Conference paper

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Applications of *H*-phosphonates for C element bond formation

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Abstract: The readily accessible and inexpensive dialkyl *H*-phosphonates are important building blocks for organic synthesis. This review specifically covers our recent work on the application of *H*-phosphonates as reactants for C–P bond formation, and as promoters for quinoline *N*-oxides to synthesize 2-functionalized quinolines.

Keywords: application; *H*-phosphonates; ICPC-22; organophosphorus; quinoline *N*-oxides.

Introduction

Organophosphorus compounds have been widely applied in the field of organic chemistry, biochemistry, and photoelectric materials. Due to the importance of these compounds, the development of novel and efficient synthetic strategies for the construction of organophosphorus compounds have drawn much attention in the past decades, including the well-known Michaelis–Arbuzov reaction [1, 2], Hirao cross-coupling [3, 4], Atherton–Todd reaction [5–9], and Kabachnik–Fields reaction [10–16]. Particularly, dialkyl *H*-phosphonates are an important class of building blocks for the synthesis of organophosphorus compounds, which have been applied for the synthesis of α-aminophosphonic acids, bisphosphonates, alkynylphosphonates, poly(alkylene *H*-phosphonate)s, etc. (Scheme 1) [17].

In the recent years, the research groups of Han [18–21], Zhao et al. [22–25], Yang et al. [26, 27], Xiao et al. [28, 29], Wu et al. [30, 31], Zou et al. [32–35], Toste et al. [36], Montchamp [37–39], and others have made critical and promising contributions in developing the novel synthetic methods in organophosphorus chemistry. For example, the tautomeric equilibrium of dialkyl *H*-phosphonates between their phosphite form and phosphonate form, namely the tricoordinated phosphorus form and the tetracoordinated phosphorus form (Scheme 2), makes this compound a highly intriguing building block. In the past several years, our research

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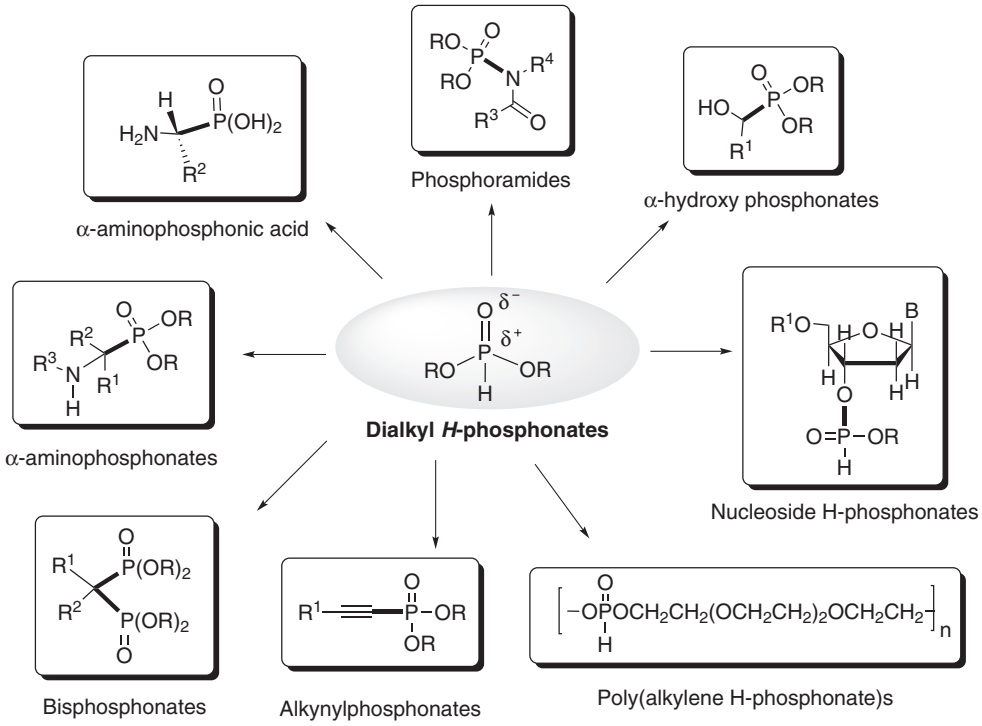
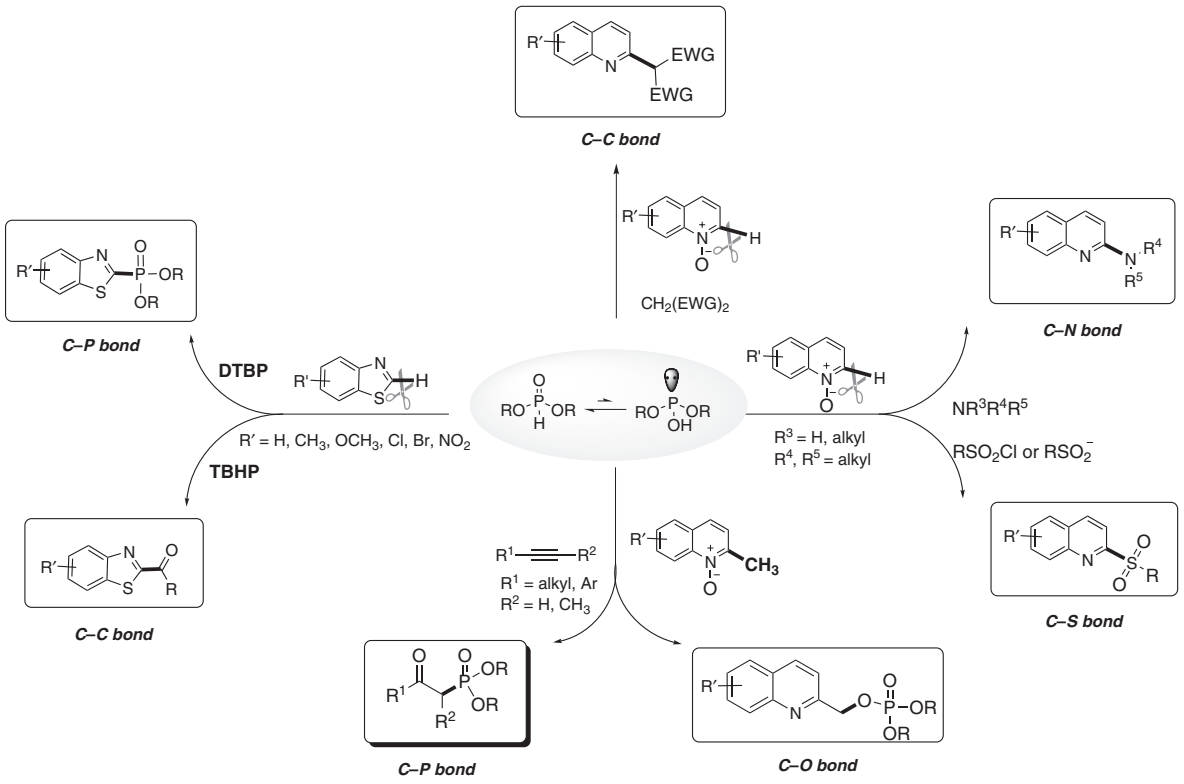


Scheme 1: Application of *H*-phosphonates as building blocks.



Scheme 2: Application of *H*-phosphonates for C element bond formation.

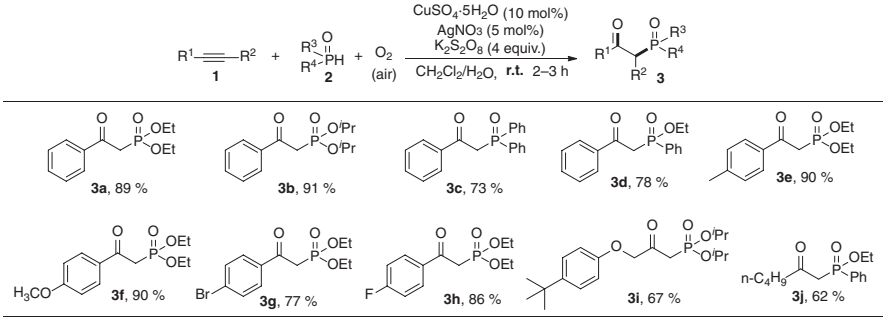
group of Zhengzhou University devoted our efforts to the exploration of novel application of *H*-phosphonates for organic synthesis. Herein, the recent advances of the application of *H*-phosphonates as a reactant or promoter for C–P, C–C, C–N, C–S and C–O bond formation are summarized using representative results from our lab (Scheme 2).

H-Phosphonates as reactant for C–P bond construction

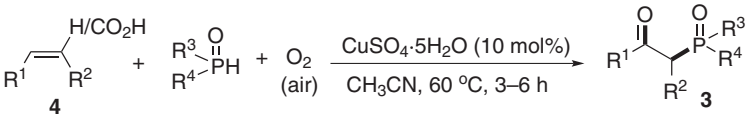
β-Ketophosphonates are a significant class of organic intermediates for various transformations, and also exhibit interesting bioactivities and prominent metal-complexing abilities. Due to their importance, various methods have been developed by using Arbuzov reaction [2], LDA-mediated acylation reaction [40], $PdCl_2$-catalyzed reaction [41], and Cu–Fe catalytic system [42]. In our reported system, a convenient synthetic approach via the one-pot aerobic reaction of alkynes with dialkyl *H*-phosphonates and oxygen in the air was developed (Scheme 3) [43]. In the presence of $AgNO_3$ (5.0 mol%), $CuSO_4 \cdot 5H_2O$ (10.0 mol%) and $K_2S_2O_8$ (4 equiv.), in the mixture solvent, i.e. CH_2Cl_2/H_2O (v/v = 1/1), a wide variety of β-ketophosphonates were prepared at room temperature for 3 h at room temperature. The substrate scope of the reaction was broad, with a variety of alkynes and dialkyl *H*-phosphonates undergoing coupling in excellent yields (see Scheme 3).

Generally, α,β-alkenyl carboxylic acids and alkenes are cheaper than corresponding alkynes. Inspired by the above-mentioned results, we then extended the similar methodology to synthesize β-ketophosphonates from α,β-alkenyl carboxylic acids or alkenes rather than terminal alkynes [44]. After the optimization of reaction conditions, we found that only $CuSO_4 \cdot 5H_2O$ (10.0 mol%) was needed for the reaction of α,β-alkenyl carboxylic acids (or alkenes) and dialkyl *H*-phosphonates in CH_3CN at 60 °C for 6 h (Scheme 4). Importantly, CH_3CN was demonstrated to be a unique solvent for this transformation, and no reaction was observed when the reaction was conducted in other solvents like THF, DMF, EtOH, 1,4-dioxane, EtOAc, etc. Therefore, it was proposed that the complex $[Cu(MeCN)_n]^{2+}$, *in situ* generated from Cu^{2+} and CH_3CN, probably was the active catalytic species. The oxygen (O_2) in air was initially trapped by $[Cu(MeCN)_n]^{2+}$ to form active oxygen complex $[\cdot O–O–Cu(MeCN)_n]$, by which an efficient cascade decarboxylation-oxyphosphorylation reaction was thus triggered.

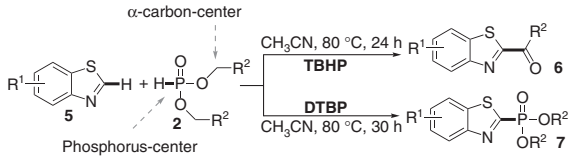
On the other hand, the reactive sites of dialkyl *H*-phosphonates could be the α-carbon-center or the phosphorus-center (Scheme 5). When the benzothiazoles **5** and *H*-phosphonates **2** were applied as substrates



Scheme 3: Selected examples of the synthesis of β-ketophosphonates via the reaction of alkynes and *H*-phosphonates.



Scheme 4: Reaction of α,β-alkenyl carboxylic acids (or alkenes) and H-phosphonates.

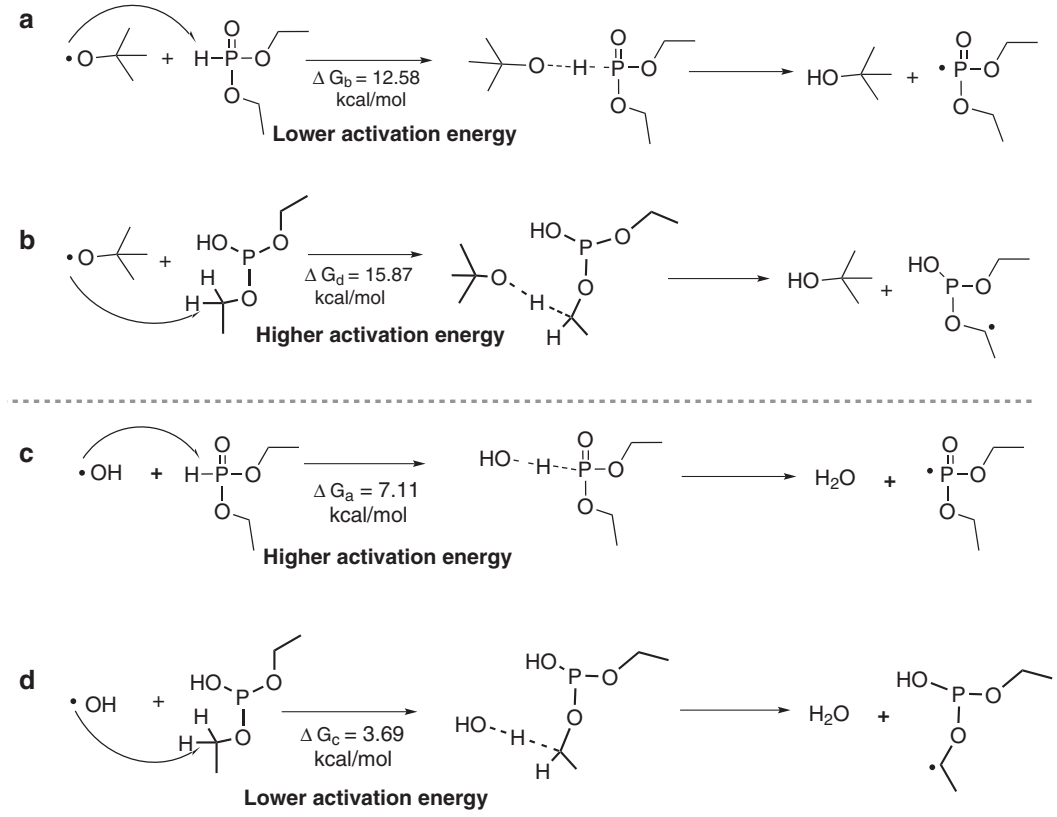


Scheme 5: Reaction of benzothiazoles and *H*-phosphonates.

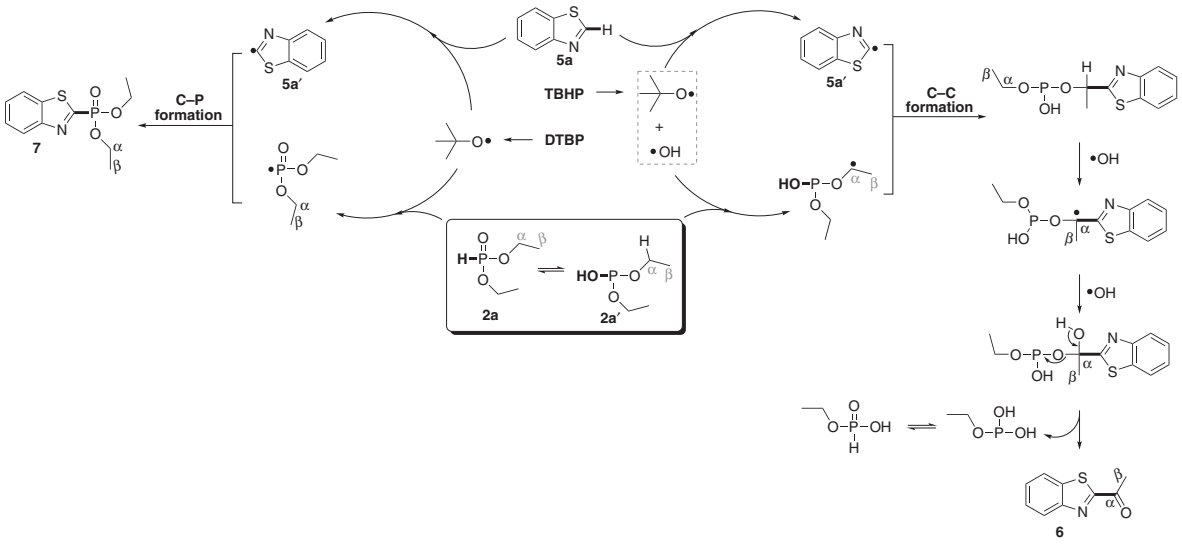
under oxidative conditions, it was unexpectedly found that the dialkyl *H*-phosphonate **2** was a switchable synthetic precursor for the C_2-acylation of benzothiazoles and C_2-phosphonation of benzothiazoles. Accordingly, two important benzothiazole derivatives, i.e. 2-acylbenzothiazoles **6** and dialkyl benzothiazol-2-ylphosphonates **7** were synthesized. After optimization of the reaction conditions, *tert*-butyl hydroperoxide (TBHP) and di-*tert*-butyl peroxide (DTBP) proved to be the optimal oxidant in CH_3CN at 80 °C for the selective C_2-acylation or C_2-phosphonation of benzothiazoles, respectively [45].

In these reactions, oxidants were converted into radicals, e.g. HO· and ^{t}BuO·. By using density functional theory (DFT) calculation, the free energy barriers for the possible proton transfer pathways were 12.58, 15.87, 7.11, and 3.69 kcal/mol, respectively. These results suggested that the phosphorus-centered phosphonate radical can be easily generated in the presence of ^{t}BuO· (Scheme 6, a vs b); while the α-carbon-centered phosphite radical can be easily generated in the presence of HO· (Scheme 6, c vs d), which is in good agreement with the experimental results.

The proposed reaction mechanism in Scheme 7 showed that the C–P bond formation was achieved by the reaction of phosphorus-centered phosphonate radical and the radical **5a′**. While the C–C bond formation was achieved by the reaction of α-carbon-centered phosphite radical and the radical **5a′**.



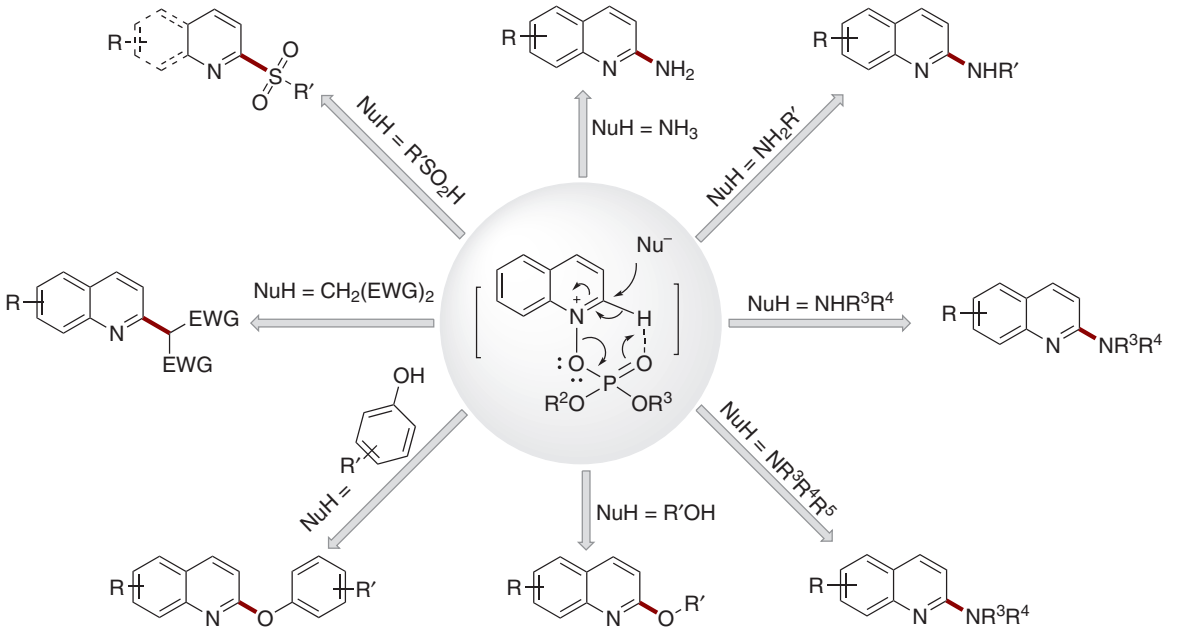
Scheme 6: Proton transfer pathways and the corresponding free energy barriers.



Scheme 7: Proposed reaction mechanism.

H-Phosphonates as promoter for the transformation of heteroaromatic *N*-oxides

Heteroaromatic *N*-oxides such as pyridine *N*-oxides, quinoline *N*-oxides, often serve as important intermediates for the activation and functionalization of the corresponding parent ring [46]. Subsequently, numerous efforts have been devoted to the development of novel and efficient methods for the transformation of heteroaromatic *N*-oxides [47]. In the course of our continuing efforts in developing reactions of *H*-phosphonates [48–50], we have discovered that *H*-phosphonates are a class of powerful activator for heteroaromatic *N*-oxides. By using *H*-phosphonates as mediator, functionalization of quinoline *N*-oxides such as 2-amination, 2-alkylation, 2-sulfonation, 2-aryloxylation etc. were achieved (Scheme 8).



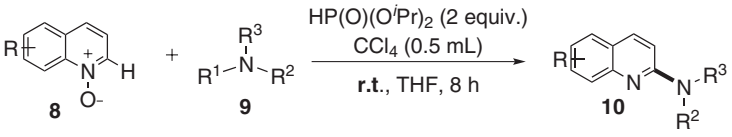
Scheme 8: Overview of *H*-phosphonates mediate for the transformation of heteroaromatic *N*-oxides.

Firstly, we established a straightforward one-pot reaction for the synthesis of 2-(dialkylamino)quinolines at room temperature *via* the reaction of quinoline *N*-oxides and trialkylamines in the presence of diisopropyl *H*-phosphonate and CCl_4 (Scheme 9) [51]. Compared with the previous reported methods for indirect *N*-dialkylamination of quinoline, this strategy has great advantages including high efficiency, readily available starting materials and reagents, and mild reaction conditions.

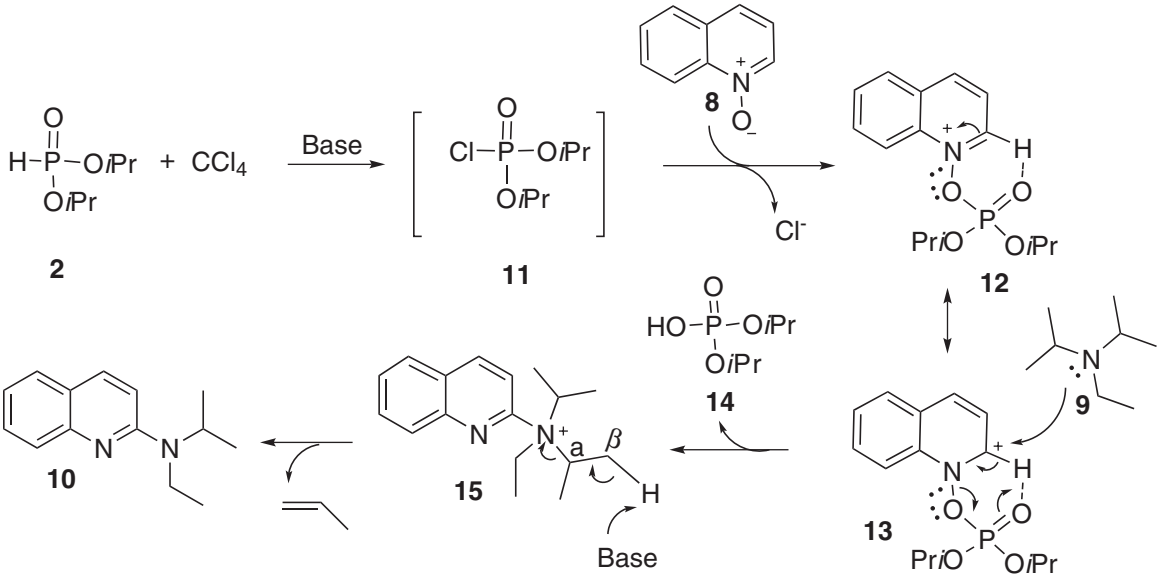
Based on the experimental results, a plausible mechanism was proposed. As shown in Scheme 10, the *H*-phosphonate **2** was firstly converted into the reactive dialkyl chlorophosphate **11** in the presence of CCl_4 and triethylamine, as in the Atherton–Todd reaction. Subsequently, the addition of the intermediate **11** and quinoline *N*-oxide **8** afford the quinolinium cation **12** (or **13**), in which an energetically favorable six-membered ring was formed due to the intramolecular hydrogen bond. Subsequently, addition of tertiary amine **9** with **13** generated the intermediate **15** by releasing phosphate **14**. Finally, deprotonation of **15** by the amine as base led to the desired product **10**.

However, the above-mentioned metal-free synthetic strategy cannot synthesize 2-alkyl(aryl)aminoquinolines and 2-aminoquinolines. Subsequently, primary amines and secondary amines were successfully employed as substrate for the construction of 2-aminoquinolines derivatives. After optimization of the reaction conditions, the one-pot reaction of quinoline *N*-oxides with ammonia, primary amines and secondary amines were achieved in the presence of K_2CO_3 (2 equiv.), diethyl *H*-phosphonate (2 equiv.) and CCl_4 (0.5 mL) for 3 h at room temperature (Scheme 11). A large variety of 2-dialkylaminoquinolines as well as 1-dialkylaminoisoquinolines were successfully synthesized [52].

Following the success of the 2-amination of quinoline *N*-oxides by using primary, secondary and tertiary amines as nucleophiles, we further using *H*-phosphonate as the activator of quinoline *N*-oxides to explored the C–C, C–O, C–S bond formation at C-2 position from the reaction of quinoline *N*-oxides with different



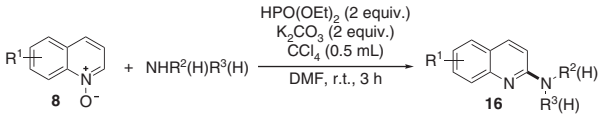
Scheme 9: *H*-Phosphonate-mediated amination of quinoline *N*-oxides with tertiary amines.



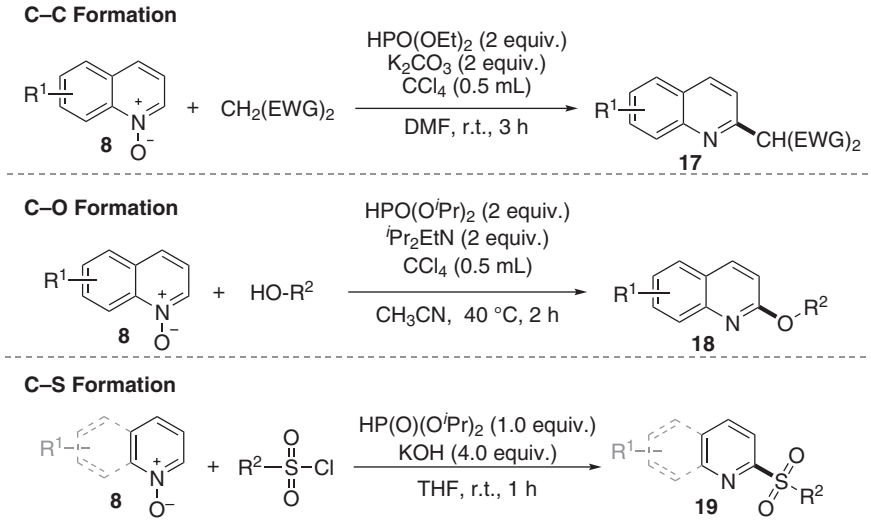
Scheme 10: Proposed mechanism.

nucleophiles including active methylene compounds [52], phenols (or alcohols) [53], and sulfonyl chlorides (or sulfinate salts) [54] (Scheme 12).

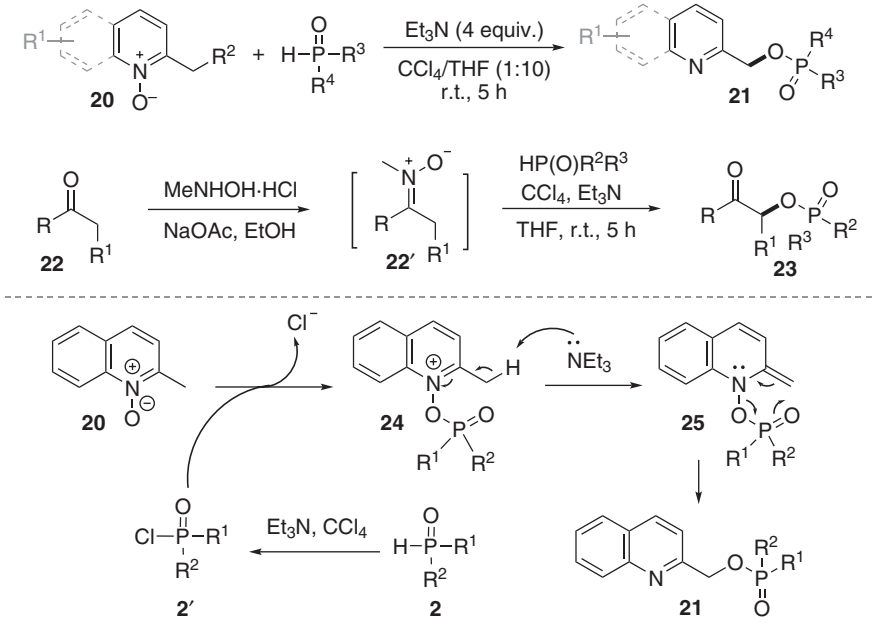
Moreover, when 2-methylquinoline *N*-oxides **20** were applied as substrates with dialkyl *H*-phosphonates in the presence of CCl_4 and Et_3N, the novel multiheteroatom (N, O and P) [3,3]-sigmatropic rearrangement



Scheme 11: *H*-Phosphonate-mediated amination of quinoline *N*-oxides with secondary and primary amines.



Scheme 12: *H*-Phosphonate-mediated transformation of quinoline *N*-oxides.



Scheme 13: *H*-Phosphonate in the [3,3]-sigmatropic rearrangement and the proposed mechanism.

were observed giving 2-(*N*-heteroaryl) methyl phosphates **21** [55]. Additionally, the biologically attractive α-keto phosphates **23** could also be synthesized by reaction of nitrones **22′** with dialkyl *H*-phosphonates by using this protocol at room temperature. The preliminary mechanistic studies showed that the dialkyl *H*-phosphonate **2** initially reacts with CCl_4 and Et_3N to form dialkylchlorophosphate **2′**. Then the nucleophilic addition-elimination of 2-methyl quinolone *N*-oxide **20** to **2′** would give intermediate **24**. Subsequently, Et_3N removes the acidic hydrogen of **24**, giving intermediate **25** which undergoes spontaneous [3,3]-rearrangement leading to the formation of product **21** (Scheme 13).

Conclusion

In summary, from the above-mentioned advances in the application of *H*-phosphonates, it can be concluded that the *H*-phosphonates are a class of useful feedstocks for the construction of C–P bond and activation of quinoline *N*-oxides for the synthesis of 2-functionalized quinolines. Such findings will open new avenues for the application of *H*-phosphonates in organic synthesis.

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References

[1] A. K. Bhattacharya, G. Thyagarajan. *Chem. Rev.* **81**, 415 (1981).
[2] B. A. Arbusow. *Pure Appl. Chem.* **9**, 307 (1964).
[3] T. Hirao, T. Masunaga, Y. Ohshiro, T. Agawa. *Synthesis* **1981**, 56 (1981).
[4] M. C. Kohler, J. G. Sokol, R. A. Stockland. *Tetrahedron Lett.* **50**, 457 (2009).
[5] S. Li, T. Chen, Y. Saga, L.-B. Han. *RSC Adv.* **5**, 71544 (2015).
[6] B. Kaboudin, A. Donyavi, F. Kazemi. *Synthesis* **50**, 170 (2018).
[7] S. S. Le Corre, M. Berchel, H. Couthon-Gourves, J.-P. Haelters, P.-A. Jaffres. *Beilstein J. Org. Chem.* **10**, 1166 (2014).
[8] P. A. Volkov, N. N. Pogodaeva, N. I. Ivanova, K. O. Khrapova, L. I. Larina, B. G. Sukhov, Y. V. Gatilov, N. K. Gusarova, B. A. Trofimov. *Tetrahedron Lett.* **55**, 4927 (2014).
[9] X. Chen, Y. Yu, L. Qu, X. Liao, Y. Zhao. *Synth. Commun.* **34**, 493 (2004).
[10] Y. H. Wu, Q. L. Wu, W. P. Wang, X. C. Wang, Z. J. Quan. *Adv. Synth. Catal.* **360**, 2382 (2018).
[11] E. D. Matveeva, T. A. Podrugina, E. V. Tishkovskaya, L. G. Tomilova, N. S. Zefirov. *Synlett*. 2321 (2003).
[12] X. Cheng, R. Goddard, G. Buth, B. List. *Angew. Chem. Int. Ed.* **47**, 5079 (2008).
[13] M. Ohara, S. Nakamura, N. Shibata. *Adv. Synth. Catal.* **353**, 3285 (2011).
[14] M. P. Placidi, M. Botta, F. K. Kalman, G. E. Hagberg, Z. Baranyai, A. Krenzer, A. K. Rogerson, I. Toth, N. K. Logothetis, G. Angelovski. *Chem. Eur. J.* **19**, 11644 (2013).
[15] S. T. Disale, S. R. Kale, S. S. Kahandal, T. G. Srinivasan, R. V. Jayaram. *Tetrahedron Lett.* **53**, 2277 (2012).
[16] Z. Qu, X. Chen, J. Yuan, Y. Bai, T. Chen, L. Qu, F. Wang, X. Li, Y. Zhao. *Tetrahedron* **68**, 3156 (2012).
[17] K. D. Troev. *Chemistry and Application of H-Phosphonates*, Elsevier Science Ltd, Amsterdam (2006).
[18] Y. Zhu, T. Chen, S. Li, S. Shimada, L.-B. Han. *J. Am. Chem. Soc.* **138**, 5825 (2016).
[19] T. Hirai, L.-B. Han. *J. Am. Chem. Soc.* **128**, 7422 (2006).
[20] L.-B. Han, C. Zhang, H. Yazawa, S. Shimada. *J. Am. Chem. Soc.* **126**, 5080 (2004).
[21] X. Ma, Q. Xu, H. Li, C. Su, L. Yu, X. Zhang, H. Cao, L.-B. Han. *Green Chem.* **20**, 3408 (2018).
[22] W. Miao, Y. Gao, X. Li, Y. Gao, G. Tang, Y. Zhao. *Adv. Synth. Catal.* **354**, 2659 (2012).
[23] P. Zhang, L. Zhang, Y. Gao, J. Xu, H. Fang, G. Tang, Y. Zhao. *Chem. Commun.* **51**, 7839 (2015).
[24] H. Zhang, W. Li, C. Zhu. *J. Org. Chem.* **82**, 2199 (2017).
[25] P. Zhang, J. Ying, G. Tang, Y. Zhao. *Org. Chem. Front.* **4**, 2054 (2017).
[26] Y.-N. Ma, S.-X. Li, S.-D. Yang. *Acc. Chem. Res.* **50**, 1480 (2017).
[27] Y.-M. Li, M. Sun, H.-L. Wang, Q.-P. Tian, S.-D. Yang. *Angew. Chem. Int. Ed.* **52**, 3972 (2013).

[28] H. M. Guo, Q. Q. Zhou, X. Jiang, D. Q. Shi, W. J. Xiao. *Adv. Synth. Catal.* **359**, 4141 (2017).
[29] J. Xuan, T.-T. Zeng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao. *Chem. Eur. J.* **21**, 4962 (2015).
[30] W. C. Yang, P. Dai, K. Luo, Y. G. Ji, L. Wu. *Adv. Synth. Catal.* **359**, 2390 (2017).
[31] W.-C. Yang, K. Wei, X. Sun, J. Zhu, L. Wu. *Org. Lett.* **20**, 3144 (2018).
[32] W.-B. Sun, J.-F. Xue, G.-Y. Zhang, R.-S. Zeng, L.-T. An, P.-Z. Zhang, J.-P. Zou. *Adv. Synth. Catal.* **358**, 1753 (2016).
[33] X.-Q. Pan, L. Wang, J.-P. Zou, W. Zhang. *Chem. Commun.* **47**, 7875 (2011).
[34] J.-A. Li, P.-Z. Zhang, K. Liu, A. Shoberu, J.-P. Zou, W. Zhang. *Org. Lett.* **19**, 4704 (2017).
[35] C.-K. Li, D.-L. Zhang, O. O. Olamiji, P.-Z. Zhang, A. Shoberu, J.-P. Zou, W. Zhang. *Synthesis* **50**, 2968 (2018).
[36] Y. He, H. Wu, F. D. Toste. *Chem. Sci.* **6**, 1194 (2015).
[37] O. Berger, J.-L. Montchamp. *Chem. Rec.* **17**, 1203 (2017).
[38] H. C. Fisher, O. Berger, F. Gelat, J.-L. Montchamp. *Adv. Synth. Catal.* **356**, 1199 (2014).
[39] O. Berger, C. Petit, E. L. Deal, J.-L. Montchamp. *Adv. Synth. Catal.* **355**, 1361 (2013).
[40] K. M. Maloney, J. Y. L. Chung. *J. Org. Chem.* **74**, 7574 (2009).
[41] X. Li, G. Hu, P. Luo, G. Tang, Y. Gao, P. Xu, Y. Zhao. *Adv. Synth. Catal.* **354**, 2427 (2012).
[42] W. Wei, J.-X. Ji. *Angew. Chem. Int. Ed.* **50**, 9097 (2011).
[43] X. Chen, X. Li, X.-L. Chen, L.-B. Qu, J.-Y. Chen, K. Sun, Z.-D. Liu, W.-Z. Bi, Y.-Y. Xia, H.-T. Wu, Y.-F. Zhao. *Chem. Commun.* **51**, 3846 (2015).
[44] X. Chen, X. Chen, X. Li, C. Qu, L. Qu, W. Bi, K. Sun, Y. Zhao. *Tetrahedron* **73**, 2439 (2017).
[45] X.-L. Chen, X. Li, L.-B. Qu, Y.-C. Tang, W.-P. Mai, D.-H. Wei, W.-Z. Bi, L.-K. Duan, K. Sun, J.-Y. Chen, D.-D. Ke, Y.-F. Zhao. *J. Org. Chem.* **79**, 8407 (2014).
[46] E. N. da Silva Junior, G. A. M. Jardim, R. S. Gomes, Y.-F. Liang, L. Ackermann. *Chem. Commun.* **54**, 7398 (2018).
[47] G. Yan, A. J. Borah, M. Yang. *Adv. Synth. Catal.* **356**, 2375 (2014).
[48] X. Li, X.-L. Chen, Q. Zhang, L.-B. Qu, W.-Z. Bi, K. Sun, J.-Y. Chen, X. Chen, Y.-F. Zhao. *RSC Adv.* **5**, 5004 (2015).
[49] J.-Y. Chen, X.-L. Chen, X. Li, L.-B. Qu, Q. Zhang, L.-K. Duan, Y.-Y. Xia, X. Chen, K. Sun, Z.-D. Liu, Y.-F. Zhao. *Eur. J. Org. Chem.* **2015**, 314 (2015).
[50] H. Ma, S. Liu, S. Zhu, W. Bi, X. Chen, Y. Zhao. *Phosphorus, Sulfur Silicon Relat. Elem.* **192**, 887 (2017).
[51] X. Chen, X. Li, Z. Qu, D. Ke, L. Qu, L. Duan, W. Mai, J. Yuan, J. Chen, Y. Zhao. *Adv. Synth. Catal.* **356**, 1979 (2014).
[52] W.-Z. Bi, K. Sun, C. Qu, X.-L. Chen, L.-B. Qu, S.-H. Zhu, X. Li, H.-T. Wu, L.-K. Duan, Y.-F. Zhao. *Org. Chem. Front.* **4**, 1595 (2017).
[53] W.-Z. Bi, C. Qu, X.-L. Chen, L.-B. Qu, Z.-D. Liu, K. Sun, X. Li, Y.-F. Zhao. *Eur. J. Org. Chem.* **2017**, 5125 (2017).
[54] K. Sun, X.-L. Chen, X. Li, L.-B. Qu, W.-Z. Bi, X. Chen, H.-L. Ma, S.-T. Zhang, B.-W. Han, Y.-F. Zhao, C.-J. Li. *Chem. Commun.* **51**, 12111 (2015).
[55] Y. Yang, C. Qu, X. Chen, K. Sun, L. Qu, W. Bi, H. Hu, R. Li, C. Jing, D. Wei, S. Wei, Y. Sun, H. Liu, Y. Zhao. *Org. Lett.* **19**, 5864 (2017).