-one **2a** could be replaced with a different cyclopropenone **2b** (product **3bb**).

In order to demonstrate the practicality of our reaction, a 1 mmol scale batch was conducted for product **3aa**. This product was thus obtained in remarkably preserved 94% isolated yield

Scheme 2. Scope, Isolated Yields[a]



[a]All reactions were carried out on a 0.2 mmol scale for 15 h under the standard conditions. [b]The reaction was carried out at 70 °C.

(320 mg) in moreover only 1 mL of chloroform. In addition, the X-ray diffraction analysis of product **3ca** confirmed the structural interpretation, in particular its fused cyclic nature (Figure 1).

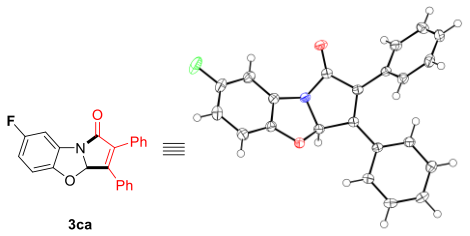


Figure 1. X-ray structure of product **3ca** (CCDC: 2093753), ORTEP view,[11] 50% probability level.

Based on some literature precedents,[12] we assume that the phosphine organocatalyst activates the strained and electrophilic cyclopropenone to form zwitterionic intermediate **I**, which would then progress to ketene ylide intermediate **II** (Scheme 3). The latter species would then undergo a nucleophilic dearomative attack from the benzoxazole coupling partner to generate intermediate **III**. This would rapidly cyclize

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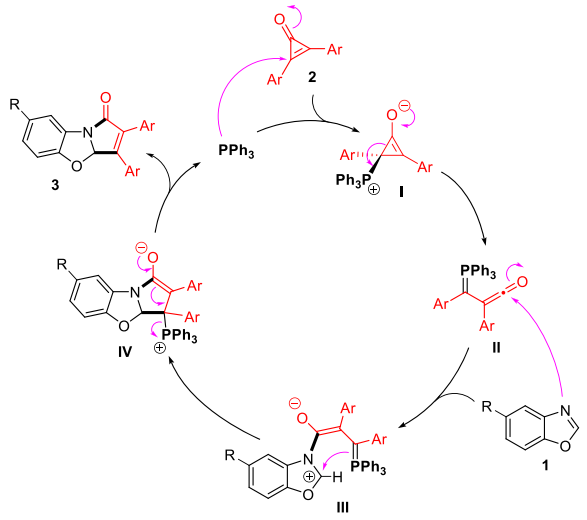
Scheme 3. Proposed Mechanism



to form the second C−C bond toward intermediate **IV**. Phosphine elimination would then regenerate the organocatalyst, releasing coupling product **3**.

In order to further investigate this mechanism, we then performed some key ^{31}P NMR experiments (Figure 2).

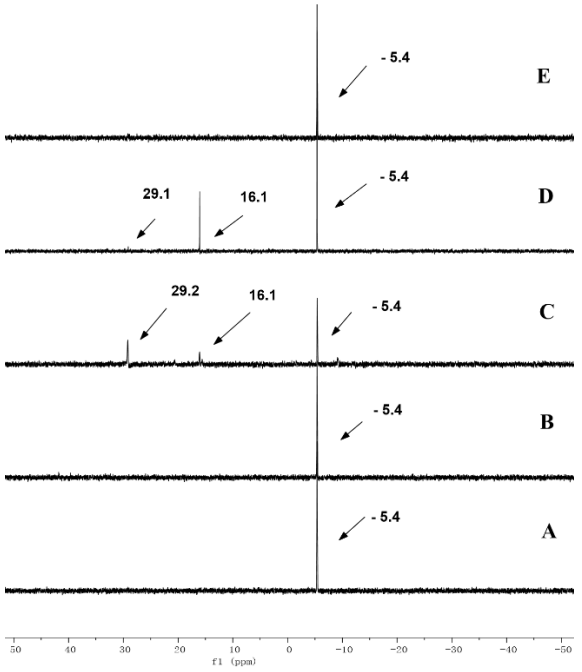
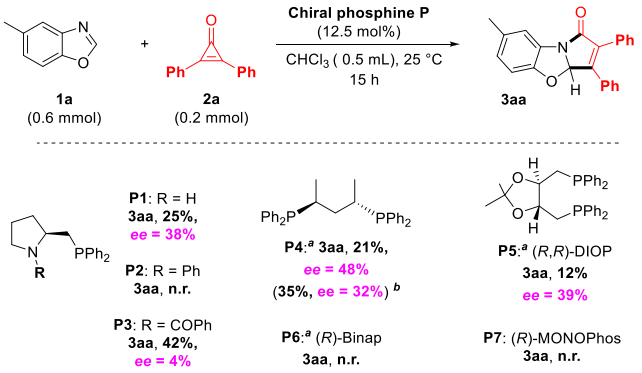


Figure 2. Comparison of the ^{31}P NMR spectra of (A) only PPh_3 in $CDCl_3$; (B) PPh_3 and **1a** (1:24); (C) PPh_3 and **2a** (1:8); (D) PPh_3, **1a**, and **2a** (1:24:8); (E) PPh_3, **1a** and **2a** (1:24:8) after the mixture was stirred for 15 h.

Experiment A shows that the ^{31}P NMR signal of PPh_3 shifts at −5.4 ppm in $CDCl_3$, a solvent which we know accommodates the reaction well (Table 1, entry 7). The addition of benzoxazole **1a** does not alter this signal, even in large excess (24 equiv, experiment B). However, the addition of strained electrophilic cyclopropenone **2a** (8 equiv) leads to the appearance of two new signals at +16.1 and +29.2 ppm, presumably corresponding to two new species (experiment C). One or both might correspond to intermediates **I** and/or **II**, as the observed chemical shifts are compatible. If one adds to this 24 equiv of benzoxazole **1a**, the signal at +29.1 ppm disappears (experiment D), demonstrating that this particular species is probably a productive intermediate of the reaction. If one stirs this mixture for another 15 h, only the PPh_3 signal remains (−5.4 ppm, experiment E), thus demonstrating the intermediacy of the noted signals in experiments C and D as well as the catalytic role of the phosphine.

Finally, because of the envisaged mechanism involving a very rigid and covalent proximity of the catalyst to the reaction sites in intermediates **II** and **III** (Scheme 3), it occurred to us that an optically active phosphine might render the reaction enantioselective.[13] In order to explore this possibility, we screened a series of commercially available chiral and optically active phosphines (phosphines **P1**−**P7**, Scheme 4). Unfortunately, none performed with an enantiomeric excess above 48% for product **3aa** (chiral phosphine **P4**) in moreover moderate yields. While we could not improve these results so far, these at least demonstrate the feasibility of an enantioselective version of this organocatalyzed synthetic method. We are currently designing and synthetizing new chiral phosphines in order to achieve this objective.

Scheme 4. Action of Optically Active Phosphine Catalysts



[a]For the diphosphines, a catalytic loading of 6.25 mol % was utilized, thus giving a 1:16 ratio versus substrate **2a**. [b]Control run under strict argon atmosphere.

In conclusion, we have developed a triphenylphosphine organocatalyzed dearomative [3 + 2] cycloaddition of benzoxazoles with 1,2-diphenylcyclopropenone. The cyclic and fused nature of the coupling product was confirmed by X-ray crystallography. Moreover, a mechanistic investigation was conducted with ^{31}P NMR, leading to important insights regarding the existence of phosphorus based catalytic intermediates. This contribution should encourage the further development of organocatalyzed C−C bond activation coupling methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c04045.

Experimental procedures, characterization, and NMR spectra of new compounds (PDF)

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Accession Codes

CCDC 2093753 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Frederic W. Patureau − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany;* orcid.org/0000-0002-4693-7240; Email: frederic.patureau@rwth-aachen.de

Authors

Xingben Wang − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany*

Congjun Yu − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany*

Iuliana L. Atodiresei − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c04045

Notes

The authors declare no competing financial interest.

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