http://dx.doi.org/10.5935/0103-5053.20140294

J. Braz. Chem. Soc., Vol. 26, No. 3, 405-410, 2015.
Printed in Brazil - ©2015 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Communication

Asymmetric Synthesis of Highly Functionalized Cyclohexa-1,3-dienes via Organocatalyzed One-Pot Three-Component Domino Reaction of Malononitrile with α,β-Unsaturated Imines

Wei Chen,[a] Ren-Zun Zhang,[b] Xiao-Yan Lu[,c] and Jian-Wu Xie*[,b]*

[a]*Zhejiang Pharmaceutical College, Ningbo 315100, People's Republic of China*

[b]*Key Laboratory of the Ministry of Education for Advanced Catalysis Materials, Department of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua 321004, People's Republic of China*

[c]*Ningbo No. 2 Hospital, Ningbo 315010, People's Republic of China*

The enantioselective synthesis of highly functionalized cyclohexa-1,3-dienes was achieved via an organocatalytic one-pot three-component domino reaction. In addition, a possible mechanism accounting for the reaction was proposed.

Keywords: organocatalytic, domino reactions, quinidine, cyclohexa-1,3-dienes

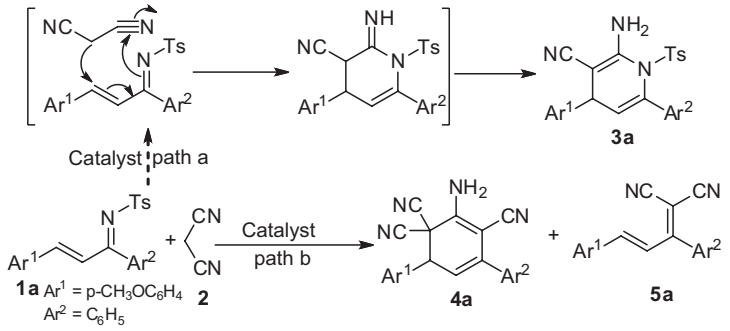
Introduction

Regio-, chemo-, and enantioselective construction of six-membered carbocycles is one of the most fundamental and important issues in synthetic organic chemistry because of the importance and prevalence of these motifs in many biologically active natural products and drug molecules.[1] Intermolecular annulation reaction is one of the most ideal processes for the rapid and selective construction of complex cyclic structures in a one-pot manner from relatively simple building blocks.[2,3] While the annulation approaches to construct six-membered carbocycles have typically relied on the [4 + 2] and [5 + 1]-modes[4,5] and to the best of our knowledge, there is no report on the direct enantioselective organocatalytic [1 + 3 + 2]-processes for the synthesis of chiral six-membered carbocycles. In addition, multicomponent domino reactions (MDRs), in which more than one bond is being formed in a multistep one-pot reaction sequence are of great importance in organic chemistry because they have several advantages over a series of individual reactions.[6-8] First, multicomponent domino reactions allow construction of complex structures in as few steps as possible. In theory, they also eliminate the need for a purification step (or steps). Since the intermediates are not isolated it becomes easier to work with sensitive or unstable intermediates. Finally, employing multicomponent domino reactions will reduce the amount of waste formed and save on cost and amounts of reagents, solvents, time. In connection with our continuous interest in organocatalysis, and on the basis of our recent achievement,[9] we report herein an alternative approach to the synthesis of highly functionalized cyclohexa-1,3-dienes by an enantioselective organocatalytic one-pot three-component domino [1 + 3 + 2] pathway using commercially available, low cost quinidine as the organocatalyst.

*e-mail: xiao_yan_lu@163.com, xiejw@zjnu.cn

Results and Discussion

N-Sulfonyl-1-aza-1,3-dienes, which were found by Boger *et al.*[10] to participate as a 4π component in organic synthesis, have been well demonstrated as versatile electrophiles in cycloaddition reactions such as [4 + 2], [3 + 2], [2 + 2], etc., as well as 1,2- and 1,4-addition reactions.[11] Many nucleophiles have been reported in the addition reactions involving *N*-sulfonyl-1-aza-1,3-dienes.[10] However, to the best of our knowledge, malononitriles have never been reported to date as nucleophiles for the asymmetric addition to *N*-sulfonyl-1-aza-1,3-dienes. We envisioned the reaction sequence involving Michael addition of *N*-sulfonyl-1-aza-1,3-dienes **1** to malononitrile **2** by using *H*-bonding activation, followed by subsequent intramolecular cyclization of the resulting adducts as a facile and efficient approach to the piperidine derivatives (Scheme 1, path a), which may be useful in the total synthesis of natural products and medicinal chemistry (Scheme 1). To our surprise, no desired product **3a** was



Scheme 1. Potential strategies for the cyclization of α,β-unsaturated imines with malononitrile.

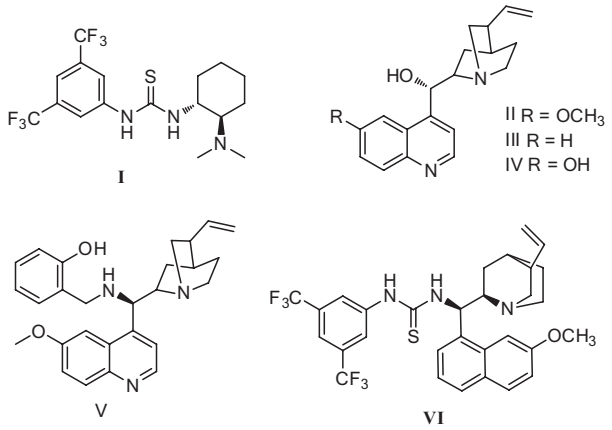


Figure 1. Structures of organocatalysts **I**-**VI**.

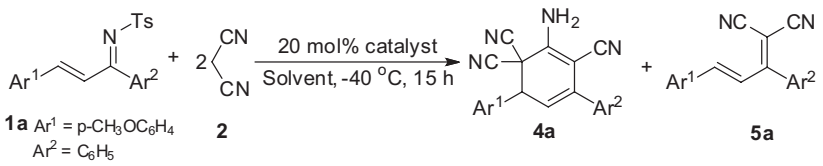
observed, but cyclohexa-1,3-diene **4a**, which was isolated in the presence of the organocatalysts **I**-**VI** (Figure 1) in dichloromethane (DCM) at –40 °C (Scheme 1, path b). Notably, **5a** was also isolated as a byproduct in low yield.

Subsequently, investigations were carried out in order to find the optimal reaction conditions for the formation of enantiomeric piperidine derivatives **3** and the *N*-sulfonyl-1-aza-1,3-diene **1a** was chosen as a model substrate. The reaction was first carried out in the presence of the organocatalysts **I**-**VI** in DCM at –40 °C. We first investigated the catalytic activity of organocatalysts for the multicomponent domino annulation of *N*-sulfonyl-1-aza-1,3-diene **1a** with malononitrile **2**. A few representative results are shown in Table 1. We tended to activate both donors and acceptors to promote this transformation and the multicomponent domino annulation was first catalyzed by thiourea-tertiary amine **I**. The reaction proceeded smoothly and cyclohexa-1,3-diene **4a** was obtained in moderate yield, while the enantiomeric excess (ee) was very low (Table 1, entry 1). Cinchona alkaloids have appeared to be efficient organocatalysts in asymmetric transformations since the basic tertiary nitrogen of cinchona alkaloids could activate nucleophiles by deprotonation, whereas the secondary hydroxyl group would serve as hydrogen-bonding donor in the activation of electrophiles such as α,β-unsaturated carbonyl compounds or nitroalkenes. As such, quinidine **II** and cinchonine **III** were screened and better results were obtained (Table 1, entries 2-3).

Especially, quinidine II exhibited excellent catalytic activity and even much higher enanotioselectivity (72% ee) was obtained (Table 1, entry 2). Catalysts IV-VI derived from cinchona alkaloids were also found to be highly active catalysts, product **4a** was obtained in moderate yield, while the ee was very low (Table 1, entries 4-6). In the next stage of the studies, different solvents and temperatures were screened. The reaction proceeded smoothly and afforded moderate yields (10-44%) and varied enantioselectivities (Table 2, entries 7-13) in different solvents. However, chlorinated solvents were the most useful in terms of enantioselectivities and yields (Table 1, entries 2 and 14). Notably, the multicomponent domino annulation worked very well in chloroform ($CHCl_3$) to afford **4a** with high enantioselectivity in 46% yield (Table 1, entry 14) and chloroform turned out to be the solvent of choice and was used for temperature screening. By lowering the reaction temperature to –50 °C, high enantioselectivity (89% ee) and a moderate yield (42%) were obtained in the presence of quinidine II (Table 1, entry 15). Based on the above screened results, the optimal reaction conditions of 1 eq. **1** and 2.5 eq. **2** in chloroform with 20 mol% quinidine II at –50 °C were established.

With the optimized conditions in hand, we investigated the scope of the reaction. The results are summarized in Table 2. Various substituted *N*-sulfonyl-1-aza-1,3-dienes **1a**-**l** were treated with malononitrile **2**. The reaction proved to be general, since moderate yields (31-53%) and high enantioselectivities (81-91% ee) were observed in all cases. The position of the substituent on the aromatic ring had no significant influence on the stereochemical outcome of the reaction. Moreover, the multicomponent domino annulation with *N*-sulfonyl-1-aza-1,3-dienes bearing either electron-withdrawing or electron-donating substituents proceeded without noticeable changes in yield or stereoselectivity. *N*-sulfonyl-1-aza-1,3-dienes with electron withdrawing

Table 1. Screening of the reaction conditions of malononitrile **3** with *N*-sulfonyl-1-aza-1,3-diene **2a** catalyzed by **1**[a]



entry	Catalyst	Solvent	**4a** yield[b] / %	ee[c] / %	**5a** yield[b] / %
1	**I**	DCM	49	21	23
2	**II**	DCM	47	72	Trace
3	**III**	DCM	44	43	10
4	**IV**	DCM	41	0	11
5	**V**	DCM	46	27	Trace
6	**VI**	DCM	36	0	14
7	**II**	THF	34	0	19
8	**II**	Toluene	31	43	15
9	**II**	EtOH	44	0	10
10	**II**	CH_3CN	10	0	23
11	**II**	Et_2O	39	9	13
12	**II**	*n*-Hexane	23	0	27
13	**II**	EtOAc	30	24	15
14	**II**	$CHCl_3$	46	83	Trace
15[d]	**II**	$CHCl_3$	42	89	Trace

[a]Reactions performed with 0.1 mmol of **1a**, 0.25 mmol malononitrile, 20 mol% catalyst in different solvents at –40 °C; [b]isolated yield; [c]determined by chiral high-performance liquid chromatography (HPLC) analysis; [d]at –50 °C.

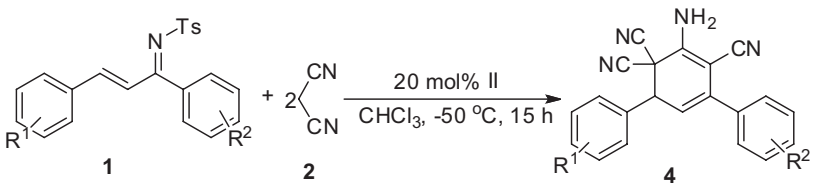
substituents on the *ortho*, *meta* or *para* positions afford cyclohexa-1,3-dienes **4** with slightly inferior yields and enantioselectivities (Table 2, entries 7-9). The opposite configuration of cyclohexa-1,3-diene **4a** was obtained with slightly inferior enantioselectivity when the multicomponent domino annulation was catalyzed by quinine.

This catalytic cascade is a three-component annulation comprising a *N*-sulfonyl-1-aza-1,3-diene, two malononitriles and a simple chiral tertiary amine, which is capable of catalyzing each step of this triple cascade. To obtain mechanistic information about the enantioselective multicomponent domino annulation, several control experiments were conducted. The reaction proceeded smoothly between **6l** and malononitrile **2** in good yield under the same reaction conditions, while the enantioselectivity is very low (Scheme 2). Even when *p*-toluenesulfonamide ($TsNH_2$) was added as an additive, the enantioselectivity is very poor (Scheme 2). The sulfonyl group proved to be a key group in the *N*-sulfonyl-1-aza-1,3-dienes **1** in the enantioselective multicomponent domino annulation. On the basis of the above observations and previous studies,[3] a possible mechanism for the present tertiary amine-catalyzed three-component cascade annulation was proposed (Scheme 3). We propose a stepwise mechanism in which the rate-determining step consists of a dual Brønsted base/hydrogen-bonding activation step involving both the *N*-sulfonyl-1-aza-1,3-dienes **1** and malononitrile **2**. First, malononitrile **2** was deprotonated by the quinidine nitrogen atom to generate an ion pair, while the hydroxyl group coordinates to the oxygen atom of the sulfonyl group, bringing the two reactants into close proximity. Next, attack of the nucleophile on the *N*-sulfonyl-1-aza-1,3-dienes **1** generates intermediate **A** followed by Knoevenagel condensation to produce intermediate **B**. Then, further intramolecular cyclization reactions occurred, followed by proton transfer of the resulting adducts as a facile and efficient approach to the target compounds **4** (Scheme 2). In addition, the molecular structure of enantiopure **4l** has been firmly determined by X-ray (Figure 2). The enantiopure crystals of **4** suitable for determination of the absolute configuration were not obtained in our lab.

Crystallographic data

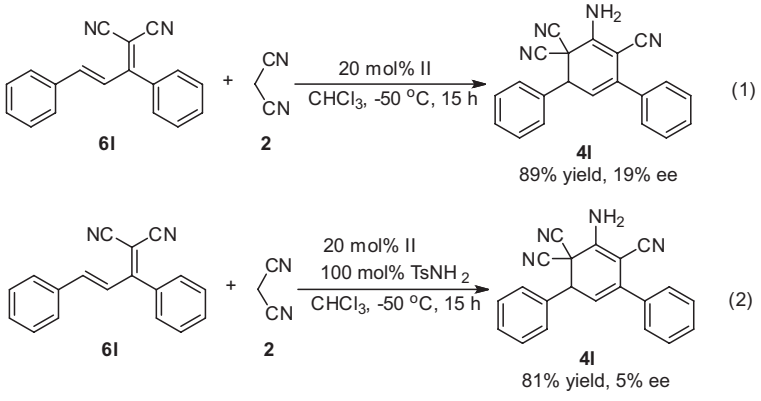
Crystal data for **4l**: $C_{21}H_{14}N_4$ (322.36); monoclinic; P2(1)/c; a = 7.995(10) Å, b = 13.031(16) Å, c = 16.63(2) Å; V = 1733(4) Å^3; Z = 12; specimen 0.326 × 0.312 × 0.218 mm^3;

Table 2. Quinidine-catalyzed reaction of *N*-sulfonyl-1-aza-1,3-dienes **1** with malononitrile **2**[a]



entry	R_1	R_2	**2**	**4**	Yield[b] / %	ee[c] / %
1	*p*-OMe	H	**1a**	**4a**	42	89
2	*p*-OMe	*p*-Cl	**1b**	**4b**	45	90
3	*p*-OMe	*p*-Br	**1c**	**4c**	40	86
4	*p*-OMe	*p*-Me	**1d**	**4d**	31	89
5	H	*p*-OMe	**1e**	**4e**	31	87
6	*p*-F	*p*-OMe	**1f**	**4f**	50	91
7	*p*-Cl	*p* -OMe	**1g**	**4g**	47	86
8	*o*-Cl	*p*-OMe	**1h**	**4h**	41	84
9	*m*-Cl	*p*-OMe	**1i**	**4i**	40	81
10	*p*-Br	*p*-OMe	**1j**	**4j**	43	88
11	*p*-Me	*p*-OMe	**1k**	**4k**	37	90
12	H	H	**1l**	**4l**	53	91
13[d]	*p*-OMe	H	**1a**	**4a**	31	–86

[a]Reactions performed with 0.1 mmol of **1a**, 0.25 mmol malononitrile, 20 mol% catalyst in different solvents at –50 °C; [b]isolated yield; [c]determined by chiral HPLC analysis; [d]catalyzed by quinine.

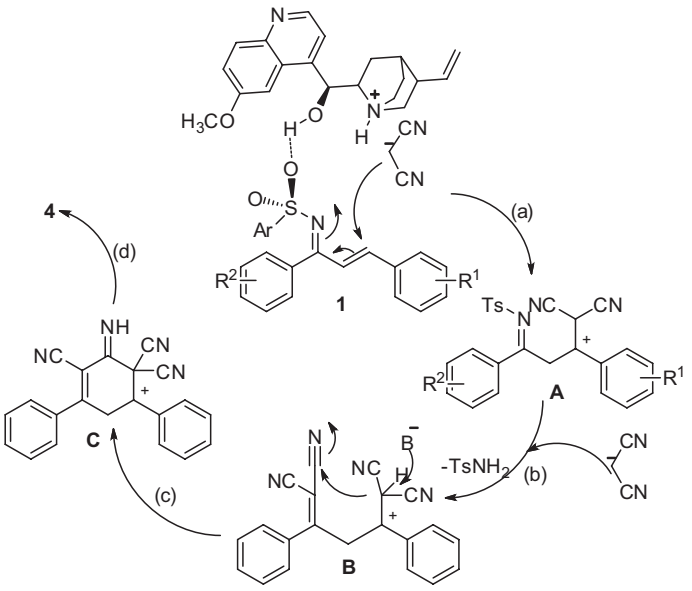


Scheme 2.

T = 296(2) K; SIEMENS P4 diffractometer; absorption coefficient 0.076 mm^{-1}; reflections collected 9576; independent 3046 [R(int) = 0.0272]; refinement by full-matrix least-squares on F^2, data/restraints/parameters 3046/0/227; goodness-of-fit on F^2 = 1.026; final *R* indices [$I > 2\sigma(I)$] R1 = 0.0380, wR2 = 0.0905; *R* indices (all data) R1 = 0.0602, wR2 = 0.1016; largest diff. peak and hole 0.166 and –0.123 e $Å^{-3}$. CCDC 1035842 contains the supplementary crystallographic data for the structure of **4l**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

Conclusions

In summary, a concise and stereoselective methodology for the synthesis of highly substituted carbocycles has been developed. Further investigation on the application of the present strategy to construct complex organic molecules is currently underway.



Scheme 3. Plausible mechanism.

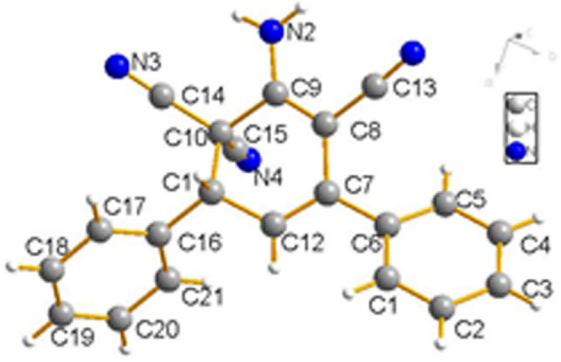


Figure 2. Molecular structure of enantiopure **4l** (ellipsoids with 50% probability).

Experimental

Nuclear magnetic resonance (NMR) spectra were recorded with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts were reported in parts *per* million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26, DMSO δ 2.50), carbon (chloroform δ 77.0, DMSO δ 39.5). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Optical rotations were measured in $CHCl_3$ solution at 589 nm and 20 °C. Enantiomeric excess was determined by high-performance liquid chromatography (HPLC) analysis on Chiralcel IC, OD and Chiralpak AD columns. Infrared (IR) spectra were recorded using a Perkin-Elmer 1600 Series FTIR. Electrospray ionization-high resolution mass spectrometry (ESI-HRMS) was measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer. Chloroform was distilled from CaH_2. The *N*-sulfonyl-1-aza-1,3-dienes were easily prepared according to Carretero and co-workers' procedure.[12]

General procedure for the one-pot domino reaction of *N*-tosyl-1-aza-1,3-dienes and malononitrile

To a solution of *N*-sulfonyl-1-aza-1,3-dienes **1a** (0.10 mmol) in $CHCl_3$ (0.5 mL) was added catalyst **II** (6.5 mg, 20 mol%) at –50 °C under N_2. Then, a solution of malononitrile **2** (42 μL, 0.25 mmol) in anhydrous $CHCl_3$ (1.5 mL) was added. Subsequently, $CHCl_3$ (0.5 mL) was also added. The mixture was kept at the temperature until the reaction was completed. Then the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **4**.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

The authors gratefully acknowledge financial support from the Zhejiang Provincial Natural Science Foundation of China (LQ13B020005), Ningbo Natural Science Foundation (2012A610175), the Foundation of Zhejiang Educational Committee (Y201226178), Zhejiang Pharmaceutical Association (2011ZYY 18 and 2014ZYY 34) and Ningbo No. 2 Hospital.

References

1. For selected reviews, see: Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R.; *Chem. Rev.* **2007**, *107*, 3286; Pihko, A. J.; Koskinen, A. M. P.; *Tetrahedron* **2005**, *61*, 8769; Marco-Contelles, J.; Molina, M. T.; Anjum, S.; *Chem. Rev.* **2004**, *104*, 2857; Ferrero, M.; Gotor, V.; *Chem. Rev.* **2000**, *100*, 4319; Mehta, G.; Srikrishna, A.; *Chem. Rev.* **1997**, *97*, 671 and references cited therein.
2. Trost, B. M.; *Angew. Chem., Int. Ed.* **1995**, *34*, 259; Trost, B. M.; *Science* **1991**, *254*, 1471.
3. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H.; *Acc. Chem. Res.* **2008**, *41*, 40; Wender, P. A.; Croatt, M. P.; Witulski, B.; *Tetrahedron* **2006**, *62*, 7505.
4. For recent selected reviews, see: Merino, P.; Marqués-López, E.; Tejero, T.; Herrera, R. P.; *Synthesis* **2010**, 1; Reymond, S.; Cossy, J.; *Chem. Rev.* **2008**, *108*, 5359; Takao, K.; Munakata, R.; Tadano, K.; *Chem. Rev.* **2005**, *105*, 4779; Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G.; *Angew. Chem., Int. Ed.* **2002**, *41*, 1668; Corey, E. J.; *Angew. Chem., Int. Ed.* **2002**, *41*, 1650; Winkler, J. D.; *Chem. Rev.* **1996**, *96*, 167.
5. For recent selected reviews on the construction of carbocycles by other approaches, see: Moyano, A.; Rios, R.; *Chem. Rev.* **2011**, *111*, 4703; Leemans, E.; D'hooghe, M.; De Kimpe, N.; *Chem. Rev.* **2011**, *111*, 3268; Rubin, M.; Rubina, M.; Gevorgyan, V.; *Chem. Rev.* **2007**, *107*, 3117; Madsen, R.; *Eur. J. Org. Chem.* **2007**, 399; Nicolaou, K. C.; Bulger, P. G.; Sarlah, D.; *Angew. Chem., Int. Ed.* **2005**, *44*, 4490; Gibson, S. E.; Lewis, S. E.; Mainolfi, N. J.; *J. Organomet. Chem.* **2004**, *689*, 3873; Overman, L. E.; Pennington, L. D.; *J. Org. Chem.* **2003**, *68*, 7143; Hartley, R. C.; Caldwell, S. T.; *J. Chem. Soc., Perkin Trans. 1* **2000**, 477; Tietze, L. F.; Schünke, C.; *Eur. J. Org. Chem.* **1998**, 2089; Taber, D. F.; Joshi, P. V. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., ed.; Wiley-VCH: Weinheim, 2005.
6. Meijere, A. D.; Zezschwitz, P. V.; Bräse, S.; *Acc. Chem. Res.* **2005**, *38*, 413; Hussain, M. M.; Walsh, P. J.; *Acc. Chem. Res.* **2008**, *41*, 883; Sun, X. L.; Tang, Y.; *Acc. Chem. Res.* **2008**, *41*, 937; Wasike, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C.; *Chem. Rev.* **2005**, *105*, 1001; Trost, B. M.; Frontier, A. J.; *J. Am. Chem. Soc.* **2000**, *122*, 11727; Trost, B. M.; Gutierrez, A. C.; Livingston, R. C.; *Org. Lett.* **2009**, *11*, 2539; Touré, B. B.; Hall, D. G.; *Chem. Rev.* **2009**, *109*, 4439; Ganem, B.; *Acc. Chem. Res.* **2009**, *42*, 463.
7. Santra, S.; Andreana, P. R.; *Angew. Chem., Int. Ed.* **2011**, *50*, 9418; Dömling, A.; Wang, W.; Wang, K.; *Chem. Rev.* **2012**, *112*, 3083; Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A.; *Chem. Rev.* **2011**, *111*, 6984; Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S.; *J. Am. Chem. Soc.* **2011**, *133*, 5784.
8. Zhu, J. P.; Bienaymé, H.; *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2004; Tietze, L. F.; Brasche, G.; Gericke, K.; *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; Tietze, L. F.; *Chem. Rev.* **1996**, *96*, 115.
9. Chen, W.; Yu, W.-G.; Shi, H.-B.; Lu, X.-Y.; *Chem. Pap.* **2012**, *66*, 308.
10. Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M.; *J. Am. Chem. Soc*. **1991**, *113*, 1713; Boger, D. L.; Corbett, W. L.; *J. Org. Chem*. **1993**, *58*, 2068 and references cited therein; Jiang, X.-X.; Wang, R.; *Chem. Rev.* **2013**, *113*, 5515; Clark, R. C.; Pfeiffer, S. S.; Boger, D. L.; *J. Am. Chem. Soc.* **2006**, *128*, 2587; Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schürmann, M.; Preut, H.; Jacob, T.; Arndt, H.-D.; *J. Am. Chem. Soc.* **2008**, *130*, 13219; Esquivias, J.; Arrayás, R. G.; Carretero, J. C.; *J. Am. Chem. Soc.* **2007**, *129*, 1480; Ma, C.; Gu, J.; Teng, B.; Zhou, Q.-Q.; Li, R.; Chen, Y.-C.; *Org. Lett.* **2013**, *15*, 6206; Gu, J.; Ma, C.; Li, Q.-Z.; Du, W.; Chen, Y.-C.; *Org. Lett.* **2014**, *16*, 3986.
11. Monbaliu, J. M.; Masschelein, K. G. R.; Stevens, C. V.; *Chem. Soc. Rev.* **2011**, *40*, 4708; Li, J.-L.; Liu, T.-Y.; Chen, Y.-C.; *Acc. Chem. Res.* **2012**, *45*, 1491; Oberg, K. M.; Rovis, T.; *J. Am. Chem. Soc.* **2011**, *133*, 4785; Colby, D. A.; Bergman, R. G.; Ellman, J. A.; *J. Am. Chem. Soc.* **2006**, *128*, 5604; Shapiro, N. D.; Toste, F. D.; *J. Am. Chem. Soc*. **2008**, *130*, 9244; He, M.; Struble, J. R.; Bode, J. W.; *J. Am. Chem. Soc.* **2006**, *128*, 8418; Groenendaal, B.; Ruijter, E.; Orru, R. V. A.; *Chem. Commun.* **2008**, 5474.
12. Esquivias, J.; Arrayás, R. G.; Carretero, J. C.; *J. Am. Chem. Soc.* **2007**, *129*, 1450.

Submitted: October 23, 2014
Published online: December 16, 2014