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ARTICLE

C3-H Methylenephosphonylation of Azaarenes Enabled by Catalyst-controlled Regioselective Cyclizative Rearrangement

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The incorporation of phosphonate moieties into azaarenes via C-H functionalization is of paramount importance in pharmaceutical research, yet it remains a formidable synthetic challenge. Herein, we report an intermolecular cyclizative rearrangement approach for the efficient site-selective methylenephosphonylation of diverse azaarenes. This reaction proceeds via an orchestrated cascade sequence comprising regioselective 1,3-dipolar cycloaddition, [3,5]-sigmatropic rearrangement, and selective C-C bond cleavages. As a Lewis acid catalyst, $ZnBr_2$ is crucial to this transformation: it not only delivers high conversion but also controls the regioselectivity of the initial cyclization, which in turn dictates the chemoselectivity of the entire process. This protocol is applicable to late-stage functionalization of various pharmaceuticals and ligands, and facilitates further product diversification for advanced uses. This reaction represents the first example of the C-H methylenephosphonylation of arenes.

Introduction

Phosphonates represent essential structural motifs in biological systems, where they govern a multitude of metabolic processes.[1-2] Among them, azaarenes bearing methylenephosphonate moieties have emerged as core scaffolds in a number of pharmaceuticals and functional materials, endowed with diverse bioactivities such as antimicrobial,[3] anticancer,[4] thrombin inhibitory,[5] and 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) inhibitory properties,[6] alongside their utility as precursors to photosensitizers (Figure 1a).[7-8] Accordingly, the functionalization of diverse azaarenes with methylenephosphonate moieties is of paramount importance for the development of novel drug candidates. Conventional methods for the methylenephosphonylation of azaarenes rely heavily on stepwise transformation strategies, which necessitate prefunctionalization of azaarenes at the target site, followed by sequential cross-coupling or S_N2 reactions (Figure 1b).[7-10] Direct and site-selective C–H methylenephosphonylation undoubtedly represents one of the most straightforward and efficient pathways to this goal. Nevertheless, to the best of our knowledge, such transformations remain unexplored, mainly hampered by the scarcity of efficient synthetic protocols, insufficient control of selectivity, and challenging compatibility issues (Figure 1b).

Azaarene *N*-oxides are readily accessible via the oxidation of parent azaarenes and act as versatile 1,3-dipoles in a broad range of reactions, thus offering a straightforward and modular platform for the site-selective functionalization of azaarenes.[11-14] However, previous reports predominantly limited to *ortho*-functionalization, and methodologies enabling selective functionalization at other positions remain scarce,[15-17] particularly for C3-H bond functionalization.[18-23] In this context, Maulide and coworkers reported an elegant *meta*-selective alkyne oxyarylation of pyridine and quinoline *N*-oxides to afford metyrapone analogues, albeit needing 200 °C at microwave irradiation to achieve sufficient stepwise reactivity (Figure 1c).[22] While the use of more electron-deficient alkynes, such as diacetylene dicarboxylate (DAAD), can indeed significantly lower the reaction temperature, it diverts the reaction toward completely distinct pathway. As documented by Hamana in 1983, such conditions lead exclusively to the formation of benzazepine derivatives (Figure 1c).[24] Both reactions proceed through a cascade of 1,3-dipolar cycloaddition and [3,5]-sigmatropic rearrangement, generating **Int-1** and **Int-2** as the respective intermediates. Notably, in both cases, the regioselectivity in the initial 1,3-dipolar cycloaddition is not a concern (**Int-1**), since the alkynes employed are either electronically differentiated unsymmetric alkynes or symmetric electron-deficient alkynes. Moreover, the observed chemodivergence arises from divergent C-C bond cleavage in **Int-2**, a process that is also clearly substrate-controlled. Inspired by these studies, we hypothesized that catalyst regulation of chemoselectivity might allow the realization of C3-H methylenephosphonylation of azaarenes. To this end, we

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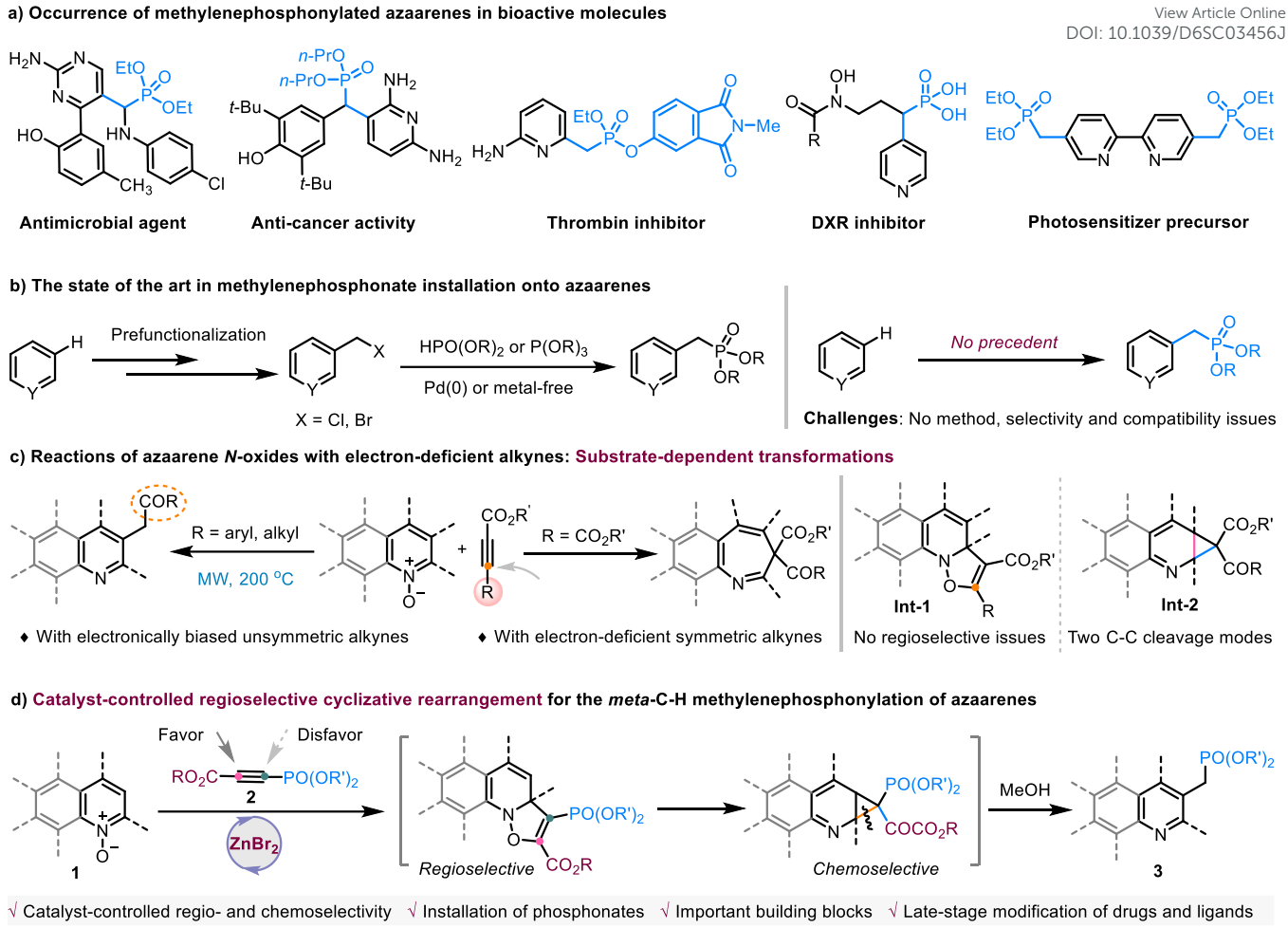

Figure 1. C-H methylenephosphonylation of azaarenes.

sought a simple, readily available phosphonate-substituted alkyne bearing an electron-withdrawing group (EWG) at the other terminus, and under such circumstances, alkynyl phosphonate bearing an ester moiety represents the optimal choice[25]. Nevertheless, the realization of this transformation poses substantial challenges. Beyond reaction reactivity, particular attention must be paid to the regioselectivity of the initial cyclization (**Int-1**) and the chemoselectivity of the subsequent step (**Int-2**), which directly dictate the product distribution. Achieving catalyst-controlled selectivity in place of substrate control would undoubtedly expand the synthetic scope of this transformation, yet it is clearly a formidable task. In line with our research interest in rearrangement-based heterocyclic chemistry,[23,26-33] we herein report the successful realization of this endeavor. Specifically, the Lewis acid catalyst $ZnBr_2$ not only ensures the reactivity of the reaction but also guarantees its chemoselectivity, thus providing a modular and general synthesis of C3-methylenephosphonylated derivatives **3** from readily available azaarene *N*-oxides **1** and alkynes **2** (Figure 1d). Notably, this protocol allows for the direct one-pot conversion of unmasked azaarenes to product **3**, with its practical utility corroborated by gram-scale synthesis and late-stage modification of diverse drug molecules and ligands. This method also addresses the gap whereby existing *meta*-functionalization strategies, such as transition-metal-catalyzed C-H activation,[34-37] temporary dearomatization-rearomatization,[38-50] ring-opening-ring-closing,[51-55] organocatalytic cyclizative rearrangement,[23] and radical coupling,[56-62] cannot directly introduce phosphonyl moieties into azaarenes.

Results and discussion

Reaction optimization

Quinoline *N*-oxide **1a** and methyl 3-(diethoxyphosphoryl)propiolate **2a** were chosen as model substrates to assess the viability of the proposed rearrangement reaction (Table 1). When the reaction was carried out in THF at 80 °C, two compounds (**3a'** and **4a**) were observed. Notably, **3a'** is derived from our desired reaction pathway via intermediates **Int-1a** and **Int-2a**, whereas **4a** originates from a distinctly different pathway involving reversed

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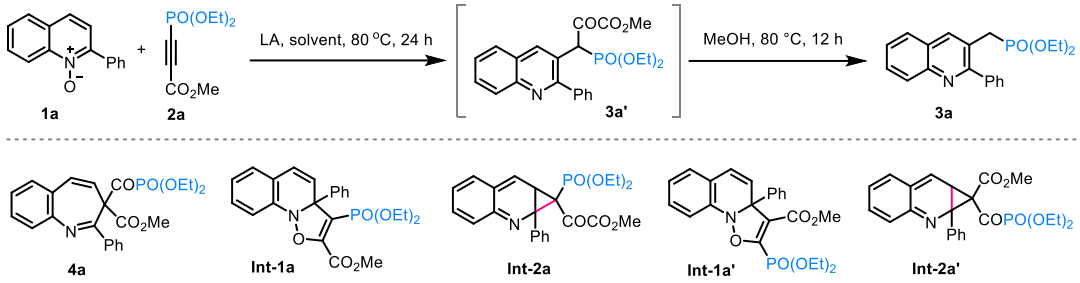
Table 1. Optimization of reaction conditions[a]



Entry	Solvent	LA (20 mol%)	Yield of **3a** (%)[a]	Ratio of **3a**/**4a**[b]
1	THF	/	10	1:2
2	toluene	/	23	1:1
3	DCE	/	16	1:2
4	MeCN	/	9	1:4
5	dioxane	/	25	1:1
6	dioxane	$Cu(OTf)_2$	34	>20:1
7	dioxane	$Ni(OTf)_2$	35	10:1
8	dioxane	$Mg(OTf)_2$	40	7:1
9	dioxane	$Sc(OTf)_3$	40	>20:1
10	dioxane	$Zn(OTf)_2$	50	>20:1
11	dioxane	$ZnCl_2$	65	>20:1
12	dioxane	$ZnBr_2$	71	>20:1
13[c]	dioxane	$ZnBr_2$	78	>20:1
14[d]	dioxane	$ZnBr_2$	83	>20:1
15[e]	dioxane	$ZnBr_2$	82	>20:1

[a]Reaction conditions for **3a**: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), LA (0.02 mmol, 20 mol%), solvent (c 0.1 M), 80 °C, 24 h, then add MeOH (0.5 mL), 80 °C, 12 h. [b]Reaction conditions for **4a**: **1a** (0.1 mmol, 1 equiv.), **2a** (0.15 mmol, 1.5 equiv.), LA (0.02 mmol, 20 mol%), solvent (1 mL), 80 °C, 24 h. [c]$ZnBr_2$ (0.03 mmol, 30 mol%). [d]$ZnBr_2$ (0.04 mmol, 40 mol%). [e]$ZnBr_2$ (0.05 mmol, 50 mol%). LA: Lewis acid.

regiocyclization (**Int-1a'**) and internal C-C bond cleavage (**Int-2a'**). Additionally, we did not observe the corresponding benzazepine derivative formed by the ring expansion of intermediate **Int-2a**. Treating with MeOH, the unstable compound **3a'** could be efficiently converted into the desired methylenephosphonylated product **3a**, while **4a** underwent complete decomposition. Indeed, these two reaction pathways are mutually competitive, and the undesired pathway leading to the ring-expanded product **4a** is significantly more favorable. To better delineate the selectivity between the two pathways, the relatively stable products **3a** and **4a** were individually isolated from parallel experiments, affording a ratio of 1:2 in THF and an overall low reaction yield of **3a** (entry 1, Table 1). Notably, other alkynes **2** with the ester group replaced by alkyl or aryl moieties were found to be inert to this reaction. Subsequently, various solvents such as toluene, 1,2-dichloroethane (DCE), acetonitrile (MeCN) and dioxane all failed to significantly improve the chemoselectivity and yield (entries 2-5). We postulated that employing a Lewis acid catalyst might address this issue, given its ability to increase alkyne electrophilicity by means of chelation effect. Furthermore, the inherent differences in the coordination behavior of ester and phosphonate groups may further boost reaction chemoselectivity via site-selective coordination. Gratifyingly, the addition of a catalytic amount (20 mol%) of Lewis acids indeed significantly improved the yield of **3a** while simultaneously suppressing the formation of byproduct **4a** (entries 6–12), and $ZnBr_2$ gave the best reaction outcomes in terms of both chemoselectivity and yield (**3a**/**4a** > 20/1, 71% yield, entry 12). Ultimately, elevating $ZnBr_2$ loading further improved reaction efficiency (entries 13-15), with 40 mol% $ZnBr_2$ affording the desired product in 83% yield (entry 14).

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Moreover, $ZnBr_2$ is a commercially available and extremely inexpensive reagent ($23/Kg, Leyan.com). The enhanced chemoselectivity should originate from the much stronger

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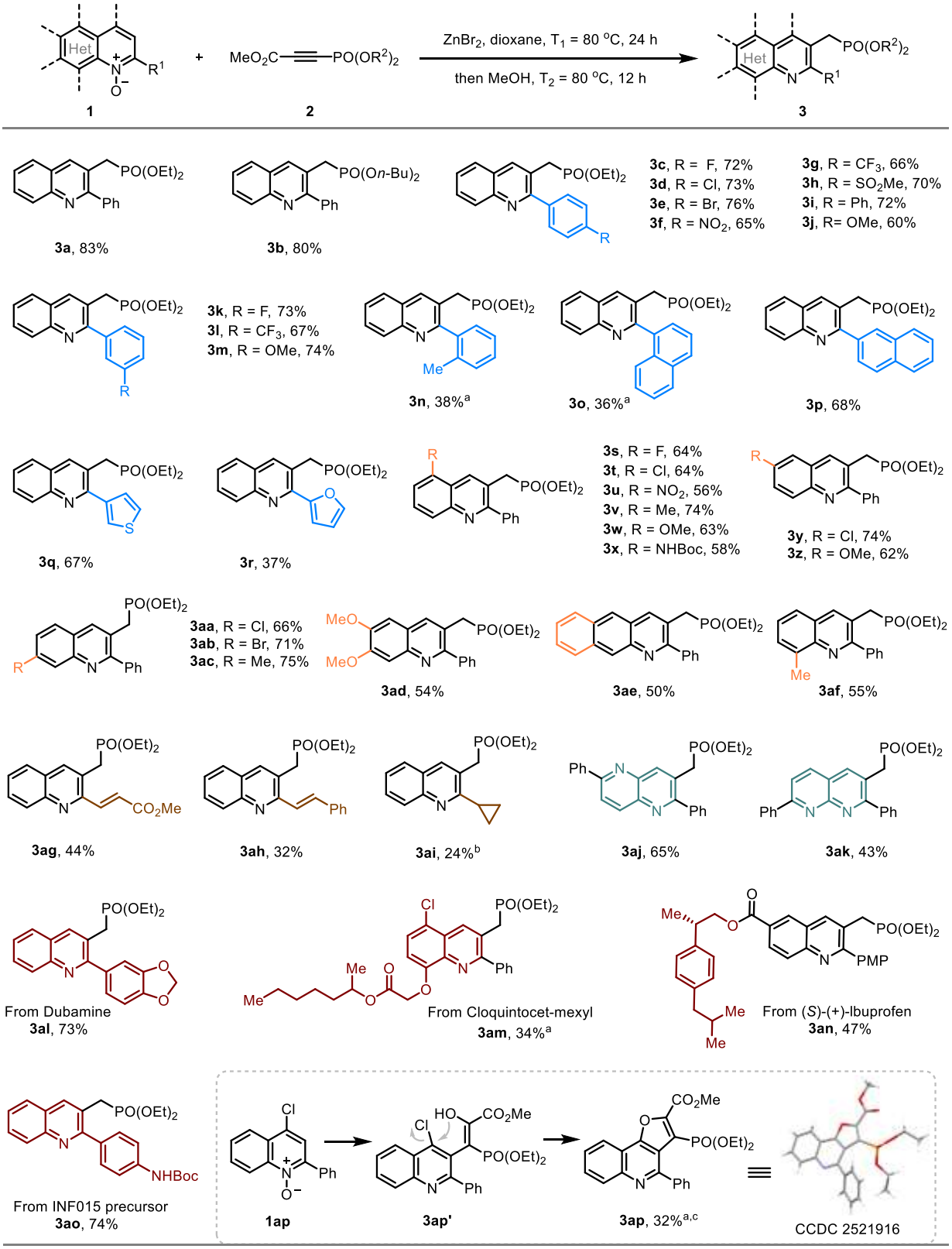

Figure 2. The substrate scope of quinolines. Standard conditions: *N*-oxides **1** (0.1 mmol), alkynes **2** (0.15 mmol), $ZnBr_2$ (0.4 equiv.), dioxane (*c* 0.1 M), 80 °C, 24 h; then MeOH (0.5 mL), 80 °C, 12 h. [a]T_1 = 120 °C. [b]MeOH (0.5 mL) and CH_3CO_2H (0.1 mmol) were added. [c]Without addition of MeOH.

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coordination ability of the phosphate moiety relative to the ester group toward the zinc complex. In addition, other alkynes are less effective than the ester-substituted phosphonylated alkynes (listed in Table S2).

Substrate scope investigation

With the optimized reaction conditions in hand, the substrate scope of this C3-methylenephosphonylation reaction was then investigated (Figure 2). Unfortunately, the unsubstituted quinoline *N*-oxide afforded no target product (listed in Table S2), instead it underwent decomposition possibly due to the instability of the dearomatized intermediates involved in this cyclizative rearrangement. With respect to the ester moieties in substrate **2**, modification of the alkyl substituent from ethyl to *n*-butyl resulted in the formation of product **3b** with an 80% yield. Various C2-aryl substituents bearing halogens (F, Cl, Br), electron-withdrawing groups (NO_2, CF_3, SO_2Me) and electron-donating groups (OMe, Ph) were well compatible with the optimized conditions, affording the desired products (**3c**-**3m**, **3p**) in good yields (60-76%). Additionally, *ortho*-methylphenyl- and 1-naphthyl-substituted quinoline *N*-oxides underwent

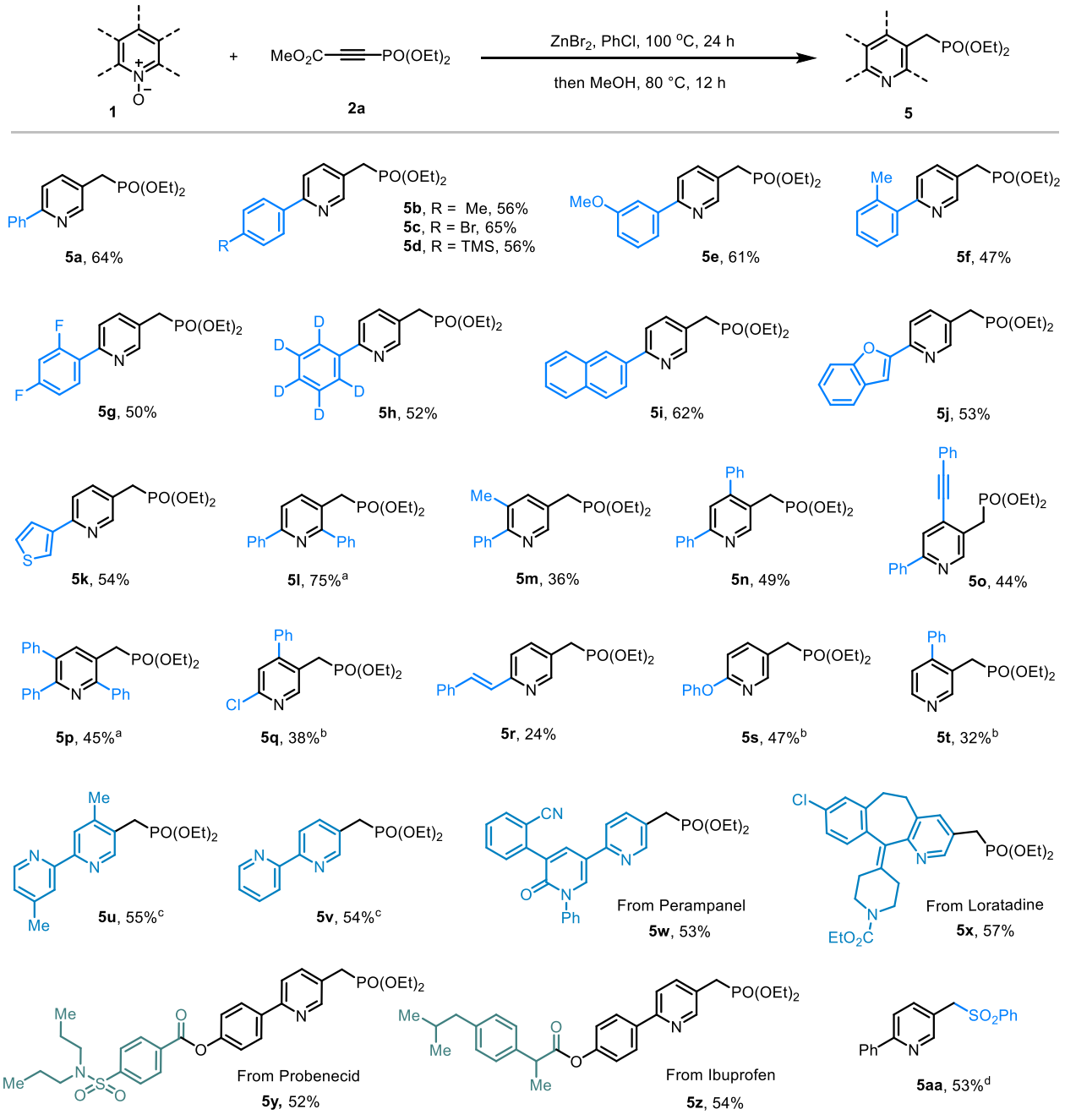

Figure 3. The substrate scope of pyridines. Standard conditions: *N*-oxide **1** (0.1 mmol), alkyne **2** (0.2 mmol), $ZnBr_2$ (0.02 mmol), PhCl (*c* 0.1 M), 100 °C, 24 h; then MeOH (0.5 mL), 80 °C, 12 h. [a]120 °C for the first step. [b]Et_3N (0.15 mmol) were added for the second step. [c]Without $ZnBr_2$. [d]Using **2d** instead of **2a**.

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conversion to the expected products (**3n**, **3o**) with diminished yields (38% and 36%, respectively), presumably due to steric hindrance. Heterocyclic substituents such as 2-thienyl and 2-furyl could undergo this reaction smoothly (**3q**-**3r**). Moreover, a wide range of substituents including functional groups (fluoro, chloro, methoxy, nitro, *tert*-butyl carbamate) located at the C5, C6, C7, and C8 positions of the benzocyclic moiety were found to be well-tolerated (**3s**-**3af**). In addition to aryl groups, 2-alkenyl- and 2-alkyl-substituted azaarenes were also compatible with the reaction, albeit with slightly reduced yields (**3ag**-**3ai**). Other bicyclic azaarenes, such as 1,5-naphthyridine (**1aj**) and 1,8-naphthyridine (**1ak**), also underwent this C3-methylenephosphonylation reaction without event. Remarkably, the incorporation of methylenephosphonate into biologically active quinoline-containing drugs, such as Dubamine, INF 015 precursor, Cloquintocet-mexyl derivative and (*S*)-(+)-Ibuprofen derivative, was also achieved in moderate to good yields (**3al-3ao**, 34-74%), demonstrating the great potential of this protocol in site-selective late-stage modification of structurally complex molecules. Interestingly, the use of 4-chloro-substituted quinoline *N*-oxide led to the formation of the synthetically useful furo[3,2-*c*]quinoline scaffold (**3ap**),[63,64] which is proposed to arise from the intramolecular oxo-cyclization of the enol intermediate **3ap'**. This result implies the reaction pathway of this C3-H methylenephosphonylation.

The pyridine derivatives were further investigated as substrates in this reaction. They were found to exhibit relatively lower reactivity toward this transformation; accordingly, the reaction conditions were slightly modified to afford good results

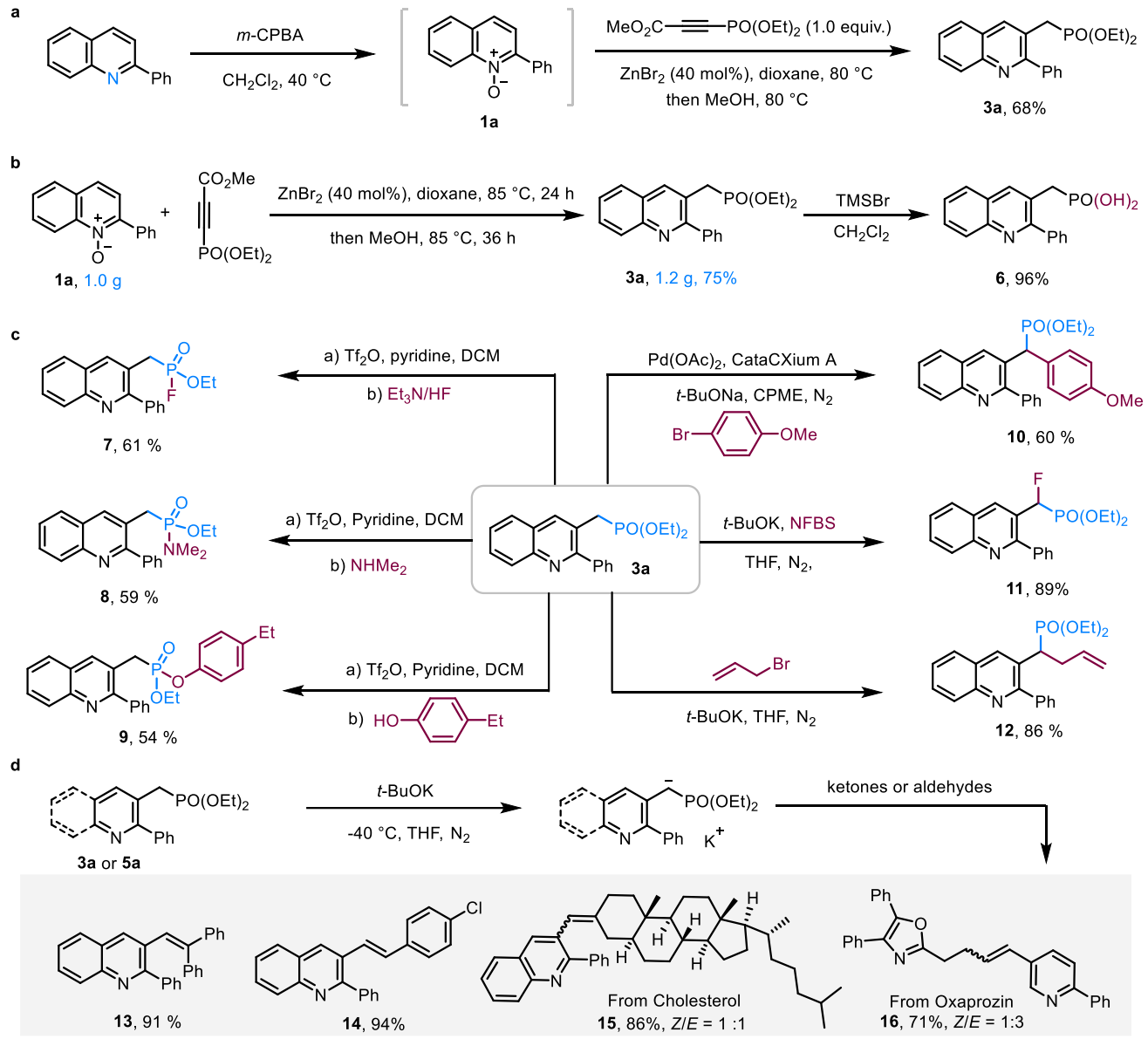

Figure 4. One-pot reaction from 2-phenylquinoline, scale-up reaction and synthetic transformation of 3a and 5a.
CataCxium A: butyldi-1-adamantylphosphine; CPME: cyclopentyl methyl ether; NFBS: *N*-fluorobenzenesulfonimide.

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(see supplementary Table 1). Under optimal conditions (Figure 3), 2-phenylpyridine *N*-oxide could react with alkyne **2a** to give desired product **5a** in 64% yield. And no regioisomeric C3-functionalized product was detected, which is likely attributed to steric hindrance during the initial 1,3-dipolar cycloaddition step. We also examined unsubstituted pyridine *N*-oxide substrate under standard conditions and no desired product was produced (listed in Table S2) Other 2-aryl substituents bearing electron-donating, electron-withdrawing, and electron-neutral groups at different positions were also viable, affording products **5b**-**5f** in moderate to good yields. Moreover, good yields were achieved when 2,4-difluorophenyl, deuterated phenyl (d_5-phenyl), or aromatic heterocyclic substituents (2-benzofuranyl, 3-thienyl) were employed (**5g**-**5k**). 2,6-Diphenyl pyridine gave even higher yield (**5l**, 75%). Additionally, both disubstituted and trisubstituted pyridines with diverse functional groups were well-tolerated under the optimized conditions (**5m**-**5q**). Moreover, 2- alkenyl- and 2-phenoxy-substituted pyridines were also viable in this cyclizative rearrangement protocol, affording the desired products (**5r** and **5s**) in moderate yields. To our delight, bipyridines, which serve as versatile ligands in various catalytic reactions,[65] were smoothly converted to C3-methylenephosphonated derivatives in good yields (**5u**, **5v**). Alternatively, 4-phenylpyridine *N*-oxide afforded **5t** in 32% yield, 3-phenylpyridine-derived *N*-oxide was also evaluated and only a trace amount of desired product was detected (listed in Table S2). Furthermore, late-stage C-H functionalization of complex drugs bearing diverse sensitive functional groups was achieved. Specifically, Perampanel-, Loratadine-, Probenecid- and Ibuprofen-derived *N*-oxides delivered the corresponding products efficiently (**5w**-**5z**). To further verify the generality of this cyclizative rearrangement strategy, we investigated sulfur-containing alkyne analogue bearing a benzenesulfonyl group. Under standard conditions, the reaction with 2-phenylpyridine *N*-oxide successfully delivered the target methylenesulfonated product **5aa** in 53% yield.

Synthetic transformations

To further expand the utility of this protocol, the one-pot synthesis of **3a** directly from 2-phenylquinoline was investigated. This approach proved feasible, affording desired product **3a** with high efficiency (68% yield, Figure 4a). Moreover, the gram-scale reaction of **1a** with **2a** afforded **3a** in 75% yield, demonstrating the scalability of this method (Figure 4b).

Hydrolysis of **3a** with TMSBr gave its phosphoric acid **6** in excellent yield. Subsequently, a series of synthetic transformations were conducted to explore the synthetic

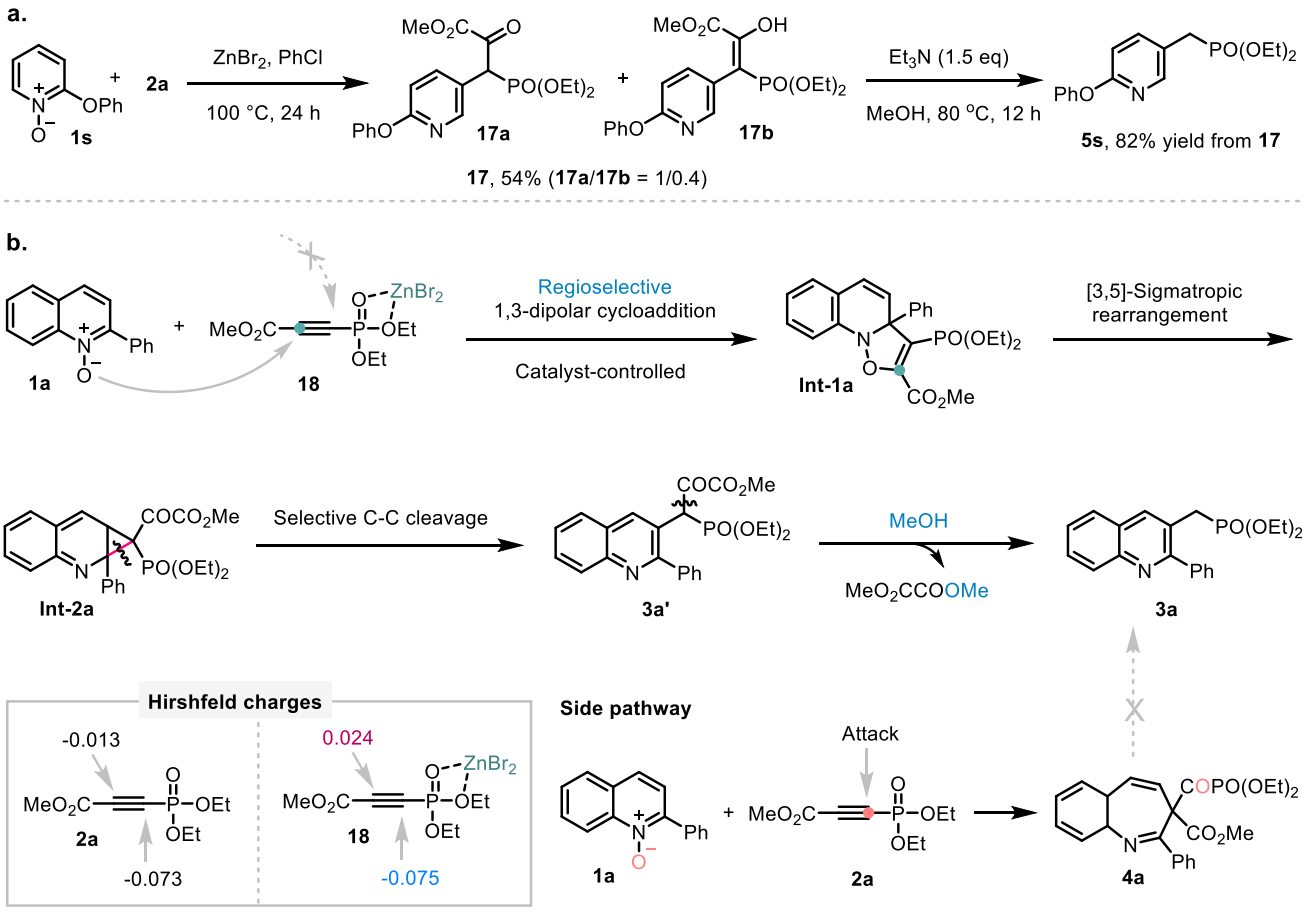

Figure 5. Control experiments and possible reaction pathway.

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versatility of product **3a** (Figure 4c). Fluorinated phosphonate **7** was obtained via Tf_2O activation followed by nucleophilic substitution with $Et_3N{\cdot}HF$ as the fluoride source. Likewise, the reaction of **3a** with dimethylamine and 4-ethylphenol afforded the corresponding products **8** and **9**, respectively. In addition, phosphonate **3a** underwent a palladium-catalyzed cross-coupling reaction, affording α-aryl phosphonate **10** in 60% yield. Furthermore, fluoro and allyl groups were efficiently installed at the α-position of methylenephosphonate **3a** to afford products **11** and **12** in high yields (Figure 4c). Finally, the potential of *meta*-methylenephosphonated azaarenes as Horner-Wadsworth-Emmons (HWE) reagents was evaluated.[66] Both benzophenone and 4-chlorobenzaldehyde were smoothly converted to C3-alkenylquinoline derivatives **13** and **14**, respectively, with good efficiency. Compound **3a** could also react with a cholesterol-derived cyclic ketone, furnishing alkenyl product **15** in high yield. When biologically active Oxaprozin-derived alkyl aldehyde was engaged in the HWE reaction, the corresponding alkenyl pyridine **16** was likewise obtained efficiently (Figure 4d). Collectively, these transformations showcase the practicality of our protocol as well as the great potential of the products to serve as important building blocks for further diversfications.

Mechanism studies

Control experiments were performed to provide insights into the reaction mechanism. Using 2-phenoxypyridine *N*-oxide **1s** as the substrate to react with alkyne **2a** under standard conditions, the key intermediate **17** was isolated in 54% yield. ^{1}H and ^{31}P NMR analysis revealed a mixture of ketone and enolate tautomers with a ratio of 1:0.4. Furthermore, treating **17** with Et_3N in MeOH at 80 ºC afforded desired **5s** in high yield (Figure 5a). These results are consistent with the observations from the reaction of quinoline **1a** in Table 1. Moreover, the formation of **3ap** via the in situ trapping of the key enol intermediate (**3ap'**) from 4-Cl-substituted quinoline **1ap** (Figure 2) is also consistent with the above experimental results.

On the basis of experimental results (Table 1, Figures 2, 3, 5a) and literature precedents,[22,24,26] a plausible reaction pathway is proposed in Figure 5b. $ZnBr_2$ exhibits a stronger coordination with the phosphonate moiety, which not only activates alkyne **2a** but also enhances the electron density difference between the two Csp centers of the alkyne. Coordination of $ZnBr_2$ to the phosphonate group activates the alkyne moiety, as evidenced by changes in the Hirshfeld charges at the α and β positions of **2a** before and after coordination. This further promotes the selective nucleophilic attack of the oxyanion from **1a**, enabling a highly regioselective 1,3-dipolar cycloaddition process (**Int-1a**). A sequential cascade involving [3,5]-sigmatropic rearrangement and external C-C bond cleavage via intermediate **Int-2** afforded key intermediate **3a'** bearing a reactive ketoester moiety. Finally, GC-MS analysis of the crude reaction mixture detected a signal assigned to dimethyl oxalate (MeO_2CCO_2Me). This result reveals that the ketoester group was removed with the aid of excess methanol, affording the desired product **3a**. On the other hand, in the absence of the Lewis acid catalyst ($ZnBr_2$), a side reaction pathway occurred, arising from the *α*-attack of phosphonated alkyne **2a** and furnishing the benzazepine product **4a**, which could not be further converted to **3a**. The regioselective cycloaddition controlled by the Lewis acid catalyst, along with the subsequent two selective C-C bond cleavages, collectively ensures the chemoselectivity of the entire reaction.

Conclusions

In conclusion, we report the first *meta*-C-H methylenephosphonylation of azaarenes via Lewis acid-catalyzed regioselective intermolecular cyclizative rearrangement, using readily available azaarene *N*-oxides and phosphonate-substituted alkynes as substrates. $ZnBr_2$ is indispensable for this transformation, ensuring both high reactivity and excellent chemoselectivity. This protocol features a broad substrate scope, remarkable functional group compatibility, and high efficiency in the late-stage functionalization of drugs and ligands. The resulting products serve as versatile synthetic linchpins for divergent synthesis of phosphorus-containing compounds and alkenylated azaarenes. This method provides a valuable perspective for the introduction of other heteroatoms onto azaarenes.

Author contributions

H. W. and Y.-P. H. conceived and designed the project. D. L. conducted all experimental investigations and data collection. F.-Z. L. performed the DFT theoretical calculations. D. L. drafted the original manuscript. H. W. and Y.-P. H. supervised the whole project and revised the manuscript. All authors discussed the results and commented on the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Further details of the experimental procedure, copies of ^{1}H, ^{13}C ^{19}F and ^{31}P NMR, X-ray crystallographic data and computational details are available in the ESI.

Acknowledgements

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Further details of the experimental procedure, copies of 1H, 13C 19F and 31P NMR, X-ray crystallographic data and computational details are available in the ESI.