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MS 4A-PROMOTED AQUEOUS PHOSPHO-ALDOL-BROOK REARRANGEMENT REACTION OF ISATINS

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Abstract – An efficient, simple, environment-friendly, and low-cost protocol for the hydrophosphonation of isatins using inexpensive and non-toxic MS 4A as a recyclable additive in water has been developed. This protocol is also suitable for the aldol reaction of isatin with acetone or acetophenone.

α-Hydroxyphosphonate derivatives have garnered significant attention for their diverse biological activities such as anticancer, antifungal, antibacterial, anti-inflammatory, and antiviral activities.[1–5] These derivatives are widely used in pharmaceutical applications, including enzyme inhibitors of renin,[6] EPSP synthase,[7] and HIV protease.[8] In addition, several studies have reported that α-oxindole-phosphonates could be obtained from α-hydroxyphosphates via the Brook rearrangement reaction in the presence of specific bases (Figure 1).[9–12] Furthermore, α-oxindole-phosphonates are also useful synthetic intermediates of α-substituted phosphonyl compounds.[13-16] Recently, Miao *et al.*[13] (Scheme 1c) and Guiry *et al.*[14] used α-oxindole-phosphonates as synthetic intermediates to construct tetrabenzohydrofuran spirooxindoles and α-aryl oxindoles, respectively.

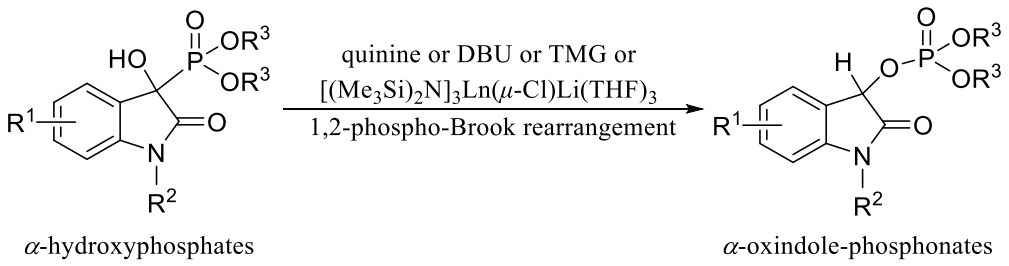
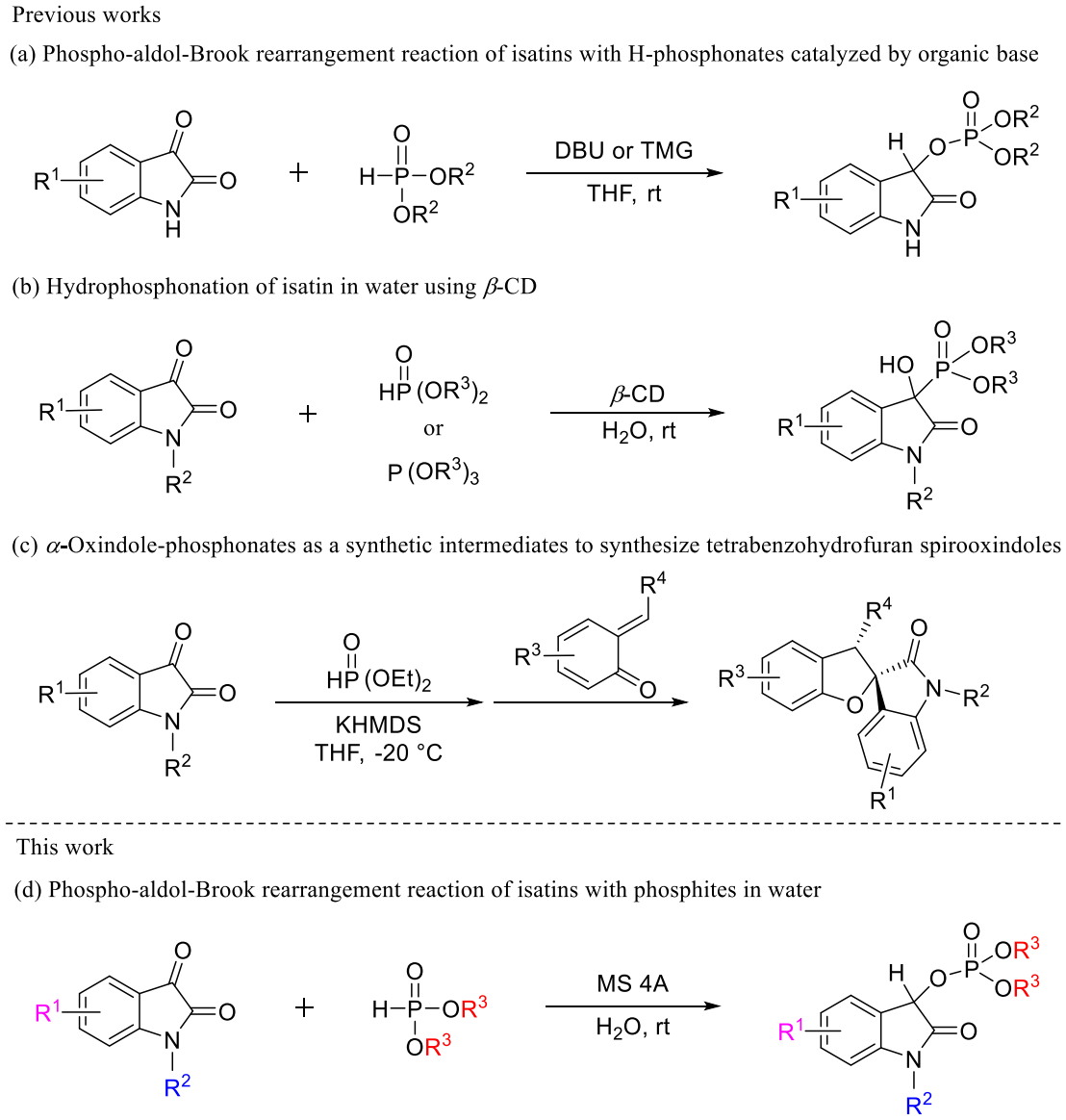


Figure 1. α-Hydroxyphosphates and α-oxindole-phosphonates

For the aforementioned reasons, many protocols have been reported for the hydrophosphonation of isatins, such as nano-rod ZnO,[17] Amberlyst-15,[18] strong organic base (Scheme 1a),[9] γ-Fe_2O_3-immobilized

1,5,7-triazabicyclo[4.4.0]dec-5-ene,[19] PEG-400,[20] Cu catalyst,[21] and *n*-BuLi.[22] These protocols also resulted in the corresponding product in high yields, but were limited to the use of metal catalysts or strong bases, toxic solvents, heating and sonication conditions, and high cost of reactants.

From the perspective of green chemistry,[23] it is considerable to use water rather than organic solvents.[24] However, to the best of our knowledge, there is only one protocol of the hydrophosphonation of isatins in water using *β*-CD with heating pretreatment that has been reported (Scheme 1b).[25] Therefore, the hydrophosphonation of isatin with a simpler experimental operation in water requires further research.

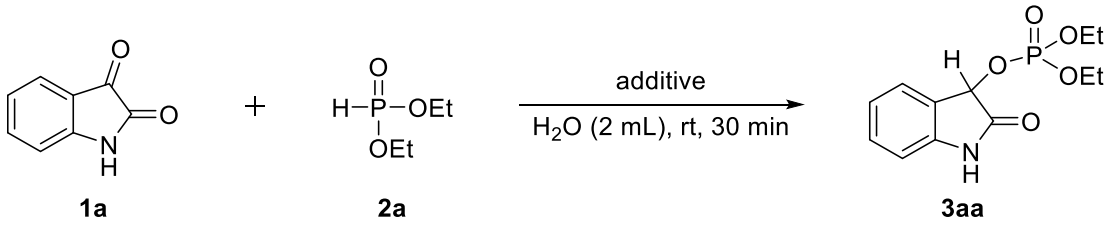


Scheme 1. Previous works and this work

On the other hand, molecular sieves (MS) are deemed as good additives not only for their dehydration property and weak basicity for promoting reactions, but also for their inexpensiveness, non-toxicity, and

recyclability.[26,27] Based on the aforementioned background, in this paper, we wish to report an efficient, simple, environment-friendly, and low-cost protocol for the hydrophosphonation of isatins using inexpensive and non-toxic MS 4A as a recyclable additive in water (Scheme 1d). This protocol is also suitable for the aldol reaction of isatin with acetone or acetophenone.

Table 1. Optimization of reaction conditions[a]



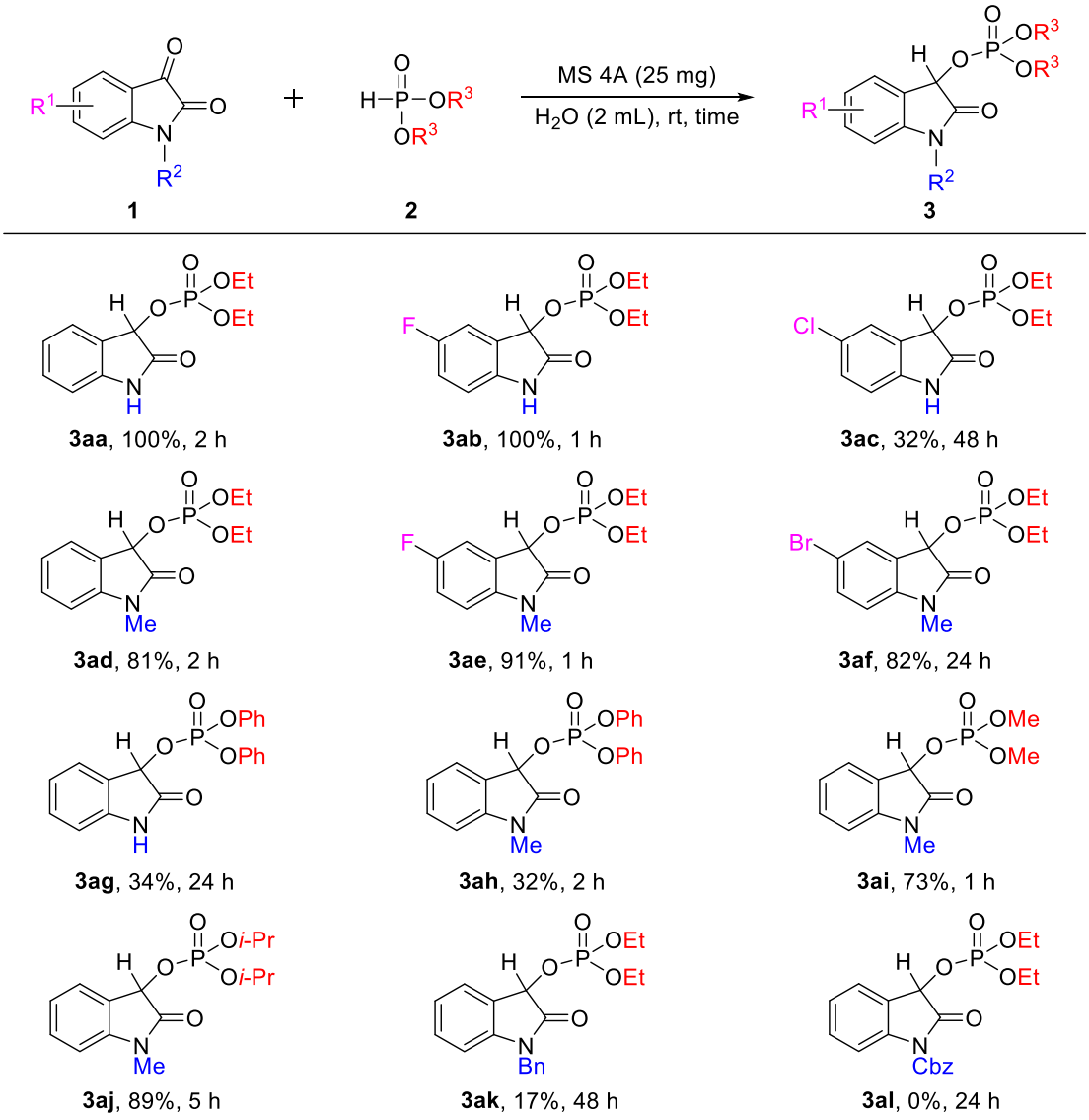
1a **2a** **3aa**

Entry	Additive	Yield[b]/%
1	MS 3A (10 mg)	38
2	MS 4A (10 mg)	49
3	MS 5A (10 mg)	23
4	MS 13X (10 mg)	41
5	NaOH (1 M)	0
6	none	0
7	MS 4A (1 mg)	3
8	MS 4A (5 mg)	35
9	MS 4A (15 mg)	58
10	MS 4A (20 mg)	66
11	MS 4A (25 mg)	83
12	MS 4A (50 mg)	82
14	MS 4A (75 mg)	75
15	MS 4A (100 mg)	74
16[c]	MS 4A (25 mg)	84
17[c, d]	MS 4A (25 mg)	88
18[c, e]	MS 4A (25 mg)	100
19[c, e, f]	MS 4A (25 mg)	89

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), and H_2O (2 mL) at rt for 30 min. [b]Isolated yield. [c]0.12 mmol **2a** was used. [d]1 h. [e]2 h. [f]Commercially MS dried up by a heat gun without being powered by a mortar prior to use.

Initially, isatin **1a** (0.1 mmol) was reacted with diethyl phosphite **2a** (0.15 mmol) in H_2O with various MS (Table 1, Entries 1-4). MS 4A resulted in the desired product **3aa** in the highest yield compared to other MS (Entry 2). No desired product was obtained when NaOH (1 M) was used as an additive or no additive (Entries 5 and 6). The effect of the amount of MS 4A was also tested, and the yield of product **3aa** was improved up to 83% (Entries 7-15). Decrease of diethyl phosphite **2a** from 0.15 to 0.12 mmol did not affect the yield of product **3aa** (Entry 16). Longer reaction times improved yields (Entries 16-18). Quantitative **3aa** was obtained when 0.12 mmol diethyl phosphite **2a** was used, and the reaction time was

extended to 2 h (Entry 18). MS without being powdered by a mortar decreased yield to 89% (Entry 19). Overall, the optimal reaction conditions were determined to be isatin **1** (0.1 mmol), phosphite **2** (0.12 mmol) with MS 4A (25 mg) in water (2 mL) at rt.

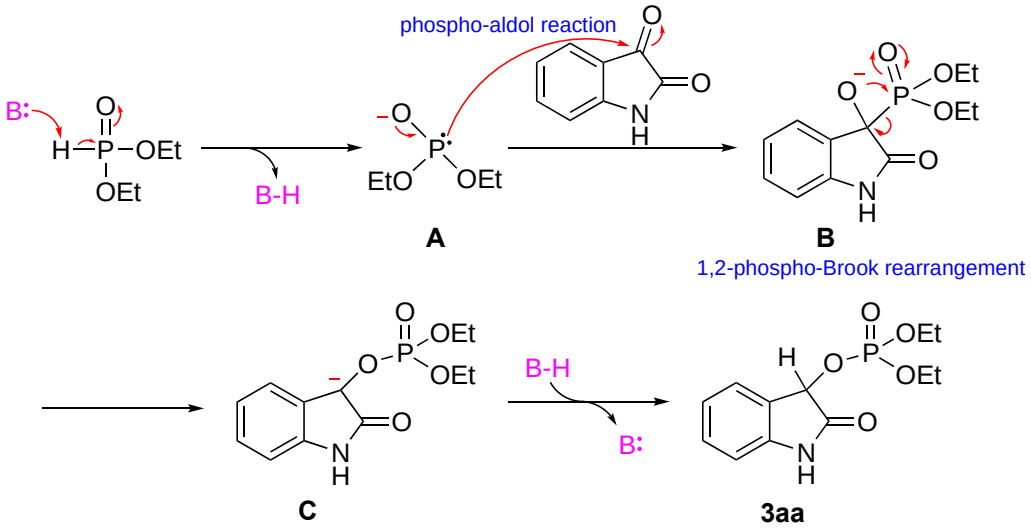


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), and MS 4A (25 mg) in H_2O (2 mL) at rt. [b]Isolated yield.

Scheme 2. Substrate scope of isatins and phosphites[a,b]

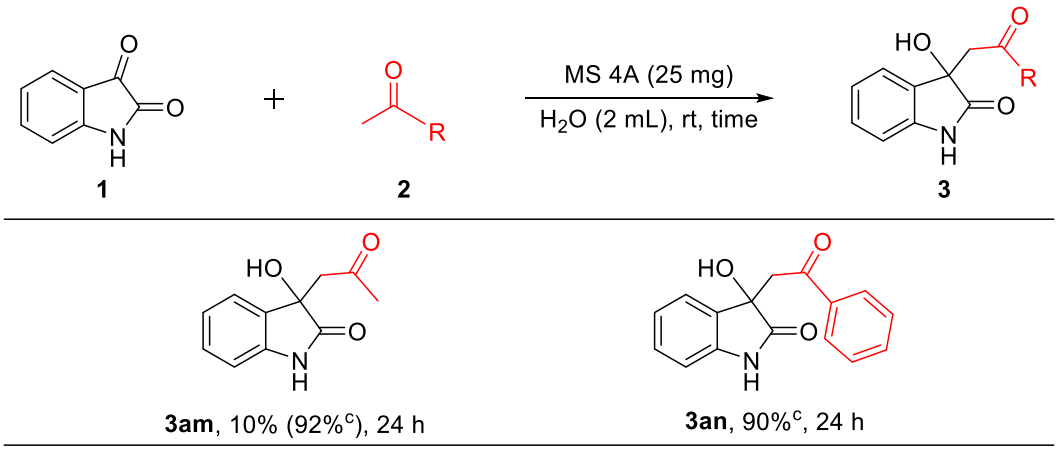
With the optimal reaction conditions in hand, we subsequently investigated the phospho-aldol-Brook rearrangement reaction of isatins **1** with phosphites **2** (Scheme 2). Isatins bearing halogen atoms, such as fluoro-, resulted in the corresponding products in quantitative and excellent yields in a short reaction time, respectively (**3ab** and **3ae**). However, the chloro-atom lowered the dispersibility of isatin in water to afford a 32% yield (**3ac**). *N*-Methylisatin and halogen-substituted *N*-methylisatin resulted in the desired products in high yields (**3ad-3af**). The aromatic group-substituted phosphite, for instance, diphenyl

phosphite resulted in the desired product in moderate yields (**3ag** and **3ah**). Fortunately, dimethyl phosphite and diisopropyl phosphite also reacted with *N*-methylisatin to provide the corresponding products in good to high yields (**3ai** and **3aj**). Poor results were obtained when benzyl-protected and benzyloxycarbonyl-protected isatins were used (**3ak** and **3al**).



Scheme 3. Proposed reaction mechanism

Considering previous studies,[28,29] the proposed reaction mechanism is shown in Scheme 3. First, diethyl phosphite was deprotonated by MS 4A, which is a weak base to generate intermediate **A**. Second, the aldol reaction occurred between intermediate **A** and isatin to generate alkoxide **B**. Thereafter, the 1,2-phospho-Brook rearrangement reaction proceeded in alkoxide **B** to yield intermediate **C**. Finally, product **3aa** was obtained after protonation.



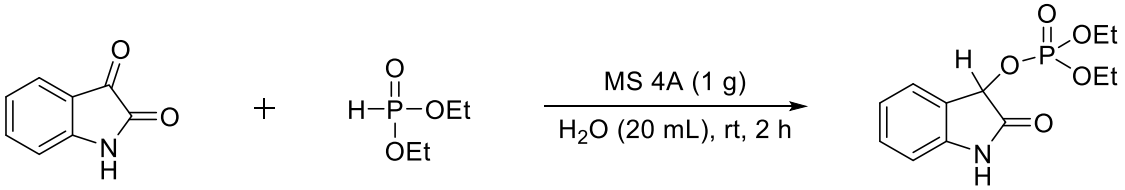
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), and MS 4A (25 mg) in H_2O (2 mL) at rt. [b]Isolated yield. [c]1 mmol **2** was used.

Scheme 4. MS 4A-promoted aldol reaction of isatin with ketones[a,b]

Furthermore, the aldol reaction of isatin with acetone or acetophenone also occurred via this procedure (Scheme 4). Isatin reacted with acetone under the optimized reaction conditions to result in the corresponding product in only 10% yield because of the lack of acetone. An increase in acetone to 10 equivalents afforded the product in 92% yield (**3am**). The desired product was obtained in 90% yield under the same reaction conditions when 10 equivalents of acetophenone were used (**3an**).

Finally, we also conducted gram-scale recovery/reuse experiments under the optimized reaction conditions using recycled MS 4A several times (Table 2). Phospho-aldol-Brook rearrangement product **3aa** was obtained in 96% yield in the first run (Entry 1). After each reaction, the MS 4A was washed with MeOH and H_2O three times. To our satisfaction, the corresponding product **3aa** was obtained in excellent yield even after four runs (Entries 2-4).

Table 2. Gram-scale recovery/reuse experiments[a,b]



1a 1.03 g, 7 mmol + **2a** 1.2 eq. → **3aa**

Entry	Run	Yield[c]/%
1	1st	96
2	2nd	98
3	3rd	95
4	4th	93

[a]Reaction conditions: **1a** (7 mmol), **2a** (8.4 mmol), and MS 4A (1 g) in H_2O (20 mL) at rt for 2 h. [b]The recovered MS 4A was washed with MeOH and H_2O. [c]Isolated yield.

In conclusion, we developed an efficient, simple, environment-friendly, and low-cost protocol for the hydrophosphonation of isatins using inexpensive and non-toxic MS 4A as a recyclable additive in water. Gram-scale recovery/reuse experiments indicated that large-scale synthesis is possible and that MS 4A can be used as a recyclable additive. This protocol can also be used for the reaction of isatin with acetone or acetophenone. Further investigations for extending reactions in water to the development of green chemistry are currently underway in our laboratory.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded in 500 MHz and 125 MHz, respectively, using a Bruker spectrometer. Chemical shifts are expressed in parts per million (δ-value), using TMS as an internal standard. IR spectra were recorded on a Bruker TENSOR 27 spectrometer using KBr discs. MS was powdered by a mortar and dried up by a heat gun prior to use. All reactions were performed under open air condition.

General Procedure for Synthesis of Products 3. In a 30 mL two-necked flask, isatins **1** (0.1 mmol) and phosphites **2** (0.12 mmol), H_2O (2 mL) was added in the presence of MS 4A (25 mg). The reaction mixture was stirred at rt. After the reaction, the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and saturated brine, then dried with Na_2SO_4. After filtration, the solvents were removed by evaporation under reduced pressure. The residue was purified by thin-layer chromatography (TLC) with hexane/EtOAc = 3/1 to afford the corresponding products **3**.

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SUPPORTING INFORMATION

Supplementary data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27427/104/1

REFERENCES

1. P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193.
2. A. H. Kategaonkar, R. U. Pokalwar, S. S. Sonar, V. U. Gawali, B. B. Shingate, and M. S. Shingare, *Eur. J. Med. Chem.*, 2010, **45**, 1128.
3. N. Zuo and H. W. He, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2008, **183**, 621.
4. S. R. Malwal, L. Chen, H. Hicks, F. Qu, W. Liu, A. Shillo, W. X. Law, J. Zhang, N. Chandnani, X. Han, Y. Zheng, C. C. Chen, R. T. Guo, A. Abdelkhalek, M. N. Seleem, and E. Oldfield, *J. Med. Chem.*, 2019, **62**, 2564.
5. Z. Rádai and G. Keglevich, *Molecules*, 2018, **23**, 1493.
6. D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, C. A. Free, W. L. Rogers, S. A. Smith, J. M. DeForrest, R. S. Oehl, and E. W. Petrillo, *J. Med. Chem.*, 1995, **38**, 4557.

7. M. J. Miller, D. S. Braccolino, D. G. Cleary, S. D. Corey, J. L. Font, K. J. Gruys, C. Y. Han, K. C. Lin, P. D. Pansegrau, J. E. Ream, D. Schnur, A. Shah, and M. C. Walker, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1993, **76**, 115.
8. B. Stowasser, K. H. Budt, L. Jian-Qi, A. Peyman, and D. Ruppert, *Tetrahedron Lett.*, 1992, **33**, 6625.
9. F. Wei, L. Guogui, H. Xiaofei, J. Jun, and W. Xingwang, *Chin. J. Org. Chem.*, 2014, **34**, 1177.
10. L. Wang, Z. Yao, F. Xu, and Q. Shen, *Heteroat. Chem.*, 2012, **23**, 449.
11. L. Peng, L. L. Wang, J. F. Bai, L. N. Jia, Q. C. Yang, Q. C. Huang, X. Y. Xu, and L. X. Wang, *Tetrahedron Lett.*, 2011, **52**, 6207.
12. S. Chen, S. Guo, F. He, Y. Zhang, X. Wu, and J. Wu, *Catalysts*, 2020, **10**, 1445.
13. X. Zhang, Y. Gao, Y. Liu, and Z. Miao, *J. Org. Chem.*, 2021, **86**, 8630.
14. B. V. Rokade and P. J. Guiry, *J. Org. Chem.*, 2020, **85**, 6172.
15. Y. Li, J. Jie, H. Li, H. Yang, and H. Fu, *Org. Lett.*, 2021, **23**, 6499.
16. Q. Chen, Y. Teng, and F. Xu, *Org. Lett.*, 2021, **23**, 4785.
17. M. Hosseini-Sarvari and M. Tavakolian, *Can. J. Chem.*, 2013, **91**, 1117.
18. K. U. Maheswara Rao, G. D. Reddy, and C. M. Chung, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2013, **188**, 1104.
19. X. J. Yang, *Appl. Organomet. Chem.*, 2014, **28**, 471.
20. L. Nagarapu, R. Mallepalli, U. N. Kumar, P. Venkateswarlu, R. Bantu, and L. Yeramanchi, *Tetrahedron Lett.*, 2012, **53**, 1699.
21. T. Deng, H. Wang, and C. Cai, *Org. Biomol. Chem.*, 2014, **12**, 5843.
22. C. Liu, Y. Zhang, Q. Qian, D. Yuan, and Y. Yao, *Org. Lett.*, 2014, **16**, 6172.
23. K. N. Ganesh, D. Zhang, S. J. Miller, K. Rossen, P. J. Chirik, M. C. Kozlowski, J. B. Zimmerman, B. W. Brooks, P. E. Savage, D. T. Allen, and A. M. Voutchkova-Kostal, *J. Org. Chem.*, 2021, **86**, 8551.
24. M. O. Simon and C. J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415.
25. J. Shankar, K. Karnakar, B. Srinivas, and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2010, **51**, 3938.
26. F. Chen, X. Jiang, J. C. Er, and Y. Y. Yeung, *Tetrahedron Lett.*, 2010, **51**, 3433.
27. Á. Magyar, K. Juhász, and Z. Hell, *Synthesis*, 2021, **53**, 279.
28. G. Pallikonda, R. Santosh, S. Ghosal, and M. Chakravarty, *Tetrahedron Lett.*, 2015, **56**, 3796.
29. M. Hayashi and S. Nakamura, *Angew. Chem. Int. Ed.*, 2011, **50**, 2249.