ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Jiang, Y. Yu, Y. Chen and W. Wu, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC08320J.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Dynamic Article Links ▶
View Article Online
DOI: 10.1039/C6CC08320J

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Facile Synthesis of Cyanofurans *via* Michael-Addition/Cyclization of Ene-Yne-Ketones with Trimethylsilyl Cyanide

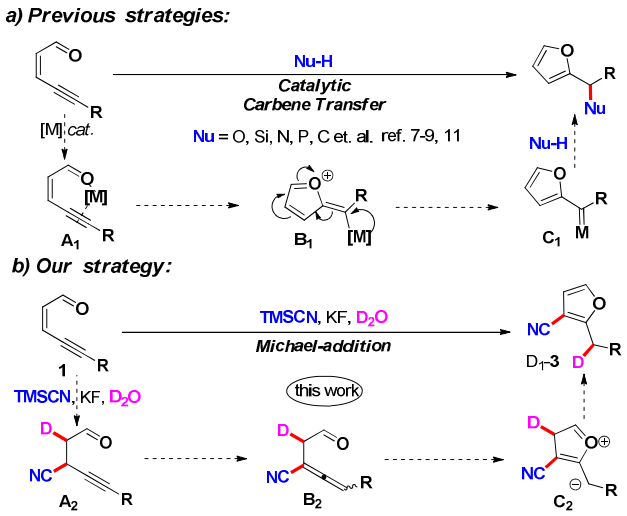
Yue Yu, Yang Chen, Wanqing Wu*, Huanfeng Jiang*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

We have developed a Michael-addition/cyclization procedure between ene-yne-ketones and TMSCN under metal-free conditions. A wide range of cyanofurans were delivered in high yields, which could be further transformed to a series of furo-furanimines, furo-pyridazines or carboxamido-furans. In addition, deuterium-labeling experiments have been conducted to clarify the reaction pathway.

Given their frequent appearance in many important pharmaceuticals[1], materials[2] and natural products[3], the efficient construction of functionalized furans is a major challenge in organic synthesis. Although many synthetic routes have been well established,[4] the development of new efficient ways to valuable furan derivatives from widely available starting materials still represents a continuing goal in the synthetic community. In particular, cyanofurans are ideal synthetic building blocks for the elaboration of more complex scaffolds, owing to the versatile chemistry of the cyano group.[5] However, synthetic methods for the formation of cyanofurans have been less explored until now.[6]

On the other hand, considerable studies have been reported for the synthesis of functionalized furans through 5-exo-dig cyclization of ene-yne-ketones in past years, in which ene-yne-ketone was mainly utilized as a carbene precursor under transition-metal-catalyzed conditions.[7] For example, Vicente, López and co-workers demonstrated that a furyl Fischer-type zinc carbenoid intermediate obtained from ene-yne-ketones underwent X-H (X = O, Si, N, Csp^2) insertions.[8] Wang and co-workers have recently reported the Pd- or Cu-catalyzed cross-coupling of terminal alkynes with ene-yne-ketones, affording conjugated enynes or allenes through a carbene migratory insertion pathway.[9] In those transformations, the alkyne moiety was activated by transition metal species at first, which then underwent 5-exo-dig cyclization to form zwitterionic intermediate $\mathbf{B_1}$ or its resonance structure, furyl metal-carbene species $\mathbf{C_1}$. In the presence of nucleophiles, species $\mathbf{C_1}$ could subsequently participate in a metal carbene migratory insertion process to give the Nu-H inserted products (Scheme 1, a). Despite the impressive progress in this field, new strategies for the transformations of ene-yne-ketones have remained underdeveloped.[10]



Scheme 1. Different strategies for the transformations of ene-yne-ketones

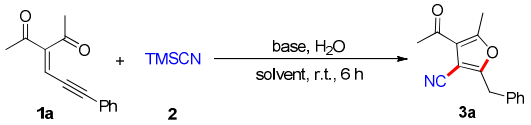
Previously, our group developed a catalyst-controlled strategy for the synthesis of various phosphorylated furans via Cu-catalyzed Csp^3-P or base promoted Csp^2-P bond construction between ene-yne-ketones and *H*-phosphonates.[11] Encouraged by this result, we herein disclose a straightforward approach for utilizing ene-yne-ketones as a Michael-addition acceptor to react with TMSCN[12], affording a series of cyanofurans. This reaction was supposed to begin with the process of Michael-addition in the presence of base and water, leading to intermediate $\mathbf{A_2}$ and allenyl intermediate $\mathbf{B_2}$. Afterwards, a nucleophilic attack by the carbonyl oxygen atom generated intermediate $\mathbf{C_2}$. Subsequent protonation and aromatization afforded the final cyanofurans (Scheme 1, b).

At the outset of this transformation, we treated ene-yne-ketone **1a** with trimethylsilyl cyanide (**2**) as the model substrates for reaction development (Table 1). Initially, **3a** was obtained in 74% yield under simple conditions that KF was used as base and 5 equiv H_2O (see Supporting Information for details) were added to CH_3CN in a test tube at room temperature for 6 h (entry 1). Subsequent survey on a series of solvents including THF, DCE, toluene, DMF, DMSO and dioxane revealed that DMF gave the best result, affording **3a** in 93% yield (entries 2-7). Screening of other bases such as CsF or KOH did not improve the yield

View Article Online
DOI: 10.1039/C6CC08320J

(entries 8-9). Finally, when the amounts of trimethylsilyl cyanide and KF decreased to 1.5 equiv, the reaction rate and conversion rate were not affected and the target product **3a** was obtained in 94% yield. Howerer, the yield would drop to 85% when the amounts were further reduced to 1.2 equiv (entry 13).

Table 1. Optimization of reaction conditions[a]

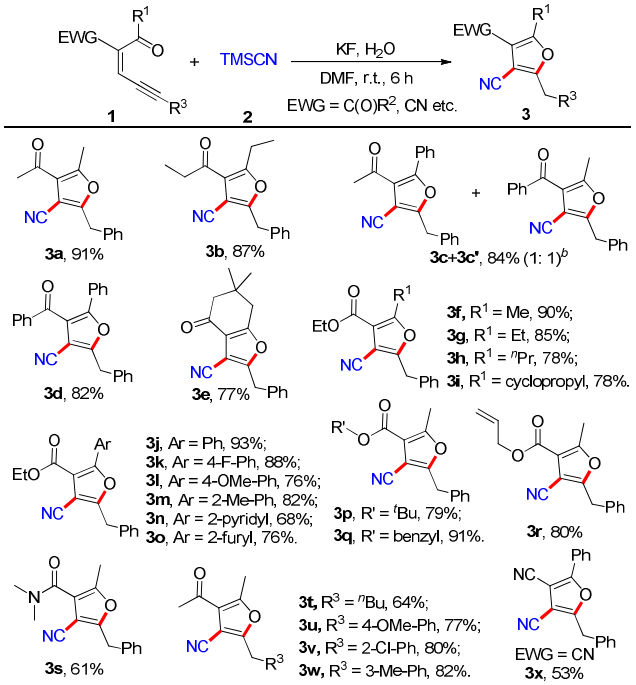


entry	base	solvent	yield of **3a** (%)[b]
1	KF	CH_3CN	74
2	KF	THF	66
3	KF	DCE	N.R
4	KF	Toluene	N.R
5	KF	DMF	93
6	KF	DMSO	68
7	KF	1,4-Dioxane	71
8	CsF	DMF	89
9	KOH	DMF	76
10[c]	**KF**	**DMF**	**94**
11[d]	KF	DMF	85

[a] Reaction conditions: All reactions were performed with **1a** (0.1 mmol), **2** (2.0 equiv), base (2.0 equiv), H_2O (5.0 equiv), 1.0 mL solvent at room temperature for 6 h unless otherwise noted. [b] Determined by GC-MS. [c] **2** (1.5 equiv), base (1.5 equiv). [d] **2** (1.2 equiv), base (1.2 equiv).

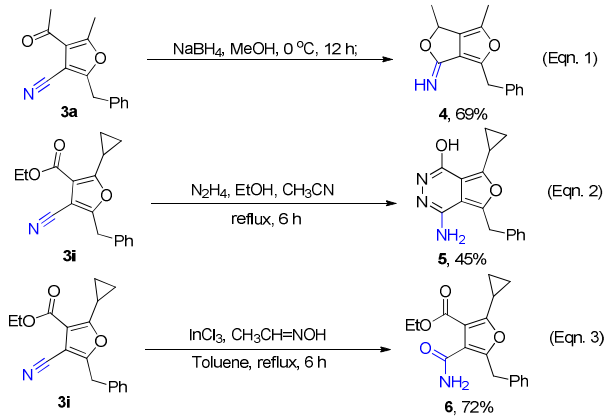
With the optimized reaction conditions in hand (Table 1, entry 10), we turned our attention to explore the scope of this transformation (Table 2). The reaction proceeded smoothly under the standard reaction conditions and afforded the products **3a-3e** in 77-91% yields when R^1 and R^2 were alkyl or phenyl groups. Notably, the mixture of (*E*)- and (*Z*)-ene-yne-ketones afforded the single products, and only 5-exo-dig cyclization occurred. Thus, to examine the nucleophilicity of different ketone carbonyl oxygen atoms, we synthesized **1c** for this transformation and the desired products **3c** and **3c'** were obtained in a total yield of 84% with a regioselectivity of 1: 1. We supposed that the steric hindrance of phenyl group made negligible influence on the inserted cyano-group in this case. To our delight, the reactions for alkoxycarbonyl-substituted ene-yne-ketones showed high functional group tolerance (such as R^2 = OEt, R^1 = Me, Et, *n*-Pr, cyclopropyl, substituted arenes, pyridyl or furyl; R^1 = Me, R^2 = *t*-Bu, benzyl or isopropyl), leading to the corresponding products **3f-3r** in good to excellent yields. When R^2 is ethyl, the reactions with electron-withdrawing groups on phenyl ring provided similar yields to those with electron-donating groups. In addition, heterocyclic group such as pyridyl and furyl were also compatible with the reaction conditions, affording the desired products **3n** and **3o** in 68% and 76% yields, respectively. Carboxamido-substituted ene-yne-ketone was also a suitable substrate for this cyclization, and the target product **3s** was isolated in 61% yield. Moreover, the reaction was found to tolerate a broad range of R^3 groups on the alkyne terminus, including alkanes and substituted arenes (**3t-3w**). It is worth mentioning that 2-benzoyl-5-phenylpent-2-en-4-ynenitrile (**1x**) could be converted into **3x** as well, albeit with relatively lower efficiency.

Table 2. Substrate scope for the synthesis of cyanofurans **3**[a]



[a] Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), KF (0.6 mmol) and H_2O (5 equiv) in 2 mL DMF at room temperature for 6 h unless otherwise noted. [b] Determined by NMR.

We next moved toward synthetic applications of cyanofurans to prepare three important intermediate scaffolds, namely, furo-furanimines[5e], furo-pyridazines[5f] and carboxamido-furans[5h], which were found as scaffolds in biologically active molecules. As shown in Scheme 2, for the synthesis of furo-furanimine, sodium borohydride was carefully added to a solution of 3-acetyl-4-cyano furan **3a** in MeOH, the target product **4** was formed in 69% yield (Scheme 2, Eqn. 1). On the other hand, the reaction of **3i** with hydrazine hydrate could easily give furo-pyridazine **5** with the yield of 76% (Scheme 2, Eqn. 2), and the hydration of **3i** catalyzed by $InCl_3$ led to carboxamido-furan **6** in 72% yield with

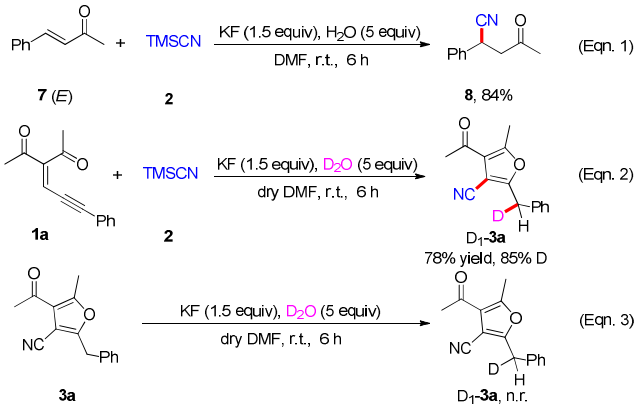


Scheme 2. Further modification on cyanofurans

View Article Online
DOI: 10.1039/C6CC08320J

the aid of acetaldoxime (Scheme 2, Eqn. 3).

To gain more insight into the mechanism of this reaction, several control experiments were performed (Scheme 3). Initially, when benzylideneacetone (**7**) was used to replace ene-yne-ketones under the standard conditions, a Michael-addition product **8** was obtained in 84% yield, indicating that the transformation could start with a Michael-addition pathway in this situation (Scheme 3, Eqn. 1).[13] The deuterium-labeling experiments were next conducted. On one hand, the reaction of **1a** and **2** was performed in dry DMF at room temperature for 6 h in the presence of KF and D_2O. It was found that the reaction afforded [D_1]-**3a** in 78% total yield with 85% D (Scheme 1, Eqn. 2). On the other hand, [D_1]-**3a** was not detected by the treatment of cyanofurans **3a** in the same conditions (Scheme 3, Eqn. 3). The structure of [D_1]-**3a** shows that one of the hydrogen atom on the methylene position comes from water. In consideration of the result of the first reaction, the most possible way is that the hydrogen atom of water inserts into the vinyl moiety of ene-yne-ketones with the CN anion via a Michael-addition and then transfer to the methylene position through a hydrogen shift during the process of aromatic isomerization (Scheme 1, b).



Scheme 3. Control experiments

In conclusion, we have established a highly efficient protocol for the synthesis of various cyanofurans via Michael-addition/cyclization of ene-yne-ketones with trimethylsilyl cyanide. These valuable products could easily transfer to other biologically active molecules such as furo-furanimines, furo-pyridazines and carboxamido-furans. Furthermore, this method features transition-metal-free, broad substrate scope, high efficiency and atom economy, which make it attractive and practical. Deuterium-labeling experiments have been conducted to clarify the reaction pathway. Further applications of this reaction is currently underway in our laboratory.

The authors thank the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21420102003 and 21490572), Pearl River S&T Nova Program of Guangzhou (201610010160) for financial support.

Notes and references

Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China. Fax: +86 20-87112906; Tel: +86 20-87112906; E-mail: cewuwq@scut.edu.cn, jianghf@scut.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

1. a) A. U. Rao, D. Xiao, X. Huang, W. Zhou, J. Fossetta, D. Lundell, F. Tian, P. Trivedi, R. Aslanian and A. Palani, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1068; b) F. Hasegawa, K. Niidome, C. Migihashi, M. Murata, T. Negoro, T. Matsumoto, K. Kato and A. Fujii, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4266; c) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**. 795; d) N. Kumari, C. B. Mishra, A. Prakash, N. Kumar, R. Mongre and P. M. Luthra, *Neurosci. Lett.*, 2014, **558**, 203.
2. a) Z. Li, H. Li, S. Chen, T. Froehlich, C. Yi, C. Schönenberger, M. Calame, S. Decurtins, S.-X. Liu and E. Borguet, *J. Am. Chem. Soc.*, 2014, **136**, 8867; b) C. Moreno-Yruela, J. Garín, J. Orduna, S. Franco, E. Quintero, J. T. L. Navarrete, B. E. Diosdado, B. Villacampa, J. Casado and R. Andreu, *J. Org. Chem.*, 2015, **80**, 12115; c) A. A. Mazurov, L. Miao, B. S. Bhatti, J.-P. Strachan, S. Akireddy, S. Murthy, D. Kombo, Y. Xiao, P. Hammond, J. Zhang, T. A. Hauser, K. G. Jordan, C. H. Miller, J. D. Speake, G. J. Gatto and D. Yohannes, *J. Med. Chem.*, 2012, **55**, 9181; d) C. Zeng, H. Seino, J. Ren, K. Hatanaka and N. Yoshie, *Macromolecules*, 2013, **46**, 1794.
3. a) J. A. Marshall, L. M. McNulty and D. Zou, *J. Org. Chem.*, 1999, **64**, 5193; b) X. Wang, K. F. Bastow, C.-M. Sun, Y.-L. Lin, H.-J. Yu, M.-J. Don, T.-S. Wu, S. Nakamura and K.-H. Lee, *J. Med. Chem.*, 2004, **47**, 5816.
4. For reviews: a) B. A. Keay, *Chem. Soc. Rev.*, 1999, **28**, 209; b) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084; c) S. F. Kirsch, *Org. Biomol. Chem.*, 2006, **4**, 2076.
5. a) M. Sun, H.-Y. Zhang, Q. Han, K. Yang and S.-D. Yang, *Chem. Eur. J.*, 2011, **17**, 9566; b) H. Shen, J. Li, Q. Liu, J. Pan, R. Huang and Y. Xiong, *J. Org. Chem.*, 2015, **80**, 7212; c) L. Zhang, Z. Peng, Q. Wen, X. Li, P. Lu and Y. Wang, *Org. Lett.*, 2016, **18**, 728; d) Q. Wen, P. Lu and Y. Wang, *Chem. Commun.*, 2015, **51**, 15378; e) J. Mangas-Sánchez, E. Busto, V. Gotor-Fernández and V. Gotor, *Org. Lett.*, 2012, **14**, 1444; f) J. Hu, Y. Wei and X. Tong, *Org. Lett.*, 2011, **13**, 3068; g) S. H. Kim, S. H. Kim, K. H. Kim and J. N. Kim, *Tetrahedron Lett.* 2010, **51**, 860; h) S. H. Kim, Y. M. Kim, H. S. Lee and J. N. Kim, *Tetrahedron Lett.* 2010, **51**, 1592; i) P. Bertus and J. Szymoniak, *J. Org. Chem.*, 2003, **68**, 7133.
6. a) X. Zhang, W. Dai, W. Wu and S. Cao, *Org. Lett.*, 2015, **17**, 2708; b) L. Wang, X. Liu, M. Wang and J. Liu, *Org. Lett.*, 2016, **18**, 2162; c) C.-J. Lee, T.-H. Chang, J.-K. Yu, G. M. Reddy, M.-Y. Hsiao and W. Lin, *Org. Lett.*, 2016, **18**, 3758; d) W. Liu and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1878.
7. a) Y. Xia, S. Qu, Q. Xiao, Z.-X. Wang, P. Qu, L. Chen, Z. Liu, L. Tian, Z. Huang, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 13502; b) T. Yao, X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 11164; c) M. J. González, E. López and R. Vicente, *Chem. Commun.*, 2014, **50**, 5379; d) S. Mata, L.A. López and R. Vicente, *Chem. Eur. J.*, 2015, **21**, 8998; e) B. Song, L.-H. Li, X.-R. Song, Y.-F. Qiu, M.-J. Zhong, P.-X. Zhou and Y.-M. Liang, *Chem. Eur. J.*, 2014, **20**, 5910; f) H. Cao, H. Zhan, J. Cen, J. Lin, Y. Lin, Q. Zhu, M. Fu and H. Jiang, *Org. Lett.*, 2013, **15**, 1080; g) J. Ma, H. Jiang and S. Zhu, *Org. Lett.*, 2014, **16**, 4472; h) D. Zhu, J. Ma, K. Luo, H. Fu, L. Zhang and S. Zhu, *Angew. Chem. Int. Ed.*, 2016, **55**, 8452.
8. a) J. González, J. González, C. Pérez-Calleja, L. A. López and R. Vicente, *Angew. Chem. Int. Ed.*, 2013, **52**, 5853; b) R. Vicente, J. González, L. Riesgo, J. González and L. A. López, *Angew. Chem. Int. Ed.*, 2012, **51**, 8063.
9. a) Y. Xia, Z. Liu, R. Ge, Q. Xiao, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, **51**, 11233; b) Y. Xia, R. Ge, L. Chen, Z. Liu, Q. Xiao, Y. Zhang and J. Wang, *J. Org. Chem.*, 2015, **80**, 7856; c) F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *J. Org. Chem.*, 2016, **81**, 3275; d) F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Org. Lett.*, 2014, **16**, 4082.
10. a) J. S. Clark, A. Boyer, A. Aimon, P. E. García, D. M. Lindsay, A. D. F. Symington and Y. Danoy, *Angew. Chem. Int. Ed.*, 2012, **51**, 12128;

View Article Online
DOI: 10.1039/C6CC08320J

b) J. S. Clark, F. Romiti, K. F. Hogg, M. H. S. A. Hamid, S. C. Richter, A. Boyer, J. C. Redman and L. J. Farrugia, *Angew. Chem. Int. Ed*., 2015, **54**, 5744; c) X. Luo, L.-S. Ge, X.-L. An, J.-H. Jin, Y. Wang, P.-P. Sun and W.-P. Deng, *J. Org. Chem*., 2015, **80**, 4611.

11. Y. Yu, S. Yi, C. Zhu, W. Hu, B. Gao, Y. Chen, W. Wu and H. Jiang, *Org. Lett*., 2016, **18**, 400.

12. a) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl and G. Liu, *Science*, 2016, **353**, 1014; b) K. Shen, X. Liu, Y. Cai, L. Lin and X. Feng, *Chem. Eur. J.*, 2009, **15**, 6008; c) Y. Wen, B. Gao, Y. Fu, S. Dong, X. Liu and X. Feng, *Chem. Eur. J*., 2008, **14**, 6789; d) F.-X. Chen, H. Zhou, X. Liu, B. Qin, X. Feng, G. Zhang and Y. Jiang, *Chem. Eur. J*., 2004, **10**, 4790; e) Z.-L. Shen, W.-J. Zhou, Y.-T. Liu, S.-J. Ji and T.-P. Loh, *Green Chem*., 2008, **10**, 283; f) H. Shen, L. Hu, Qing Liu, M. I. Hussain, J. Pan, M. Huang and Y. Xiong, *Chem. Commun*., 2016, **52**, 2776; g) P. Fontaine, A. Chiaroni, G. Masson and J. Zhu, *Org. Lett*., 2008, **10**, 1509; h) C. Zhu, F. Yuan, W. Gua and Y. Pan, *Chem. Commun*., 2003, **39**, 692; i) D. Chen and M.-H. Xu, *J. Org. Chem*., 2014, **79**, 7746; j) H. Kaise, J. Shimokawa and T. Fukuyama, *Org. Lett*., 2014, **16**, 727; k) Y.-T. He, L.-H. Li, Q. Wang, W. Wu and Y.-M. Liang, DOI: 10.1021/acs.orglett.6b02627.

13. a) Y. Tanaka, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc*., 2008, **130**, 6072; b) J. Zhang, X. Liu and Rui Wang, *Chem. Eur. J.*, 2014, **20**, 4911.