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Copper-Catalyzed Decarboxylative Hydrophosphinylation of α-Acyl-α-Diazoacetates

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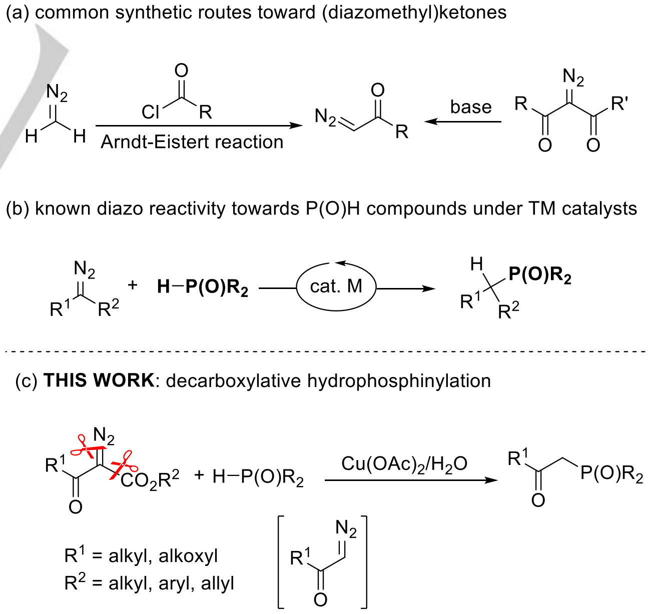
Abstract: A simple copper-catalyzed decarboxylation-denitrogenation C–P coupling reaction of α-acyl-α-diazoacetates with hydrophosphoryl compounds is reported. The reaction may proceed *via* a process involving the generation of (diazomethyl)ketones after hydrolysis in the presence of water and the hydrophosphinylation of the copper carbene intermediates. This finding may suggest the potential use of the relatively more readily available α-acyl-α-diazoacetates as replacement of (diazomethyl)ketones in some cases.

Diazo compounds represent an important class of highly reactive synthetic intermediates frequently used in organic synthesis.[1] However, most diazo compounds are known to be hazardous chemicals with relatively low stability and explosive property.[1,2] Thus, there is a continuous effort on the search for new and safer surrogates to replace the commonly used unstable diazo compounds,[3,4] and alternatively, the development of new methods and technologies that allow for safer preparation and use of these compounds.[5] However, the drawbacks remain. The use of (diazomethyl)ketones is such a case in point. These compounds are usually prepared from the well-known Arndt−Eistert reaction, namely, a reaction of an acyl chloride or mixed anhydride with an excess of the most hazardous and explosive diazomethane (Scheme 1a, left).[6] A much safer protocol might be the deformylative diazo transfer reaction, originally developed by Wolf and Yates,[7] through alkali treatment of diazo-diketone derivatives (Scheme 1a, right). The improved variation of the protocol offered by Danheiser using a one-pot trifluoroacetyl activation and diazo transfer procedure further expands the scope of the method to allow for the synthesis of vinyl α-diazoketones.[8] But regardless, alternative protocols for generation and use of these compounds remain highly desirable.

During our recent study on new synthetic methods towards organophosphorus compounds,[9, 10] we came to consider that the relatively more available and stable α-acyl-α-diazoacetates may undergo hydrolysis under suitable conditions to in-situ form terminal diazoketones, which would be captured by H-heteroatom compounds upon transition metal catalysis leading to α-functionalized ketones *via* the formation of C-heteroatom bond.[11] Accordingly, α-acyl-α-diazoacetates may be regarded as convenient precursors of some labile (diazomethyl)ketones.[12] Along this line and in keeping with our interest in C–P bond formation process,[10] we disclose herein for the first time a new Cu-catalyzed decarboxylative hydrophosphinylation reaction of α-acyl-α-diazoacetates with hydrophosphoryl compounds, leading to the formation of α-phosphinyl ketones (Scheme 1c).[13] It is noted that the transition-metal (TM) catalyzed hydrophosphinylation reaction of diazo compounds has been studied to some extent.[14] Nevertheless, most of the reactions proceed through the P(O)–H insertion into the metal-carbene intermediates, thus resulting in the normal denitrogenative C–P coupling products (Scheme 1b). To the best of our knowledge, such a decarboxylative hydrophosphinylation process has not been reported. In addition, although recent reports have already shown a wide range of new transformations for the synthesis of α-phosphinyl arylketones, alkyl-substituted products (R^1 = Alkyl group, Scheme 1c) have been seldom obtained with these methods.[13]


(a) common synthetic routes toward (diazomethyl)ketones

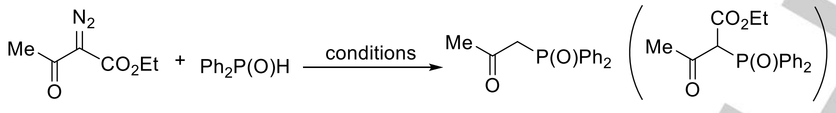
(b) known diazo reactivity towards P(O)H compounds under TM catalysts

(c) **THIS WORK**: decarboxylative hydrophosphinylation

R^1 = alkyl, alkoxyl
R^2 = alkyl, aryl, allyl

Scheme 1. The decarboxylative hydrophosphinylation of α-acyl-α-diazoacetates.

Table 1. Optimization on the copper-catalyzed reaction of **1a** and **2a.**[a]



1a **2a** **3a** **4a**

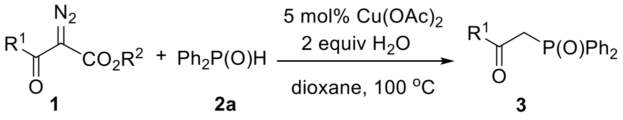
Entry	Catalyst	Solvent	Additive	**3a** (yield%)[b]	**4a** (yield%)[b]
1	$CuSO_4$	dioxane	K_2CO_3	-	-
2	$CuSO_4$	dioxane	K_2CO_3[c]	-	-
3	$CuSO_4$	dioxane	NaOH	-	trace
4	$CuSO_4$	dioxane	H_2O	59	-
5	$Cu(OAc)_2$	dioxane	H_2O	75	-
6	$CuCl_2$	dioxane	H_2O	74	-
7	CuI	dioxane	H_2O	44	-
8	$Cu(MeCN)_4PF_6$	dioxane	H_2O	54	-
9	$Cu(OAc)_2$	THF	H_2O	74	-
10	$Cu(OAc)_2$	toluene	H_2O	43	20
11	$Cu(OAc)_2$	DCE	H_2O	42	16
12	$Cu(OAc)_2$	MeCN	H_2O	50	trace
13[d]	$Cu(OAc)_2$	EtOH	H_2O	-	-
14	$Cu(OAc)_2$	dioxane	H_2O[e]	72	-
15	$Cu(OAc)_2$	H_2O		-	-

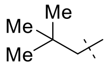
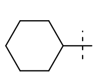
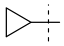
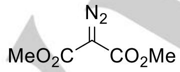
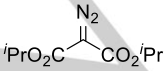
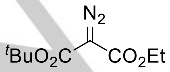
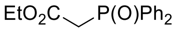
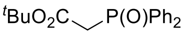
[a] Unless otherwise noted, a mixture of **1a** (0.2 mmol), **2a** (1.2 equiv), [Cu] (5 mol%), solvent (1 mL) and additive (2 equiv) was heated in a Schlenk tube under N_2. [b] Isolated yields. [c] 2 equiv of H_2O were added. [d] ethyl diphenylphosphinate was obtained as the product. [e] 8 equiv of H_2O.

α-Acyl-α-diazoacetates are isolated stabilized diazo compounds, and can be readily obtained from acylacetic esters *via* a diazo transfer reaction using sulfonyl azide reagents.[15] We initially chose α-acetyl-α-diazoacetate (**1a**) and diphenylphosphine oxide (**2a**) as model substrates to examine the reaction under various conditions. We questioned if the presence of an inorganic base would trigger the occurring of the decarboxylation process. However, the experiments showed that the use of inorganic bases such as NaOH and K_2CO_3 were incompatible with the copper-catalyzed conditions (Table 1, entries 1-3).[16] Interestingly, when two equivalents of water were added instead, the reaction gave rise to **3a** in 59% yield efficiently in the presence of 5 mol% $CuSO_4$ (Table 1, entry 4). With these encouraging results, we then examined the catalytic activity of other bench-available copper catalysts in the presence of water. The reaction catalyzed by $Cu(OAc)_2$ and $CuCl_2$ gave the product **3a** in much better the yields (Table 1, entries 5 and 6). However, copper(I) salts such as CuI and $Cu(MeCN)_4PF_6$ were proven less effective and gave **3a** in moderate yields (Table 1, entries 7 and 8). Particularly, a considerable amount of unknown precipitate was observed in the reaction using CuI as the catalyst. Furthermore, the transformation appears to be solvent-dependent. The reaction performed in THF gave **3a** in a similar yield (Table 1, entry 9), whereas the reactions in other solvents including toluene, DCE and MeCN gave a mixture of **3a** and **4a** (Table 1, entries 10-12). When EtOH was used as a solvent, no C–P coupled product was detected, but ethyl diphenylphosphinate was obtained as the major product (Table 1, entry 13). In addition, the expected product was not formed either, when water was used as a solvent. This was attributed to the fact that the copper catalyst decomposed as the formation of bronze copper metal was observed in the reaction (Table 1, entry 15). Therefore, the best result was obtained when dioxane was used as the solvent; a clean transformation was achieved, and **3a** was obtained in 75% yield (Table 1, entry 5).

Table 2 summarized the results of the $Cu(OAc)_2$-catalyzed decarboxylative hydrophosphinylation reactions of a variety of α-acyl-α-diazoacetates with diphenylphosphine oxide (**2a**) under the optimal conditions. First, a series of different alcohol-derived α-acetyl-α-diazoacetates **1a**-**1e** served as good precursors for the reaction, giving rise to the expected product **3a** in good to high yields (entries 1-5). Amongst, 4-bromobenzyl α-acetyl-α-diazoacetate **1e** showed a relatively higher reactivity, and the reaction proceeded more efficiently and completed in 1 h to give **3a** in 71% yield, probably due to the ease of hydrolysis of the 4-bromobenzyl group. Notably, *p*-tolyl α-acetyl-α-diazoacetate (**1f**) also participated well in the reaction although a somewhat lower yield was obtained (entry 6). Other α-acyl-α-diazoacetates by varying the substituent R^1 (**1g**: n-Bu, **1h**: Bn, **1i**: neopentyl, **1j**: cyclohexyl, and **1k**: cyclopropyl) were also synthesized, and subjected to reaction with **2a** under the optimal conditions. The corresponding products **3b**-**3f** were all effieciently generated in good to high yields (entries 7-11). In addition, dimethyl 2-diazomalonate **1l** and diisopropyl 2-diazomalonate **1m** were also suitable substrates for this transformation, delivering the products **3g** and **3h** in 70% and 83% yields, respectively. When an asymmetric diazomalonate **1n** was employed, a mixture of products **3i** and **3j** were formed as expected (entry 14).

Table 2. The reaction scope with respect to diazodicarbonyl compounds[a]

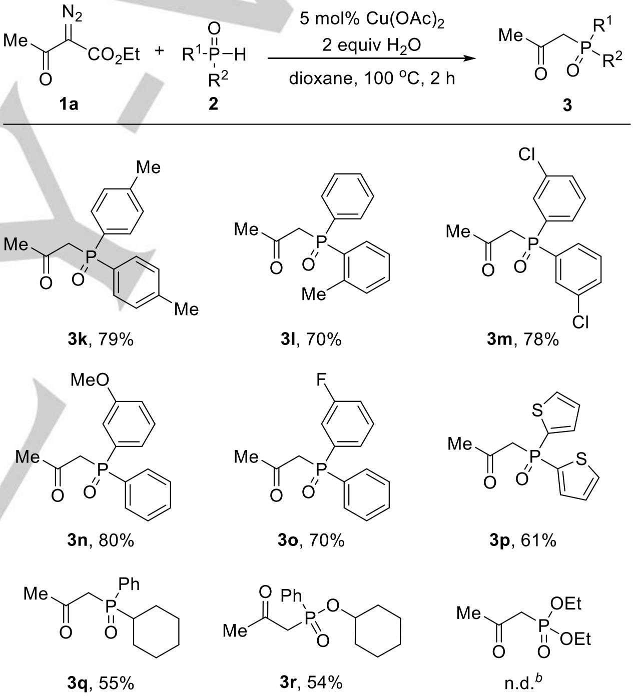


entry	1	R^1	R^2	3, yield (%)
1	**1a**	Me	Et	**3a**, 75
2	**1b**	Me	Me	**3a**, 63
3	**1c**	Me	^{i}Pr	**3a**, 83
4	**1d**	Me	^{t}Bu	**3a**, 72
5	**1e**	Me	^{p}BrC$_6$H$_4$CH$_2$	**3a**, 71
6	**1f**	Me	^{p}Tol	**3a**, 63
7	**1g**	^{n}Bu	Et	**3b**, 70
8	**1h**	Bn	Et	**3c**, 75
9	**1i**		Et	**3d**, 74
10	**1j**		Et	**3e**, 70
11	**1k**		Et	**3f**, 80
12	**1l**			**3g**, 70
13	**1m**			**3h**, 83
14	**1n**			 **3i**, 58 +  **3j**, 16

[a] Unless otherwise noted, a mixture of **1** (0.2 mmol), **2a** (1.2 equiv), [Cu] (5 mol%), solvent (1 mL) and water (2 equiv) was heated to 100 ºC for 3 h in a Schlenk tube under N$_2$. [b] Isolated yields. [c] 1 h.

The reaction was successfully extended to include some other hydrophosphoryl compounds as substrates (Table 3). Diarylphosphine oxides bearing electron-donating and electron-withdrawing substitutes on the phenyl rings all reacted smoothly with **1a** to provide the expected products **3k**-**3o** in moderate to high yields. A thiophene-substituted H-phosphine oxide also participated well in the reaction to give **3p** in 61% yield. In addition, cyclohexyl(phenyl)phosphine oxide and cyclohexyl phenylphosphinate were also applicable to this transformation, yielding **3q** and **3r** in 55% and 54% yield, respectively. The reaction of diethyl phosphonate however did not give any identifiable product.

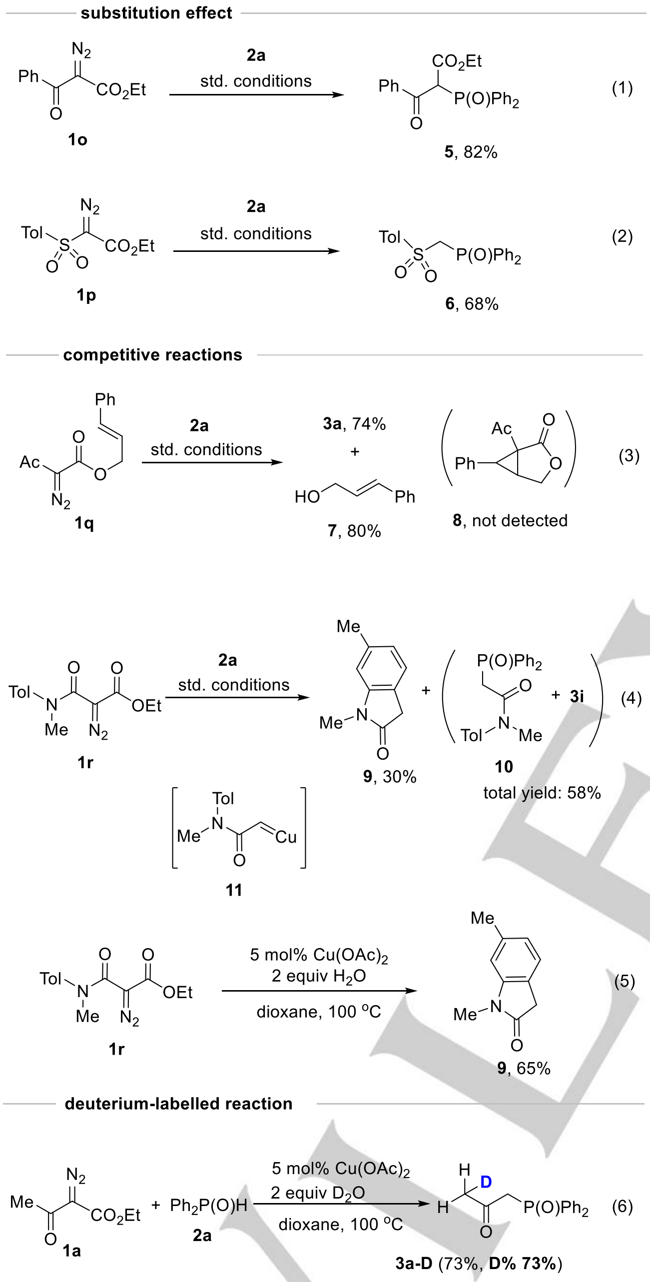
Table 3. The reaction scope with respect to hydrophosphoryl compounds[a]



[a] Unless otherwise noted, a mixture of **1a** (0.2 mmol), **2** (0.24 mmol), Cu(OAc)$_2$ (5 mol%), water (0.4 mmol) and dioxane (1 mL) was heated in a sealed Schlenk tube for 3 h. Isolated yields are given. [b] No identifiable product was obtained.

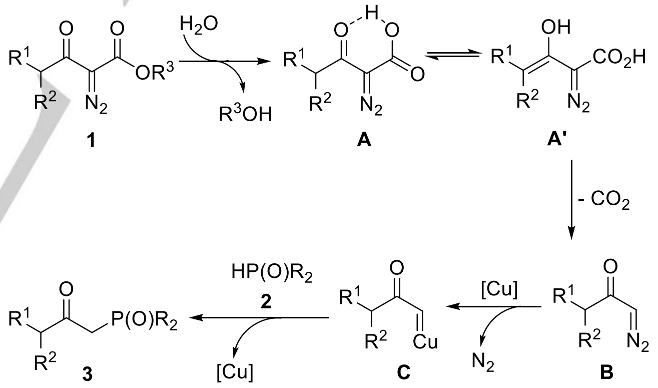
It is worth mentioning that the reaction of α-benzoyl-α-diazoacetate **1o** and **2a** did not generate decarboxylative C–P coupling product under the present conditions, but the normal insertion product **5** was obtained in a high yield (Scheme 2, eq.1). The reactions conducted at higher concentrations or in the presence of more equivalents of water also gave **5** in high yields.[17] In contrast, the reaction of ethyl 2-diazo-2-tosylacetate (**1p**) remained to deliver the decarboxylative C–P coupling product **6** in 68% yield (Scheme 2, eq. 2). These results indicated a substituent effect of the reaction, the reason of which however remains to be clarified.

To obtain more insight into the reaction mechanism, we also prepared two diazodicarbonyl compounds bearing more reaction points to probe possible competitive reactions, i.e., an allyl 2-diazo-3-oxobutanoate (**1q**) and ethyl 2-diazo-3-(methyl(*p*-tolyl)amino)-3-oxopropanoate (**1r**). Although substrate **1q** was known as a good precusor for the intramolecular cyclopropanation reaction under the copper or rhodium catalysis,[18] the reaction with **2a** under the present conditions only gave the decarboxylative C–P coupling product **3a** in 74% yield with high selectivity, and the [2+1] cycloadduct **8** was not formed (Scheme 2, eq. 3).[19] These results indicate that the hydrolysis of the ester group may take place faster under the present conditions. On the other hand, the reaction of **1r** turned out to be much more complicated, yielding a mixture of the cyclized product **9**, with the decarboxylative C–P coupling product **10** and a deamidative product **3i** (Scheme 2, eq. 4). The results suggest the competative intramolecular arylation of the possible copper-carbene intermediate **11** may take place in the reaction. Indeed, the reaction of **1r** catalyzed by 5 mol% Cu(OAc)$_2$ in the presence of 2 equiv of water without adding **2a** delievered the product **9** cleanly in 65% yield (Scheme 2, eq. 5). Finally, we performed the catalytic reaction of **1a** and **2a** using D_2O instead of H_2O (Scheme 2, eq. 6). Interestingly, in the presence of 2 equiv of D_2O, the reaction afforded the product **3a-D** in 73% yield with a deuteration of ca. 73% at the γ-C position (the calculated deuteration rate refers to one H atom of the methyl group). While the loss of deuterium atoms at the α-C position was probably due to deuterium-hydrogen exchange during the purification process on silica gel column chromatography, we reasoned that the incorporation of deuterium at the γ-C position indicated the existance of an enol-keto tautomerization with respect to the acetyl moiety during the reaction.



Scheme 2. The control experiments.

Based on the obtained results and literature precedents,[14] a tentative mechanism is proposed in Scheme 3. Firstly, the hydrolysis of α-acyl-α-diazoacetate **1** takes place to give an α-diazoacetoacetic acid intermediate **A** under the reaction conditions.[20] The tautomerization between **A** and the enol form **A'** may exist to some extent because of activation of the carbonyl group by intramolecular hydrogen bond. Decarboxylation of the intermediate **A** then gives the (diazomethyl)ketone **B**, which reacts with the copper catalyst to generate the copper-carbene intermediate **C**. The subsequent hydrophosphinylation reaction of **C** finally gives the product **3** and regenerates the copper catalyst (Scheme 3).



Scheme 3. The proposed mechanism.

In conclusion, we have disclosed a copper-catalyzed decarboxylative hydrophosphinylation reaction between α-acyl-α-diazoacetates and hydrophosphoryl compounds. The study does not only provide a new alternative way to generate (α-alkylphosphinyl)ketones, but may also suggest the possible use of relatively more readily available and stable α-acyl-α-diazoacetates instead of α-diazoketones in some cases. Further study on the applications of the method as well as the reaction mechanism will be pursued.

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Keywords: copper catalysis • hydrophosphinylation • decarboxylation • C–P bond • α-acyl-α-diazoacetates

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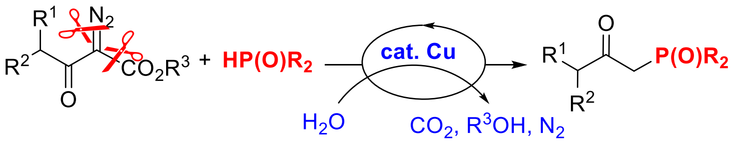
Entry for the Table of Contents

Key Topic: Decarboxylative hydrophosphinylation



A simple Cu-catalyzed decarboxylative hydrophosphinylation of α-acyl-α-diazoacetates with hydrophosphoryl compounds is developed *via* a process of the generation of (diazomethyl)ketones and the subsequent C–P coupling. The findings imply the potential use of the relatively more readily available α-acyl-α-diazoacetates as replacement of (diazomethyl)ketones in some cases.