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# Access to functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines via tandem addition-cyclization/cross-coupling reactions

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ABSTRACT

Tandem addition-cyclization reactions of various 2-alkynylbenzenamines with $CS_2$ lead to the formation of 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazines under mild conditions. The reactions showed moderate to excellent yields and were highly regiospecific, and only the six-membered ring was generated via 6-*exo*-dig S-cyclization. The reaction can be transferred to highly functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines via CuI-catalyzed crossing-coupling and reductive coupling reactions.



## 1. Introduction

2-Alkynylbenzenamines are useful synthetic intermediates as they possess two reactive sites, a nucleophile ($-NH_2$) and a triple bond. It is well-known that alkynes possessing a nucleophile in proximity to the triple bond can construct diverse heterocycles via transition metal- or Lewis acid-catalyzed intramolecular annulation in an efficient way. Based on 2-alkynylbenzenamines, various heterocycles have been reported for the construction of privileged molecular entries, such as indole,[1] quinoline,[2] quinazolinone,[3] benzoxazine,[4] 4*H*-benzo[*d*][1,3]thiazin-2-amine,[5] and 1*H*-benzo[*d*] [1,3]thiazine.[6] Moreover, 2-alkynylbenzenamine can be easily prepared by classical Pd/Cu-catalyzed Sonogashira reaction using 2-iodoaniline and terminal alkyne as readily available starting materials. Therefore, as a useful synthetic intermediate, 2-alkynylbenzenamine has attracted considerable attention in the fields of organic and medicinal chemistry.

Heterocycles having a privileged scaffold are systems of great interest due to their promising biological activity and the applications in synthetic materials.[7] As a privileged fragment, 4*H*-benzo[*d*][1,3]thiazine core can be found in many biologically active molecules.[8] The synthesis of 4*H*-benzo[*d*][1,3]thiazine has been a major area of focus for synthetic organic chemists, and several efficient synthetic routes for the preparation of 4*H*-benzo[*d*][1,3]thiazine have been developed.[6,9] As part of a continuing effort in our laboratory toward the development of novel natural product-like compounds,[10] we recently reported the practical routes for the generation of 2,4-dihydro-1*H*-benzo[*d*][1,3]thiazines via silica gel-promoted[6a] or AgOTf-catalyzed[6b] tandem addition-cyclization reactions of 2-alkynylbenzenamines with isothiocyanates. Very recently, we described the synthesis of 4-methylene-4*H*-benzo[d][1,3]thiazine via a tandem reaction of 1-(2-alkynylphenyl)ketoxime with Lawesson's reagent catalyzed by $InCl_3$ and cyanuric chloride.[11] Herein, we would like to report the synthesis of 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazines starting from 2-alkynylbenzenamines with $CS_2$, and the further transformation to highly functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines.

## 2. Results and discussions

Initially, we used 2-alkynylbenzenamine **1a** with carbon disulfide as the starting materials and AgOTf as catalyst, DBU as base in DMSO at room temperature. However, only trace 4-benzylidene-4*H*-benzo[*d*][1,3]thiazine **2a** was observed, most starting material **1a** was recovered (Table 1, entry 1). Z-Configuration of the product **2a** was verified by X-ray diffraction analysis. Then different solvents, such as DMF, $CH_3CN$, and $CH_2Cl_2$ were also tried in the reaction, and DMF was demonstrated to be the best choice and gave the desired product **2a** as a single stereoisomer, characterized by $^1H$ NMR, in 56% yield (Table 1, entries 2–4). Next, the bases were examined in the reaction. The results demonstrated that the organic

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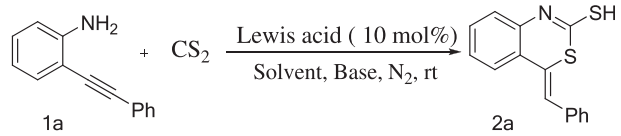
**Table 1**
Conditions screening for Ag-catalyzed tandem reaction of 2-alkynylbenzenamine **1a** with $CS_2$[a]



1a 2a

| Entry | Catalyst | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | AgOTf | DBU | DMSO | Trace |
| 2 | AgOTf | DBU | DMF | 56 |
| 3 | AgOTf | DBU | $CH_3CN$ | Trace |
| 4 | AgOTf | DBU | $CH_2Cl_2$ | Trace |
| 5 | AgOTf | $Et_3N$ | DMF | 65 |
| 6 | AgOTf | DABCO | DMF | 67 |
| 7 | AgOTf | $Cs_2CO_3$ | DMF | 11 |
| 8 | AgOTf | $Na_2CO_3$ | DMF | 15 |
| 9 | AgOTf | $NaHCO_3$ | DMF | 35 |
| 10 | AgOTf | NaOH | DMF | 30 |
| 11 | AgOTf | t-BuOK | DMF | 54 |
| 12 | AgOAc | DABCO | DMF | 73 |
| 13 | $Ag_2CO_3$ | DABCO | DMF | 86 |
| 14 | $AgNO_3$ | DABCO | DMF | 95 |
| 15 | $AgNO_3$[c] | DABCO | DMF | 95 |
| 16 | $AgNO_3$[d] | DABCO | DMF | 62 |
| 17 | — | DABCO | DMF | 50 |

[a] Reaction conditions: 2-alkynylbenzenamine **1a** (0.3 mol), $CS_2$ (10.0 equiv), [Ag] (10 mol %), base (1.2 equiv), solvent (1 mL) rt, 24 h.
[b] Isolated yield based on 2-alkynylbenzenamine **1a**.
[c] $AgNO_3$ (5 mol %).
[d] $AgNO_3$ (2 mol %).

bases were more efficient than inorganic bases, for example, $Et_3N$ and DABCO increased the yield of product **2a** to 65% and 67%, respectively (Table 1, entries 5 and 6); however, inorganic bases, such as $Cs_2CO_3$, $Na_2CO_3$, $NaHCO_3$, and NaOH, most of them dramatically decreased the yield of the product **2a** (Table 1, entries 7–10). Other silver salts, such as AgOAc, $Ag_2CO_3$, and $AgNO_3$ were also screened in the reaction, which revealed that $AgNO_3$ provided the best yield and just a single stereoisomer (Table 1, entries 12–14). The same result was observed when the catalytic amount of $AgNO_3$ was reduced to 5 mol % (Table 1, entry 15). The investigation showed that further decreasing the amount of $AgNO_3$ (2 mol %) gave moderate (62%) isolated yield (Table 1, entry 16). Blank experiment showed that Lewis acid $AgNO_3$ was necessary in the reaction in order to obtain good yield (Table 1, entry 17).Fig. 1.

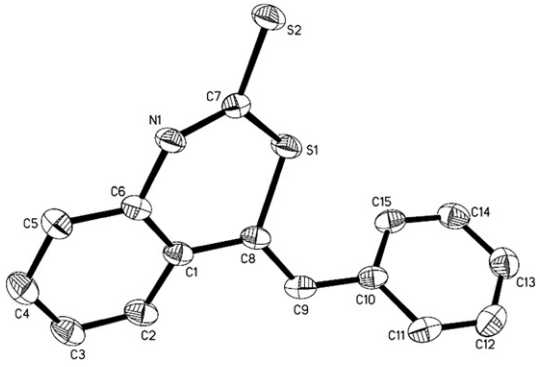
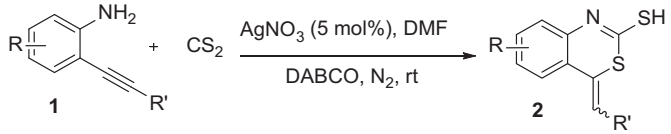



**Fig. 1.** X-ray ORTEP illustration of compound **2a**.

To evaluate the generality of this method, the scope of the reaction was investigated under optimized conditions [$AgNO_3$ (5 mol %) as a catalyst, DABCO as a base, DMF as solvent, at room temperature under $N_2$], and the results are summarized in Table 2. Most reactions proceeded smoothly to give rise to the corresponding products **2** in moderate to good yields. The reactions of carbon disulfide with various substituted 2-alkynylbenzenamines **1** were examined. When R′ group attached on the triple bond was an aryl group with electron-withdrawing groups (such as F), moderate yields were observed (Table 2, entries 2 and 3). The reaction of **1b** with $CS_2$ was completed within 24 h to afford the desired product **2b** as a single stereoisomer in 65% yield. However, good results were displayed, when it was replaced by electron-donating groups (Table 2, entries 4 and 5). For instance, reaction of carbon disulfide with 2-alkynylbenzenamine **1d** afforded the desired product **2d** in 80% yield (Table 2, entry 2), and 86% yield of product **2e** was obtained when 2-alkynylbenzenamine **1e** was employed in the reaction. As expected, other 2-alkynylbenzenamines **1f**–**o**, with electron-rich or electron-poor substituent (Me, F, Cl) on aromatic ring all showed good tolerance (Table 2, entries 6–13). For example, reaction of 4-fluoro-substituted 2-alkynylbenzenamine **1i** with $CS_2$ gave rise to the corresponding product **2i** in 73% yield (Table 2, entry 9). A 76% yield was obtained when 4-methyl-substituted 2-alkynylbenzenamine **1j** was utilized as substrate (Table 2, entry 11). When R′ was replaced by aliphatic group, such as cyclopropyl group, the reactions gave the corresponding products in moderate yields (Table 2, entries 14 and 15).

**Table 2**
$AgNO_3$-catalyzed tandem reactions of 2-alkynylbenzenamines **1** with $CS_2$



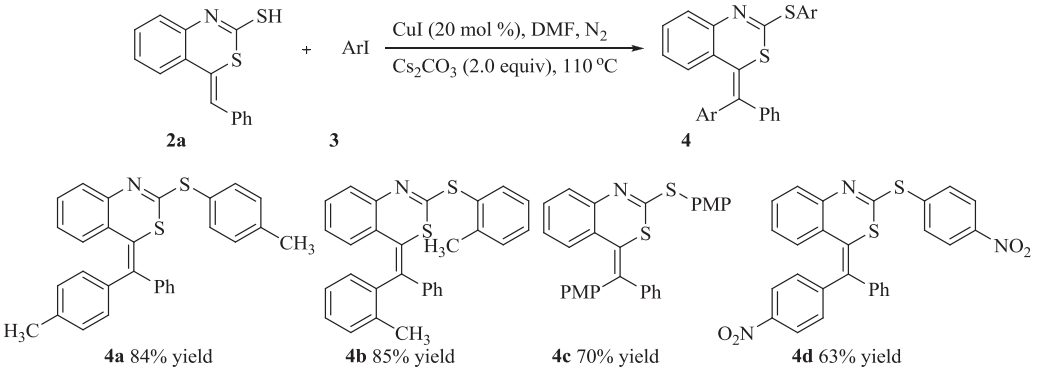
1 2

| Entry | R/**1** | R′ | Product **2** | Yield (%)[a] (*Z*/*E*)[b] |
|---|---|---|---|---|
| 1 | H/**1a** | $C_6H_5$ | **2a** | 95 |
| 2 | H/**1b** | 4-$FC_6H_4$ | **2b** | 65 |
| 3 | H/**1c** | 3-$FC_6H_4$ | **2c** | 42 (75/25) |
| 4 | H/**1d** | 4-$C_2H_5C_6H_4$ | **2d** | 80 (87/13) |
| 5 | H/**1e** | 4-$MeOC_6H_4$ | **2e** | 86 (82/18) |
| 6 | 4-Cl/**1f** | $C_6H_5$ | **2f** | 54 |
| 7 | 4-Cl/**1g** | 4-$MeOC_6H_4$ | **2g** | 55 (82/18) |
| 8 | 4-F/**1h** | $C_6H_5$ | **2h** | 51 |
| 9 | 4-F/**1i** | 4-$MeOC_6H_4$ | **2i** | 73 |
| 10 | 4-F/**1j** | 4-$FC_6H_4$ | **2j** | 58 (91/9) |
| 11 | 4-$CH_3$/**1k** | $C_6H_5$ | **2k** | 76 |
| 12 | 4-$CH_3$/**1l** | 4-$FC_6H_4$ | **2l** | 52 |
| 13 | 4-$CH_3$/**1m** | 4-$MeOC_6H_4$ | **2m** | 52 (81/19) |
| 14 | H/**1n** | Cyclopropyl | **2n** | 40 (83/17) |
| 15 | 4-F/**1o** | Cyclopropyl | **2o** | 41 (72/28) |

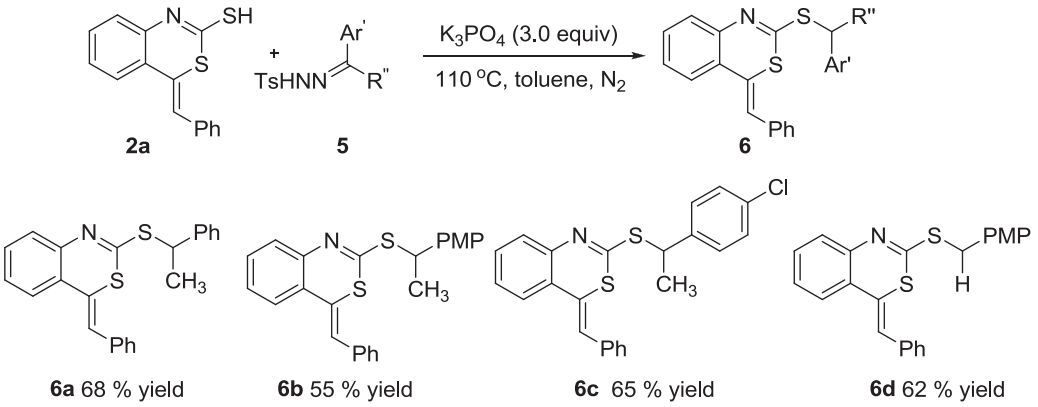
[a] Reaction conditions: 2-alkynylbenzenamine **1** (0.3 mol), $CS_2$ (10.0 equiv), $AgNO_3$ (5 mol %), DABCO (1.2 equiv), DMF (1 mL), rt. Isolated yield based on 2-alkynylbenzenamine **1**.
[b] Characterized the ratio of the stereoisomer **2** by $^1H$ NMR.

After the successful generation of 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazine **2**, we considered to introduce more diversity into the 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazine scaffold via CuI-catalyzed crossing-coupling reactions. Thus, we explored the possibility of the CuI-catalyzed cross-coupling reactions of **2a** with aryl iodides **3** for the synthesis of highly functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines **4**. The reactions were performed at 110 °C catalyzed by CuI (20 mol %) in DMF in the presence of $Cs_2CO_3$ as base (Scheme 1). The results showed that all reactions proceeded smoothly to generate the desired products **4** in moderate to good yields. The limititation of the protocol is that selective coupling of thiol and olefin couldn't be realized under the conditions.

Recently, we reported a metal-free procedure for the synthesis of thioethers via base-promoted reductive coupling of tosylhydrazones with thiols.[12] Therefore, the similar reductive coupling of tosylhydrazones with 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazine **2a** were also examined (Scheme 2). Under the optimized conditions, the reductive coupling reactions proceeded well to generate the intriguing target products **6** in moderate yields.




**Scheme 1.** Synthesis of highly functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazine **4** via CuI-catalyzed cross-coupling reactions.




**Scheme 2.** Metal-free reductive coupling between 4-benzylidene-4*H*-benzo[*d*][1,3]thiazine-2-thiol **2a** and tosylhydrazones **5**.

In summary, we have described a novel and efficient method for the synthesis of 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazines via $AgNO_3$-catalyzed tandem reaction from readily available starting materials, 2-alkynylbenzenamines and $CS_2$. The reactions showed moderate to excellent yields and were highly regiospecific, and only the six-membered ring was generated via 6-*exo*-dig S-cyclization. In addition, further transformation of 2-mercapto-4-benzylidene-4*H*-benzo[*d*][1,3]thiazines to highly functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines has been developed via crossing-coupling reaction and reductive coupling reaction in moderate to good yields. Application of 2-alkynylbenzenamine in other transformations is ongoing currently in our laboratory, and the results will be reported in due course.

## 3. Experimental section

### 3.1. General

General experimental procedure for tandem addition-cyclization of 2-alkynylbenzenamines (1) with $CS_2$: A solution of 2-alkynylbenzenamines **1** (0.30 mmol), $CS_2$ (3.0 mmol, 10 equiv), $AgNO_3$ (5 mol %), DABCO (1.2 equiv) in DMF (2.0 mL) was stirred at room temperature. After completion of reaction as indicated by TLC, the reaction was quenched with water (10 mL), extracted with EtOAc (2×10 mL), and dried by anhydrous $Na_2SO_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding 4-benzylidene-4*H*-benzo[*d*][1,3]thiazine **2a**.

*3.1.1. 4-Benzylidene-4H-benzo[d][1,3]thiazine-2-thiol (**2a**).* Yield: 95%, $^1$H NMR (400 MHz, DMSO) $\delta$=7.27–7.32 (m, 3H), 7.37–7.39 (m, 1H), 7.43–7.48 (m, 5H), 7.79 (d, $J$=8.0 Hz, 1H), 12.92 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=118.2, 120.5, 125.2, 125.6, 125.8, 127.9, 128.3, 129.1, 130.2, 134.8, 135.6, 187.2; HRMS (ESI) calcd for $C_{15}H_{12}NS_2$ $(M+H)^+$ 270.0411; found, 270.0385.

*3.1.2. Crystal data and structure refinement for **2a**.* Empirical formula: $C_{15}H_{11}NS_2$ (Formula weight: 269.37); Temperature: 298(2) K; Wavelength: 0.71073 A; Crystal system, space group Triclinic, P-1; Unit cell dimensions: $a$=8.1866(10) A, $\alpha$=83.049(2)°, $b$=8.7350(10) A, $\beta$=76.325(2)°, $c$=10.0235(12) A, $\gamma$=67.924(2)°, Volume: 644.99(13)° $A^3$; $Z$=2, Calculated density: 1.387 $Mg/m^3$; Absorption coefficient: 0.392 $mm^{-1}$; F(000): 280; Crystal size: 0.28×0.25×0.22 mm; Theta range for data collection: 2.52–25.50 deg.; Limiting indices: −9<=h<=9, −10<=k<=10, −12<=l<=10; Reflections collected/unique: 5391/2358 [$R$(int)=0.0199]; Completeness to theta=25.50: 98.3%; Absorption correction: semi-empirical from equivalents; max. and min. transmission: 0.9188 and 0.8983. Refinement method: full-matrix least-squares on $F^2$. Data/restraints/parameters: 2358/1/167; Goodness-of-fit on $F^2$: 1.106, Final $R$ indices [$I>2\sigma$ ($I$)]: $R1$=0.0418, $\omega R2$=0.1479. $R$ indices (all data): $R1$=0.0489, $\omega R2$=0.1820. Largest diff. peak and hole: 0.354 and −0.328 e $A^{-3}$

*3.1.3. 4-(4-Fluorobenzylidene)-4H-benzo[d][1,3]thiazine-2-thiol (**2b**).* Yield: 65%, $^1$H NMR (400 MHz, DMSO) $\delta$=7.25 (s, 1H), 7.26–7.35 (m, 4H), 7.45 (t, $J$=8.0 Hz, 1H), 7.51–7.54 (m, 2H), 7.77 (d, $J$=8.0 Hz, 1H), 12.88 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=115.2 (d, $^2J_{CF}$=22.0 Hz), 118.2, 120.5, 124.0, 125.1, 125.6, 125.8, 130.2, 131.3 (d, $^3J_{CF}$=8.0 Hz), 131.4, 135.6, 161.4 (d, $^1J_{CF}$=245.0 Hz), 187.0; HRMS (ESI) calcd for $C_{15}H_{11}FNS_2$ $(M+H)^+$: 288.0317; found, 288.0320.

*3.1.4. 4-(3-Fluorobenzylidene)-4H-benzo[d][1,3]thiazine-2-thiol (**2c**).* Yield: 42%, $^1$H NMR (400 MHz, DMSO) $\delta$=7.00–7.03 (m, 1H),

7.21–7.34 (m, 5H), 7.44–7.53 (m, 2H), 7.80 (d, $J$=8.0 Hz, 1H), 12.90 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=114.8 (d, $^{2}J_{CF}$=21.0 Hz), 115.7 (d, $^{2}J_{CF}$=22.0 Hz), 118.3, 120.1, 123.6, 125.2, 125.3, 125.8, 127.2, 130.4 (d, $^{3}J_{CF}$=9.0 Hz), 130.5 (d, $^{3}J_{CF}$=9.0 Hz), 135.7, 137.2 (d, $^{3}J_{CF}$=8.0 Hz), 161.9 (d, $^{1}J_{CF}$=243.0 Hz), 186.6; HRMS (ESI) calcd for $C_{15}H_{11}FNS_2$ $(M+H)^+$: 288.0317; found, 288.0326.

*3.1.5. 4-(4-Ethylbenzylidene)-4H-benzo[d][1,3]thiazine-2-thiol (**2d**).* Yield: 80%, $^1$H NMR (400 MHz, DMSO) $\delta$=1.20 (t, $J$=8.0 Hz, 3H), 2.64 (q, $J$=8.0 Hz, 2H), 7.12 (s, 1H), 7.26–7.35 (m, 4H), 7.37–7.45 (m, 3H), 7.76 (d, $J$=8.0 Hz, 1H), 12.89 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=15.4, 28.0, 118.2, 120.8, 124.8, 125.2, 125.3, 125.8, 127.8, 129.3, 130.1, 132.3, 135.6, 143.9, 187.5; HRMS (ESI) calcd for $C_{17}H_{16}NS_2$ $(M+H)^+$: 298.0724; found, 298.0711.

*3.1.6. 4-(4-Methoxybenzylidene)-4H-benzo[d][1,3]thiazine-2-thiol (**2e**).* Yield: 86%, $^1$H NMR (400 MHz, DMSO) $\delta$=3.81 (s, 3H), 7.04 (d, $J$=8.0 Hz, 2H), 7.14 (d, $J$=8.0 Hz, 1H), 7.19 (s, 1H), 7.25–7.31 (m, 2H), 7.43 (d, $J$=8.0 Hz, 2H), 7.73 (d, $J$=8.0 Hz, 1H), 12.88 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=54.6, 113.2, 117.6, 120.5, 122.7, 124.6, 124.7, 125.3, 126.9, 129.3, 130.2, 134.9, 158.3, 187.0; HRMS (ESI) calcd for $C_{16}H_{14}NOS_2$ $(M+H)^+$: 300.0517; found, 300.0530.

*3.1.7. 4-Benzylidene-6-chloro-4H-benzo[d][1,3]thiazine-2-thiol (**2f**).* Yield: 54%, $^1$H NMR (400 MHz, DMSO) $\delta$=7.29–7.34 (m, 2H), 7.37–7.39 (m, 2H), 7.47–7.52 (m, 4H), 7.89 (s, 1H), 13.01 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=119.9, 122.3, 124.7, 126.6, 128.2, 128.3, 128.4, 129.3, 129.8, 129.9, 134.5, 134.6, 187.28; HRMS (ESI) calcd for $C_{15}H_{11}ClNS_2$ $(M+H)^+$: 304.0021; found, 303.9997.

*3.1.8. 4-(4-Methoxybenzylidene)-6-chloro-4H-benzo[d][1,3]thiazine-2-thiol (**2g**).* Yield: 55%, $^1$H NMR (400 MHz, DMSO) $\delta$=3.81 (s, 3H), 7.04(d, $J$=8.0 Hz, 2H), 7.27–7.29 (m, 2H), 7.44–7.49 (m, 3H), 7.82 (s, 1H), 12.97 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=55.2, 113.8, 119.8, 121.7, 122.9, 124.6, 126.6, 127.2, 129.5, 129.7, 131.0, 134.3, 159.1, 187.64; HRMS (ESI) calcd for $C_{16}H_{13}ClNOS_2$ $(M+H)^+$: 334.0127; found, 334.0138.

*3.1.9. 4-Benzylidene-6-fluoro-4H-benzo[d][1,3]thiazine-2-thiol (**2h**).* Yield: 51%, $^1$H NMR (400 MHz, DMSO) $\delta$=7.34–7.40 (m, 4H), 7.47 (m, 3H), 7.71 (d, $J$=8.0 Hz, 1H), 12.92 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=111.6 (d, $^{2}J_{CF}$=25.0 Hz), 117.2 (d, $^{2}J_{CF}$=25.0 Hz), 120.3 (d, $^{3}J_{CF}$=9.0 Hz), 122.4 (d, $^{3}J_{CF}$=9.0 Hz), 124.6, 126.3, 128.2, 128.4, 129.2, 132.3, 134.6, 159.4 (d, $^{1}J_{CF}$=242.0 Hz), 186.5; HRMS (ESI) calcd for $C_{15}H_{11}FNS_2$ $(M+H)^+$: 288.0317; found, 288.0325.

*3.1.10. 4-(4-Methoxybenzylidene)-6-fluoro-4H-benzo[d][1,3]thiazine-2-thiol (**2i**).* Yield: 73%, $^1$H NMR (400 MHz, DMSO) $\delta$=3.81 (s, 3H), 7.05 (d, $J$=8.4 Hz, 1H), 7.23 (s, 1H), 7.31 (d, $J$=6 0.0 Hz, 4H), 7.45 (d, $J$=8.4 Hz, 1H), 7.67 (d, $J$=9.6 Hz, 1H), 12.93 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=55.2, 111.5 (d, $^{2}J_{CF}$=24.0 Hz), 113.9, 114.2 (d, $^{2}J_{CF}$=27.0 Hz), 116.7, 120.2, 123.0 (d, $^{3}J_{CF}$=8.0 Hz), 126.3, 127.2, 130.9, 132.2, 159.1, 159.5 (d, $^{1}J_{CF}$=240.0 Hz), 186.8; HRMS (ESI) calcd for $C_{16}H_{13}FNOS_2$ $(M+H)^+$: 318.0423; found, 318.0438.

*3.1.11. 4-(4-Fluorobenzylidene)-6-fluoro-4H-benzo[d][1,3]thiazine-2-thiol (**2j**).* Yield: 58%, $^1$H NMR (400 MHz, DMSO) $\delta$=7.26–7.33 (m, 5H), 7.53–7.56 (m, 2H), 7.69 (d, $J$=8.0 Hz, 1H), 12.95 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=111.6 (d, $^{2}J_{CF}$=25.0 Hz), 115.5 (d, $^{2}J_{CF}$=22.0 Hz), 117.4 (d, $^{2}J_{CF}$=24.0 Hz), 120.3(d, $^{3}J_{CF}$=9.0 Hz), 122.4 (d, $^{3}J_{CF}$=8.0 Hz), 124.5, 125.2, 131.2, 131.4 (d, $^{2}J_{CF}$=9.0 Hz), 132.3, 159.5 (d, $^{1}J_{CF}$=242.0 Hz), 161.5 (d, $^{1}J_{CF}$=242.0 Hz), 186.3; HRMS (ESI) calcd for $C_{15}H_{10}F_2NS_2$ $(M+H)^+$: 306.0223; found, 306.0220.

*3.1.12. 4-Benzylidene-6-methyl-4H-benzo[d][1,3]thiazine-2-thiol (**2k**).* Yield: 76%, $^1$H NMR (400 MHz, DMSO) $\delta$=2.34 (s, 3H), 7.19–7.26 (m, 3H), 7.35–7.37 (m, 1H), 7.42–7.47 (m, 4H), 7.61 (s, 1H), 12.81 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=20.5, 118.2, 120.3, 124.7, 125.3, 125.9, 127.9, 128.4, 129.2, 130.8, 133.5, 134.9, 135.3, 186.4; HRMS (ESI) calcd for $C_{16}H_{14}NS_2$ $(M+H)^+$: 284.0568; found, 284.0540.

*3.1.13. 4-(4-Fluorobenzylidene)-6-methyl-4H-benzo[d][1,3]thiazine-2-thiol (**2l**).* Yield: 52%, $^1$H NMR (400 MHz, DMSO) $\delta$=2.34 (s, 3H), 7.20 (d, $J$=8.0 Hz, 1H), 7.25 (s, 1H), 7.26 (d, $J$=8.0 Hz, 1H), 7.31 (t, $J$=8.8 Hz, 2H), 7.50–7.54 (m, 2H), 7.60 (s, 1H), 12.89 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=21.0, 115.9 (d, $^{2}J_{CF}$=21.0 Hz), 118.7, 120.7, 124.1, 125.7, 126.3, 131.4, 131.8 (d, $^{3}J_{CF}$=8.0 Hz), 131.9, 134.0, 135.8, 161.9 (d, $^{1}J_{CF}$=245.0 Hz), 186.6; HRMS (ESI) calcd for $C_{16}H_{13}FNS_2$ $(M+H)^+$: 302.0473; found, 302.0482.

*3.1.14. 4-(4-Methoxybenzylidene)-6-methyl-4H-benzo[d][1,3]thiazine-2-thiol (**2m**).* Yield: 52%, $^1$H NMR (400 MHz, DMSO) $\delta$=2.33 (s, 3H), 3.81 (s, 3H), 6.86 (d, $J$=8.0 Hz, 1H), 7.04 (d, $J$=8.0 Hz, 2H), 7.14–7.24 (m, 3H), 7.43 (d, $J$=8.4 Hz, 2H), 7.56 (s, 1H), 12.81 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=20.5, 55.2, 113.8, 118.1, 120.8, 123.5, 124.8, 125.2, 127.5, 130.5, 130.8, 133.4, 135.3, 158.9, 186.5; HRMS (ESI) calcd for $C_{17}H_{16}NOS_2$ $(M+H)^+$: 314.0673; found, 314.0683.

*3.1.15. 4-(Cyclopropylmethylene)-4H-benzo[d][1,3]thiazine-2-thiol (**2n**).* Yield: 40%, $^1$H NMR (400 MHz, DMSO) $\delta$=0.60–0.64 (m, 2H), 0.92–0.94 (m, 2H), 1.60–1.63 (m, 1H), 5.69 (d, $J$=8.0 Hz, 1H), 7.16 (t, $J$=8.0 Hz, 1H), 7.23 (d, $J$=8.0 Hz, 1H), 7.32 (t, $J$=8.0 Hz, 1H), 7.50 (d, $J$=8.0 Hz, 1H), 12.56 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=7.7, 11.5, 118.1, 120.3, 122.0, 124.1, 125.6, 129.2, 130.5, 135.2, 188.5; HRMS (ESI) calcd for $C_{12}H_{12}NS_2$ $(M+H)^+$: 234.0411; found, 234.0390.

*3.1.16. 4-(Cyclopropylmethylene)-6-fluoro-4H-benzo[d][1,3]thiazine-2-thiol (**2o**).* Yield: 41%, $^1$H NMR (400 MHz, DMSO) $\delta$=0.62–0.64 (m, 2H), 0.90–0.95 (m, 2H), 1.59–1.62 (m, 1H), 5.79 (d, $J$=10.0 Hz, 1H), 7.17–7.33 (m, 2H), 7.40 (dd, $J$=10.0, 2.4 Hz, 1H), 12.69 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$=8.3, 12.2, 111.1 (d, $^{2}J_{CF}$=25.0 Hz), 116.8 (d, $^{2}J_{CF}$=23.0 Hz), 120.6 (d, $^{3}J_{CF}$=8.0 Hz), 121.2, 122.7 (d, $^{3}J_{CF}$=7.0 Hz), 132.7, 140.4, 159.9 (d, $^{1}J_{CF}$=241.0 Hz), 188.3; HRMS (ESI) calcd for $C_{12}H_{11}FNS_2$ $(M+H)^+$: 252.0317; found, 252.0325.

General procedure for synthesis of highly functionalized 4*H*-benzo[*d*][1,3]thiazines (**4**) via CuI-catalyzed crossing-coupling reactions: A solution of 4*H*-benzo[*d*][1,3]thiazines **2** (0.30 mmol), aryl iodine (ArI) (0.9 mmol, 3.0 equiv), CuI catalyst (20 mol %), $Cs_2CO_3$ (0.6 mmol, 2.0 equiv) in DMF (2.0 mL) was stirred at 110 °C under $N_2$ for overnight. After completion of reaction as indicated by TLC, the reaction was cooled to room temperature and quenched with water (10 mL), extracted with EtOAc (2×10 mL), and dried by anhydrous $Na_2SO_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding functionalized 4*H*-benzo[*d*][1,3]thiazines **4**.

*3.1.17. 4-(Phenyl(p-tolyl)methylene)-2-(p-tolylthio)-4H-benzo[d][1,3]thiazine (**4a**).* Yield: 84%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=2.21 (s, 3H), 2.38 (s, 3H), 6.79 (d, $J$=8.4 Hz, 2H), 6.88 (d, $J$=8.0 Hz, 2H), 7.20 (d, $J$=8.0 Hz, 2H), 7.25–7.28 (m, 2H), 7.33 (t, $J$=8.0 Hz, 1H), 7.38–7.45 (m, 5H), 7.52 (t, $J$=8.4 Hz, 1H), 7.72 (d, $J$=8.4 Hz, 1H), 8.25 (d, $J$=8.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=20.5, 21.0, 125.7, 126.3, 126.6, 127.8, 127.9, 128.5, 129.0, 129.1, 129.2, 129.5, 132.7, 134.8, 135.3, 136.4, 138.2, 138.3, 139.4, 147.4, 159.7; HRMS (ESI) calcd for $C_{29}H_{24}NS_2$ $(M+H)^+$: 450.1350; found, 450.1334.

*3.1.18. 4-(Phenyl(o-tolyl)methylene)-2-(o-tolylthio)-4H-benzo[d][1,3]thiazine (**4b**).* Yield: 85%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=2.16 (s,

3H), 2.34 (s, 3H), 6.61 (d, *J*=8.0 Hz, 1H), 6.85 (t, *J*=7.6 Hz, 1H), 6.97 (t, *J*=7.6 Hz, 1H), 7.03 (d, *J*=7.2 Hz, 1H), 7.19–7.25 (m, 3H), 7.32–7.42 (m, 6H), 7.51–7.55 (m, 2H), 7.69 (d, *J*=8.4 Hz, 1H), 8.21 (d, *J*=8.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=20.4, 21.0, 125.9, 126.3, 126.4, 126.5, 126.6, 127.3, 128.2, 128.3, 128.5, 128.7, 129.1, 129.4, 129.6, 129.7, 130.0, 130.3, 130.4, 136.2, 136.4, 136.5, 137.0, 139.0, 140.3, 143.3, 148.0, 159.8; HRMS (ESI) calcd for $C_{29}H_{24}NS_2$ $(M+H)^+$: 450.1350; found, 450.1303.

*3.1.19. 4-((4-Methoxyphenyl)(phenyl)methylene)-2-(4-methoxyphenylthio)-4H-benzo[d][1,3]thiazine (**4c**).* Yield: 70%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=3.68 (s, 3H), 3.82 (s, 3H), 6.61 (d, *J*=8.8 Hz, 2H), 6.84 (d, *J*=8.4 Hz, 2H), 6.92 (d, *J*=8.4 Hz, 2H), 7.21–7.28 (m, 2H), 7.34–7.41 (m, 4H), 7.45 (d, *J*=8.8 Hz, 2H), 7.52 (t, *J*=7.6 Hz, 1H), 7.71 (d, *J*=8.4 Hz, 1H), 8.34 (d, *J*=8.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=55.3, 55.4, 114.4, 114.6, 121.3, 126.0, 126.7, 127.0, 127.1, 128.2, 128.3, 129.0, 129.5, 130.1, 131.0, 136.8, 137.1, 138.1, 141.0, 147.9, 158.4, 160.2, 160.6; HRMS (ESI) calcd for $C_{29}H_{24}NO_2S_2$ $(M+H)^+$, 482.1248; found, 482.1253.

*3.1.20. 4-((4-Nitrophenyl)(phenyl)methylene)-2-(4-nitrophenylthio)-4H-benzo[d][1,3]thiazine (**4d**).* Yield: 63%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=6.98 (d, *J*=9.2 Hz, 2H), 7.25 (d, *J*=7.6 Hz, 2H), 7.41–7.51 (m, 4H), 7.68 (t, *J*=7.6 Hz, 2H), 7.76 (d, *J*=8.8 Hz, 2H), 7.83 (d, *J*=8.4 Hz, 1H), 7.96 (d, *J*=8.8 Hz, 2H), 8.17 (d, *J*=8.4 Hz, 1H), 8.25 (d, *J*=8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=123.6, 124.1, 126.1, 127.0, 127.1, 127.6, 128.6, 129.1, 129.2, 129.5, 130.6, 134.9, 135.7, 137.7, 139.6, 139.7, 145.6, 145.9, 147.7, 147.8, 158.1; HRMS (ESI) calcd for $C_{27}H_{18}N_3O_4S_2$ $(M+H)^+$, 512.0739; found, 512.0750.

General procedure for synthesis of functionalized 4*H*-benzo[*d*][1,3]thiazines (**6**) via metal-free reductive coupling reactions of 2-mercapto-4*H*-benzo[*d*][1,3]thiazines (**2**) with tosylhydrazones (**5**): a mixture of 2-mercapto-4*H*-benzo[*d*][1,3]thiazines **2** (0.3 mmol), tosylhydrazone **5** (0.6 mmol, 2.0 equiv), $K_3PO_4$ (0.9 mmol, 3.0 equiv) in toluene (2.0 mL) was stirred at 110 °C for 24 h under $N_2$. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature. After adding ethyl acetate (10 mL), the organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated under reduced vacuum. The residue was then purified by flash chromatography on silica gel to afford product **6**.

*3.1.21. 4-Benzylidene-2-(1-phenylethylthio)-4H-benzo[d][1,3]thiazine (**6a**).* Yield: 68%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=1.77 (d, *J*=7.2 Hz, 3H), 5.27 (q, *J*=7.2 Hz, 1H), 7.06 (s, 1H), 7.28–7.33 (m, 5H), 7.37–7.45 (m, 8H), 7.54 (d, *J*=7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=22.0, 45.2, 122.9, 124.7, 126.2, 126.7, 127.3, 127.4, 127.5, 127.7, 128.2, 128.5, 129.3, 129.6, 135.4, 142.3, 142.5, 157.6; HRMS (ESI) calcd for $C_{23}H_{20}NS_2$ $(M+H)^+$: 374.1037; found, 374.1025.

*3.1.22. 4-Benzylidene-2-(1-(4-methoxyphenyl)ethylthio)-4H-benzo[d][1,3]thiazine (**6b**).* Yield: 55%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=1.74 (d, *J*=7.2 Hz, 3H), 3.77 (s, 3H), 5.22 (q, *J*=7.2 Hz, 1H), 6.83 (d, *J*=8.4 Hz, 2H), 7.05 (s, 1H), 7.27–7.42 (m, 10H), 7.53 (d, *J*=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=22.1, 44.8, 55.2, 113.9, 122.9, 124.7, 126.3, 126.6, 127.3, 127.4, 127.7, 128.2, 128.6, 129.3, 129.6, 134.2, 135.5, 142.5, 157.7, 158.9; HRMS (ESI) calcd for $C_{24}H_{22}NOS_2$, $(M+H)^+$: 404.1143; found, 404.1150.

*3.1.23. 4-Benzylidene-2-(1-(4-chlorophenyl)ethylthio)-4H-benzo[d][1,3]thiazine (**6c**).* Yield: 65%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=1.63 (d, *J*=7.2 Hz, 3H), 5.13 (q, *J*=7.2 Hz, 1H), 6.97 (s, 1H), 7.08–7.23 (m, 5H), 7.25–7.35 (m, 7H), 7.44 (d, *J*=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=21.7, 44.4, 122.9, 124.7, 126.0, 126.8, 127.3, 127.5, 127.7, 128.2, 128.6, 128.8, 129.3, 129.6, 133.1, 135.4, 141.1, 142.3, 157.2; HRMS (ESI) calcd for $C_{23}H_{19}ClNS_2$ $(M+H)^+$: 408.0647; found, 408.0653.

*3.1.24. 2-(4-Methoxybenzylthio)-4-benzylidene-4H-benzo[d][1,3]thiazine (**6d**).* Yield: 62%, $^1$H NMR (400 MHz, $CDCl_3$) $\delta$=3.67 (s, 3H), 4.34 (s, 2H), 6.73 (d, *J*=8.8 Hz, 2H), 6.97 (s, 1H), 7.17–7.25 (m, 4H), 7.26–7.35 (m, 6H), 7.44 (d, *J*=8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$=35.2, 55.2, 114.0, 122.9, 124.8, 126.1, 126.7, 127.4, 127.5, 127.7, 128.3, 129.0, 129.3, 129.7, 130.3, 135.4, 142.4, 157.9, 159.0; HRMS (ESI) calcd for $C_{23}H_{20}NOS_2$ $(M+H)^+$: 390.0986; found, 390.0974.

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## Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.098.

## References and notes

1. For some recent examples, see: (a) Nair, R. N.; Lee, P. J.; Grotjahn, D. B.; Rheingold, A. L. *Chem.—Eur. J.* **2010**, *16*, 7992; (b) Adriano, C.; Arianna, R.; Paolo, S. *Tetrahedron* **2010**, *66*, 7169; (c) Bartolo, G.; Lucia, V.; Giuseppe, S.; Raffaella, M.; Mirco, C. *Adv. Synth. Catal.* **2010**, *352*, 3355; (d) Praveen, C.; Karthikeyan, K.; Perumal, P. T. *Tetrahedron* **2009**, *65*, 9244; (e) Guo, Y.-J.; Tang, R.-Y.; Li, J.-H.; Zhong, P.; Zhang, X.-G. *Adv. Synth. Catal.* **2009**, *351*, 2615; (f) Adriano, C.; Arianna, R. *Tetrahedron Lett.* **2009**, *50*, 6877; (g) Norio, S.; Kimiyoshi, A.; Akiko, F.; Asuka, S.; Takeo, K. *J. Org. Chem.* **2008**, *73*, 4160; (h) Ye, S.; Ding, Q.; Wang, Z.; Zhou, H.; Wu, J. *Org. Biomol. Chem.* **2008**, *6*, 4406.
2. (a) Zhao, J.; Peng, C.; Liu, L.; Wang, Y.; Zhu, Q. *J. Org. Chem.* **2010**, *75*, 7502; (b) Peng, C.; Wang, Y.; Liu, L.; Wang, H.; Zhao, J.; Zhu, Q. *Eur. J. Org. Chem.* **2010**, 818; (c) Haruki, S.; Chao, P.; Mamoru, K.; Mao, M. *Synthesis* **2010**, 3091; (d) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160; (e) Du, W.; Dennis, P. C. *Org. Lett.* **2003**, *5*, 1765.
3. (a) Ana, G.; Mercedes, M.-S.; Carmen, R. C.; Gregorio, A.; Ana, B. C. *Org. Lett.* **2010**, *12*, 1900; (b) Wang, H.; Liu, L.; Wang, Y.; Zhang, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6841.
4. Takao, S.; Shohel, O.; Naoya, T.; Noriki, K.; Takashi, O. *Org. Lett.* **2011**, *13*, 1098.
5. Tang, R.-Y.; Luo, P.-S.; Zhang, X.-G.; Li, J.-H.; Zhong, P. *Synlett* **2010**, 1345.
6. (a) Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. *J. Comb. Chem.* **2010**, *12*, 370; (b) Ding, Q.; Wu, J. *J. Comb. Chem.* **2008**, *10*, 541.
7. Recent reviews for the synthesis of heterocycles: (a) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282; (b) Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564; (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140; (d) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodrıguez-Garcıa, I. *Chem. Rev.* **2008**, *108*, 3174; (e) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142.
8. (a) Matysiak, J. *Bioorg. Med. Chem.* **2006**, *14*, 2613; (b) Su, Y.; Guo, Q.; Wang, G.; Guo, S. Faming Zhuanli Shenqing Gongkai Shuomingshu Patent 1683349, 2005; Chem. Abstr. 2006, 145, 124577. (c) Hsu, W.-C.; Tao, T.-M.; Liu, K.-C. *Chin. Pharma. J.* **2005**, *57*, 43; (d) Hsu, W.-C.; Tao, T.-M.; Chou, T.-C.; Ding, Y.-A.; Liu, K.-C. *Chin. Pharma. J.* **2002**, *54*, 331; (e) Schmittel, M.; Mahajan, A.; Steffen, J.-P. *Synthesis* **2004**, 415.
9. (a) Csomós, P.; Fodor, L.; Bernáth, G.; Sinkkonen, J.; Salminen, J.; Wiinamäki, K.; Pihlaja, K. *Tetrahedron* **2008**, *64*, 1002; (b) Abaev, V. T.; Tsiunchik, F. A.; Gutnov, A. V.; Butin, A. V. *Tetrahedron Lett.* **2006**, *47*, 4029; (c) Fernandes, M. A.; Reid, D. *Synlett* **2003**, 2231; (d) Nishio, T.; Sekiguchi, H. *Heterocycles* **2002**, *58*, 203; (e) Hari, A.; Miller, B. L. *Org. Lett.* **2000**, *2*, 3667; (f) El-Desoky, S. I.; Kandeel, E. M.; Abd-el-Rahman, A. H.; Schmidt, R. R. *J. Heterocycl. Chem.* **1999**, *36*, 153; (g) Nishio, T. *J. Org. Chem.* **1997**, *62*, 1106.
10. For some selected examples, see: (a) Ding, Q.; Liu, X.; Cao, B.; Zong, Z.; Peng, Y. *Tetrahedron Lett.* **2011**, *52*, 1964; (b) Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. *Green. Chem.* **2010**, *12*, 1607; (c) Ding, Q.; Huang, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 1047; (d) Ding, Q.; He, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 587; (e) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921; (f) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850; (g) Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5439; (h) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959.
11. Qiu, G.; Hu, Y.; Ding, Q.; Peng, Y.; Hu, X.; Wu, J. *Chem. Commun.* **2011**, 9708.
12. Ding, Q.; Cao, B.; Yuan, J.; Liu, X.; Peng, Y. *Org. Biomol. Chem.* **2011**, *9*, 748.