CHEMISTRY
AN ASIAN JOURNAL
ACES
COMMUNICATION

DOI: 10.1002/asia.201301641

Phosphine-Initiated Domino Reaction: A Convenient Method for the Preparation of Spirocyclopentanones

Ling Liang, Erqing Li, Peizhong Xie, and You Huang*[a]

Abstract: An efficient synthetic approach has been developed for the construction of the spirocyclopentanone skeleton via a phosphine-catalyzed [3+2] annulation reaction. With this novel and economical protocol, various quaternary carbon-centered spirocyclopentanones could be readily obtained.

Carbocyclic spiro motifs are the structural centerpieces of biologically active products, chiral ligands, and new materials (Figure 1). For example, fredericamycin A[1], which was isolated from a new strain of *Streptomyces griseus*, exhibits antitumor activity, and dimethyl gloiosiphone A exhibits antimicrobial activity against several *Staphylcoccus*, *Bacillus*, and *Salmonella* species.[2] Furthermore, their rigid structures make them ideal candidates for the development of chiral ligands, which have been applied successfully to various reactions (Figure 1).[3] Thus, great attention has been drawn to the development of efficient methods to build these spirocyclic systems.[4]

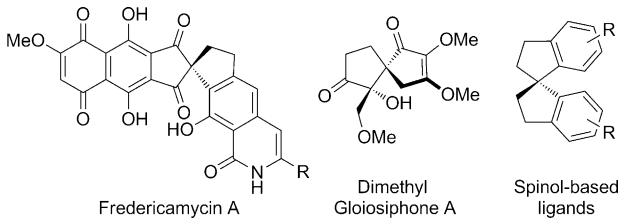
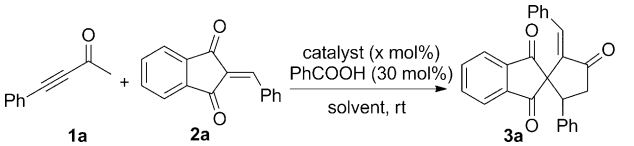


Figure 1. Representative spirocyclic compounds.

In the past decades, phosphine-catalyzed domino reactions[5] have become a powerful tool in the construction of carbo- and heterocycles.[6] While electron-deficient alkenes[7] and alkynes[8] have been well studied, little attention has been paid to ynone derivatives in organocatalytic domino reactions.[9] Recently, Tomita and Fu reported elegant intramolecular cycloaddition reactions.[10] Later on, Shi et al.[11] and Huang et al.,[12] respectively, reported on phosphine-catalyzed intermolecular [3+2] cycloaddition reactions of ynones with N-substituted isatins. Recently, asymmetric variants of the intermolecular [3+2] cycloaddition reactions of ynones have also been reported by other groups.[13] Based on these pioneering studies and our own work on phosphine-catalyzed domino reactions,[14] herein we report a phosphine-catalyzed intermolecular domino annulation reaction of ynones with 2-arylideneindane-1,3-diones that delivers efficiently spirocyclopentanones. In this reaction, air- and water-stable, inexpensive phosphine instead of sensitive metals was used as catalyst, and environmentally benign ethanol was used as solvent. The domino reaction could proceed smoothly to produce the desired adducts in excellent yields under mild conditions.

Initially, we carried out the reaction of ynone **1a** with 2-arylideneindane-1,3-dione **2a** in $CHCl_3$ in the presence of benzoic acid (30 mol%) by using 10 mol% phosphine as catalyst. Encouragingly, the annulation product **3a** was isolated in 74% yield (Table 1, entry 1). The yield could be improved to 93% by increasing the catalyst loading to 30 mol% (Table 1, entry 2). To optimize the performance of

Table 1. Optimization of reaction conditions for the domino reaction.[a]



Entry	Solvent	Cat. [%]	t	Yield[b]
1	$CHCl_3$	PPh_3 (10)	24 h	74
2	$CHCl_3$	PPh_3 (30)	20 h	93
3	$CHCl_3$	PPh_2Et (30)	20 h	83
4	$CHCl_3$	$P(p\text{-}OMePh)_3$ (30)	18 h	81
5[b]	THF	DABCO (30)	5 d	NR
6	THF	PPh_3 (30)	7 d	84
7	toluene	PPh_3 (30)	7 d	60
8	CH_2Cl_2	PPh_3 (30)	24 h	82
9	CH_3CN	PPh_3 (30)	24 h	85
10	EtOH	PPh_3 (30)	15 h	90
11[c]	EtOH	PPh_3 (30)	2 d	80

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), 30 mol% PhCOOH, 3.0 mL solvent, room temperature. [b] Isolated yields. [c] The reaction was carried out without PhCOOH.

[a] L. Liang, E. Li, P. Xie, Prof. Dr. Y. Huang
State Key Laboratory and Institute of Elemento-organic chemistry
Collaborative Innovation Center of Science and Engineering (Tianjin)
Nankai University
Tianjin 30071 (China)
Fax: (+86) 22-23503627
E-mail: hyou@nankai.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201301641.

the reaction, various catalysts and solvents were investigated (Table 1, entries 3–11). However, other phosphine catalysts did not lead to better results, and no reaction occurred when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as a catalyst (Table 1, entries 3–5). Solvent screening revealed that the solvent significantly affected the reaction performance (Table 1, entries 6–10). EtOH was identified as the optimal reaction medium for this reaction. In the absence of benzoic acid, a lower yield of product was obtained, even at a prolonged reaction time (Table 1, entry 11). In addition, the structure and stereochemistry of **3a** was determined by a combination of NMR spectroscopy, high-resolution mass spectrometry (HRMS), and single-crystal X-ray analysis (Figure 2).[15]

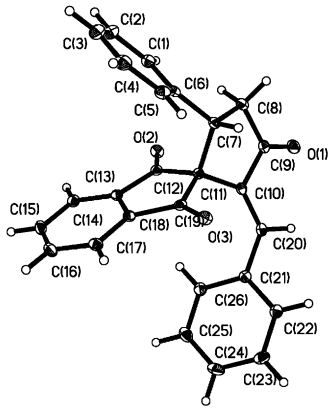
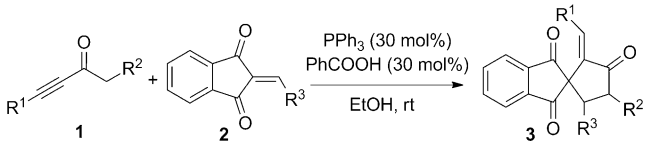


Figure 2. X-ray crystal structure of **3a**.

Table 2. Investigation of the substrate scope.[a]



Entry	R^1	R^2	R^3	t [h]	Yield[b]
1	Ph	H	C_6H_5	15	90 (**3a**)
2	Ph	H	2-Br-C_6H_4	10	93 (**3b**)
3	Ph	H	3-Br-C_6H_4	10	96 (**3c**)
4	Ph	H	4-Br-C_6H_4	10	90 (**3d**)
5	Ph	H	2-Me-C_6H_4	10	91 (**3e**)
6	Ph	H	3-Me-C_6H_4	10	95 (**3f**)
7	Ph	H	4-Me-C_6H_4	10	94 (**3g**)
8	Ph	H	4-Cl-C_6H_4	12	88 (**3h**)
9	Ph	H	4-F-C_6H_4	12	87 (**3i**)
10[c]	Ph	H	4-OMe-C_6H_4	3	90 (**3j**)
11	Ph	H	4-NO_2-C_6H_4	24	73 (**3k**)
12	Ph	H	2,4-Cl-C_6H_3	12	62 (**3l**)
13	Ph	H	2-furyl	48	87 (**3m**)
14	Ph	H	2-thienyl	53	84 (**3n**)
15	Ph	H	1-naphthyl	20	96 (**3o**)
16	Ph	H	styryl	35	89 (**3p**)
17	Ph	Me	4-Br-C_6H_4	18	95 (**3q**)
18	Ph	di-Me	4-Br-C_6H_4	18	97 (**3r**)
19	4-F-C_6H_4	H	4-Br-C_6H_4	21	83 (**3s**)
20	4-Me-C_6H_4	H	4-Br-C_6H_4	21	84 (**3t**)
21	*n*Bu	Me	4-Br-C_6H_4	22	NR (**3u**)
22[d]	Ph	H	4-Br-C_6H_4	14	86 (**3d**)

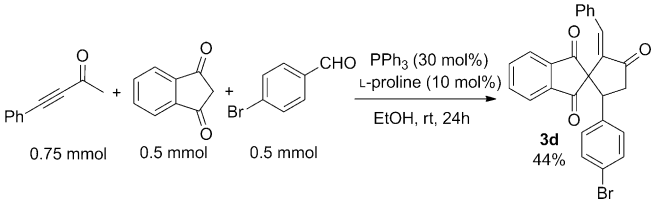
[a] Unless otherwise noted, reaction conditions were: **1a** (0.75 mmol), **2a** (0.5 mmol), 30 mol% PhCOOH, 30 mol% PPh_3, 3.0 mL solvent, room temperature. [b] Isolated yields. [c] The reaction was carried out at 70 °C at a 2:1 ratio of **1**:**2**. [d] The reaction was carried out with 3.0 mmol **2d**.

Next, the reaction of various ynones and 2-arylideneindane-1,3-diones **2** was evaluated under the optimized reaction conditions (Table 1, entry 10), and the results are shown in Table 2. In all cases, the reactions proceeded smoothly to produce the desired products in good to excellent yields (73–97%).

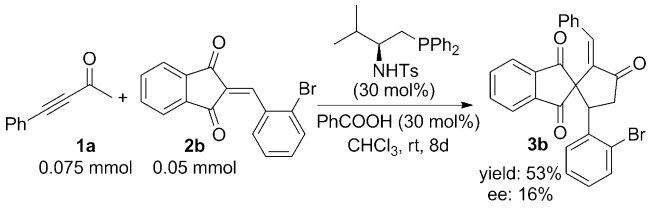
Various substrates **2** bearing diverse aromatic groups on R^3 could participate in the domino reactions to afford the corresponding products with excellent yields (Table 2, entries 2–9). In the presence of a strong electron-donating group (−OMe), an increase in temperature was required (Table 2, entry 10). It is worth noting that 2-arylideneindane-1,3-diones bearing strong electron-withdrawing groups on R^3 resulted in somewhat lower yields (Table 2, entries 11–12).2-Arylideneindane-1,3-diones bearing 2-furyl, 2-thiophenyl, and 2-naphthyl also gave rise to the desired products in high yields, albeit at prolonged reaction times (Table 2, entries 13–15). Pleasingly, a substrate with a vinylic group could participate in the reaction efficiently (Table 2, entry 16). Different ynones were also probed, and products were obtained with excellent yields (Table 2, entries 17–20). When 1-phenylpent-1-yn-3-one was used, **3q** was obtained as a single isomer (Table 2, entry 17). The steric hindrance at the α position of the ynone only slightly influenced the reaction (Table 2, entry 18). Unfortunately, when R^1 was *n*-butyl, no reaction occurred. Furthermore, for one representative example, we showed that the reaction could be carried out on a gram scale to afford the desired product **3d** without loss of reactivity (entry 22).

In further studies, we were delighted to find that the reaction of ynone **1a**, indane-1,3-dione, and *p*-Br-benzaldehyde in the presence of a catalytic amount of L-proline (10 mol%) and PPh_3 (30 mol%) at room temperature in EtOH furnished the desired product **3d** in 44% yield (Scheme 1). In this multicomponent reaction, multiple stereocenters were generated in a single step.

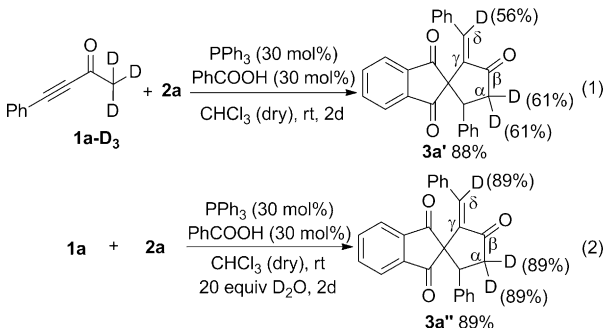
To demonstrate the practicality of our method, the asymmetric variant of this domino reaction was also investigated in a basic manner, with L-valine-derived phosphine[16] as a catalyst (Scheme 2). In this reaction, **3b** was obtained with



Scheme 1. One-pot reaction.



Scheme 2. Reaction catalyzed by L-valine-derived phosphine.

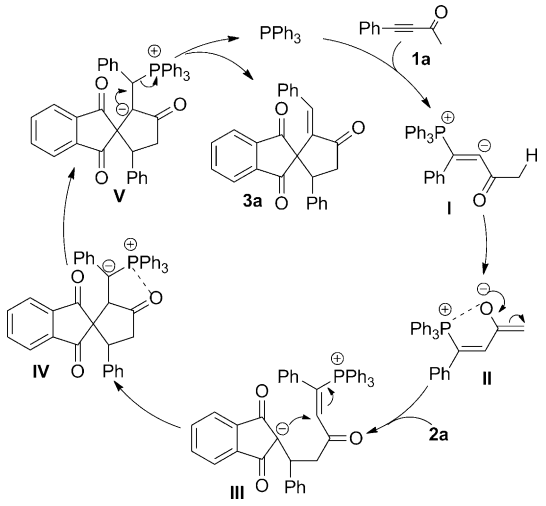


Scheme 3. Control experiments.

a promising enantiomeric excess of 16% and a yield of 53%.

Next, control experiments were carried out to investigate the reaction mechanism (Scheme 3). As previously mentioned, the additive accelerates the reaction (Table 1, entries 10 and 11). We speculated that the proton migration process might be accelerated by PhCOOH. To examine this possibility, **1a**-D_3 was synthesized, and the reaction was carried out in dry $CHCl_3$. In this reaction, deuterated product **3a′** was obtained in 88% yield, and deuterium was found not only at the α carbon but also at the δ carbon. This result indicated that the deuterium atom at the δ position came from the α position. Furthermore, when the reaction was carried out in the presence of 20 equivalents of D_2O, deuterated product **3a″** was obtained in 89% yield, and 89% deuterium was incorporated in the product **3a″** both at the α and δ positions, respectively. This result shows that the reaction first undergoes a rapid H/D exchange at the α position of the ynone to produce **1a**-D_3;[17] accordingly, a similar result was obtained for the two different control experiments.

On the basis of the above experimental results and previous studies,[10–13] we propose a plausible reaction mechanism for the domino reaction (Scheme 4). The reaction was rationalized to proceed in a tandem manner. First, the nucleophilic attack of the phosphine catalyst on ynone **1a** generates the intermediate **I**, which subsequently undergoes a proton shift (mediated by benzoic acid and ethanol)[18] and produces the enolate **II**. Subsequently, enolate **II** nucleophilically adds to 2-arylideneindane-1,3-dione **2a** to furnish intermediate **III**. Intramolecular nucleophilic addition of the carbanion to the double bond then delivers cyclic intermediate **IV**. Finally, proton migration (assisted by benzoic acid



Scheme 4. The proposed reaction mechanism.

and ethanol) and elimination of the catalyst yield the final product **3a**. An analogous mechanistic proposal pertaining to the synthesis of spirocyclic oxindoles has been postulated by other groups during the preparation of this manuscript.[19]

In theory, there are three possible structures for the intermediate **II** generated from ynones and phosphine (Figure 2). On the basis of the results obtained by DFT calculations, we found that the thermodynamically most stable structure is **II** because a significant intramolecular P–O interaction stabilizes this intermediate (Figure 3). The short P–O distance be-

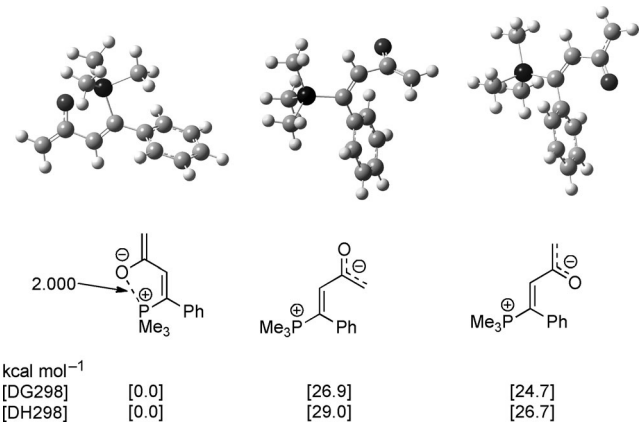


Figure 3. DFT-computed relative enthalpies and free energies of three possible structures of intermediate II.

tween the phosphorus and carbonyl oxygen atoms is 2.000 Å.[20] The excellent stereoselectivity in the [3+2] process might thus be attributed to the P–O interaction, which exists in the reaction steps (intermediates II–V).

In summary, we have successfully developed an environmentally friendly synthetic strategy for preparing highly functionalized spiro-cyclopentanones in good to excellent yields; this transformation constructed two new bonds and one ring with both reactants being completely used. The re-

action can be performed in the environmentally benign solvent ethanol and showed good functional group tolerance. Readily available starting materials, mild reaction condition, and an inexpensive catalyst make this reaction valuable in synthetic chemistry. We expect that this protocol could be potentially applied to the synthesis of carbocyclic spiro motifs present in natural products.

Experimental Section

Ynones **1** (0.75 mmol), 2-arylideneindane-1,3-diones **2** (0.5 mmol), and benzoic acid (30 mol%) were dissolved in EtOH (3.0 mL). Subsequently, PPh_3 (30 mol%) was added, and the reaction mixture was stirred at room temperature. After complete conversion, as indicated by thin-layer chromatography (TCL), all volatiles were removed in vacuo, and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1).

Acknowledgements

This work was supported financially by the National Natural Science Foundation of China (21172115, 20972076) and the Research Fund for the Doctoral Program of Higher Education of China (20120031110002).

Keywords: annulation · domino reaction · phosphine · spiro compounds · ynone

[1] Isolation and structure elucidation: a) R. C. Pandey, M. W. Toussaint, R. M. Stroshane, C. C. Kalita, A. A. Aszalos, A. L. Garretson, T. T. Wei, K. M. Byme, R. F. Geoghegan, R. J. White, *J. Antibiot.* **1981**, *34*, 1389; b) R. Miosra, R. C. Pandey, B. D. Hilton, P. P. Roller, J. V. Silverton, *J. Antibiot.* **1987**, *40*, 786.

[2] J. L. Chen, M. F. Moghaddam, W. H. Gerwick, *J. Nat. Prod.* **1993**, *56*, 1205.

[3] For some selected examples: a) J.-H. Xie, Q.-L. Zhou, *Acc. Chem. Res.* **2008**, *41*, 581; b) K.-L. Ding, Z.-B. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32; c) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie, Q.-L. Zhou, *Nat. Chem.* **2010**, *2*, 546; d) S.-F. Zhu, X.-G. Song, Y. Li, Y. Cai, Q.-L. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 16374; e) I. Čorić, S. Müller, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 17370; f) M. M. Coulter, K. G. M. Kou, B. Galligan, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16330.

[4] For reviews: a) S. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165; b) R. Pradhan, M. Patra, A. K. Behera, B. K. Mishra, R. K. Behera, *Tetrahedron* **2006**, *62*, 779; c) M. Sannigrahi, *Tetrahedron* **1999**, *55*, 9007; d) A. P. Krapcho, *Synthesis* **1978**, 77; e) A. P. Krapcho, *Synthesis* **1976**, 425.

[5] For reviews on Domino reactions: a) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237; b) B. Westermann, M. Ayaz, S. S. Van Berkel, *Angew. Chem. Int. Ed.* **2010**, *49*, 846; *Angew. Chem.* **2010**, *122*, 858; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; *Angew. Chem.* **2007**, *119*, 1590; d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

[6] For selected reviews on phosphine-containing Lewis base catalyzed reactions, see: a) P. Xie, Y. Huang, *Eur. J. Org. Chem.* **2013**, 6213; b) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174; c) C. Gomez, J.-F. Betzer, A. Voituriez, A. Marinetti, *ChemCatChem* **2013**, *5*, 1055; d) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; e) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140; f) V. Nair, R. S. Menon, A. R. Sreekanth, N. Abhilash, A. T. Biji, *Acc. Chem. Res.* **2006**, *39*, 520; g) X. Lu, Y. Du, C. Lu, *Pure Appl. Chem.* **2005**, *77*, 1985; h) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535.

[7] For examples of phosphine-catalyzed reactions of allenes: a) X. Chen, M. Wen, S. Ye, Z. Wang, *Org. Lett.* **2011**, *13*, 1138; b) Y. Sun, X. Guan, M. Shi, *Org. Lett.* **2010**, *12*, 5664; c) T. Wang, S. Ye, *Org. Lett.* **2010**, *12*, 4168; d) X. Zhang, L. Yang, X. Tong, *J. Am. Chem. Soc.* **2010**, *132*, 2550; e) H. Guo, Q. Xu, O. Kwon, *J. Am. Chem. Soc.* **2009**, *131*, 6318; f) X. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc.* **2003**, *125*, 4716; g) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906.

[8] For examples of phosphine-catalyzed reactions of alkynes: a) Z. Xu, X. Lu, *J. Org. Chem.* **1998**, *63*, 5031; b) L.-G. Meng, P. Cai, Q. Guo, S. Xue, *J. Org. Chem.* **2008**, *73*, 8491; c) S. Gabillet, D. Lecerclé, O. Loreau, M. Carboni, S. Dezard, J.-M. Gomis, F. Taran, *Org. Lett.* **2007**, *9*, 3925; d) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12928; e) V. Sriramurthy, O. Kwon, *Org. Lett.* **2010**, *12*, 1084.

[9] a) A. Siby, O. Loreau, F. Taran, *Synthesis* **2009**, 2365; b) F. Silva, M. Sawicki, V. Gouverneur, *Org. Lett.* **2006**, *8*, 5417.

[10] a) H. Kuroda, I. Tomia, T. Endo, *Org. Lett.* **2003**, *5*, 129; b) J. E. Wilson, J. Sun, G. C. Fu, *Angew. Chem. Int. Ed.* **2010**, *49*, 161; *Angew. Chem.* **2010**, *122*, 165.

[11] Z. Lian, M. Shi, *Eur. J. Org. Chem.* **2012**, 581.

[12] L. Yang, P. Xie, E. Li, Y. Huang, R. Chen, *Org. Biomol. Chem.* **2012**, *10*, 7628.

[13] a) Z. Lian, M. Shi, *Org. Biomol. Chem.* **2012**, *10*, 8048; b) D. B. Ramachary, C. Venkaiah, P. M. Krishna, *Chem. Commun.* **2012**, *48*, 2252; c) D. B. Ramachary, C. Venkaih, R. Madhavachary, *Org. Lett.* **2013**, *15*, 3042.

[14] a) X. Meng, Y. Huang, R. Chen, *Chem. Eur. J.* **2008**, *14*, 6852; b) X. Meng, Y. Huang, R. Chen, *Org. Lett.* **2009**, *11*, 137; c) X. Meng, Y. Huang, H. Zhao, P. Xie, J. Ma, R. Chen, *Org. Lett.* **2009**, *11*, 991; d) P. Xie, Y. Huang, R. Chen, *Org. Lett.* **2010**, *12*, 3768; e) J. Ma, P. Xie, Y. Huang, R. Chen, *Chem. Eur. J.* **2011**, *17*, 7418; f) P. Xie, Y. Huang, W. Lai, X. Meng, R. Chen, *Org. Biomol. Chem.* **2011**, *9*, 6707; g) P. Xie, Y. Huang, R. Chen, *Chem. Eur. J.* **2012**, *18*, 7362; h) C. Hu, Z. Geng, J. Ma, Y. Huang, R. Chen, *Chem. Asian J.* **2012**, *7*, 2032; i) E. Li, P. Xie, L. Yang, L. Liang, Y. Huang, *Chem. Asian J.* **2013**, *8*, 603; j) E. Li, Y, Huang, L, Liang, P. Xie, *Org. Lett.* **2013**, *15*, 3138.

[15] CCDC 938814 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

[16] a) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders, H. Sasai, *Angew. Chem. Int. Ed.* **2012**, *51*, 5423; *Angew. Chem.* **2012**, *124*, 5519; b) Z. Jin, R. Yang, Y. Du, B. Tiwari, R. Ganguly, Y. R. Chi, *Org. Lett.* **2012**, *14*, 3226.

[17] I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696.

[18] a) Y.-Z. Xia, Y. Liang, Y.-Y. Chen, M. Wang, L. Jiao, F. Huang, S. Liu, Y.-H. Liang, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3470; b) P. Xie, W. Lai, Z. Geng, Y. Huang, R. Chen, *Chem. Asian J.* **2012**, *7*, 1533.

[19] a) D. B. Ramachary, C. Venkaiah, P. M. Krishna, *Org. Lett.* **2013**, *15*, 4714; b) Q.-F. Zhou, X.-P. Chu, F.-F. Ge, C. Li, T. Lu, *Mol. Diversity* **2013**, *17*, 563.

[20] a) The DFT calculations were carried out by using the Gaussian 03 program: Gaussian 03; revision E.01, M. J. Frisch, et al., Gaussian, Inc., Wallingford, CT, **2004**. See the Supporting Information for the full reference; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

Received: December 10, 2013
Published online: February 23, 2014