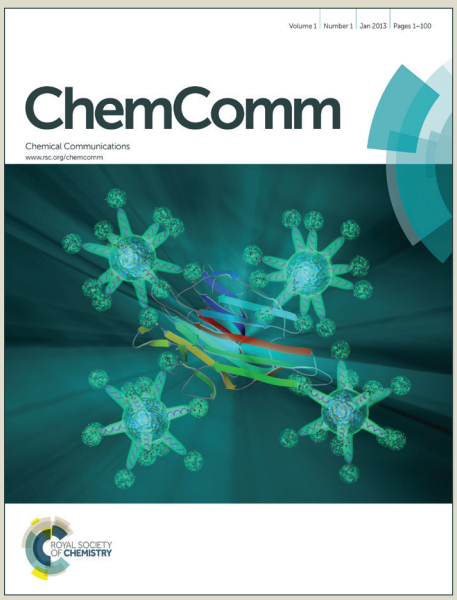
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Copper(II) perchlorate-promoted tandem reaction of internal alkynol and salicyl *N*-tosylhydrazone: direct access to isochromeno[3,4-*b*]chromene

Hai Xiao Siyang, Xu Rui Wu, Xiao Yue Ji, Xin Yan Wu and Pei Nian Liu*

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

Copper(II) perchlorate-promoted tandem reaction of internal alkynol and salicyl *N*-tosylhydrazone provides a novel, concise method for constructing isochromeno[3,4-*b*]chromene in 35-94% yields. The tandem reaction involves cycloisomerization, formal [4+2] cycloaddition and elimination process.

Heteroannular ketals are synthetically and pharmaceutically important structural motifs present in a wide range of natural products.[1] For example, [3,4-*b*]ketals form the scaffold of numerous natural products with useful biological activities, such as dipyranosides **I**, key precursors for ansamycins,[2] sapogenin triterpene **II**, from *Emmenospermum pancherianum*,[3] and the antimalarial macralstonidine **III**, from *Alstonia* (Figure 1).[4]

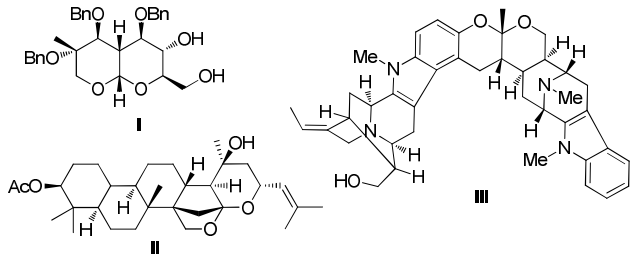
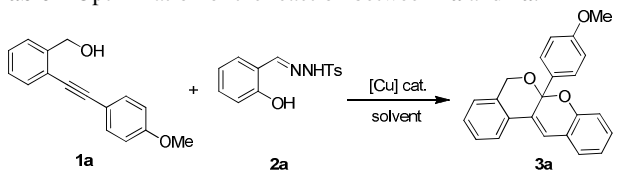


Figure 1 Natural products containing the [3,4-*b*]ketal moiety.

Numerous researchers have explored ways to synthesize these natural ketal-like derivatives. Although these efforts have led to creative strategies to construct spiroketals,[1a,d,e,f] heteroannular ketals such as fused pyranobenzopyrans remain a challenge. The methodologies reported to date involve cyclization reaction promoted by radicals,[5] acid,[6] or Me_3SiI,[7] or conducted under Diels-Alder,[8] Heck,[9] or Lewis-acid catalyzed conditions.[10] Most of these methods require numerous steps and a preformed tetrahydropyran derivatives as substrates, or more than stoichimetric amount of Lewis acid is needed. Therefore, developing new synthetic methods to construct fused pyranobenzoyran derivatives would be an important advance.

The reactivity of alkynol-based systems has made them one of the most prevalent organic synthons for generating diverse structures as furans, pyrans and ketals, as well as many other heterocyclic systems and natural products.[11] However, most syntheses involving alkynols rely on noble-metal catalysts, making them much more expensive than copper-based methods. Meanwhile, alternative and novel protocols employing salicyl *N*-tosylhydrazones and terminal alkynes were reported for constructing heterocycles.[12] In a continuation of our work on the development of new synthetic application based on alkynols,[13] we report here a copper perchlorate-promoted tandem reaction of internal alkynol with salicyl *N*-tosylhydrazone, which provides a novel, concise synthetic route to the heteroannular ketal isochromeno[3,4-*b*]chromene.

Table 1 Optimization of the reaction between **1a** and **2a**.[a]



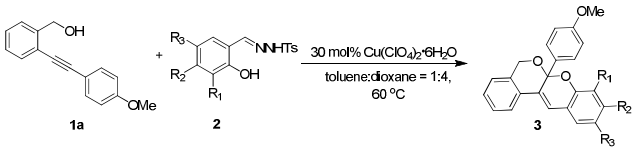
Entry	Catalyst / mol%	Solvent	*T* °C	*t* h	**3a**[b] %
1	$Cu(OTf)_2$ / 20	dioxane	100	2	40
2	CuI / 20	dioxane	100	10	0
3	$CuSO_4{\cdot}5H_2O$ / 20	dioxane	100	18	<5
4	$CuCl_2{\cdot}2H_2O$ / 20	dioxane	100	20	25
5	$Cu(NO_3)_2{\cdot}3H_2O$ / 20	dioxane	100	20	18
6	$[Cu(CH_3CN)_4]PF_6$ / 20	dioxane	100	5	<5
7	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	dioxane	100	6	43
8	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	CH_3CN	100	20	22
9	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	Toluene	100	3.5	46
10	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	THF	100	20	37
11	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	CH_3NO_2	100	3.5	27
12	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	DCE	100	3.5	35
13	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	DMSO	100	24	0
14[c]	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	Toluene	100	0.5	52
15[c]	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	Toluene	60	15	60
16[d]	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	Toluene	60	20	67
17[d,e]	$Cu(ClO_4)_2{\cdot}6H_2O$ / 20	Toluene/dioxane	60	24	66
18[d,e]	$Cu(ClO_4)_2{\cdot}6H_2O$ / 30	Toluene/dioxane	60	24	78
19[d,f]	**$Cu(ClO_4)_2{\cdot}6H_2O$ / 30**	**Toluene/dioxane**	**60**	**11**	**94**

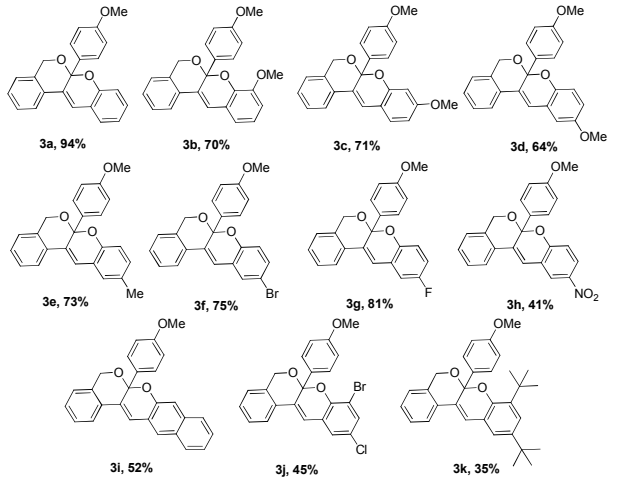
[a] Reactions were performed in sealed tubes containing **1a** (0.3 mmol), **2a** (0.36 mmol), and solvent (2 mL) under Ar, unless noted otherwise. [b] Isolated yield. [c] **1a** (0.3 mmol) and **2a** (0.6 mmol). [d] **1a** (0.6 mmol) and **2a** (0.3 mmol). [e] Toluene:dioxane = 1:1 (v/v, 2 mL). [f] Toluene:dioxane = 1:4 (v/v, 2 mL).

As indicated in Table 1, our study started with the $Cu(OTf)_2$-mediated reaction of internal alkynol **1a** with salicyl *N*-tosylhydrazone **2a** at 100 °C in dioxane. Using 0.2 equiv. of $Cu(OTf)_2$ generated the corresponding isochromeno[3,4-*b*]chromene **3a** in 40% isolated yield (entry 1). The structure of **3a** was confirmed by single-crystal X-ray diffraction analysis (see

Supporting Information, CCDC number: 997620). We then screened various reaction conditions to optimize the catalytic process. Among the copper catalysts tested, $Cu(ClO_4)_2{\cdot}6H_2O$ proved to be the best one, increasing the yield to 43% (entries 2-7). Among the solvents tested, toluene performed well to afford the product in 46% yield (entries 8-13). We also carried out the experiments with different reactant ratios: changing the ratio of **1a:2a** from 1:1.2 to 1:2 increased yield to 52% (entry 14). Lowering the temperature to 60 °C further increased the yield to 60% (Table 1, entry 15). The reaction proceeded more efficiently to give 67% yield at this temperature when we reversed the ratio of **1a:2a** to 2:1 (entry 16). When the solvent was changed to a 1:1 (v/v) mixture of toluene and dioxane and the catalyst load was increased to 0.3 equiv of $Cu(ClO_4)_2{\cdot}6H_2O$, the reaction generated **3a** in better 78% yield (entries 17 and 18). Altering the solvent ratio of toluene and dioxane to 1:4 further improved the reaction and **3a** was isolated in 94% yield (entry 19).

Table 2 Reaction of internal alkynol **1a** with various salicyl *N*-tosylhydrazones **2** in the presence of $Cu(ClO_4)_2{\cdot}6H_2O$.[a]

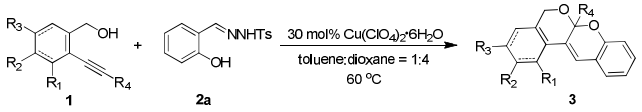


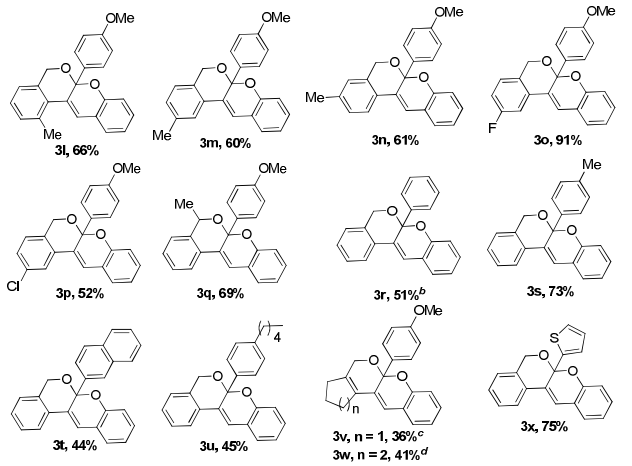


[a] Reactions were conducted at 60 °C for 11 h using **1a** (0.6 mmol), **2** (0.3 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (30 mol%), and a 1:4 (v/v) mixture of toluene:dioxane (2 mL). Isolated yields are shown.

Using the optimized reaction conditions (**1a**:**2a** = 2:1, 30 mol% $Cu(ClO_4)_2{\cdot}6H_2O$, 1:4 (v/v) mixture of toluene:dioxane, 11 h, 60 °C), we explored the scope and limitations of the tandem vinylation-cyclization coupling. Various substituted salicyl *N*-tosylhydrazones **2** were reacted with **1a** to form isochromeno[3,4-*b*]chromene (Table 2). Salicyl *N*-tosylhydrazones with electron-donating groups at the *ortho*, *meta*, and *para* positions were effective, affording the corresponding isochromeno[3,4-*b*]chromenes **3b**-**d** in 64-71% yields. Salicyl *N*-tosylhydrazones bearing the electron-donating Me group or electron-withdrawing Br or F groups at position R^3 reacted smoothly with **1a** to furnish products **3e-g** in 73–81% yields. However, placing the strongly electron-withdrawing *nitro* group at position R^3 made the reaction sluggish, generating **3h** in only 41% yield. Further examination of the scope of *N*-tosylhydrazones showed that a naphthalene-based substrate generated the product **3i** in only 52% yield. Disubstituted substrates hampered the formation of the desired products, and reacting 3,5-disubstituted salicyl *N*-tosylhydrazone with **1a** delivered the corresponding **3j** in only 45% yield. Similarly, steric hindrance in the substrates meant that **3k** was generated in only 35% yield.

Table 3 Reaction of various internal alkynols **1** with salicyl *N*-tosylhydrazone **2a** in the presence of $Cu(ClO_4)_2{\cdot}6H_2O$.[a]



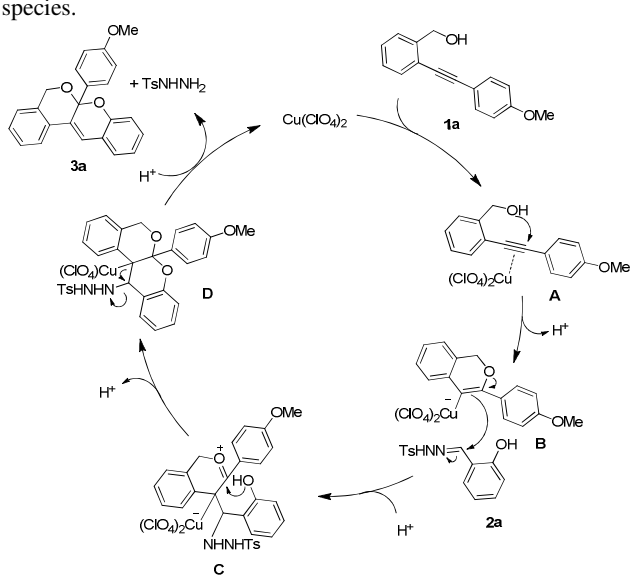


[a] Reactions were conducted under Ar at 60 °C for 11 h using **1** (0.6 mmol), **2a** (0.3 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (30 mol%), and a 1:4 (v/v) mixture of toluene:dioxane (2 mL), unless otherwise noted. Isolated yields are shown. [b] The reaction was performed at 80 °C for 20 h. [c] The reaction was performed at 80 °C in toluene (2 mL) for 4 h. [d] The reaction was performed at 80 °C for 8 h.

To explore the full scope of the reaction, we examined the ability of various substituted alkynols **1** to react with salicyl *N*-tosylhydrazone **2a** (Table 3). Internal alkynols **1** bearing electron-donating Me groups at positions R^1, R^2, and R^3 reacted well to afford the products **3l-3n** in 60-66% yields. A substrate carrying a F at position R^2 generated **3o** in 91% yield, while alkynol substituted with Cl group generated **3p** in 52% yield. Substituting the benzylic methylene of the substrate with a Me group led to formation of **3q** in 69% yield. The reaction also proceeded with (2-(phenylethynyl)phenyl)methanol, giving **3r** in 51% yield, while using (2-(*p*-tolylethynyl)phenyl)methanol gave **3s** in 73% yield. Naphthyl and 4-pentylphenyl alkynols also reacted, though they generated the corresponding products **3t** and **3u** in only 44% and 45% yields, respectively. Internal alkynols bearing non-benzeniod bridges such as cyclopentene and cyclohexene were also suitable for the reaction, and the products **3v** and **3w** were generated in 36% and 41% yields, respectively. Moreover, the alkynol containing heterocyclic thiophenyl group also worked well to deliver **3x** in 75% isolated yield, although alkynols substituted by alkyl group such as hexyl or alkenyl group such as 1-cyclohexene could not give the desired products.

We propose a tentative mechanism for the copper(II) perchlorate-promoted tandem reaction of internal alkynol and salicyl *N*-tosylhydrazone to generate isochromeno[3,4-*b*]chromene (Scheme 1). Coordination between the triple bond of **1a** and $Cu(ClO_4)_2{\cdot}6H_2O$ (**A**) enhances the electrophilicity of the alkyne. Intramolecular addition of the hydroxyl group to the electron-deficient alkyne generates vinylcopper species **B**, based on previous reports of large-scale, Cu(II)-catalyzed preparation of 2,3-dimethylfuran,[14] Pd-catalyzed cycloisomerization[15] and Au- or Pt-catalyzed cycloisomerization.[16] If 3 equiv. ^{t}BuOK or

Cs_2CO_3 was added to the reaction mixture, no product **3a** could be observed. Moreover, when salicylaldehyde was used instead of salicyl *N*-tosylhydrazone under optimal condition, product **3a** could be obtained in lower 71% yield. So, intermediate **B** is proposed to be trapped by **2a** to afford intermediate **C** rather than in situ generated diazo substrate after deprotanation.[12] Then, intermediate **D** is generated after the acetalization[17] with release of a proton. Subsequent cleavage of the carbon-copper bond[18] and acid-promoted elimination of $TsNHNH_2$ affords the desired isochromeno[3,4-*b*]chromene **3a** and regenerates the catalytic species.



Scheme 1 The proposed mechanism

In summary, we have developed a novel, concise catalytic tandem reaction that provides direct access to isochromeno[3,4-*b*]chromene from available internal alkynol and salicyl *N*-tosylhydrazone using copper(II) perchlorate. This methodology tolerates a broad array of substitutions on functional salicyl *N*-tosylhydrazone, and internal alkynols can be applied well. The use of inexpensive copper(II) perchlorate makes this method preferable to standard approaches based on noble-metal catalysts. This tandem reaction involves cycloisomerization, formal [4+2] cycloaddition and elimination process. Further investigations focused on expanding our methodology with alkynols are undergoing in our laboratories.

This work was supported by NSFC/China, NCET (NCET-13-0798), the Innovation Program of Shanghai Municipal Education Commission (Project No. 12ZZ050), the Basic Research Program of the Shanghai Committee of Sci. & Tech. (Project No. 13NM1400802) and the Fundamental Research Funds for the Central Universities.

Notes and references

Shanghai Key Laboratory of Functional Materials Chemistry, Key Lab for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Meilong Road 130, Shanghai 200237, China, Fax: (+) 86-21-64250552, E-mail: liupn@ecust.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data for all products, crystal data and structure refinement of product **3a** (CCDC number: 997620), copies of ^1H and ^{13}C NMR spectra of all products. See DOI: 10.1039/b000000x/

1 Selected reviews, see: (a) F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617; (b) D. O'Hagan, *Nat. Prod. Rep.*, 1995, **12**, 1; (c) R. D. Norcross and I. Paterson, *Chem. Rev*. 1995, **95**, 2041; (d) J. E. Aho, P. M. Pihko and T. K. Rissa, *Chem. Rev.* 2005, **105**, 4406; (e) B. R. Raju and A. K. Saikia, *Molecules*, 2008, **13**, 1942; (e) S. Favre, P. Vogel and S. Gerber-Lemaire, *Molecules*, 2008, **13**, 2570; (f) J. Sperry, Z. E. Wilson, D. C. K. Rathwell and M. A. Brimble, *Nat. Prod. Rep.*, 2010, **27**, 1117.

2 (a) B. Fraser-Reid, L. Magdzinski, B. F. Molino and D. R. Mootoo, *J. Org. Chem.* 1987, **52**, 4495; (b) D. R. Mootoo and B. Fraser-Reid, *J. Org. Chem.* 1989, **54**, 5548.

3 G. V. Baddeley, J. J. H. Simes and T.-H. Ai, *Aust. J. Chem.* 1980, **33**, 2071.

4 E. E. Waldner, M. Hesse, W. I. Taylor and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 1926.

5 (a) C. Audin, J.-M. Lancelin and J.-M. Beau, *Tetrahedron Lett.*, **1988**, 29, 3691; (b) N. Moufid, Y. Chapleur and P. Mayon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 999; (c) O. Rhode and H. M. R. Hoffmann, *Tetrahedron*, 2000, **56**, 6479.

6 (a) T. Mikami, A. Katoh and O. Mitsunobu, *Tetrahedron Lett.*, 1990, **31**, 539; (b) N. Beaulieu, R. A. Dickinson and P. Deslongchamps, *Can. J. Chem.*, 1980, **58**, 2531; (c) P. Duhamel, A. Deyine, G. Dujardin, G. Plé and J.-M. Poirier, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2103.

7 F. Wang, M. Qu, X. Lu, F. Chen and M. Shi, *Chem. Commun.*, 2012, **48**, 6259.

8 (a) C. Taillefumier, Y. Chapleur, D. Bayeul and A. Aubry, *J. Chem. Soc., Chem. Commun.*, 1995, 937; (b) C. Taillefumier and Y. Chapleur, *Can. J. Chem.*, 2000, **78**, 708; (c) R. S. Kumar, R. Nagarajan and P. T. Perumal, Synthisis, 2004, 949; (d) J. Wang, F.-X. Xu, X.-F. Lin and Y.-G. Wang, *Tetrahedron Lett.*, 2008, **49**, 5208. For selected examples about hetero Diels-Alder reaction, see: (e) L. Diao, C. Yang and P. Wan, *J. Am. Chem. Soc.*, 1995, **117**, 5369; (f) R. M. Jones, C. Selenski and T. R. R. Pettus, *J. Org. Chem.*, 2002, **67**, 6911.

9 A. Tenaglia and F. Karl, *Synlett*, 1996, 327.

10 Selected examples, see: (a) J. S. Yadav, B. V. S. Reddy, L. Chandraiah, B. Jagannadh, S. K. Kumar and A. C. Kunwar, *Tetrahedron Lett.*, 2002, **43**, 4527; (b) J. S. Yadav, B. V. S. Reddy, M. Aruna, C. Venugopal, T. Ramalingam, S. K. Kumar and A. C. Kunwar, *J. Chem. Soc., Perkin Trans. 1*, 2002, 165; (c) M. Anniyappan, D. Muralidharan and P. T. Perumal, *Tetrahedron*, 2002, **58**, 10301; (d) J. S. Yadav, B. V. S. Reddy, C.Madhuri, G. Sabitha, B. Jagannadh, S. K. Kumar and A. C. Kunwar, *Tetrahedron Lett.*, 2001, **42**, 6381; (e) J.-i. Matsuo, S. Sasaki, H. Tanaka and H. Ishibashi, *J. Am. Chem. Soc.*, 2008, **130**, 11600; (f) M. M. A. R. Moustafa, A. C. Stevens, B. P. Machin and B. L. Pagenkopf, *Org. Lett.*, 2010, **12**, 4736.

11 Selected reviews, see; (a) B. Alcaide, P. Almendros and J. M. Alonso, *Org. Biomol. Chem.*, 2011, **9**, 4405; (b) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev.*, 2011, **111**, 1657; (c) B. Alcaide, P. Almendros and J. M. Alonso, *Molecules*, 2011, **16**, 7815; (d) S. F. Tlais and G. B. Dudley, *Beilstein J. Org. Chem.*, 2011, **7**, 570; (e) X. Zeng, *Chem. Rev.*, 2013, **113**, 6864.

12 (a) L. Zhou, Y. Shi, Q. Xiao, Y. Liu, F. Ye, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 968; (b) N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang and B. D. Bruin, *J. Am. Chem. Soc.*, 2014, **136**, 1090.

13 (a) P. N. Liu, F. H. Su, T. B. Wen, H. H.-Y. Sung, I. D. Williams and G. Jia, *Chem. Eur. J.*, 2010, **16**, 7889; (b) D. Y. Li, X. S. Shang, G. R. Chen and P. N. Liu, *Org. Lett.*, 2013, **15**, 3848; (c) H. X. Siyang, X. R. Wu, H. L. Liu, X. Y. Wu and P. N. Liu, *J. Org. Chem.*, 2014, **79**, 1505.

14 D. Végh, P. Zalupsky and J. Kováč, *Synth. Commun.*, 1990, **20**, 1113.

15 B. Gabriele, G. Salerno and E. Lauria, *J. Org. Chem.*, 1999, **64**, 7687.

16 (a) Y. Liu, F. Song, Z. Song, M. Liu and B. Yan, *Org. Lett.*, 2005, **7**, 5409. (b) J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez and F. J. Fañanás, *Angew. Chem. Int. Ed.*, 2006, **45**, 2091.

17 Selected examples of asymmetric Mannich-Ketalization reaction, see: (a) M. Rueping and M.-Y. Lin, *Chem. Eur. J.*, 2010, **16**, 4169; (b) H. Wu, Y.-P. He and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 460.

18 For computational studies on the cycloisomerization of W-alkynols, see: (a) T. Sordo, P. Campomanes, A. Diéguez, F. Rodríguez and F. J. Fañanás, *J. Am. Chem. Soc.*, 2005, **127**, 944; (b) J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, T. Sordo and P. Campomanes, *Chem. Eur. J.*, 2005, **11**, 5735.