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The copper-catalyzed radical aminophosphinoylation of maleimides with anilines and diarylphosphine oxides†

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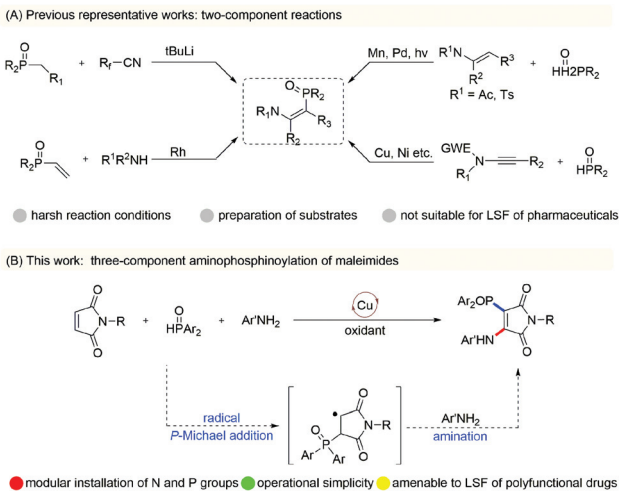
The copper-catalyzed radical multi-component coupling of maleimides, anilines, and diarylphosphine oxides has been realized, providing the rapid synthesis of a library of aminophosphinoylated maleimides, with the formation of C–N and C–P bonds. The remarkable feature of the current multi-component reaction was that five clinical drug molecules containing sulfonamide and arylamine functional groups underwent chemo-selective radical vinylphosphinoylation to access sterically congested products. Most impressively, this transformation worked on a wide range of substrates and showed good functional group tolerance.

Introduction

Recent studies have shown that β-phosphoryl enamines, owing to their unique structural characteristics, play an irreplaceable role in the fields of organic ligands, candidate pharmaceutical molecules and material chemistry.[1] Thus, tremendous efforts have been devoted to designing valuable synthetic approaches for enriching the diversity and applicability of their derivatives.[2] The initial studies involved Rh-catalyzed hydroaminovinylation of vinylphosphonate with alkyl amines,[3] condensation of alkyl phosphonates with a Michael receptor[4] and hydrophosphorylation of ynamides.[5] However, these approaches require expensive metal catalysts and involve the use of harsh reaction conditions that would impede the discovery of new drugs. In recent years, direct C–H phosphorylation of enamides by way of various catalytic pathways has also attracted considerable attention (Scheme 1A).[6] These described protocols rely on the preparation of substrates, a requirement of stoichiometric Mn or silver oxidant in some cases, and usually have the nitrogen atom of the starting material protected by electron-deficient groups under oxidative reaction conditions. These two-component reactions are key ways to prepare β-phosphoryl enamines, but three-component cascade reactions remain elusive. There is a considerable need to develop a clever complementary strategy for enriching the chemistry of β-phosphoryl enamines and achieving late-stage functionalization of polyfunctional drugs.

Recently, we and other groups have demonstrated copper-catalyzed oxidative aminofunctionalizations of maleimides,[7] and in these transformations have achieved *in situ* formation of enamine intermediates from the oxidative amination of maleimides with electron-rich secondary alkylamines, followed by copper-catalyzed oxidative cross-coupling with various nucleophilic reagents with high reaction efficiency. The success of these multi-component reactions lies in the secondary alkylamines being more nucleophilic than the other nucleophiles. It is difficult to get aromatic amines with low



Scheme 1 The synthetic strategy for the preparation of β-phosphoryl enamines.

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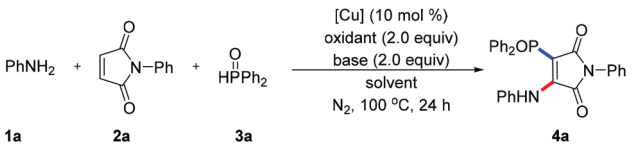
nucleophilicity to participate in the difunctionalization reactions of maleimides when using this strategy. In light of the significance of maleimide chemistry and the requirement of β-phosphoryl enamines, we wondered whether copper-catalyzed radical aminophosphinoylation of maleimides could be developed by performing radical addition of phosphinoyl with maleimide and then amination reactions (Scheme 1B). This protocol could overcome the intrinsic reactivity of anilines and provide a new strategy to afford the β-phosphoryl enamine motif. However, the preparation of aminophosphinoylated maleimides using the above-mentioned transformation is extremely challenging, mainly due to the well-developed and incidental copper-catalyzed oxidative dehydrogenation coupling of anilines to lead to aromatic azo compounds,[8] hydrophosphinylation of H-phosphonates with electron-deficient alkenes,[9] oxidative N–P cross-coupling between H-phosphonates and anilines,[10] and homo-dehydrogenative P–P and P–O–P coupling of H-phosphonates.[11]

Results and discussion

We used inexpensive and readily available aniline **1a**, *N*-phenyl maleimide **2a**, and diphenylphosphine oxide **3a** as a model substrate, and performed the radical multi-component aminophosphinoylation to examine our assumptions (Table 1, for details see ESI†). Based on our previous experience with maleimide chemistry, we focused on the inexpensive copper catalysts. After simple optimization of reaction conditions, we found that using DTBP as a free radical oxidant and CuCl as a catalyst, the desired product **4a** was obtained with a yield of 11% (entry 1). Using other oxidants, namely 70% TBHP, $K_2S_2O_8$, $Mn(OAc)_3$ and TBPB, each led to lower yields than did using DTBP (entries 2–5). Some undesired byproduct from the *P*-Michael addition of maleimide was formed during reaction optimization. In other words, aniline did not rapidly capture the carbon free radical intermediate, thus reducing the efficiency of the conversion of the raw materials. Therefore, organic and inorganic bases commonly used in the laboratory were screened (entries 6–9); use of Li_2CO_3 as the base improved the yield of the target product, and the reaction became relatively clean. The choice of reaction solvent was found to be very important for accessing the target product. Replacing CH_3CN with a CH_3CN/toluene mixture increased the yield to 61% (entry 10). Subsequently, we re-screened a series of useful copper salts and found that $CuCl_2$ showed the best catalytic performance (entry 11). Next, some additives or ligands were included in the catalytic system in an attempt to improve the yield of the target product. Surprisingly, introduction of the bidentate ligand 1,10-phen led to a sharp drop in yield (entry 12), which may have been due to the ligand having coordinated the copper ion and reducing its Lewis acidity. In addition, the current radical cascade reaction was found to be insensitive to the reaction atmosphere, and product in considerable yield was still obtained under oxygen conditions (entry 13).

As illustrated in Scheme 2, the multi-component radical aminophosphinoylation reaction was found to provide a concise pathway to construct a comprehensive library of aminophosphinoylated maleimides. At first, *N*-phenyl maleimide and diphenylphosphine oxide were used as cross-coupling partners. A range of arylamines having different substituents with distinct electronic properties effectively participated in the current transformation. Specifically, a wide range of common functional groups, namely methyl (**4b–4e**), ester (**4f**), trifluoromethoxy (**4h**), trifluomethylthio (**4i**), methoxyl (**4j**), halogen (**4k–4m**), sulfonyl (**4n**), acyl (**4o**) and trifluoromethyl (**4p**) groups, were nicely accommodated in these reactions. However, *ortho*-substituted arylamine substrates provided the corresponding products in relatively low yields (**4d–4g**), which may have been due to steric repulsion. Most importantly, 4-iodoaniline delivered the anticipated vinylphosphinoylation product (**4m**) with high reaction efficiency, highlighting the powerful generality and appeal of the late-stage modification of the achieved products. Additionally, the practicability of this reaction was demonstrated on the 5 mmol reaction scale, with the target product **4a** obtained in 70% yield. Alkyl amines did not act as efficient coupling partners, probably due to the oxidative dehydrogenation of alkyl amines having resulted in their decompositions into aldehyde byproducts under oxidizing conditions.[10] Note that the current multi-component reaction was found to not be limited to *N*-aryl substituted maleimide, and *N*-alkyl maleimides proved to be entirely compatible with the reaction and afforded the corresponding products in good to excellent yields. We have prepared a series of *N*-benzyl substituted maleimide substrates (**4s–4ac**) containing

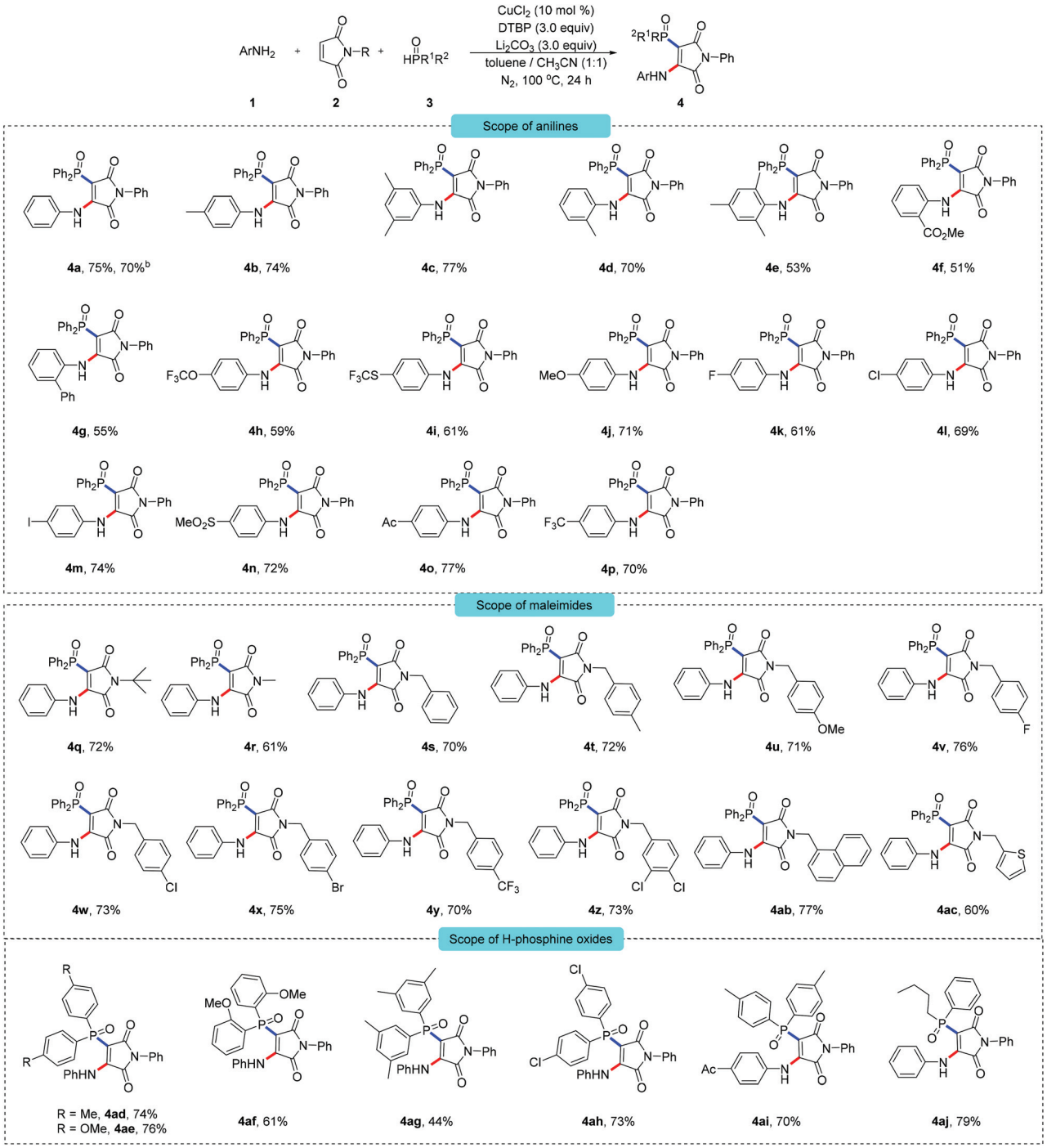
Table 1 Reaction optimization[a]



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

Entry	Catalyst	Solvent	Oxidant	Base	Yield[b] (%)
1	CuCl	MeCN	DTBP		11
2	CuCl	MeCN	70% TBHP		0
3	CuCl	MeCN	$K_2S_2O_8$		10
4	CuCl	MeCN	$Mn(OAc)_3$		5
5	CuCl	MeCN	TBPB		0
6	CuCl	MeCN	DTBP	Li_2CO_3	49
7	CuCl	MeCN	DTBP	Na_2CO_3	0
8	CuCl	MeCN	DTBP	K_2CO_3	0
9	CuCl	MeCN	DTBP	Cs_2CO_3	0
10	CuCl	MeCN/PhMe = 1 : 1	DTBP	Li_2CO_3	61
11	**$CuCl_2$**	**MeCN/PhMe = 1 : 1**	**DTBP**	**Li_2CO_3**	**75**
12[c]	$CuCl_2$	MeCN/PhMe = 1 : 1	DTBP	Li_2CO_3	45
13[d]	$CuCl_2$	MeCN/PhMe = 1 : 1	DTBP	Li_2CO_3	70

[a] Standard reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), copper salt (0.02 mmol), oxidant (0.6 mmol), and base (0.6 mmol) in solvent (2.0 mL) under N_2, heated at 100 °C for 24 h. [b] Isolated yield. [c] 10% 1,10-phen as a ligand. [d] Under an O_2 atmosphere.



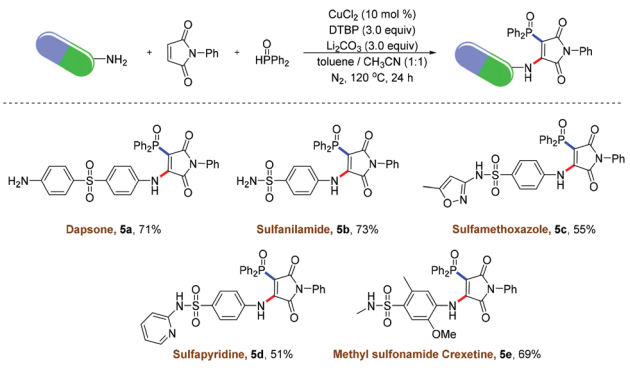
Scheme 2 The radical aminophosphinoylation of maleimides, anilines, and diarylphosphine oxides.

important functional groups suitable for this reaction and yielding good reaction efficiency. The oxidative aminophosphinoylation could be performed using polychlorinated maleimide as an electrophile (**4z**). Furthermore, the aminophosphinoylation coupling of electron-rich heteroaryl-substituted maleimide (**4ac**) was also feasible when using the optimal reaction conditions and the anticipated product was provided with a useful yield. To broaden the significant applicability of this protocol, methyl (**4ad**, **4ag**), methoxyl (**4ae**, **4af**) and chlorine (**4ah**)-substituted diarylphosphine oxides were tested for the current reaction conditions, and found to be suitable—with the corresponding products isolated in good yields. We also conducted an orthogonal experiment. Using a combination of different arylamines and organic phosphines effectively enriched the molecular library of aminophosphinoylated maleimides (**4ai**).

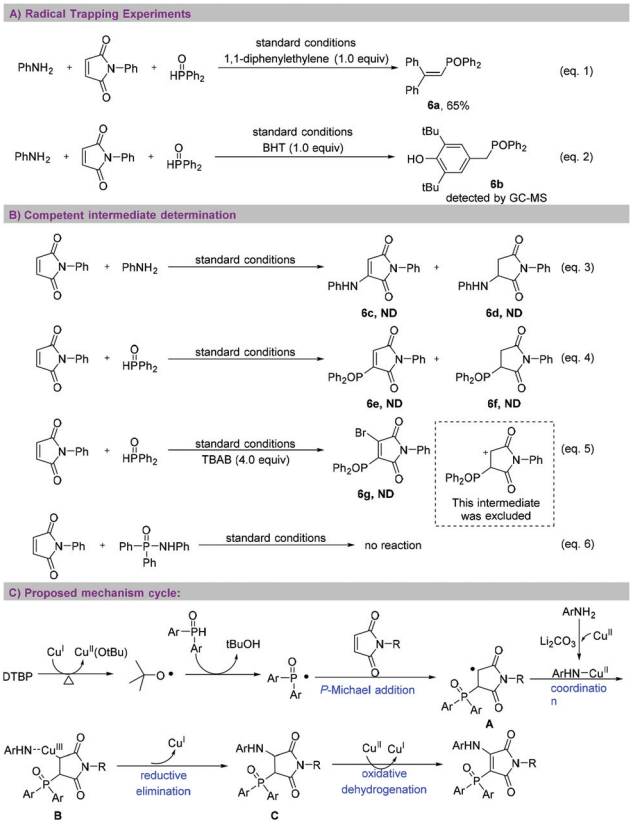
Another aspect of the multi-component reaction that we noticed was that dialkylphosphites such as diethyl phosphite and diisopropyl phosphite were unsuitable for this transformation and did not give aminophosphonated products.

To highlight the practical application of the strategy involving radical aminophosphinoylation of maleimide, we sought to examine the late-stage modification of pharmaceuticals bearing sulfonamide and arylamine functional groups. As shown in Scheme 3, dapsone (**5a**), a sulfone drug used to treat acne vulgaris, was handily achieved using the above-mentioned protocol, which provided an efficient pathway for the discovery of a therapeutic agent for bacterial infection. Sulfanilamide (**5b**), an anti-vulvovaginal candidiasis drug, was readily converted into the desired product with unique chemoselectivity by carrying out a radical vinylphosphinoylation. Sulfamethoxazole (**5c**), an oral sulfonamide antibiotic, was highly compatible with the reaction and gave the expected product in an acceptable yield. The sulfonamide antibiotic sulfapyridine (**5d**), commonly used to treat dermatitis herpetiformis, was also compatible and provided the vinylphosphinoylated product in good yield. Furthermore, the vinylphosphinoylated methyl sulfonamide clisetine was successfully obtained in 69% yield.

To investigate whether the aminophosphinoylation of maleimide occurred through a free radical reaction process, as shown in Scheme 4, we selected BHT and 1,1-diphenyl ethylene as free radical scavengers and performed two control experiments (eqn (1) and (2)). In these cases, the desired conversion reaction was completely inhibited, and radical adduct **6a** was isolated in 65% yield and radical adduct **6b** was detected using GC-MS. Next, we studied the sequence of the multi-component reaction (eqn (3) and (4)). The reaction of *N*-phenyl maleimide with aniline or diphenylphosphine oxide under the standard reaction conditions showed hardly any nucleophilic addition and oxidative coupling products. Next, TBAB was added to the reaction between *N*-phenyl maleimide and diphenylphosphine oxide under the standard reaction conditions (eqn (5)); no bromophosphinoylated product **6g** was generated. This experimental result excluded the formation of a carbocation intermediate.[12] Finally, no reaction occurred between *N*,*P*,*P*-triphenylphosphinic amide and



Scheme 3 Synthetic applications.



Scheme 4 Mechanistic considerations and control experiments.

N-phenyl maleimide (eqn (6)). This result indicated the untenability of this transformation to progress by way of the insertion into the maleimide carbon–carbon double bond of an N–P bond. Based on the aforementioned experimental results, a tentative mechanism for aminophosphinoylation reaction was derived, as shown in Scheme 4C. According to this mechanism, single-electron oxidation of organophosphorus with DTBP generates phosphinoyl radicals in the presence of copper salt,[13] followed by nucleophilic addition of maleimides with *P*-centered radical to form alkyl radical **A**.[14] Then, the coordination between **A** and copper-aniline complex affords trivalent copper intermediate **B**,[15] which undergoes reductive elimination to yield α,β-aminophosphinoylation product **C**. Finally according to the mechanism, copper-promoted oxidative dehydrogenation of **C** accesses the desired product.[16]

Conclusions

In summary, the concise and straightforward copper-catalyzed radical aminophosphinoylation of maleimides with anilines and diarylphosphine oxides was achieved, and a library of aminophosphinoylated maleimides with unique structures was efficiently constructed. Most impressively for this multi-component reaction was the ability to use it to effectively achieve chemo-selective radical vinylphosphinoylations of various drug

molecules bearing multiple sulfonamide and arylamine functional groups, providing an available pathway for the discovery of new maleimide candidate drugs. Notably, this reaction was found to display a wide range of applications, excellent tolerance of functional groups, and good atom economy during synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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