RSC Advances

This article can be cited before page numbers have been issued, to do this please use: G. Tang, J. Wu, Y. Gao, X. Zhao, L. Zhang, W. Chen and Y. Zhao, *RSC Adv.*, 2015, DOI: 10.1039/C5RA22570A.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA22570A

Journal Name

RSCPublishing

COMMUNICATION

Copper-Catalyzed Cycloaddition between Hydrogen Phosphonates and Activated Alkenes: Synthesis of Phosphonoisoquinolinediones

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

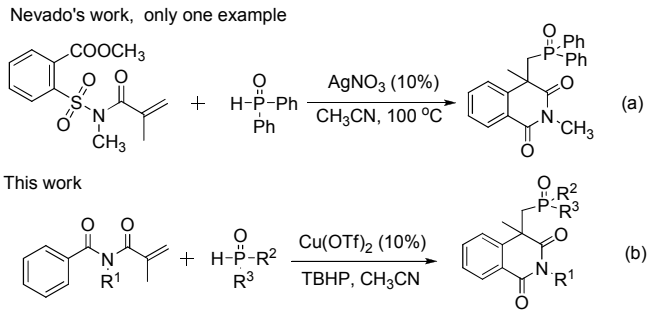
www.rsc.org/

Ju Wu,[a] Yuzhen Gao,[a] Xin Zhao,[a] Liangliang Zhang,[a] Weizhu Chen,[a,b] Guo Tang,[a,*] and Yufen Zhao[a]

A new, general method for the synthesis of phosphonoisoquinolinediones has been achieved via copper-catalyzed phosphonation-cyclization of various methacryloylbenzamides with P(O)H compounds. This transformation allows the direct formation of a P-C bond and the construction of an isoquinolinedione ring in one reaction.

As one of the most important heterocyclic compounds, substituted isoquinolinedione derivatives are important scaffolds in a broad array of biologically active compounds. Over the last 20 years, more isoquinolinedione-containing compounds as drug candidates have increased greatly.[1] Thus, the development of new methods for their synthesis has been a major focus of study.[2] Among the synthetic methods to obtain isoquinolinedione derivatives, the difunctionalization reaction of alkenes through a radical process is well known, including direct intramolecular aryltrifluoromethylation [2d] and arylphosphonylation [3] of activated alkenes.

As we know, organophosphorus compounds have broad applications in the fields of organic synthesis, pharmaceuticals and agrochemicals owing to its unique properties.[4] Heterocyclic phosphonate compounds are ubiquitous and exhibit interesting biological activities and potential pharmaceutical applications.[5] If both phosphonyl group and isoquinolinedione structural motif can be simultaneously introduced into organic compounds, a series of new isoquinolinedione-containing organophosphorus compounds might be expected, and might provide an opportunity to introduce phosphonyl group into the original lead compounds or drugs to adjust their bioactivity. However, the efficient synthesis of molecules bearing both isoquinolinedione motif and phosphonyl group is quite rare. In 2014, Nevado group reported that the reaction of methyl 2-(N-methacryloyl-N-methylsulfamoyl)benzoate with diphenylphosphine oxide in the presence of silver salt led to phosphonoisoquinolinedione.[3] Only one example was provided (Scheme 1 a). Herein, we report the successful realization of this concept with the introduction of phosphonyl radicals for the flexible synthesis of unprecedented phosphonoisoquinolinediones with a quaternary carbon centre. This transformation allows the direct formation of a P-C bond and the construction of a heterocyclic ring in one reaction.

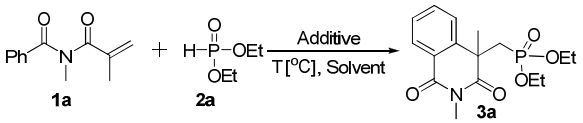


Scheme 1. Synthetic routes to phosphonoisoquinolinediones.

This idea was first examined by using N-methacryloyl-N-methylbenzamide (**1a)** and diethyl *H*-phosphonate (**2a)** as reaction partners (table 1). It has been found that many salts such as copper,[6] silver[7] and manganese[8] can work with $R_2P(O)H$ to form the corresponding phosphonyl radical which promoted phosphonyl radical addition chemistry. In the beginning, various silver and manganese catalysts were tested and all gave moderate yields (entries 1-4, Table 1). In these processes, manganese is used in excess (3 equivalents), which is quite wasteful. For a practical reaction, using readily available and low-cost catalyst for this transformation would be appealing. Gratifyingly, the combined use of $Cu(OAc)_2$ and TBHP (*tert*-butylhydroperoxide) gave **3a** in 40% yield (entry 6). Subsequently, various Cu(II) salts were further checked and the results showed that $Cu(OTf)_2$ was more effective to give the desired product (entries 5-9). However, the attempt to decrease the amount of $Cu(OTf)_2$ was failed (entry 10). Moreover, the yield was reduced to 43% under air (entry 11). Low yield was afforded without copper salt or TBHP (entries 12 and 13). Cu(I) salt and Cu powder couldn't execute this reaction efficiently (entries 14 and 15). After optimization of the reaction conditions, we established an efficient route to the phosphonation–annulation of methacryloylbenzamides (entry 9, table 1).

View Article Online
DOI: 10.1039/C5RA22570A Journal Name

Table 1. Optimization of reaction conditions.[a]

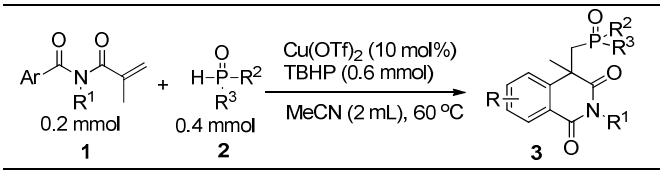


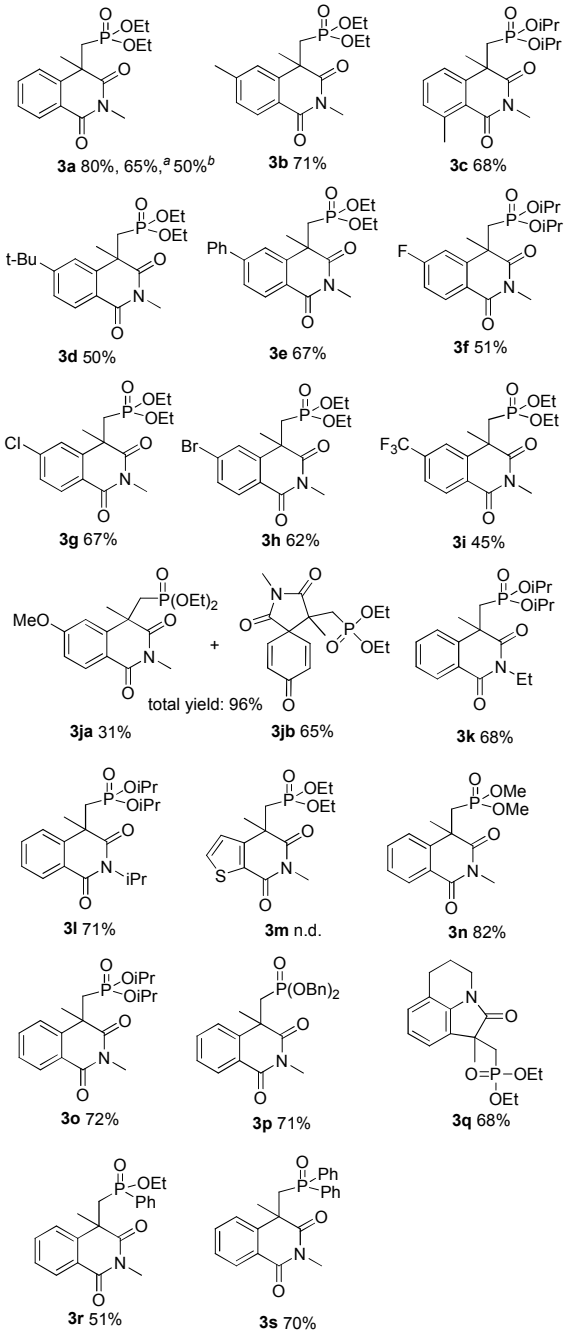
Entry	Additive (equiv)	Solvent	T (°C)	Yield(%)
1	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	60	63
2	$Mn(OAc)_3 \cdot 2H_2O$ (3)	HOAc	70	59
3	$AgNO_3$(0.05)+$Mg(NO_3)_2 \cdot 6H_2O$(0.5)	CH_3CN	100	62
4	$AgNO_3$(0.1)+$Mg(NO_3)_2 \cdot 6H_2O$(0.5)	CH_3CN	100	65
5	$Cu(OAc)_2$ (0.1)+TBHP (3)	CH_3CN	60	40
6	$CuCl_2$ (0.1)+TBHP (3)	CH_3CN	60	15
7	$CuSO_4 \cdot 5H_2O$ (0.1)+TBHP (3)	CH_3CN	60	20
8	$Cu(NO_3)_2 \cdot 3H_2O$ (0.1)+TBHP (3)	CH_3CN	60	48
9	**$Cu(OTf)_2$ (0.1)+TBHP (3)**	**CH_3CN**	**60**	**83**
10	$Cu(OTf)_2$ (0.05)+TBHP (3)	CH_3CN	60	70
11[b]	$Cu(OTf)_2$ (0.1)+TBHP (3)	CH_3CN	60	43
12	TBHP (3)	CH_3CN	60	34
13	$Cu(OTf)_2$ (0.2)	CH_3CN	60	0
14	CuCl (0.1)+TBHP (3)	CH_3CN	60	15
15	Cu powder(0.1)+TBHP (3)	CH_3CN	60	5

[a] *Reaction conditions*: **1a** (0.2 mmol), **2a** (0.4 mmol), additive in solvent (2.0 mL) stirring under nitrogen for 24 h. Oil bath temperature. Yields were determined by ^{31}P NMR based on Ph_3PO as internal standard. [b] Unde air.

With this preliminary result in hand, the results of phosphonation–annulation for methacryloylbenzamides **1** with different H–phosphonates **2** can be summarized as follows. As shown in Table 2, a variety of functional groups on the phenyl ring of methacryloylbenzamides were compatible under this procedure, affording the desired products in moderate to good yields. The alkyl and phenyl substituted benzamide substrates, such as *para*-methyl, *ortho*-methyl, *para*-*tert*-butyl and *para*-phenyl on the aryl ring, reacted with **2a** efficiently and gave the desired products **3b-3e** in good yields. Halogen atoms such as fluoro, chloro, and bromo on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **3f-3h** in moderate to good yields, which could allow for further synthetic transformations. Benzamide substrates bearing CF_3 group reacted smoothly to give the corresponding product in moderate yield (**3i**). When N-methacryloyl-4-methoxy-N-methylbenzamide reacted with **2a**, we acquired both the normal coupling product **3ja** and the dearomatization product **3jb** as a 1:2 mixture in 96% total yield. The product **3jb** was formed by annulation of alkenyl radical with the aryl ring at the carbon atom directly attached to the carbonyl atom to form 1,3,8-trioxo-2-azaspiro compound.[9] The reactivity of N-alkyl substituted substrates was further explored. More bulk alkyl groups at the nitrogen atom such as ethyl and isopropyl groups react with diethyl H-phosphonate (**2a**) furnishing the corresponding isoquinolinedione **3k** and **3l** in 68% and 71% yields, respectively. N-Methacryloyl-N-methylthiophene-2-carboxamide gave a complicated mixture, no **3m** was obtained. Dimethyl, diisopropyl, and dibenzyl H–phosphonates could be also used as substrates, generating the corresponding products (**3n-3p**) in good yields. 1-Methacryloyl-1,2,3,4-tetrahydroquinoline was also a suitable acceptor to extend the applicability of the current method, and led to the formation of product (**3q**) in 68% yield. It is worth noting that ethoxyphenylphosphine oxide and diphenylphosphine oxide can be also applied in the preparation of the corresponding phosphonoisoquinolinediones in moderate yields (**3r** and **3s**).

Table 2. Reaction scope study.





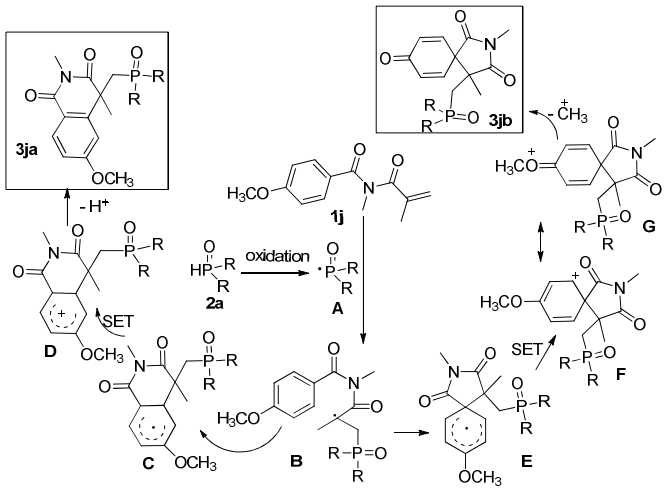
[a] *Reaction conditions*: **1a** (10 mmol), **2a** (20 mmol), $Cu(OTf)_2$ (1.0 mmol), TBHP(30 mmol), CH_3CN (30 mL) stirring under nitrogen for 30 h. [b] **1a** (10 mmol), **2a** (20 mmol), $Cu(OTf)_2$ (0.5 mmol), TBHP(30 mmol), CH_3CN (30 mL) stirring under nitrogen for 30 h.

In order to demonstrate the practical application of this method, N-methacryloyl-N-methylbenzamide (**1a**, 10 mmol) was employed

View Article Online
DOI: 10.1039/C5RA22570A COMMUNICATION

in a gram-scale reaction and delivered **3a** in 65% yield (Table 2). When the loading of $Cu(OTf)_2$ was reduced to 5 mol%, the reaction also afforded **3a** in 50% yield.

No desired product was obtained when 2.0 equiv of TEMPO was added in the reaction of **1a** with **2a** under the optimal conditions. This result indicates that the phosphonyl radicals may be intercepted by TEMPO. According to our previous Cu(II)–TBHP catalytic reaction mechanism study,[6a,c] a plausible mechanism is proposed as shown in Scheme 2. Initially, the reaction of P(O)H **1** with Cu(II) salt and TBHP generates phosphonyl radical **A** which then goes through intermolecular addition onto the carbon-carbon double bond of **2** to produce alkyl radical **B**. Followed by intramolecular attack of the radical **B** on the pendant aromatic ring subsequently provides radical **C**. Subsequently, phosphonoisoquinolinedione **3ka** is formed through oxidation-deprotonation reaction. Alternatively, alkyl radical **B** attacks the aryl ring at the carbon atom directly attached to the carbonyl group to form radical **E**. Cationic intermediate **F** is formed through single-electron oxidation which could afford resonance structure **G**. The intermediate **G** converts into the product **3kb** *via* demethylation.



Scheme 2. Proposed reaction mechanism.

In conclusion, we have successfully developed a facile catalytic method for the preparation of phosphonoisoquinolinediones *via* phosphonation-cyclization of various methacryloylbenzamides with P(O)H compounds. This method provides a rapid access to a broad spectrum of phosphonoisoquinolinediones in moderate to good yields. Moreover, the use of inexpensive Cu(II) catalyst, using readily-prepared methacryloylbenzamides and P(O)H compounds mean that this facile protocol will be attractive for academia and industry.

Acknowledgements

We acknowledge financial support from the Chinese National Natural Science Foundation (21173178, 21232005, 21375113), J1310024, the National Basic Research Program of China (2012CB821600), and the Program for Changjiang Scholars and Innovative Research Team in University.

Notes and references

[a] Department of Chemistry, College of Chemistry and Chemical Engineering, and the Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, Fujian 361005, China Fax: (86)592-2185780; E-mail: t12g21@xmu.edu.cn

[b] The Third Institute of Oceanography of the State Oceanic Administration, Xiamen, Fujian 361005, China

Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra of compounds **3a-3s**. See DOI: 10.1039/c000000x/

1 (*a*) M. Paige, G. Kosturko, G. Bulut, M. Miessau, S. Rahim, J. A. Toretsky, M. L. Brown and A. Uren, *Bioorg. Med. Chem.,* 2014, **22**, 478; (*b*) M. Billamboz, V. Suchaud, F. Bailly, C. Lion, J. Demeulemeester, C. Calmels, M. L. Andréola, F. Christ, Z. Debyser and P. Cotelle, *ACS Med. Chem. Lett.*, 2013, **4**, 606; (*c*) L. Chen, M. Conda-Sheridan, P. V. N. Reddy, A. Morrell, E.-J. Park, T. P. Kondratyuk, J. M. Pezzuto, R. B. van Breemen and M. Cushman, *J. Med. Chem.*, 2012, **55**, 5965; (*d*) M. Billamboz, F. Bailly, C. Lion, N. Touati, H. Vezin, C. Calmels, M. L. Andréola, F. Christ, Z. Debyser and P. Cotelle, *J. Med. Chem.*, 2011, **54**, 1812; (*e*) A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, V. Barone, P. La Colla and R. Loddo, *J. Med. Chem.*, 2002, **45**, 5217.

2 (*a*) M. Billamboz, F. Bailly, M. L. Barreca, L. De Luca, J.-F. Mouscadet, C. Calmels, M.-L. Andréola, M. Witvrouw, F. Christ, Z. Debyser and P. Cotelle *J. Med. Chem.*, 2008, **51**, 7717; (*b*) J. J. Medvedev, M. V. Meleshina, T. L. Panikorovskii, C. Schneider, V. A. Nikolaev, *Org. Biomol. Chem.,* 2015, **13**, 9107; (*c*) M. C Garcia-Gonzalez, E. Hernandez-Vazquez, , R. E. Gordillo-Cruz and L. D. Miranda, *Chem. Commun*., 2015, **51**, 11669; (*d*) L. Zheng, C. Yang, Z. Z. Xu, F. Gao and W. Xia, *J. Org. Chem*., 2015, **80**, 5730; (*e*) C. Yang, X. Zhang, D. Zhang-Negrerie, Y. Du, K. Zhao, *J. Org. Chem*., 2015, **80**, 5320; (*f*) J. Shi, J. Zhou, Y. Yan, J. Jia, X. Liu, H. Song, H. E. Xu, W. Yi, *Chem. Commun*., 2015, **51**, 668.

3 W. Kong, E. Merino and C. Nevado, *Angew. Chem. Int. Ed.*, 2014, **53**, 5078.

4 (*a*) T. Baumgartner, R. Réau, *Chem. Rev.,* 2006, **106**, 4681; (*b*) H. A. McManus, P. J. Guiry, *Chem. Rev.,* 2004, **104**, 4151; (*c*) M. N. Birkholz, Z. Freixa, P. W. N. M. van Leeuwen, *Chem. Soc. Rev.,* 2009, **38**, 1099.

5 A. Arnone, P. Bravo, M. Frigerio, F. Viani and C. Zappalà, *Synthesis,* 1998, 1511; *(b)* H. Krawczyk, K. Wasek, J. Kedzia, J. Wojciechowski and W. M. Wolf, *Org. Biomol. Chem.,* 2008, **6**, 308; *(c)* A. Arnone, P. Bravo, M. Frigerio, A. Mele, B. Vergani and F. Viani, *Eur. J. Org. Chem.,* 1999, 2149; *(d)* M. Frings, I. Thomé, I. Schiffers, F. Pan and C. Bolm, *Chem. Eur. J*., 2014, **20**, 1691; *(e)* A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova and V. S. Petrosyan, *Heteroatom Chemistry*, 2008, **19**, 418; *(f)* P. Dauban and R. H. Dodd, *J. Org. Chem.,* 1997, **62**, 4277; *(g)* R. Mansueto, V. Mallardo, F. M. Perna, A. Salomone and V. Capriati, *Chem. Commun.,* 2013, **49**, 10160.

6 (*a*) P. Zhang, L. Zhang, Y. Gao, J. Xu, H. Fang, G. Tang and Y. Zhao, *Chem. Commun*., 2015, **51**, 7839; (*b*) H. Y. Zhang, L. L. Mao, B. Yang and S. D. Yang, *Chem. Commun*., 2015, **51**, 4101; (*c*) Z. Zhao, W. Xue, Y. Gao, G. Tang and Y. Zhao, *Chem. Asian J.,* 2013, **8**, 713; (*d*) B. Xiong, X. Feng, L. Zhu, T. Chen, Y. Zhou, C. T. Au and S. F. Yin, *ACS Catal.,* 2015, **5**, 537; (*e*) M. Zhou, M. Chen, Y. Zhou, K. Yang, J. Su, J. Du and Q. Song, *Org. Lett.,* 2015, **17**, 1786.

7 (*a*) Y. M. Li, M. Sun, H. L. Wang, Q. P. Tian and S. D. Yang, *Angew. Chem. Int. Ed.,* 2013, **52**, 3972; (*b*) B. Zhang, C. G. Daniliuc and A. Studer, *Org. Lett.,* 2014, **16**, 250; (*c*) M. C. Lamas and A. Studer, *Org. Lett.,* 2011, **13**, 2236; (*d*) 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, and Y. F. Zhao, *Chem. Commun*., 2015, **51**, 3846; (*e*) Z. Z. Zhou, D. P. Jin, L. H. Li, Y. T. He, P. X. Zhou, X. B. Yan, X. Y. Liu and Y. M. Liang, *Org. Lett.,* 2014, **16**, 5616.

8 (*a*) B. B. Snider, *Chem. Rev.*, 1996, **96**, 339; (*b*) W. Liu, D. Zell, M. John, L. Ackermann, *Angew. Chem., Int. Ed.,* 2015, **54**, 13; (*c*) X. Li, J. Xu, Y. Gao, H. Fang, G. Tang and Y. Zhao, *J. Org. Chem*., 2015, **80**, 2621; (*d*) Y. Gao, J. Xu, P. Zhang, H. Fang, G. Tang and Y. Zhao, *RSC Adv.,* 2015, **5**, 36167; (*e*) H. C. Fisher, O. Berger, F. Gelat and J. L. Montchamp, *Adv. Synth. Catal.,* 2014, **356**, 1199; (*f*) D. P. Li, X. Q. Pan,L. T. An, J. P. Zou, and W. Zhang, *J. Org. Chem*., 2014, **79**, 1850; (*g*) X. H. Cao, X. Pan, P. J. Zhou, J. P. Zou and O. T. Asekun, *Chem. Commun*., 2014, **50**, 3359; (*h*) S. F. Zhou, D. P. Li, K. Liu, J.

View Article Online
DOI: 10.1039/C5RA22570A
Journal Name

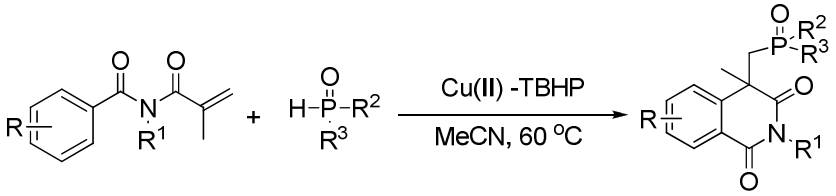
P. Zou, and O. T. Asekun, *J. Org. Chem*., 2015, **80**, 1214; (*i*) Y. Gao, X. Li, J. Xu, Y. Wu, W. Chen, G. Tang and Y. Zhao, *Chem. Commun.,* 2015, **51**, 1605.

9 (*a*) G. Han, Q. Wang, Y. Liu and Q. Wang, *Org. Lett.,* 2014, **16**, 5914; (*b*) G. Han, Y. Liu and Q. Wang, *Org. Lett.,* 2014, **16**, 3188.

View Article Online
DOI: 10.1039/C5RA22570A

Copper-Catalyzed Cycloaddition between Hydrogen Phosphonates and Activated Alkenes: Synthesis of Phosphonoisoquinolinediones

Ju Wu,[a] Yuzhen Gao,[a] Xin Zhao,[a] Liangliang Zhang,[a] Weizhu Chen,[a,b] Guo Tang,[a,*] and Yufen Zhao[a]



A new and general method for the synthesis of phosphonoisoquinolinediones has been achieved through copper-catalyzed phosphonation-cyclization of various methacryloylbenzamides with P(O)H compounds.