HETEROCYCLES, Vol. 98, No. 5, 2019, pp. 667 - 673. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 24th January, 2019, Accepted, 29th March, 2019, Published online, 23rd April, 2019
DOI: 10.3987/COM-19-14046

CATALYST-FREE TANDEM REACTION FOR THE SYNTHESIS OF TETRAHYDRO-1,2,3-TRIAZINE DERIVATIVES

Kewei Wang,[1] Huijun Liu,[1] Yong Guo,[1] Gang Yi,[2]* Zhifang Jia,[1]* and Feng Feng[1]

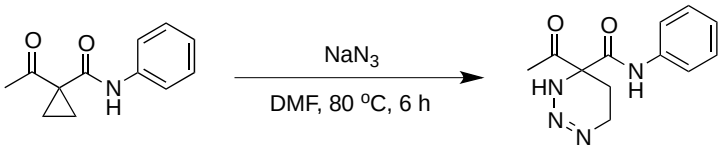
[1]Department of Chemistry and Chemical Engineering, Shanxi Datong University, Datong, 037009, China. jiazhifang2006@163.com [2]Shandong Dongyue Organosilicon Materials Co., Ltd., Zibo, 256401, China. yigang009@163.com

Abstract – A simple and efficient method for the synthesis of tetrahydro-1,2,3-triazine derivatives was developed through a one-pot ring-opening/ring-closing tandem reaction. By the tandem reaction, various previously unreported tetrahydro-1,2,3-triazines were prepared by cyclopropane derivatives and NaN_3 with 90–97% yields under the catalyst-free conditions.

Tetrahydro-1,2,3-triazines as an important constituent of pharmaceutical molecules are of interest for the modern organic synthesis because of their biological activity.[1] To date, the synthetic methods of tetrahydro-1,2,3-triazines mainly contain the follows: (1) the cyclization of azide and Grignard reagent;[2] (2) the cyclization of enediynyl azides;[3] (3) the multi-step reaction from tetrahydropyrimidin-2(1*H*)-one.[4] Although these methods have got remarkable results, some disadvantages still exist, such as harsh reaction conditions, hardly available substrates, and complex synthetic steps. Therefore, an efficient, facile, and general synthetic method of tetrahydro-1,2,3-triazine is needed.

Tandem reaction not only improves the overall efficiency of synthetic reactions by omitting the step of isolating the intermediate, but also reduces environment pollution by consuming less toxic solvents in the operation.[5] However, a problem of catalyst incompatibility generally exists because a multistep tandem reaction usually requires different catalysts in various steps, sometimes even cooperating catalysts with antagonistic groups.[6] Therefore, to solve this problem, an scientific solution is to explore catalyst-free tandem reaction systems except exploiting multifunctional catalysts.[7] In other words, developing catalyst-free tandem reaction system not only solves the catalyst incompatibility problem but also offers a clean approach for organic synthesis. Herein, a simple and efficient strategy for synthesizing tetrahydro-1,2,3-triazine compounds was developed (**Scheme 1**). A series of tetrahydro-1,2,3-triazines was efficiently synthesized by cyclopropane derivatives and NaN_3 through a ring-opening/ring-closing

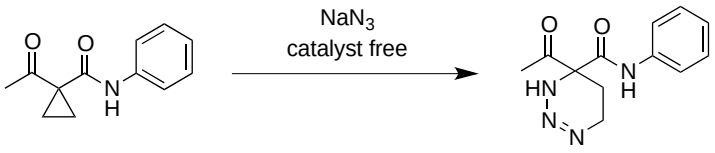
tandem reaction under the catalyst-free conditions.



1a **2a**

Scheme 1. One-pot tandem reaction for the synthesis of tetrahydro-1,2,3-triazine derivative **2a**

Table 1. Synthesis of tetrahydro-1,2,3-triazine derivative **2a** through a one-pot tandem reaction



1a **2a**

Entry[a]	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	DMF	60	6	62
2	DMF	80	6	97
3	$MeNO_2$	80	6	14
4	EtOH	80	6	trace
5	DCE	80	6	trace
6	THF	60	6	0
7	MeCN	80	6	9
8	DMSO	80	6	trace
9	toluene	80	6	0
10	DMF	80	4	79

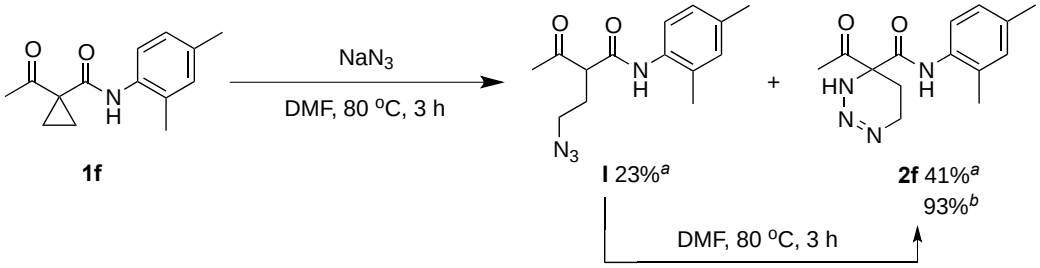
[a] **1a** (1.0 mmol), NaN_3 (1.2 mmol), solvent (1 mL). [b] Isolated yield.

In the preparation methods of tetrahydro-1,2,3-triazines, a favorite strategy is the cyclization of enediynyl azides,[3] in which azides as starting materials always should be prepared by NaN_3 and halogenated compounds.[8] However, most of organic azides are instable so that they are easy to explode during their storage, transportation, and operation.[9] Therefore, we designed a tandem reaction to directly synthesize tetrahydro-1,2,3-triazine, in which the organic azide as an intermediate need not to be isolated. Since the ring-opening reaction of cyclopropanes is easy to occur, we initially chose cyclopropane derivative **1a** as starting material to react with NaN_3 in *N*,*N*-dimethylformamide (DMF) at 60 °C for 6 h. To our delight, the desired product **2a** was obtained in 62% yield (**Table 1**, entry 1). The reaction temperature rose to 80 °C, the yield of **2a** increased from 62% to 97% accordingly (entry 2). The reaction solvents were then screened. The yields of **2a** were quite poor (< 15%), whether the reaction was performed in the polar

solvents ($MeNO_2$, EtOH, MeCN, and DMSO) or the weak polar solvents (DCE, THF, and toluene) (entries 3–9). After optimizing the reaction time (entry 10), the optimal reaction conditions were finally determined: **1a** (1.0 mmol), NaN_3 (1.2 mmol), DMF (1 mL), 80 °C, 6 h (entry 2).

In order to shed light on the reaction mechanism, some control reactions were performed (**Scheme 2**). Under the optimal conditions, an intermediate with yield of 23% was obtained with the generation of **2f** (yield of 41%) when cyclopropane derivative **1f** reacted with NaN_3 at 80 °C for 3 h. After the verifications by ^1H and ^{13}C NMR spectra, the intermediate structure was confirmed as organic azide **I**. Moreover, the intermediate **I** was isolated and was then used as substrate directly react at 80 °C for 3 h in DMF without adding any catalyst and reactant, only the target product **2f** was generated with the isolated yield of 93% (The yield of **2f** was calculated based on **I**). These results indicate that the reaction could be a one-pot tandem reaction, containing 1) the nucleophilic addition reaction of **1f** and NaN_3; 2) intramolecular condensation of **I** and proton exchange; 3) tautomerism (**Figure 1**).

With the optimized conditions in hand, we then explored the scope of the reaction substrates. As shown in **Table 2**, when the cyclopropane derivatives containing electron-donating groups (–OMe, –Me) at the



[a] The isolated yields were obtained from NaN_3 and **1f** in DMF at 80 °C for 3 h.
[b] The isolated yield (basd on **I**) was obtained directly from **I** in DMF at 80 °C for 3 h.

Scheme 2. Control reactions of the tandem reaction

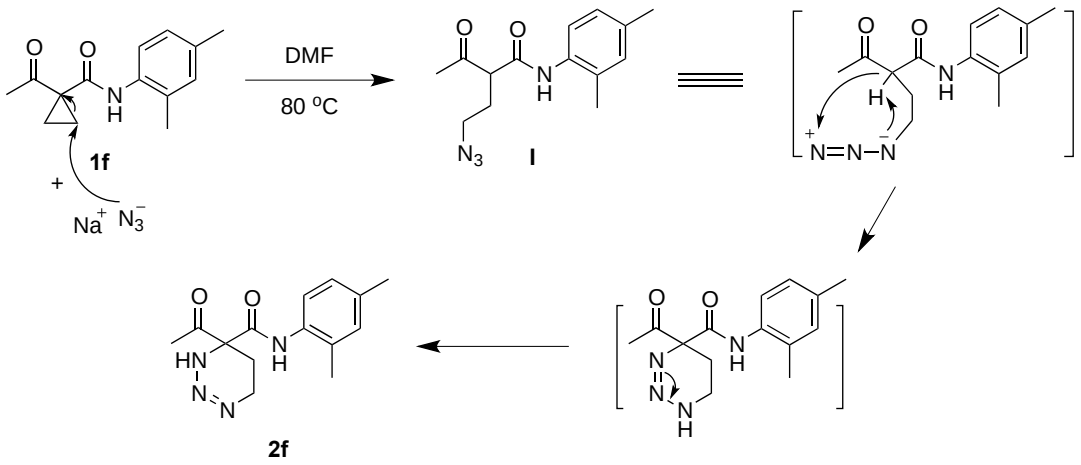
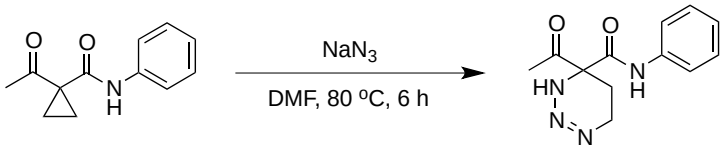
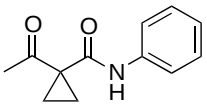
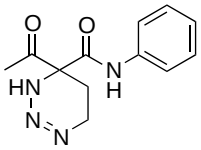
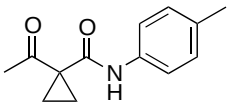
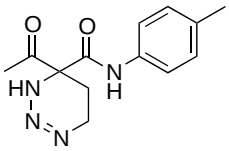
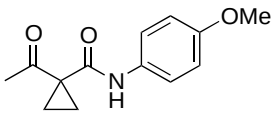
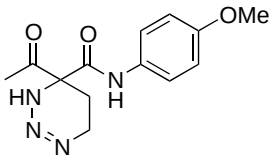
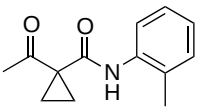
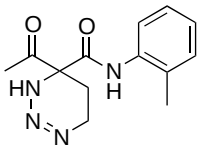
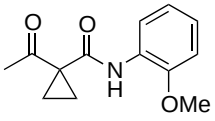
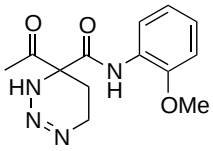
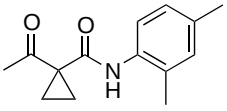
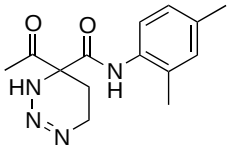
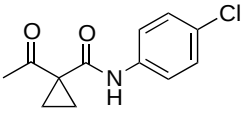
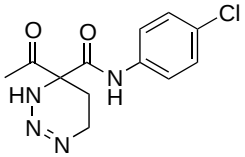
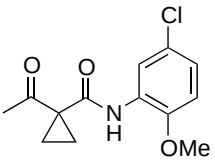
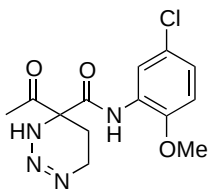
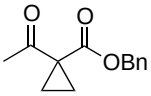
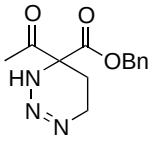


Figure 1. Proposed reaction mechanism

Table 2. Synthesis tetrahydro-1,2,3-triazine derivatives **2a–i**



1a-i **2a-i**

Entry[a]	Substrate		Product		Yield[b] (%)
1[c]		**1a**		**2a**	94
2		**1b**		**2b**	93
3		**1c**		**2c**	96
4		**1d**		**2d**	94
5		**1e**		**2e**	90
6		**1f**		**2f**	92
7		**1g**		**2g**	90
8		**1h**		**2h**	91
9		**1i**		**2i**	92

[a] **1a** (1.0 mmol), NaN_3 (1.2 mmol), DMF (1 mL). [b] Isolated yield. [c] The reaction was performed on a 10.0 mmol scale.

phenyls were used as substrates, the reaction proceeded smoothly. Moreover, high yields of the expected products **2b–f** were obtained, whether the electron-donating group is at *ortho*- or *para*-position of acylamino group. In addition, the substrates with electron-withdrawing group (–Cl) also gave the desired compound **2g** without significantly affecting the reaction yield (entry 7). The starting material **1h** containing both electron-withdrawing group (–Cl) and electron-donating group (–OMe) was also investigated. The yield of product **2h** reached up to 91% (entry 8). In particular, benzoyloxycarbonyl-substituted cyclopropane substrate **1i** participated readily in the tandem reaction, producing the corresponding product in high yields (**2i**). To investigate the general application of the synthesis strategy, we increased the model reaction scale to 10 mmol, and the similar yield of **2a** was generated (**Table 2**, entry 1).

In summary, a simple and efficient method for the synthesis of tetrahydro-1,2,3-triazines was developed through a ring-opening/ring-closing tandem reaction. Using this method, various tetrahydro-1,2,3-triazine derivatives were synthesized with high yields under the catalyst-free conditions.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-500 or AV-400 spectrometer. High-resolution mass spectra (HRMS) were obtained on Brüker Compass Data Analysis 4.0. All of the chemicals were of reagent grade and used as received without further purification.

Starting Materials. Cyclopropane derivatives **1a–i** were synthesized in accordance with the previously reported procedure.[10] All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Tetrahydro-1,2,3-triazines (2)

4-Acetyl-*N*-phenyl-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2a). In a typical reaction, NaN_3 (78 mg, 1.2 mmol) was slowly added into a solution of cyclopropane derivative **1a** (203 mg, 1.0 mmol) and DMF (1 mL). The mixture was stirred about 6 h at 80 ºC. After the reaction, the mixture was cooled to room temperature and poured into water (3 mL). Afterwards, the mixture was extracted with CH_2Cl_2 (3 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 for 10 h. All of the organic phases were then concentrated, and isolated with preparative thin-layer chromatography (TLC) (eluting solvent: EtOAc/petroleum ether = 1/3 v/v). Then the product **2a** was obtained (239 mg, 97%). Colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, TMS): δ = 8.76 (s, 1H), 7.54–7.52 (m, 2H), 7.33 (t, *J* = 10.0 Hz, 2H), 7.15 (t, *J* = 5.0 Hz, 1H), 5.10 (s, 1H), 3.46–3.43 (m, 2H), 2.55 (s, 3H), 2.50–2.47 (m, 1H), 2.30–2.27 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.3, 166.6, 136.5, 128.9, 124.9, 119.6, 83.0, 46.2, 35.9, 24.5 ppm; HRMS (ESI): *m/z*: calcd for $C_{12}H_{14}N_4NaO_2$: 269.1014 $[M + Na]^+$; found: 269.1011.

4-Acetyl-*N*-(*p*-tolyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2b). Colorless oil. ^{1}H NMR

(500 MHz, $CDCl_3$, 20 °C, TMS): δ = 8.68 (s, 1H), 7.41 (d, *J* = 2.5 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 5.07 (s, 1H), 3.46–3.43 (m, 2H), 2.55 (s, 3H), 2.50–2.45 (m, 1H), 2.32 (s, 3H), 2.30–2.26 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.8, 166.8, 135.0, 134.4, 129.8, 120.1, 83.4, 46.7, 36.3, 25.0, 21.1 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{16}N_4NaO_2$: 283.1171 $[M + Na]^+$; found: 283.1164.

4-Acetyl-*N*-(4-methoxyphenyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2c). Colorless liquid. ^1H NMR (500 MHz, $CDCl_3$, 20 °C, TMS): δ = 8.64 (s, 1H), 7.43 (d, *J* = 10.0 Hz, 2H), 6.87 (d, *J* = 10.0 Hz, 2H), 5.06 (s, 1H), 3.79 (s, 3H), 3.46–3.43 (m, 2H), 2.55 (s, 3H), 2.50–2.47 (m, 1H), 2.30–2.27 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.5, 166.3, 156.7, 129.7, 121.9, 114.0, 82.9, 55.3, 46.3, 35.9, 24.5 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{16}N_4NaO_3$: 299.1120 $[M + Na]^+$; found: 299.1112.

4-Acetyl-*N*-(*o*-tolyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2d). Colorless oil. ^1H NMR (500 MHz, $CDCl_3$, 20 °C, TMS): δ = 8.74 (s, 1H), 7.92–7.90 (m, 1H), 7.25–7.18 (m, 2H), 7.11–7.08 (m, 1H), 5.11 (s, 1H), 3.49–3.46 (m, 2H), 2.56 (s, 3H), 2.52–2.47 (m, 1H), 2.35–2.29 (m, 1H), 2.26 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.8, 166.8, 134.7, 130.6, 128.6, 126.8, 125.5, 121.7, 83.4, 46.4, 36.2, 25.8, 17.4 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{16}N_4NaO_2$: 283.1171 $[M + Na]^+$; found: 283.1165.

4-Acetyl-*N*-(2-methoxyphenyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2e). Colorless liquid. ^1H NMR (500 MHz, $CDCl_3$, 20 °C, TMS): δ = 9.36 (s, 1H), 8.31–8.29 (m, 1H), 7.08–7.05 (m, 1H), 6.96–6.93 (m, 1H), 6.88–6.86 (m, 1H), 5.07 (s, 1H), 3.87 (s, 3H), 3.45–3.42 (m, 2H), 2.53 (s, 3H), 2.50–2.31 (m, 1H), 2.31–2.27 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.5, 166.6, 148.5, 126.5, 124.7, 120.9, 119.4, 110.1, 83.4, 55.7, 46.5, 36.1, 24.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{16}N_4NaO_3$: 299.1120 $[M + Na]^+$; found: 299.1117.

4-Acetyl-*N*-(2,4-dimethylphenyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2f). Colorless liquid. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.64 (s, 1H), 7.71 (d, *J* = 8.00 Hz, 1H), 7.03–7.00 (m, 2H), 5.09 (s, 1H), 3.48–3.45 (m, 2H), 2.55 (s, 3H), 2.52–2.45 (m, 1H), 2.34–2.27 (m, 4H), 2.20 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 212.3, 166.8, 135.3, 132.1, 131.3, 128.9, 127.3, 122.0, 83.4, 46.5, 36.2, 24.8, 20.9, 17.4 ppm; HRMS (ESI): *m/z*: calcd for $C_{14}H_{18}N_4NaO_2$: 297.1327 $[M + Na]^+$; found: 297.1320.

4-Acetyl-*N*-(4-chlorophenyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2g). Colorless liquid. ^1H NMR (500 MHz, $CDCl_3$, 20 °C, TMS): δ = 8.79 (s, 1H), 7.51–7.48 (m, 2H), 7.31 (d, *J* = 8.00 Hz, 2H), 5.10 (s, 1H), 3.46 (t, *J* = 6.00 Hz, 2H), 2.55 (s, 3H), 2.52–2.45 (m, 1H), 2.32–2.25 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.2, 166.9, 135.3, 130.1, 129.2, 121.0, 83.2, 46.4, 36.0, 24.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{12}H_{13}ClN_4NaO_2$: 303.0625 $[M + Na]^+$; found: 303.0627.

4-Acetyl-*N*-(5-chloro-2-methoxyphenyl)-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxamide (2h). Colorless liquid. ^1H NMR (500 MHz, $CDCl_3$, 20 °C, TMS): δ = 9.37 (s, 1H), 8.39 (s, 1H), 7.05–7.03 (m,

1H), 6.80–6.78 (m, 1H), 5.07 (s, 1H), 3.88 (s, 3H), 3.47–3.44 (m, 2H), 2.55 (s, 3H), 2.50–2.45 (m, 1H), 2.33–2.29 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ = 206.4, 167.1, 147.3, 127.6, 126.3, 124.6, 119.7, 111.1, 83.7, 56.3, 46.6, 36.3, 24.8 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{15}ClN_4NaO_3$: 333.0730 $[M + Na]^+$; found: 333.0724.

Benzyl 4-acetyl-3,4,5,6-tetrahydro-1,2,3-triazine-4-carboxylate (2i). Colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38–7.32 (m, 5H), 5.13 (s, 2H), 5.07 (s, 1H), 3.94–3.91 (m, 2H), 3.54–3.51 (m, 2H), 2.35 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.2, 167.3, 136.5, 128.6, 128.2, 128.1, 91.8, 65.5, 49.5, 30.6, 18.9 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{15}N_3NaO_3$: 284.1011 $[M + Na]^+$; found: 284.1007.

ACKNOWLEDGEMENT

The authors thank the Applied Basic Research Foundation of Shanxi (201801D221096) and the Industrial Research Foundation of Datong (2018013) for financial support, and also the Young Foundation of Shanxi Datong University (2012Q18 and 2011Q10).

REFERENCES

1. G. Cirrincione, A. M. Almerico, P. Barraja, P. Diana, A. Lauria, A. Passannanti, C. Musiu, A. Pani, P. Murtas, C. Minnei, M. E. Marongiu, and P. L. Colla, *J. Med. Chem.*, 1999, **42**, 2561.
2. B. F. Schmidt, E. J. Snyder, R. M. Carroll, D. W. Farnsworth, C. J. Michejda, and R. H. Smith, *J. Org. Chem.*, 1997, **62**, 8660.
3. A. Basak, S. K. Roy, S. Das, A. B. Hazra, S. C. Ghosh, and S. Jha, *Chem. Commun.*, 2007, 622.
4. L. Legentil, B. Lesur, and E. Delfourne, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 427.
5. Y. Yue, X. Guo, Z. Chen, L. Yang, and W. Hu, *Tetrahedron Lett.*, 2008, **49**, 6862.
6. (a) E. Merino, E. Verde-Sesto, E. M. Maya, A. Corma, M. Iglesias, and F. Sánchez, *Appl. Catal. A: Gen.*, 2014, **469**, 206; (b) K. Wang, Z. Jia, X. Yang, L. Wang, Y. Gu, and B. Tan, *J. Catal.*, 2017, **348**, 168.
7. (a) B. Liu, C. Wattanaprayoon, S. C. Oh, L. Emdadi, and D. Liu, *Chem. Mater.*, 2015, **27**, 1479; (b) H. Yang, L. Fu, L. Wei, J. Liang, and B. P. Binks, *J. Am. Chem. Soc.*, 2015, **137**, 1362; (c) Z. Jia, K. Wang, B. Tan, and Y. Gu, *ACS Catal.*, 2017, **7**, 3693.
8. (a) Z.-Y. Chen and M.-J. Wu, *Org. Lett.*, 2005, **7**, 475; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2596.
9. J. P. Costantino, H. W. Richter, C. H. L. Go, and W. H. Waddell, *J. Am. Chem. Soc.*, 1985, **107**, 1744.
10. R. Zhang, Y. Liang, G. Zhou, K. Wang, and D. Dong, *J. Org. Chem.*, 2008, **73**, 8089.