Beilstein Journal of Organic Chemistry

New simple synthesis of ring-fused 4-alkyl-4*H*-3,1-benzothiazine-2-thiones: Direct formation from carbon disulfide and (*E*)-3-(2-aminoaryl)acrylates or (*E*)-3-(2-aminoaryl)acrylonitriles

Qiuping Ding*, Yuqing Lin, Guangni Ding, Fumin Liao, Xiaoyan Sang and Yi-Yuan Peng*

Full Research Paper

Open Access

Address:
Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry & Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, China

Email:
Qiuping Ding* - dqpjxnu@gmail.com; Yi-Yuan Peng* - yiyuanpeng@yahoo.com

* Corresponding author

Keywords:
4*H*-3,1-benzothiazine-2-thione; carbon disulfide; (*E*)-3-(2-aminoaryl)acrylate; (*E*)-3-(2-aminoaryl)acrylonitrile; Michael addition

Beilstein J. Org. Chem. **2013,** *9,* 460–466.
doi:10.3762/bjoc.9.49

Received: 17 December 2012
Accepted: 01 February 2013
Published: 01 March 2013

Associate Editor: T. P. Yoon

Abstract

A new simple and efficient method to construct ring-fused 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives has been developed from carbon disulfide and (*E*)-3-(2-aminoaryl)acrylates or (*E*)-3-(2-aminoaryl)acrylonitriles under mild conditions, without the need for a metal catalyst. The newly developed method tolerates a wide range of substrates in moderate to excellent yields. Moreover, this method is advantageous over previous ones for the easy synthesis of reactants.

Introduction

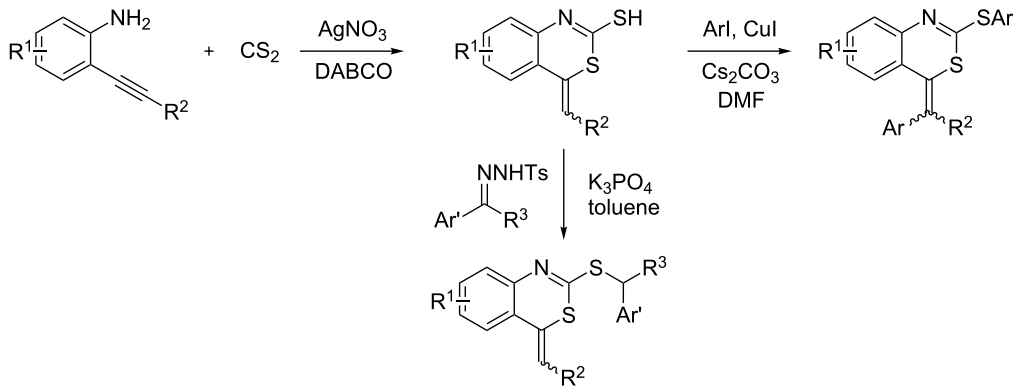
Molecules containing the 4*H*-3,1-benzothiazine moiety have received considerable interest from the chemical and medicinal community due to their promising biological activity [1-4] and the applications in recording and photographic materials [5-8]. A number of efficient approaches for their preparation have been reported in the literature [9-15]. 4-Alkyl-4*H*-3,1-benzothiazine-2-thiones are an important class of 4*H*-3,1-benzothiazine derivatives. Therefore, 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives are also of potential biological importance. However, only a few practical routes for the synthesis of this class of 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives have been reported [16,17]. Although Kobayashi and co-workers have reported the synthesis of 2-(2-thioxo-4*H*-3,1-benzothiazin-4-yl)acetic acid derivatives by the reaction of 3-(2-isothiocyanatophenyl)prop-2-enoates with sodium sulfide, this method suffers from the tedious synthesis of the substrates prepared in four steps from 2-iodoaniline [16]. Molina et al. also described the preparation of 4*H*-3,1-benzothiazine-2-thione derivatives by

intramolecular heteroconjugate addition of carbodiimides or isothiocyanates bearing one *o*-substituted α,β-unsaturated carbonyl fragment promoted by the CS_2/TBAF system [17]. However, both the low yields (30–60%) of the products and the substrate limitations outweigh their advantages. As part of a continuing effort in our laboratory toward the development of novel natural-product-like compounds [18-22], we recently reported the practical synthesis of 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazines starting from 2-alkynylbenzenamines with CS_2, and further transformations to highly functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines (Scheme 1) [9].

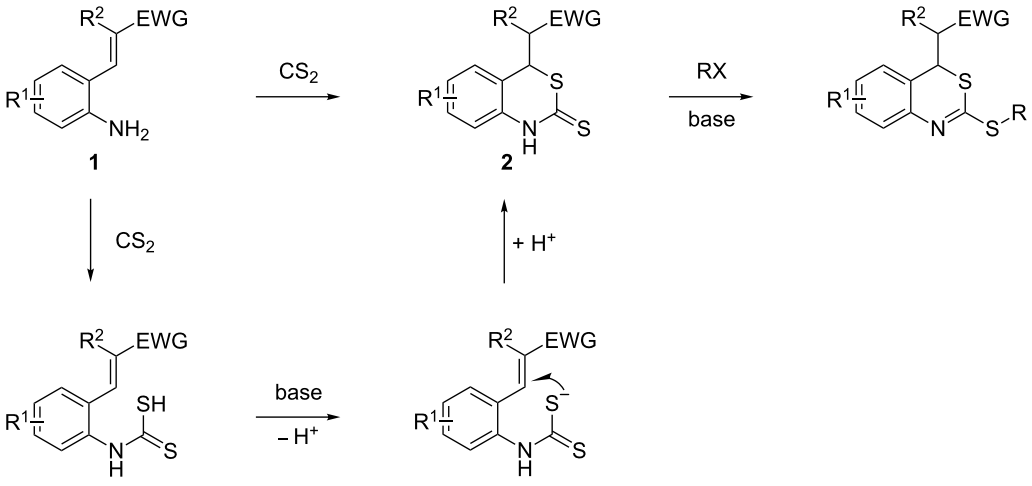
Promoted by these results, we envisioned that (*E*)-3-(2-aminoaryl)acrylates or (*E*)-3-(2-aminoaryl)acrylonitriles could also be utilized as starting substrates for the synthesis of N-heterocycles. Therefore, we focused on the *o*-amino-α,β-unsaturated compound **1** (Scheme 2), which would be expected to construct 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives through a one-pot base-promoted intermolecular addition/intramolecular Michael addition reaction.

Results and Discussion

In our initial study, we examined the tandem reaction with various bases and solvents to optimize the reaction conditions. (*E*)-Butyl 3-(2-aminophenyl)acrylate (**1a**) was chosen as a model substrate, and the results are summarized in Table 1. Among the bases screened, DABCO was found to be superior to the other organic or inorganic bases, although DBU, Et_3N, and KOH also provided good results (Table 1, entries 1–6). However, no product could be detected in the absence of base (Table 1, entry 7). When a catalytic amount of DABCO (20 mol %) was used, only a 69% yield of product **2a** was obtained. Subsequently, the study results showed that the amount of CS_2 had a great effect on the reaction (Table 1, entry 1 versus entries 8–10). To reduce the amount of CS_2, we finally



Scheme 1: $AgNO_3$-catalyzed tandem reaction of 2-alkynylbenzenamines with CS_2 and their further transformation.

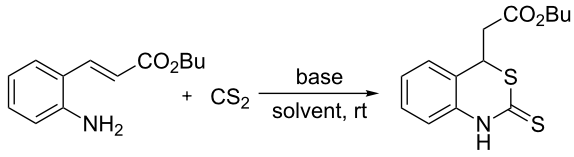


Scheme 2: Concept for the construction of 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives.

chose 4.0 equiv of CS_2. The results also suggested that the solvent was crucial for this transformation. Low-polar solvents such as toluene and CH_2Cl_2 inhibited the reaction (Table 1, entry 11 and entry 12). Among the polar solvents screened (Table 1, entries 13–16), DMSO was the best, affording the desired product in 88% yield (Table 1, entry 13). When the reaction was performed at 60 °C in a sealed tube, the yield of product **2a** decreased to 65% after a similar reaction time (Table 1, entry 17).

With the preliminary optimized reaction conditions in hand, we next tested the generality of the (*E*)-3-(2-aminoaryl)acrylates (Table 2). As expected, a series of functional groups on the phenyl ring of the (*E*)-butyl 3-(2-aminoaryl)acrylates, such as methyl, chloro, fluoro, and nitro were compatible in this procedure, and the corresponding desired products **2b**–**2e** were isolated in 36–86% yields. In general, substrates with electron-donating (methyl) and weakly or moderately electron-withdrawing groups (F, Cl) showed good results in the transformation. For instance, (*E*)-butyl 3-(2-amino-5-methylphenyl)acrylate (**1b**) reacted with CS_2 leading to the corresponding product **2b** in 75% yield (Table 2, entry 2). A slightly higher yield was obtained when (*E*)-butyl 3-(2-amino-5-fluorophenyl)acrylate (**1d**) was used as a replacement in the above reaction (86% yield, Table 2, entry 4). It is worth noting that a substrate with strongly electron-withdrawing group (nitro) gave a low yield 36% of the product **2e**. Further exploration indicated that various alkyl (methyl, ethyl, *tert*-butyl) 3-(2-aminophenyl)acrylates **1** were suitable reactants in the transformation, and the desired products **2f**–**2j** were obtained in moderate to good yields (Table 2, entries 6–10). When (*E*)-ethyl 3-(2-aminophenyl)acrylate (**1g**) was employed in the reaction, the corresponding product **2g** was isolated in 80% yield (Table 2,

Table 1: Exploring variation of the base and other conditions for the construction of 4-alkyl-4*H*-3,1-benzothiazine-2-thiones.[a]

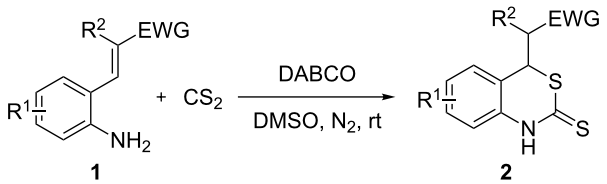


1a **2a**

entry	base	solvent	yield[b] (%)
1	DBU	DMF	80
2	Et_3N	DMF	76
3	Na_2CO_3	DMF	65
4	$NaHCO_3$	DMF	60
5	KOH	DMF	82
6	DABCO	DMF	85
7	—	DMF	—
8[c]	DABCO	DMF	83
9[d]	DABCO	DMF	84
10[e]	DABCO	DMF	44
11[d]	DABCO	toluene	—
12[d]	DABCO	CH_2Cl_2	trace
13[d]	DABCO	DMSO	88
14[d]	DABCO	1,4-dioxane	45
15[d]	DABCO	CH_3CN	50
16[d]	DABCO	THF	30
17[d,f]	DABCO	DMSO	65

[a]Reaction conditions: (*E*)-butyl 3-(2-aminophenyl)acrylate (**1a**, 0.3 mmol), CS_2 (3 mmol, 10.0 equiv), base (0.3 mmol), rt, 2 d. [b]Isolated yield based on **1a**. [c]CS_2 (1.8 mmol, 6.0 equiv). [d]CS_2 (1.2 mmol, 4.0 equiv). [e]CS_2 (0.9 mmol, 3.0 equiv). [f]Reaction performed in DMSO at 60 °C in sealed tube.

Table 2: Preparation of 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives **2**.[a]



1 **2**

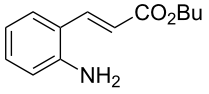
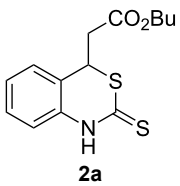
entry	substrate **1**	product **2**	yield[b] (%)
1	 **1a**	 **2a**	88

Table 2: Preparation of 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives **2**.[a] (continued)

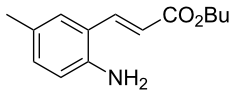
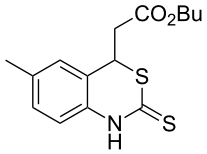
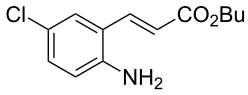
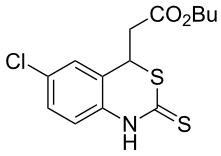
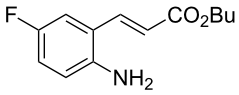
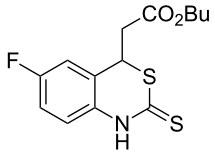
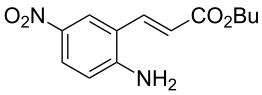
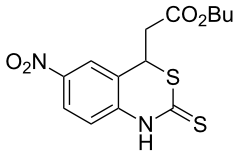
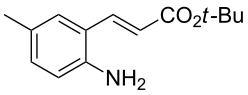
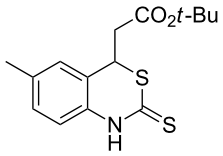
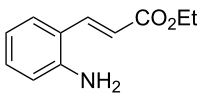
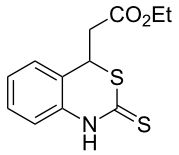
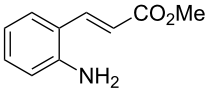
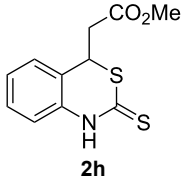
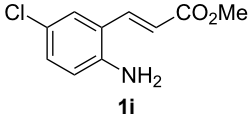
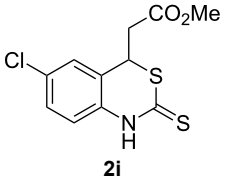
2	 **1b**	 **2b**	75
3	 **1c**	 **2c**	73
4	 **1d**	 **2d**	86
5	 **1e**	 **2e**	36
6	 **1f**	 **2f**	87
7	 **1g**	 **2g**	80
8	 **1h**	 **2h**	60
9	 **1i**	 **2i**	72

Table 2: Preparation of 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives **2**.[a] (continued)

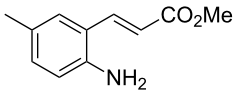
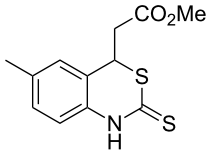
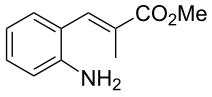
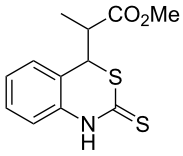
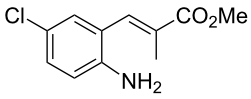
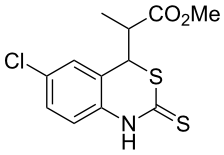
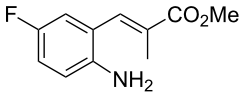
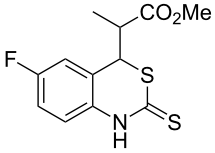
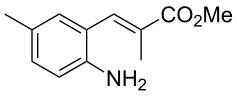
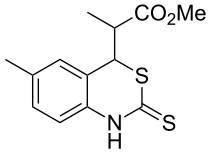
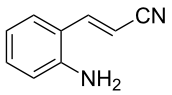
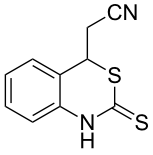
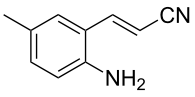
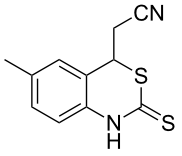
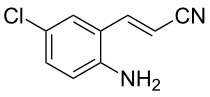
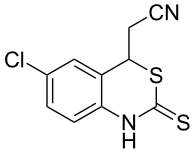
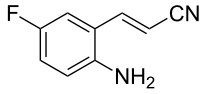
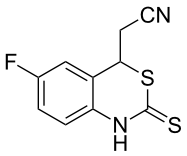
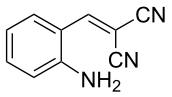
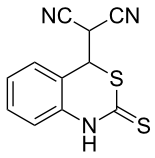
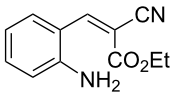
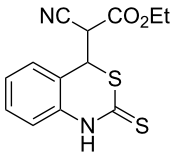
10	 **1j**	 **2j**	71
11	 **1k**	 **2k**	74
12	 **1l**	 **2l**	55
13	 **1m**	 **2m**	54
14	 **1n**	 **2n**	74
15	 **1o**	 **2o**	90
16	 **1p**	 **2p**	75
17	 **1q**	 **2q**	44

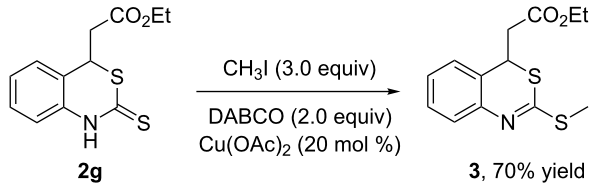
Table 2: Preparation of 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives **2**.[a] (continued)

18	 **1r**	 **2r**	53
19	 **1s**	 **2s**	NR
20	 **1t**	 **2t**	NR

[a]Reaction conditions: substrate **1** (0.3 mmol), CS_2 (1.2 mmol, 4.0 equiv), base (0.3 mmol, 1.0 equiv), rt, 2 d. [b]Isolated yield based on **1**.

entry 7). We next examined the reaction of (*E*)-methyl 3-(2-aminophenyl)-2-methylacrylates **1k–1n** with different substituents on the phenyl ring, and the desired products **2k–2n** were isolated in 54–74% yield (Table 2, entries 11–14). Furthermore, the reaction conditions proved to be useful for (*E*)-3-(2-aminoaryl)acrylonitriles (**1o–1r**, Table 2, entries 15–18). For instance, (*E*)-3-(2-aminophenyl)acrylonitrile (**1o**) reacted with CS_2 affording the expected product **2o** in excellent 90% yield (Table 2, entry 15). However, it was found that reactants 2-(2-aminobenzylidene)malononitrile (**1s**) and ethyl 3-(2-aminophenyl)-2-cyanoacrylate (**1t**) were not workable under the standard conditions (Table 2, entries 19 and 20).

The 2-(2-thioxo-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl)acetate **2** could be further elaborated by alkylation with alkyl halide. For example, compound **2g** reacted with iodomethane to afford the expected ethyl 2-(2-(methylthio)-4*H*-benzo[*d*][1,3]thiazin-4-yl)acetate (**3**) in 70% yield (Scheme 3).



Scheme 3: Alkylation of **2g** with iodomethane.

Conclusion

In summary, we have successfully developed a new simple and efficient method to construct ring-fused 4-alkyl-4*H*-3,1-benzothiazine-2-thione derivatives. In the context of this method, carbon disulfide reacted with (*E*)-3-(2-aminoaryl)acrylates or (*E*)-3-(2-aminoaryl)acrylonitriles under metal-free conditions at room temperature. The newly developed method tolerates a wide range of substrates in moderate to excellent yields and provides promise for further alkylation or arylation. Moreover, this method is advantageous over previous ones [16,17] for the easy synthesis of reactants.

Experimental

General

All reactions were performed in test tubes in air. Flash column chromatography was performed with silica gel (200–300 mesh). Analytical thin-layer chromatography was performed on glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at 25–35 °C. Commercial reagents and solvents were used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 at 400 MHz (^{1}H) and 100 MHz (^{13}C) at ambient temperature. Chemical shifts are reported in parts per million (ppm) on the delta scale (δ) and referenced to tetramethylsilane (0 ppm). HRMS analyses were performed in ESI mode on a Bruker mass spectrometer.

General procedure for the synthesis of 2-(2-thioxo-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl)acetate, **2**: A mixture of 3-(2-aminoaryl)acrylate **1** (0.3 mmol), CS_2 (1.2 mmol, 4.0 equiv, 91.2 mg) and DABCO (0.3 mmol, 1.0 equiv, 33.6 mg) was stirred in DMSO (2 mL) at room temperature. After completion of the reaction as indicated by TLC (about 2 d), the reaction was quenched by water and extracted with ethyl acetate. The organic layers were dried with anhydrous $MgSO_4$, the solvent was evaporated under vacuum, and the residue was isolated by column chromatography with EtOAc/petroleum ether (1/5, v/v) as eluent to yield the desired products **2**. For details, see Supporting Information File 1.

Supporting Information

Supporting Information File 1

General procedure, characterization data and copies of spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-49-S1.pdf]

Acknowledgements

Financial support from Jiangxi Educational Committee (GJJ12169), National Natural Science Foundation of China (21002042), and Open Project Program of Key Laboratory of Functional Small Organic Molecule, Ministry of Education, Jiangxi Normal University (No. KLFS-KF-201217) is gratefully acknowledged.

References

1. Nishio, T. *J. Org. Chem.* **1997,** *62,* 1106–1111. doi:10.1021/jo961704n
2. El-Desoky, S. I.; Kandeel, E. M.; Abd-el-Rahman, A. H.; Schmidt, R. R. *J. Heterocycl. Chem.* **1999,** *36,* 153–160. doi:10.1002/jhet.5570360124
3. Matysiak, J. *Bioorg. Med. Chem.* **2006,** *14,* 2613–2619. doi:10.1016/j.bmc.2005.11.053
4. Csomós, P.; Fodor, L.; Bernáth, G.; Sinkkonen, J.; Salminen, J.; Wiinamäki, K.; Pihlaja, K. *Tetrahedron* **2008,** *64,* 1002–1011. doi:10.1016/j.tet.2007.09.079
5. Obayashi, T.; Okawa, A. Laser heat-mode type recording medium with excellent high sensitivity and storage stability. JP2001253172, Sept 18, 2001.
6. Canon, K. K. Electrophotographic developers. JP59197051, Nov 8, 1984.
7. Kanagawa, A.; Sadao, I.; Keiso, S.; Hideo, U. Aufzeichnungsmaterial. DE2704724A1, Feb 4, 1977.
8. Kanagawa, A.; Sadao, I.; Keiso, S.; Hideo, U. Thiazinderivate und Verfahren zu ihrer Herstellung. DE2658246A1, July 7, 1977.
9. Ding, Q.; Liu, X.; Yu, J.; Zhang, Q.; Wang, D.; Cao, B.; Peng, Y. *Tetrahedron* **2012,** *68,* 3937–3941. doi:10.1016/j.tet.2012.03.098
10. Gimbert, C.; Vallribera, A. *Org. Lett.* **2009,** *11,* 269–271. doi:10.1021/ol802346r
11. Butin, A. V.; Tsiunchik, F. A.; Abaev, V. T.; Gutnov, A. V.; Cheshkov, D. A. *Synthesis* **2009,** 2616–2626. doi:10.1055/s-0029-1217399
12. Otani, T.; Katsurayama, S.; Ote, T.; Saito, T. *J. Sulfur Chem.* **2009,** *30,* 250–263. doi:10.1080/17415990902839443
13. Abaev, V. T.; Tsiunchik, F. A.; Gutnov, A. V.; Butin, A. V. *Tetrahedron Lett.* **2006,** *47,* 4029–4032. doi:10.1016/j.tetlet.2006.04.010
14. Fernandes, M. A.; Reid, D. H. *Synlett* **2003,** 2231–2233. doi:10.1055/s-2003-42078
15. Fathalla, W. M.; Pazdera, P. *Molecules* **2002,** *7,* 96–103. doi:10.3390/70100096
16. Fukamachi, S.; Konishi, H.; Kobayashi, K. *Helv. Chim. Acta* **2011,** *94,* 111–118. doi:10.1002/hlca.201000340
17. Tárraga, A.; Molina, P.; López, J. L. *Tetrahedron Lett.* **2000,** *41,* 4895–4899. doi:10.1016/S0040-4039(00)00756-5
18. Ding, Q.; Ji, H.; Wang, D.; Lin, Y.; Yu, W.; Peng, Y. *J. Organomet. Chem.* **2012,** *711,* 62–67. doi:10.1016/j.jorganchem.2012.03.030
19. Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. *J. Comb. Chem.* **2010,** *12,* 370–373. doi:10.1021/cc100012a
20. Ding, Q.; Cao, B.; Liu, X.; Zong, Z.; Peng, Y. *Green Chem.* **2010,** *12,* 1607–1610. doi:10.1039/c0gc00123f
21. Ding, Q.; Wang, D.; Sang, X.; Lin, Y.; Peng, Y. *Tetrahedron* **2012,** *68,* 8869–8874. doi:10.1016/j.tet.2012.08.039
22. Ding, Q.; Liu, X.; Wang, H.; Chen, M.; Peng, Y. *Synthesis* **2012,** 920–926. doi:10.1055/s-0031-1289722

License and Terms