Tetrahedron xxx (2014) 1–14

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Assembly of 4*H*-chromenes, imidazobenzothiazines and quinazolines via copper-catalyzed domino reactions using 2-halobenzyl tosylates as substrates

Mohamed A. Omar, Jürgen Conrad, Uwe Beifuss *

Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstraße 30, D-70599 Stuttgart, Germany

ARTICLE INFO

Article history:
Received 19 April 2014
Received in revised form 16 June 2014
Accepted 17 June 2014
Available online xxx

Keywords:
Copper
Chromenes
Imidazobenzothiazines
Quinazolines
Domino reaction

ABSTRACT

The use of 2-halobenzyl tosylates as substrates in copper-catalyzed domino intermolecular substitution/intramolecular arylation processes for the efficient and selective preparation of heterocycles is reported for the first time. Reaction of 2-halobenzyl tosylates with β-ketoesters delivers 4*H*-chromenes with yields ranging between 59 and 89%. Imidazobenzothiazines are formed with yields up to 82% upon reaction of 2-halobenzyl tosylates with 2-mercaptoimidazoles. When 2-halobenzyl tosylates are reacted with benzamidines the corresponding quinazolines are obtained.

1. Introduction

Over the last decade the importance of copper-catalyzed cross-couplings for the formation of C(aryl)–C, C(aryl)–O, C(aryl)–N und C(aryl)–S bonds has increased significantly.[1] The reasons for this development are that copper compounds are inexpensive and that many copper-mediated transformations can now be performed using catalytic amounts of the copper source, in the presence of cheap additives or even in their absence, and under mild reaction conditions. Moreover, most copper-catalyzed transformations do not lag behind other transition metal-catalyzed reactions with respect to yield, selectivity and functional group tolerance.[2] The potential of copper-catalyzed cross couplings can be extended considerably by combining them with reactions that are compatible with the reaction conditions of the copper-catalyzed coupling to new reaction sequences.[3] This approach has proven particularly valuable for the synthesis of heterocycles. With bifunctional substrates a large number of heterocyclic systems can be prepared with both remarkably high efficiency and selectivity.[4] Our group[5] and others[6] have reported that 2-halobenzyl halides in general and 2-bromobenzyl bromides in particular can serve as valuable dielectrophilic coupling partners for copper-catalyzed reactions with dinucleophiles for the synthesis of heterocycles by means of domino benzylation/arylation processes. Among other heterocyclic systems, 4*H*-chromenes, imidazobenzothiazines, quinazolines and quinazolinones have been obtained using this approach. 2-Bromobenzyl bromides and other 2-halobenzyl halides can be easily prepared by a number of standard procedures, such as the halogenation of 2-halotoluenes[7] or 2-halobenzylic alcohols.[8] A major disadvantage, however, is that many benzyl bromides are strong lachrymators and are also intensely irritating to skin and mucous membranes.[9] This is why we decided to evaluate whether 2-halobenzyl bromides can be replaced with the corresponding 2-halobenzyl tosylates. 2-Halobenzyl tosylates can be easily synthesized from the corresponding 2-halobenzylic alcohols.[10]

For our study, three different heterocyclic systems, namely 4*H*-chromenes, imidazobenzothiazines and quinazolines, were selected as synthetic goals. The first reason was that the successful preparation of these three heterocycles would allow us to demonstrate the utility of 2-halobenzyl tosylates as substrates for three different domino benzylation/arylation reactions, namely the domino C-benzylation/O-arylation, the domino S-benzylation/N-arylation and the domino N-benzylation/N-arylation/oxidation. The second reason was that 4*H*-chromenes, imidazobenzothiazines and quinazolines are particularly valuable heterocycles.

Due to their occurance in natural products and numerous biological and pharmaceutical activities chromenes have attracted considerable attention.[11] Some prominent examples of biologically

* Corresponding author. Fax: +49 711 459 22951; e-mail address: ubeifuss@uni-hohenheim.de (U. Beifuss).

http://dx.doi.org/10.1016/j.tet.2014.06.071
0040-4020/

active 4*H*-chromenes[12] include the antibiotic rhodomyrtone,[13] the α-glucosidase inhibitor myrtucommulone-E[14] and the apoptosis inducing agent sHA 14-1 (Fig. 1).[15] This is why the synthesis of 4*H*-chromenes is of great interest. Although several synthetic routes to this skeleton have been reported in recent years,[16] straight forward methods using readily available starting materials are still highly desired. Recently, we have found that the reaction of unsubstituted 2-bromobenzyl bromides with β-ketoesters can be used for the efficient preparation of 4*H*-chromenes using 20 mol % CuI and 4 equiv K_3PO_4 in DMF at 110 °C for 24 h.[5b]

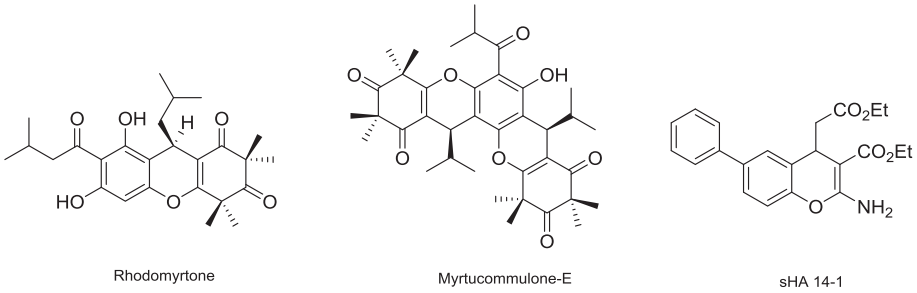


Fig. 1. Selected biologically active compounds with a 4*H*-chromene core.

Compounds with an imidazo[1,2-*a*][3,1]benzothiazine and related skeletons exhibit a number of biological activities[17] and are also of interest as materials.[18] So far, only a few methods are known for the synthesis of these heterocyclic systems. Gauthier et al. have demonstrated that imidazo[1,2-*a*][3,1]benzothiazines can be obtained in three steps by reaction between a 2-aminobenzhydrol and thiourea.[19] The reaction between 2-mercaptobenzimidazole and a pentafluorobenzyl bromide delivers a benzimidazo[1,2-*a*][3,1]benzothiazine in two steps under basic conditions.[20] Recently, Bao et al. reported the preparation of these heterocycles in one-step by a Cu(I)-catalyzed domino reaction between 2-bromobenzyl bromides and 2-mercaptoimidazoles, which involves an intermolecular *S*-benzylation followed by an intramolecular N-arylation.[6a]

Quinazolines and derivatives thereof represent an important class of *N*-heterocycles. The quinazoline moiety is not only present in many natural products[21] but is also found in a variety of drugs, such as prazosin,[22] erlotinib,[23] gefitinib,[24] lapatinib[25] and trimetrexate[26] (Fig. 2). Quinazolines possess a broad range of useful biological and pharmacological activities. Among them are antiviral,[27] antibacterial,[28] antimalarial,[29] anticancer[30] and antitubercular[31] properties. This is why even today there is a strong interest in the development of new synthetic approaches for the preparation of substituted quinazolines.[32] Among others, a number of copper-catalyzed methods have been put forward.[33–37] Most of them are based on the use of *o*-bisfunctionalized aromatic compounds, such as *o*-halobenzaldehydes,[33,34] *o*-haloaromatic ketones,[34] *o*-aminobenzoketones,[35] *o*-halobenzylbromides,[5a] 1-(2-halophenyl)methanamines[36] and (2-aminophenyl)methanols[37] as substrates.

2. Results and discussion

The reaction between 2-bromo-1-(4-methylbenzenesulfonate methyl)benzene (**1a**) and methyl acetoacetate (**2a**) was selected as a model reaction for the synthesis of 4*H*-chromene **3a**. 2-Bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) was obtained in 98% yield by reaction of 2-bromobenzylic alcohol with *p*-TsCl.[38] When 1 equiv of **1a** and 1.1 equiv of **2a** were reacted under conditions well-established for copper-catalyzed transformations in our group,[5b] i.e., with 20 mol % CuI and 4 equiv K_3PO_4 in DMF at 110 °C for 24 h, the corresponding 4*H*-chromene **3a** was formed in 64% yield (Table 1, entry 1). The successful outcome of the initial experiment encouraged us to optimize the reaction conditions. First, the reaction was performed using different bases, such as Cs_2CO_3, K_2CO_3 and DABCO. However, with none of the bases the yield achieved with K_3PO_4 could be improved (Table 1, entries 2–4). When the amount of K_3PO_4 was decreased from 4 equiv to 3 equiv the yield of **3a** dropped to 49% yield (Table 1, entry 5). Further experiments with respect to the influence of different solvents on the outcome of formation of **3a** revealed that the transformation between 1 equiv of **1a** and 2 equiv of **2a** could be run in a number of other solvents, including CH_3CN, THF, DMA and H_2O (Table 1, entries 6–9). However, the best results were obtained with CH_3CN. When the reaction was performed in CH_3CN at 90 °C, **3a** could be isolated in 72% yield (Table 1, entry 9). At 60 °C, the yield of **3a** was 54% (Table 1, entry 10). As a result, all further reactions were run in CH_3CN at 90 °C. Finally, the influence of different Cu sources on the model reaction was examined. It could be demonstrated that the transformation could not only be catalyzed by several other Cu(I) salts, such as CuCl, CuCN, Cu_2O and CuBr (Table 1, entries 11–15), but also by a number of Cu(II) salts, such as $Cu(ClO_4)_2 \cdot 6H_2O$, $Cu(OAc)_2$, $Cu(acac)_2$ (Table 1, entries 16–18) and elemental Cu (Table 1, entry 19). The best results could be achieved with CuBr as the catalyst. With 20 mol % CuBr, the yield of **3a** could be increased to 80% (Table 1, entry 14). A similar yield was observed with only 10 mol % CuBr (Table 1, entry 15). A final control experiment demonstrated that in the absence of any Cu source the yield of **3a** was negligible (Table 1, entry 20). The optimization of the model reaction between **1a** and **2a** with regard to the solvent, the base and the copper source clearly demonstrated that the highest yields of **3a** were obtained when 1 equiv of **1a** and 2 equiv of **2a** were reacted in the presence of either 10 or 20 mol % CuBr and 4 equiv K_3PO_4 in CH_3CN at 90 °C under argon for 24 h (Table 1, entries 14 and 15).

After successful optimization of the model reaction the scope of the domino process with respect to both the 2-halobenzyl tosylate and the β-ketoester was examined. First, it was studied whether the 2-bromobenzyl tosylate **1a** can be replaced with the 2-iodo- and the 2-chloro derivatives **1b** and **c** (Table 2). For this purpose, **1b** and **1c** were reacted with **2a** under the conditions established for the bromo compound. With both substrates, **3a** was formed exclusively. With the 2-iodobenzyl tosylate **1b**, the yield of the chromene **3a** could be enhanced to 82% (Table 2, entry 2) while it dropped markedly to 62% with the 2-chlorobenzyl tosylate **1c** as starting material (Table 2, entry 3). Despite the convincing result with the 2-iodobenzyl tosylate **1b** all further reactions were conducted with 2-bromobenzyl tosylates as substrates.

Next, it was demonstrated that **1a** can not only be reacted with methyl acetoacetate (**2a**), but also with ethyl acetoacetate (**2b**), *i*-propyl acetoacetate (**2c**), *t*-butyl acetoacetate (**2d**), allyl

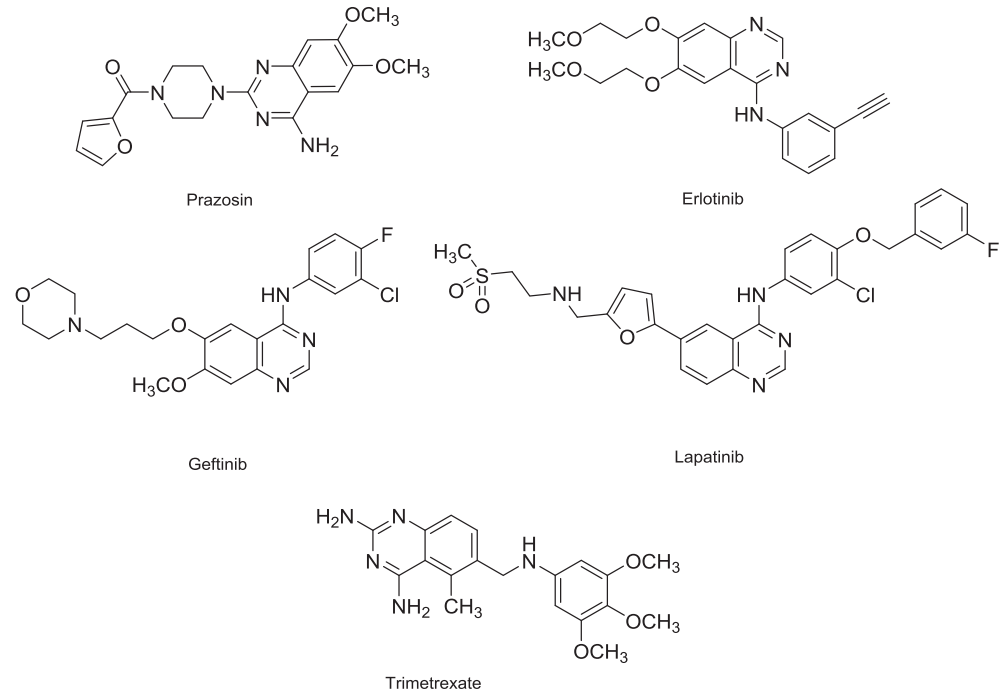
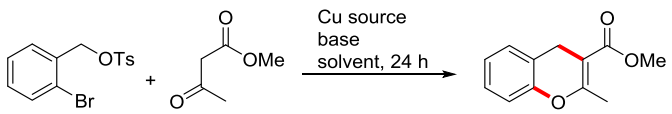


Fig. 2. Selected biologically active compounds with a quinazoline core.

Table 1
Optimization of the conditions for the copper-catalyzed reaction between **1a** and **2a**



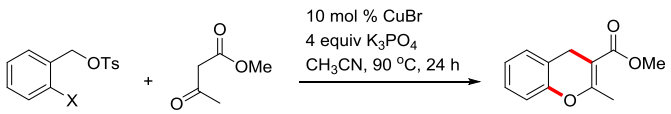
1a **2a** **3a**

Entry	Catalyst (mol %)	Base (equiv)	Solvent	*T* (°C)	Yield of **3a** (%)[d]
1	CuI (20)	K_3PO_4 (4)	DMF	110	64[a]
2	CuI (20)	Cs_2CO_3 (4)	DMF	110	58[a]
3	CuI (20)	K_2CO_3 (4)	DMF	110	43[a]
4	CuI (20)	DABCO (4)	DMF	110	20[a]
5	CuI (20)	K_3PO_4 (3)	DMF	110	49[a]
6	CuI (20)	K_3PO_4 (4)	THF	100	62[b]
7	CuI (20)	K_3PO_4 (4)	DMA	110	55[b]
8	CuI (20)	K_3PO_4 (4)	H_2O	90	19[b,c]
9	CuI (20)	K_3PO_4 (4)	CH_3CN	90	72[b]
10	CuI (20)	K_3PO_4 (4)	CH_3CN	60	54[b]
11	CuCl (20)	K_3PO_4 (4)	CH_3CN	90	25[b]
12	CuCN (15)	K_3PO_4 (4)	CH_3CN	90	46[b]
13	Cu_2O (20)	K_3PO_4 (4)	CH_3CN	90	35[b]
14	CuBr (20)	K_3PO_4 (4)	CH_3CN	90	80[b]
15	CuBr (10)	K_3PO_4 (4)	CH_3CN	90	78[b]
16	$Cu(ClO_4)_2 \cdot 6H_2O$ (10)	K_3PO_4 (4)	CH_3CN	90	37[b]
17	$Cu(AcO)_2$ (20)	K_3PO_4 (4)	CH_3CN	90	54[b]
18	$Cu(acac)_2$ (20)	K_3PO_4 (4)	CH_3CN	90	35[b]
19	Cu 99% (20)	K_3PO_4 (4)	CH_3CN	90	24[b]
20	—	K_3PO_4 (4)	CH_3CN	90	10[b]

[a] The reaction was performed using 0.5 mmol of **1a** and 0.55 mmol of **2a** in a sealed vial.
[b] The reaction was performed using 0.5 mmol of **1a** and 1 mmol of **2a** in a sealed vial.
[c] The reaction was run in a round-bottom flask under argon.
[d] Yields refer to isolated yields.

acetoacetate (**2e**), benzyl acetoacetate (**2f**) and methoxyethyl acetoacetate (**2g**) to deliver the corresponding 4*H*-chromenes **3b**–**g** with yields ranging from 66 to 79% as the sole products (Table 3, entries 2–7). It was also established that ethyl 3-oxopentanoate (**2h**), ethyl 3-oxohexanoate (**2i**) and the 4-methyl-3-oxopentanoates **2j**,**k** can be employed as β-ketoesters for the preparation of 2,3-disubstituted 4*H*-chromenes **3h**–**k** with yields ranging from 59 to 89% (Table 3, entries 8–11). Finally, it was found that the formation of 4*H*-chromenes is not restricted to unsubstituted 2-bromobenzyl tosylates. The required 2-bromobenzyl tosylate **1d** was obtained in 91% yield by reaction of the corresponding 2-bromobenzylic alcohol with *p*-TsCl. The reaction of 2-bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**) with **2a** and **2b** delivered the corresponding 4*H*-chromenes **3l** and **3m** in yields of 75 and 68%, respectively, (Table 3, entries 12 and 13).

Table 2
Reactions of 2-halobenzyl tosylates **1a**–**c** with methyl acetoacetate **2a**[a]



1 **2a** **3a**

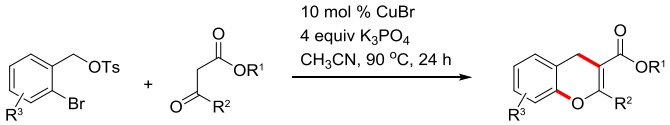
Entry	**1**	X	Yield of **3a** (%)[b]
1	**a**	Br	78
2	**b**	I	82
3	**c**	Cl	62

[a] All reactions were performed using 0.5 mmol of **1** and 1 mmol of **2a** in a sealed vial.
[b] Yields refer to isolated yields.

The reaction can be considered as domino intermolecular *C*-benzylation/intramolecular *O*-arylation. A plausible reaction mechanism for the CuBr-catalyzed domino reaction is presented in Scheme 1. It is assumed that the domino reaction starts with the intermolecular *C*-benzylation of a β-ketoester (**1a**+**2**→**4**). The second step, the intramolecular *O*-arylation between an *O*-atom of the β-ketoester moiety and the aromatic carbon carrying the halogen atom is initiated by reaction of **4** with K_3PO_4 to give the corresponding potassium enolate **A** and K_2HPO_4. Then, the oxidative addition of the arylbromide to copper takes place and **B** is formed as an intermediate. This is followed by a bromide/enolate exchange

Please cite this article in press as: Omar, M. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.071

Table 3
CuBr-catalyzed synthesis of 4*H*-chromenes **3a**–**m** from 2-halobenzyl tosylates **1a**,**d** and β-ketoesters **2a**–**k**[a]



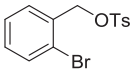
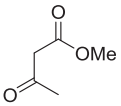
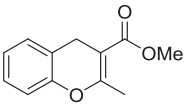
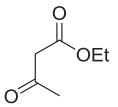
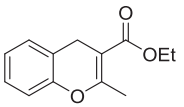
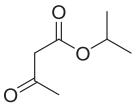
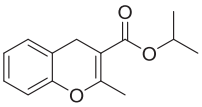
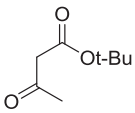
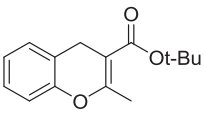
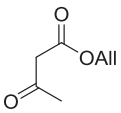
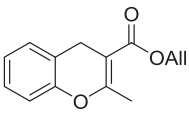
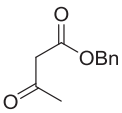
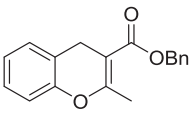
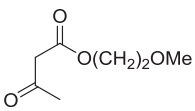
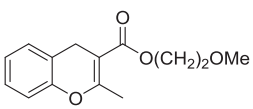
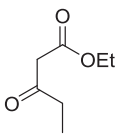
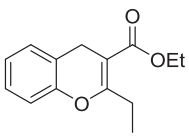
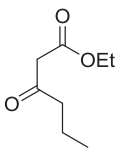
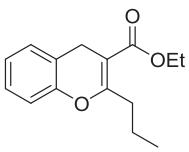
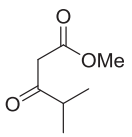
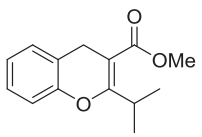
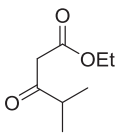
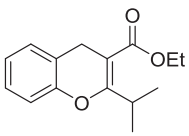
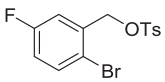
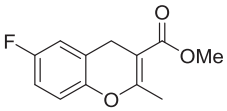
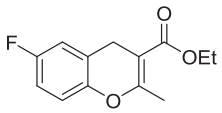
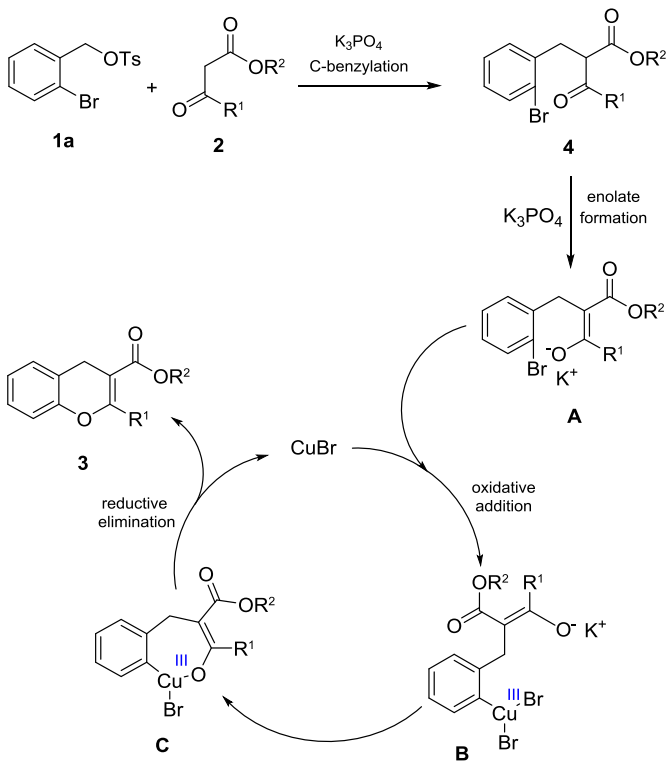
Entry	1		2		3		Yield of **3** (%)[b]
1		**1a**		**2a**		**3a**	78
2	**1a**			**2b**		**3b**	68
3	**1a**			**2c**		**3c**	70
4	**1a**			**2d**		**3d**	76
5	**1a**			**2e**		**3e**	66
6	**1a**			**2f**		**3f**	79
7	**1a**			**2g**		**3g**	66
8	**1a**			**2h**		**3h**	89
9	**1a**			**2i**		**3i**	59
10	**1a**			**2j**		**3j**	82
11	**1a**			**2k**		**3k**	78
12		**1d**	**2a**			**3l**	75

Table 3 (*continued*)

Entry	1	2	3		Yield of **3** (%)[b]
13	**1d**	**2b**		**3m**	68

[a] All reactions were performed using 0.5 mmol of **1** and 1 mmol of **2** in a sealed vial.
[b] Yields refer to isolated yields.



Scheme 1. Plausible reaction mechanism for the Cu(I)-catalyzed synthesis of the 4*H*-chromenes **3**.

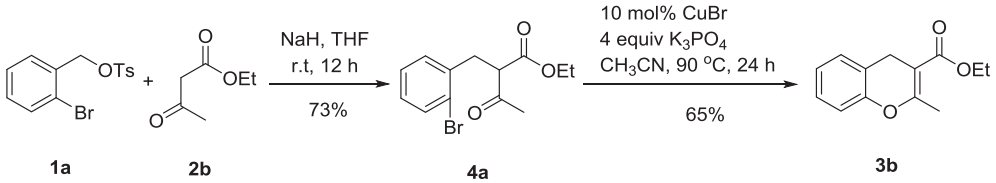
to produce the chelated copper complex **C**. In the final step, **C** undergoes reductive elimination with formation of the 4*H*-chromene **3** and regeneration of CuBr.

To support the reaction mechanism, a control experiment was performed, namely the Cu(I)-catalyzed intramolecular *O*-arylation of **4**, the proposed intermediate of the domino reaction. For this purpose, the benzylated β-ketoester **4a** was prepared by reaction of **1a** with **2b** under basic conditions (NaH) and then reacted with 10 mol % CuBr and 4 equiv K_3PO_4 in CH_3CN under argon (Scheme 2). After 24 h at 90 °C the 4*H*-chromene **3b** was isolated in 65%. The exclusive formation of **3b** is a good indicator that **4** can act as an intermediate in the 4*H*-chromene synthesis presented.

intramolecular *O*-arylation can be performed using 2-halobenzyl tosylates **1** as substrates with yields up to 89%. This means that the 2-halobenzyl halides can be replaced without any problems by the easily accessible 2-halobenzyl tosylates.

Next, it was studied whether imidazobenzothiazines **6** can be prepared by the Cu(I)-catalyzed reaction between 2-bromobenzyl tosylates **1** and 2-mercaptoimidazoles **5**. For these transformations, the Cu(I)-catalyzed reaction between 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) and 2-mercapto benzimidazole (**5a**) was selected as the model reaction. After some initial experiments it was found that benzimidazo[1,2-*a*][3,1]benzothiazine (**6a**) was formed in 77% yield when 1 equiv of **1a** was reacted with 1 equiv of **5a** in the presence of 10 mol % CuI and 3 equiv K_2CO_3 in DMSO for 20 h (Table 4, entry 1). In order to optimize the reaction, the influence of the base, the Cu-source and the reaction temperature on the outcome of the model reaction was studied. First, the reaction was performed with different bases, such as $NaHCO_3$, Cs_2CO_3, Na_2CO_3 and K_3PO_4 (Table 4, entries 2–5). It was found that the yield of **6a** could be raised to 82% when 3 equiv K_3PO_4 were employed as base (Table 4, entry 5). The yield of **6a** could not be further improved by lowering or raising the amount of K_3PO_4 (Table 4, entries 6 and 7). In the absence of any base no product formation could be observed (Table 4, entry 8). Next, the model reaction was run in the presence of 10 mol % of different Cu(I)-sources. It could be demonstrated that the reaction could also be performed with CuBr, CuCl and Cu_2O as catalyst (Table 4, entries 9–11). However, in all cases the yield was lower than with 10 mol % CuI. A reduction of the catalyst load from 10 mol % to 5 mol % CuI did not pay off, since the yield of **6a** decreased to 69% (Table 4, entry 12). A control experiment clearly demonstrated that no product was formed in the absence of any copper-source (Table 4, entry 13). Then, the transformation was studied in different solvents (Table 4, entries 14–17). The results with 1,2-DCB, and CH_3CN were promising but the yield achieved in DMSO could not be topped (Table 4, entries 14 and 17). In a final experiment the reaction temperature was lowered to 60 °C. At this temperature not even a trace of **6a** was formed (Table 4, entry 18).

With the optimized conditions in hand, the substrate scope of the imidazobenzothiazine synthesis was evaluated. It was found that in addition to the unsubstituted 2-bromobenzyl tosylate **1a** the substituted 2-bromobenzyl tosylates **1d** and **1e** could also be reacted with 2-mercaptobenzimidazole (**5a**) to give the corresponding benzimidazo[1,2-*a*][3,1]benzothiazine **6b**,**c** in yields

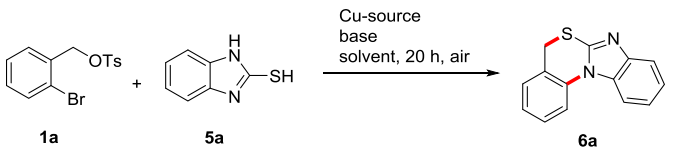


Scheme 2. Synthesis of the putative intermediate **4a** and its Cu(I)-catalyzed conversion into **3b**.

It can be stated that the Cu(I)-catalyzed synthesis of 4*H*-chromenes **3** by means of a domino intermolecular *C*-benzylation/

around 80% (Table 5, entries 2 and 3). The substrate **1e** was obtained in 97% yield by tosylation of the corresponding 2-

Table 4
Optimization of the conditions for the reaction between 2-bromobenzyl tosylate (**1a**) and 2-mercaptobenzimidazole (**5a**) for the synthesis of benzoimidazobenzothiazine (**6a**)[a]



1a **5a** **6a**

Entry	Catalyst (mol %)	Base (equiv)	Solvent	*T* (°C)	Yield of **6a** (%)[b]
1	CuI (10)	K_2CO_3 (3)	DMSO	110	77
2	CuI (10)	$NaHCO_3$ (3)	DMSO	110	59
3	CuI (10)	Cs_2CO_3 (3)	DMSO	110	69
4	CuI (10)	Na_2CO_3 (3)	DMSO	110	73
5	CuI (10)	K_3PO_4 (3)	DMSO	110	82
6	CuI (10)	K_3PO_4 (4)	DMSO	110	79
7	CuI (10)	K_3PO_4 (2)	DMSO	110	58
8	CuI (10)	—	DMSO	110	—
9	CuBr (10)	K_3PO_4 (3)	DMSO	110	68
10	CuCl (10)	K_3PO_4 (3)	DMSO	110	46
11	Cu_2O (10)	K_3PO_4 (3)	DMSO	110	61
12	CuI (5)	K_3PO_4 (3)	DMSO	110	69
13	—	K_3PO_4 (3)	DMSO	110	—
14	CuI (10)	K_3PO_4 (3)	1,2-DCB	130	71
15	CuI (10)	K_3PO_4 (3)	DMF	120	55
16	CuI (10)	K_3PO_4 (3)	H_2O	90	10
17	CuI (10)	K_3PO_4 (3)	CH_3CN	90	69
18	CuI (10)	K_3PO_4 (3)	DMSO	60	—

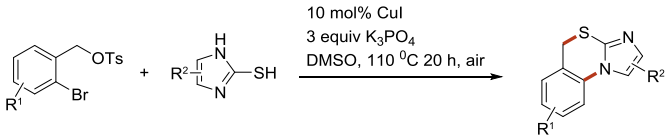
[a] All reactions were performed using 0.5 mmol of **1a** and 0.5 mmol of **5a** in a sealed vial.
[b] Yields refer to isolated yields.

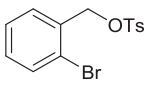
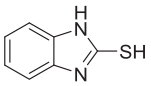
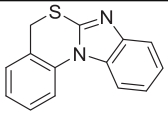
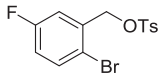
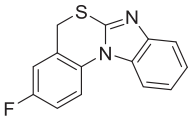
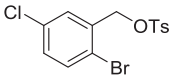
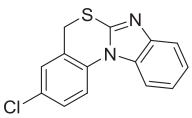
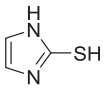
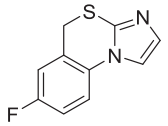
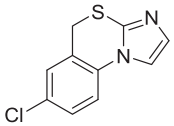
bromobenzylic alcohol. Furthermore, it was established that the reaction of the 2-bromobenzyl tosylates **1** is not restricted to 2-mercaptobenzimidazole (**5a**) as substrate but could also be achieved with 2-mercaptoimidazole (**5b**). The transformations with **1d**,**e** delivered the imidazo[1,2-*a*][3,1]benzothiazines **6d**,**e** with 79 and 73%, respectively (Table 5, entries 4 and 5).

A plausible reaction mechanism for the CuI-catalyzed domino reaction between **1a** and **5a** is given in Scheme 3. It is assumed that the reaction proceeds as a domino intermolecular *S*-benzylation/intramolecular N-arylation. It starts with the intermolecular *S*-benzylation of 2-mercaptobenzimidazole (**5a**) to give the benzyl thioether intermediate **7**. The intramolecular N-arylation between an *N*-atom of the benzimidazole ring begins with the generation of **A** and K_2HPO_4. The oxidative addition of the aryl halide to copper forms the Cu(III) intermediate **B**. This is followed by an exchange of the halide on copper for the *N*-nucleophile. The resulting intermediate **C** releases the coupling product **6a** and the Cu(I)-catalyst CuX via reductive elimination.

To support the proposed reaction mechanism of the imidazobenzothiazine synthesis, a control experiment was performed; i.e., the Cu(I)-catalyzed intramolecular N-arylation of the benzyl thioether **7**, the putative intermediate of the domino reaction. The benzyl thioether **7** was prepared selectively by *S*-benzylation of **5a** with **1a** using K_3PO_4 as a base in 62% yield (Scheme 4). Subsequently, **7** was reacted under the conditions of the CuI-catalyzed domino reaction with 10 mol % CuI and 3 equiv K_3PO_4 in DMSO at 110 °C for 20 h to deliver the imidazobenzothiazine **6a** as the only product in 77%. The exclusive formation of **6a** in high yield is a strong indication that the benzyl thioether **7** is an intermediate in the imidazobenzothiazine synthesis.

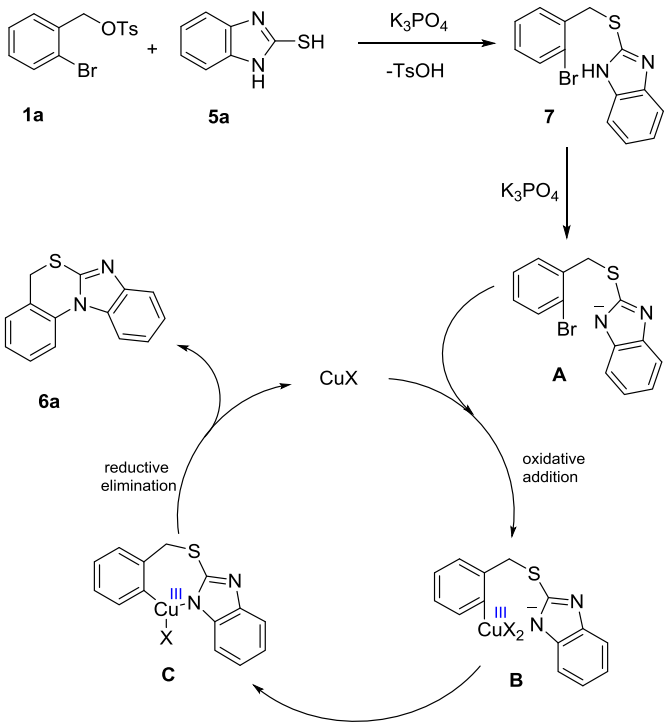
Table 5
CuI-catalyzed synthesis of imidazobenzothiazines **6a**–**e** from 2-halobenzyl tosylates **1a**,**d**,**e** and 2-mercaptoimidazoles **5a**,**b**[a]



Entry	1		5		6		Yield of **6** (%)[b]
1		**1a**		**5a**		**6a**	82
2		**1d**	**5a**			**6b**	78
3		**1e**	**5a**			**6c**	81
4	**1d**			**5b**		**6d**	79
5	**1e**		**5b**			**6e**	73

[a] All reactions were performed using 0.5 mmol of **1** and 0.5 mmol of **5** in a sealed vial.
[b] Yields refer to isolated yields.

Please cite this article in press as: Omar, M. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.071



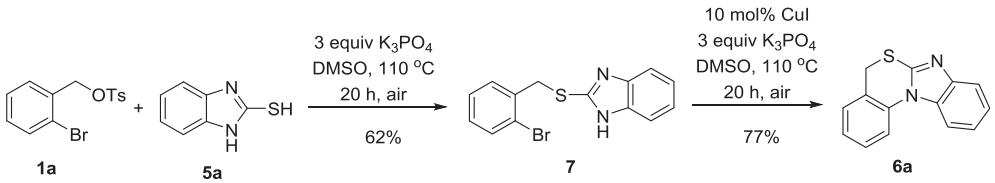
Scheme 3. Plausible reaction mechanism for the Cu(I)-catalyzed synthesis of imidazobenzothiazine **6a**.

58% yield (Table 6, entry 3). It was found that the synthesis of 2-arylquinazolines is not restricted to the unsubstituted 2-bromobenzyl tosylate (**1a**) as substrate. The substituted 2-bromobenzyl tosylates **1d** and **1e** were also tolerated. The reaction of **1d** with **8a** and **8b** gave the corresponding quinazolines **9d** and **9e** in yields of 51 and 69%, respectively, (Table 6, entries 4 and 5). The reaction of **1e** with **8a** led to the formation of **9f** in 53% yield.

Although a mechanistic investigation of the CuI-catalyzed quinazoline synthesis has not been performed, it is plausible to regard the transformation as a domino intermolecular N-benzylation/intramolecular N-arylation/oxidation.[34b,39]

The structures of all 4*H*-chromenes **3**, imidazobenzothiazines **6** and quinazolines **9** were unambiguously elucidated by NMR spectroscopy and mass spectrometry. Full assignment of the ^{1}H and ^{13}C chemical shifts and structure elucidation of all compounds was achieved by evaluating their gCOSY, gHSQC and gHMBC spectra. As an example, in the HMBC spectrum of **6e** the quaternary carbon C-3a showed ^{3}J-HMBC-correlations to protons 1-H, 2-H and 5-H. The quaternary carbon C-9a displayed strong $^{3}J_{CH}$-correlations to the protons 5-H and 6-H and finally carbon C-5a exhibited a $^{2}J_{CH}$-correlation to the proton 5-H (Fig. 3). Strong ROEs between protons 1-H and 9-H as well as between 5-H and 6-H confirmed the structure of **6e** (Fig. 3).

In case of **6a** a strong overlap of individual ^{1}H NMR resonances of the two proton aromatic spin systems (1-H)—(4-H) and (8-H)—(11-H), e.g., 1-H and 11-H, precludes an unequivocal structure elucidation (see Supplementary data Fig. 20). However, by means of the computed ^{13}C NMR chemical shifts at the DFT GIAO



Scheme 4. Synthesis of the putative intermediate **7** and its Cu(I)-catalyzed conversion into **6a**.

The Cu(I)-catalyzed synthesis of benzimidazo[1,2-*a*][3,1]benzothiazine and related skeletons **6** employing a domino intermolecular *S*-benzylation/intramolecular N-arylation can be performed with yields up to 82% when 2-halobenzyl tosylates **1** are used as substrates. The transformations with 2-halobenzyl tosylates **1** can be run with only 10 mol % of a CuI, in the absence of any additive and under air. These are clear advantages of 2-halobenzyl tosylates **1** in comparison to 2-halobenzyl halides as substrates.

Finally, it was studied whether 2-bromobenzyl tosylates **1** can also be employed as substrates for the preparation of 2-arylquinazolines **9** by copper-catalyzed reaction with benzamidines **8**. The reaction between 2-bromo-1-(4-methylbenzene sulfonatemethyl)benzene (**1a**) and benzamidine hydrochloride (**8a**) was chosen as a model reaction. When equimolar amounts of **1a** and of **8a** were reacted under conditions developed for the reactions of 1-(2-bromophenyl)methanamines with benzamidine hydrochlorides in our group,[36a] i.e., in the presence of 10 mol % CuI as a catalyst, 3 equiv K_3PO_4 as a base and 40 mol % pivalic acid as an additive in 1,2-dichlorobenzene at 110 °C for 18 h using aerial oxygen as the oxidant, 2-phenylquinazoline (**9a**) was formed in 63% yield (Table 6, entry 1). This result prompted us to synthesize some additional 2-arylquinazolines **9** (Table 6). 2-(4-Chlorophenyl)quinazoline (**9b**) was isolated in 79% yield when **1a** was reacted with 4-chlorobenzamidine hydrochloride (**8b**) (Table 6, entry 2). When **1a** was reacted with 3-methylbenzamidine hydrochloride (**8c**) the corresponding 2-(3-methylphenyl)quinazoline (**9c**) was isolated in

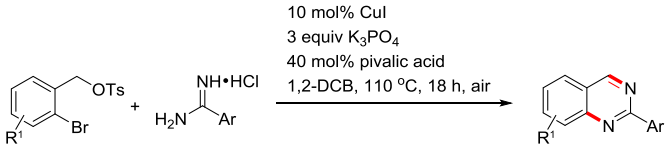
mPW1PW91/6-311++G(2d,p)//mPW1PW91/6-31G(d) level of theory[40] we were able to assign the quaternary carbons being essential for the elucidation process, e.g., C-4a (δ calcd 146.0, exptl 143.6 ppm) and C-12a (δ calcd 132.6, exptl 132.5 ppm). Similar values were obtained for compound **6b**: C-4a (δ calcd 145.8, exptl 144.8 ppm) and C-12a (δ calcd 132.5, exptl 133.5 ppm) and for compound **6c**: C-7 (δ calcd 29.8, exptl 29.8 ppm), C-4a (δ calcd 145.9, exptl 143.4 ppm) and C-12a (δ calcd 132.4, exptl 132.4 ppm). Fortunately, 1D NOE's between 1-H and 11-H in **6b** as well as **6c** could be observed at 500 MHz experimentally (Fig. 4).

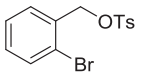
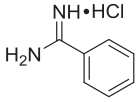
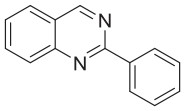
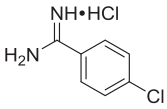
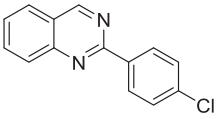
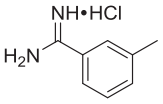
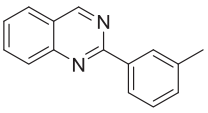
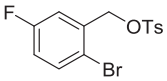
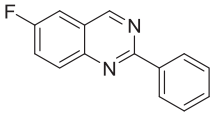
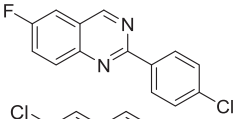
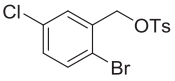
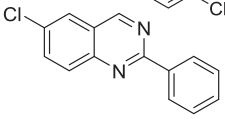
3. Conclusions

In summary, the use of easily accessible 2-halobenzyl tosylates as substrates in copper-catalyzed domino intermolecular substitution/intramolecular arylation processes for the efficient and selective preparation of 4*H*-chromenes, imidazobenzothiazines and quinazolines is reported for the first time. 4*H*-Chromenes are formed selectively in one pot with yields up to 89% as the result of a domino intermolecular *C*-benzylation/intramolecular *O*-arylation upon reaction of 2-halobenzyl tosylates with β-ketoesters. The reaction of 2-halobenzyl tosylates with 2-mercaptoimidazoles can be regarded as a domino intermolecular S-benzylation/intramolecular N-arylation and delivers imidazobenzothiazines with yields up to 82%. When 2-halobenzyl tosylates are reacted with benzamidines,

Please cite this article in press as: Omar, M. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.071

Table 6
CuBr-catalyzed synthesis of 2-arylquinazolines **9a–f** from 2-bromobenzyl tosylates **1a,d,e** and benzamidinium salts **8a–c**[a]



Entry	1		8		9		Yield of **9** (%)[b]
1		**1a**		**8a**		**9a**	63
2	**1a**			**8b**		**9b**	79
3	**1a**			**8c**		**9c**	58
4		**1d**	**8a**			**9d**	51
5	**1d**		**8b**			**9e**	69
6		**1e**	**8a**			**9f**	53

[a] All reactions were performed using 0.5 mmol of **1** and 0.5 mmol of **8** in a sealed vial.
[b] Yields refer to isolated yields.

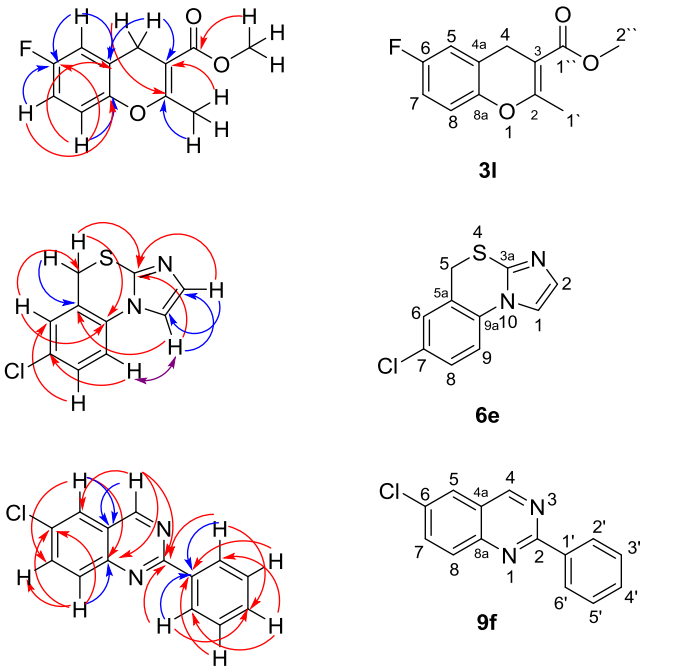


Fig. 3. Important HMBC correlations of **3l**, **6e** and **9f** (red arrows: ^3J; blue arrows: ^2J). Important ROESY correlation of **6e** (violet arrow).

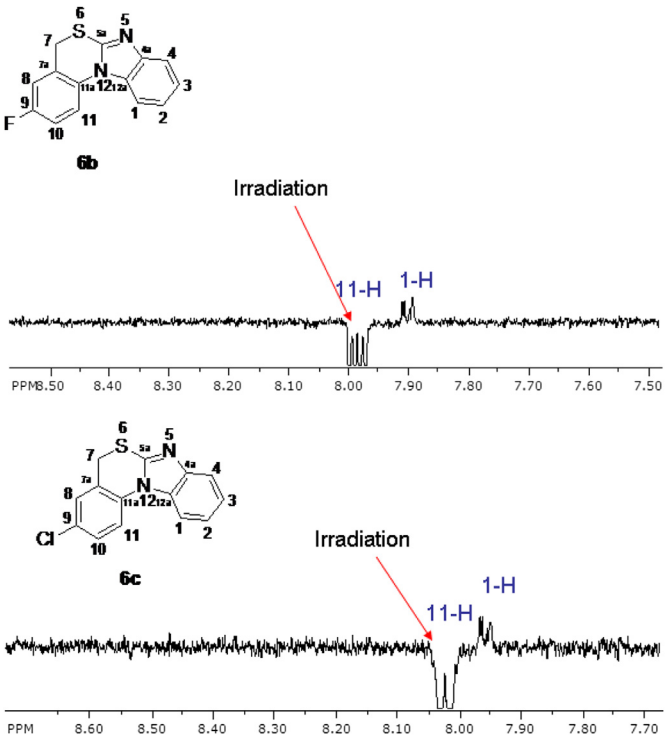


Fig. 4. Selective 1D DPFG NOESY spectrum of compounds **6b** and **6c**.

Please cite this article in press as: Omar, M. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.071

a domino N-benzylation/N-arylation/oxidation takes place and quinazolines are formed.

4. Experimental section

4.1. General

All chemicals were purchased from commercial suppliers. Solvents used in extraction and purification were distilled prior to use. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{245} aluminium plates (Merck) with visualization under UV light and by immersion in ethanolic vanillin solution followed by heating. Flash chromatography was carried out on silica gel MN 60, 0.04–0.053 mm (Macherey & Nagel). Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra of compounds **1d**, **1e**, **3l**, **3m** and **6d** were measured on a Nicolet 5700 (FT-IR spectrometer); IR spectra of all other compounds spectra were measured on a Perkin–Elmer Spectrum One (FT-IR spectrometer). ^{1}H and ^{13}C NMR spectra were recorded at 300 (75) MHz on a Varian Unity Inova instrument using $CDCl_3$ and DMSO-d_6 as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ H/C 7.26/77.00 ($CDCl_3$), 2.50/39.50 (DMSO-d_6) and 2.05/29.9 (CD_3COCD_3) relative to TMS as internal standard. HSQC-, HMBC- and COSY-spectra were recorded on an NMR spectrometer at 300 MHz. Coupling constants J [Hertz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), sex (sextet), sep (septet), m (multiplet) and br (broad). Low resolution electron impact mass spectra (MS) and exact mass electron impact mass spectra (HRMS) were recorded at 70 eV using a double-fousing sector field mass spectrometer. The intensities are reported as percentages relative to the base peak (I=100%).

4.2. Computational studies

All calculations reported in this paper were performed within density functional theory, using the Gaussian 03 package.[40d] ^{13}C NMR chemical shifts of selected compounds **6a**–**c** were calculated as follows: the rigid structures were optimized with the MM2 force field implemented in Chem3D Pro.[41] In the second step, the optimized structures were subsequently reoptimized at the AM1 level followed by the RHF/3-21G level and finally by the B3LYP/6-31G(d) level of theory within the Gaussian 03 package. In the final step, the gas-phase ^{13}C NMR chemical shifts of the reoptimizedgeometries were computed at the mPW1PW91/6-311++G(2d,p)//mPW1PW91/6-31G(d) level of theory. The references TMS and benzene for the MSTD approach according to Sarotti and Pellegrinet[40e] were computed in the same manner as for the aforementioned selected compounds. Theoretical ^{13}C NMR chemical shifts (δ_a) were derived by the following equation: $\delta_a=\sigma_{ref}-\sigma_a+\delta_{ref}$ where σ_{ref} and σ_a are the calculated NMR isotropic magnetic shielding tensors of the reference compound and carbon a of the compound of interest: σ_{TMS}=186.965 and $\sigma_{benzene}$=54.4127 at the mPW1PW91/6-311++G(2d,p)//mPW1PW91/6-31G(d) level; δ_{ref} represents the chemical shift of the reference compound δ_{TMS}=0 ppm; $\delta_{benzene}$=128.5 ppm (benzene plus TMS at 125 MHz).

4.3. General procedure I for the synthesis of 2-halobenzyl tosylates 1a–e

2-Halobenzyl tosylates **1a**–**e** were prepared from the corresponding 2-halobenzyl alcohols according to the procedure of Wallace et al.[38] *p*-TsCl (3.2 mmol) was added to a stirred solution of the 2-halobenzyl alcohol (2.7 mmol) in Et_2O (15 mL) at 0 °C. After addition of freshly powdered KOH (27 mmol) in small portions, the reaction mixture was stirred for 3 h at room temperature. The ethereal solvent was removed in vacuo and the reaction mixture was poured into water (50 mL). The precipitate formed was collected by filtration and purified by flash chromatography over silica gel.

*4.3.1. 2-Bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**).*[10e] According to general procedure I, KOH (1.5 g, 27 mmol) was added to a solution of 2-bromobenzyl alcohol (500 mg, 2.7 mmol) and *p*-TsCl (610 mg, 3.2 mmol) in Et_2O (15 mL). Flash chromatography over silica gel (petroleum ether/ethyl acetate=5:1) gave **1a** as a colourless solid in 98% yield (890 mg, 2.61 mmol): mp 79–80 °C (lit.[10e] 80.5–81.5 °C).

*4.3.2. 2-Iodo-1-(4-methylbenzenesulfonatemethyl)benzene (**1b**).* According to general procedure I, KOH (1.5 g, 27 mmol) was added to a solution of 2-iodobenzyl alcohol (632 mg, 2.7 mmol) and *p*-TsCl (618 mg, 3.2 mmol) in Et_2O (15 mL). Flash chromatography over silica gel (petroleum ether/ethyl acetate=5:1) gave **1b** as a yellow solid in 95% yield (995 mg, 2.56 mmol): mp 55–57 °C; R_f 0.56 (petroleum ether/EtOAc=5:1); IR (ATR) $\tilde{\nu}$ 1354 (C=S), 1169, 924, 885, 853, 802, 763, 666 cm^{-1}; UV (MeCN) λ_{max} (log ε) 227 (4.26) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 7.00 (ddd, ^3J (3-H, 4-H)=7.7 Hz, ^3J (4-H, 5-H)=7.7 Hz, ^3J (4-H, 6-H)=1.9 Hz, 1H, 4-H), 7.28–7.38 (overlapped, 4H, 4-H, 5-H, 3′-H and 5′-H), 7.78 (dd, ^3J (3-H, 4-H)=7.7 Hz, ^4J (3-H, 5-H)=1.9 Hz, 1H, 3-H), 7.83 (brdd, ^3J (2′-H, 3′-H)=6.4 Hz, ^3J (5′-H, 6′-H)=6.4 Hz, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 75.2 (CH_2), 98.1 (C-2), 128.1 (C-2′ and C-6′), 128.4 (C-5), 129.8 (C-3′ and C-5′), 129.9 (C-6), 130.4 (C-4), 132.9 (C-1′), 135.9 (C-1), 139.0 (C-3), 144.9 (C-4′); MS (EI, 70 eV) m/z (%) 288 (10) [M]$^+$, 261 (84) [M–I]$^+$, 188 (77), 216 (100), 155 (19) [$C_7H_7O_2S$]$^+$, 91 (38); HRMS (EI) Calculated for $C_{14}H_{13}IO_3S$ 387.9630, found 387.9640.

*4.3.3. 2-Chloro-1-(4-methylbenzenesulfonatemethyl)benzene (**1c**).* According to general procedure I, KOH (1.5 g, 27 mmol) was added to a solution of 2-chlorobenzyl alcohol (385 mg, 2.7 mmol) and *p*-TsCl (618 mg, 3.2 mmol) in Et_2O (15 mL). Flash chromatography over silica gel (petroleum ether/ethyl acetate=5:1) gave **1c** as a colourless solid in 90% yield (719 mg, 2.43 mmol): mp 91–93 °C; R_f 0.51 (petroleum ether/EtOAc=5:1); IR (ATR) $\tilde{\nu}$ 1351 (C=S), 1171, 925, 883, 857, 805, 763, 665 cm^{-1}; UV (MeCN) λ_{max} (log ε) 267 (3.04), 221 (4.23) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 7.20–7.20 (overlapped, 2H, 4-H, 5-H), 7.34–7.30 (overlapped, 3H, 6-H, 3′-H and 5′-H) 7.37 (dd, ^3J (3-H, 4-H)=7.3 Hz, ^4J (3-H, 5-H)=2.7 Hz, 1H, 3-H), 7.82 (brdd, ^3J (2′-H, 3′-H)=6.4 Hz, ^3J (5′-H, 6′-H)=6.4 Hz, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 68.8 (CH_2), 127.0 (C-5), 128.0 (C-2′ and C-6′), 129.5 (C-6), 129.8 (C-3′ and C-5′), 130.2 (C-4), 130.3 (C-3), 131.2 (C-2), 132.2 (C-1′), 133.6 (C-1), 144.9 (C-4′); MS (EI, 70 eV) m/z (%) 296 (1) [M]$^+$, 261 (1) [M–Cl]$^+$, 156 (8) [$C_7H_8O_2S$]$^+$, 141 (100) [M–$C_7H_8O_2S$]$^+$, 125 (88) [C_7H_6Cl]$^+$, 92 (23); HRMS (EI) Calculated for $C_{14}H_{13}ClO_3S$ 296.0274, found 296.0319.

*4.3.4. 2-Bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**).* According to general procedure I, KOH (1.5 g, 27 mmol) was added to a solution of 2-bromo-5-fluorobenzyl alcohol (553 mg, 2.7 mmol) and *p*-TsCl (618 mg, 2.3 mmol) in Et_2O (15 mL). Flash chromatography over silica gel (petroleum ether/ethyl acetate=5:1) gave **1d** as a colourless solid in 91% yield (880 mg, 2.45 mmol): mp 58–60 °C; R_f 0.49 (petroleum ether/EtOAc=5:1); IR (ATR) $\tilde{\nu}$ 1353 (C=S), 1174, 957, 873, 834, 661, 571 cm^{-1}; UV (MeCN) λ_{max} (log ε) 273 (3.19), 224 (4.19) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 6.90 (ddd, ^3J (3-H, 4-H)=8.3 Hz, ^3J (5-F, 4-H)=8.3 Hz, ^4J (4-H, 6-H)=3.0 Hz, 1H, 4-H), 7.12 (dd, ^3J (5-F, 6-H)=8.8 Hz, ^4J (4-H, 6-H)=2.8 Hz, 1H, 6-H), 7.34 (brdd, ^3J (2′-H, 3′-

H)=6.4 Hz, ^3J (5′-H, 6′-H)=6.4 Hz, 2H, 3′-H and 5′-H), 7.45 (brdd, ^3J (3-H, 4-H)=8.3 Hz, ^4J (5-F, 3-H)=3.5 Hz, 1H, 4-H), 7.83 (brdd, ^3J (2′-H, 3′-H)=6.4 Hz, ^3J (5′-H, 6′-H)=6.4 Hz, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 70.0 (CH_2), 116.5 (d, ^4J (C–F)=3.2 Hz, C-2), 116.8 (d, ^2J (C–F)=24.3 Hz, C-6), 117.2 (d, ^2J (C–F)=22.2 Hz, C-4), 128.0 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 132.6 (C-1′), 134.0 (d, ^3J (C–F)=8.1 Hz, C-3), 135.1 (d, ^3J (C–F)=8.1 Hz, C-1), 145.1 (C-4′), 161.9 (d, ^1J (C–F)=246.1 Hz, C-5); MS (EI, 70 eV) *m/z* (%) 357 (1) $[M]^+$, 279 (7) $[M-Br]^+$, 203 (6) $[M-C_7H_7O_2S]^+$, 187 (9), 155 (3) $[C_7H_7O_2S]^+$, 92 (11); HRMS (EI) Calculated for $C_{14}H_{12}BrFO_3S$ 357.9675, found 357.9685.

*4.3.5. 2-Bromo-5-chloro-1-(4-methylbenzenesulfonatemethyl)benzene (**1e**).* According to general procedure I, KOH (1.5 g, 27 mmol) was added to a solution of 2-bromo-5-chlorobenzyl alcohol (598 mg, 2.7 mmol) and *p*-TsCl (618 g, 2.3 mmol) in Et_2O (15 mL). Flash chromatography over silica gel (petroleum ether/ethyl acetate=5:1) gave **1e** as a colourless solid in 97% yield (970 mg, 2.6 mmol): mp 108–109 °C; R_f 0.37 (petroleum ether/EtOAc=6:1); IR (ATR) $\tilde{\nu}$ 1348 (C=S), 1187, 1121, 946, 823, 659, 561 cm^{-1}; UV (MeCN) λ_{max} (log ε) 227 (4.26) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 7.14 (dd, ^3J (3-H, 4-H)=8.3 Hz, ^4J (4-H, 6-H)=2.4 Hz, 1H, 4-H), 7.33 (overlapped, 3H, 6-H, 3′-H and 5′-H), 7.42 (brd, ^3J (3-H, 4-H)=8.3 Hz, 1H, 3-H), 7.82 (brdd, ^3J (2′-H, 3′-H)=6.5 Hz, ^3J (5′-H, 6′-H)=6.5 Hz, 2H, 2′-H and 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 70.0 (CH_2), 120.5 (C-2), 128.0 (C-2′ and C-6′), 129.7 (C-6), 129.9 (C-3′ and C-5′), 130.2 (C-4), 132.7 (C-1′), 133.7 (C-5), 133.8 (C-3), 134.7 (C-1), 145.1 (C-4′); MS (EI, 70 eV) *m/z* (%) 375 (13) $[M]^+$, 295 (64) $[M-Br]^+$, 220 (63) $[M-C_7H_7O_2S]^+$, 204 (90) $[M-C_7H_7O_3S]^+$, 155 (19) $[C_7H_7O_2S]^+$, 91 (38); HRMS (EI) Calculated for $C_{14}H_{12}BrClO_3S$ 373.9374, found 373.9353.

4.4. General procedure II for the Cu(I)-catalyzed synthesis of 4*H*-chromenes 3a–m

An oven-dried 10 mL vial was equipped with a magnetic stir bar and charged with CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), the 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene derivative **1** (0.5 mmol) and the β-ketoester **2** (1 mmol) under air. The vial was sealed, evacuated and backfilled with argon three times, then dry CH_3CN (2 mL) was added. The reaction mixture was stirred at 90 °C for 24 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (30 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue thus obtained was purified by flash column chromatography over silica gel to afford the desired product.

*4.4.1. Methyl 2-methyl-4H-chromene-3-carboxylate (**3a**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and methyl acetoacetate (**2a**) (116 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3a** as a colourless solid in 78% yield (79 mg, 0.39 mmol): mp 40–42 °C (lit.[5b] 40–42 °C).

*4.4.2. Ethyl 2-methyl-4H-chromene-3-carboxylate (**3b**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and ethyl acetoacetate (**2b**) (130 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3b** as a colourless oil in 68% yield (74 mg, 0.34 mmol).

*4.4.3. Isopropyl 2-methyl-4H-chromene-3-carboxylate (**3c**).* According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and isopropyl acetocaetae (**2c**) (147 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3c** as a colourless oil in 70% yield (81 mg, 0.34 mmol): R_f 0.54 (cyclohexane/Et_2O=5:1); IR (ATR) $\tilde{\nu}$ 2987, 1687, 1622, 1567, 1455, 1449, 1217, 1097, 939, 880, 832, 771 cm^{-1}; UV (MeCN) λ_{max} (log ε) 280 (4.12), 232 (3.97) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, ^3J (2″-H, 3″-H or 4″-H)=6.3 Hz, 6H, 3″-H and 4″-H), 2.37 (br s, 3H, 1′-H), 3.58 (s, 2H, 4-H), 5.11 (sept, ^3J (2″-H, 3″-H or 4″-H)=6.3 Hz, 1H, 2″-H), 6.90 (dd, ^3J (7-H, 8-H)=7.9 Hz, ^4J (6-H, 8-H)=1.0 Hz, 1H, 8-H), 7.01 (ddd, ^3J (5-H, 6-H)=7.3 Hz, ^3J (6-H, 7-H)=7.2 Hz, ^4J (6-H, 8-H)=1.0 Hz, 1H, 6-H), 7.09 (br d, ^3J (5-H, 6-H)=7.3, ^4J (5-H, 7-H)=1.5 Hz, 1H, 5H), 7.15 (brddd, ^3J (7-H, 8-H)=7.9 Hz, ^3J (6-H, 7-H)=7.2 Hz, ^4J (5-H, 7-H)=1.5 Hz, 1H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C-1′), 21.9 (C-2″), 22.0 (C-4″), 24.8 (C-4), 67.4 (C-2″), 101.2 (C-3), 115.9 (C-8), 120.6 (C-4a), 123.9 (C-6), 127.4 (C-7), 128.7 (C-5),150.1 (C-8a), 160.2 (C-2), 167.1 (C-1″); MS (EI, 70 eV) *m/z* (%) 232 (3) $[M]^+$, 189 (46) $[M-C_3H_7]^+$, 173 (100) $[M-OC_3H_7]^+$, 135 (10); HRMS (EI) Calculated for $C_{14}H_{16}O_3$ 232.1099, found 232.1089.

*4.4.4. tert-Butyl 2-methyl-4H-chromene-3-carboxylate (**3d**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and *tert*-butyl acetoacetate (**2d**) (158 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3d** as a colourless oil in 76% yield (93 mg, 0.38 mmol).

*4.4.5. Allyl 2-methyl-4H-chromene-3-carboxylate (**3e**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl) benzene (**1a**) (170 mg, 0.5 mmol) and allyl acetoacetate (**2e**) (142 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3e** as a colourless oil in 66% yield (75 mg, 0.32 mmol).

*4.4.6. Benzyl 2-methyl-4H-chromene-3-carboxylate (**3f**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl) benzene (**1a**) (170 mg, 0.5 mmol) and benzyl acetoacetate (**2f**) (198 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3f** as a pale yellow oil in 79% yield (110 mg, 0.39 mmol).

*4.4.7. (2-Methoxyethyl) 2-methyl-4H-chromene-3-carboxylate (**3g**).* According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and 2-methoxyethyl acetoacetate (**2g**) (165 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3g** as a colourless oil in 66% yield (82 mg, 0.33 mmol): R_f 0.42 (cyclohexane/Et_2O=5:1); IR (ATR) $\tilde{\nu}$ 3267, 2948, 1707, 1624, 1570, 1457, 1377, 1289, 1260, 1054, 877, 763 cm^{-1}; UV (MeCN) λ_{max} (log ε) 329 (3.53), 281 (3.95), 231 (3.96) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H, 1′-H), 3.41 (s, 3H, 4″-H), 3.62 (s, 2H, 4-H), 3.65 (t, ^3J (2″-H, 3″-

H)=4.7 Hz, 2H, 3″-H), 4.32 (t, ^3J (2″-H, 3″-H)=4.7 Hz, 2H, 2″-H), 6.88 (dd, ^3J (7-H, 8-H)=8.1 Hz, ^4J (6-H, 8-H)=1.1 Hz, 1H, 8-H), 7.07 (ddd, ^3J (5-H, 6-H)=7.5 Hz, ^3J (6-H, 7-H)=7.2 Hz, ^4J (6-H, 8-H)=1.1 Hz, 1H, 6-H), 7.08 (brd, ^3J (5-H, 6-H)=7.5 Hz, ^4J (5-H, 7-H)=1.5 Hz, 1H, 5-H), 7.13 (brddd, ^3J (7-H, 8-H)=8.1 Hz, ^3J (6-H, 7-H)=7.2 Hz, ^4J (5-H, 7-H)=1.5 Hz, 1H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (C-1″), 24.7 (C-4), 58.9 (C-4″), 63.2 (C-3″), 70.6 (C-2″), 100.6 (C-3), 115.9 (C-8), 120.4 (C-4a), 124.1 (C-6), 127.4 (C-7), 128.7 (C-5), 150.1 (C-8a), 161.1 (C-2), 167.5 (C-1″); MS (EI, 70 eV) *m*/*z* (%) 248 (5) $[M]^+$, 203 (3) $[M-CH_2OCH_3]^+$, 189 (57) $[M-CH_2CH_2OCH_3]^+$, 173 (100), 145 (11), 89 (11), 45 (47); HRMS (EI) Calculated for $C_{14}H_{16}O_4$ 248.1049, found 248.1035.

*4.4.8. Ethyl 2-ethyl-4H-chromene-3-carboxylate (**3h**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl) benzene (**1a**) (170 mg, 0.5 mmol) and 3-oxopentanoate (**2h**) (165 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3h** as a pale yellow solid in 89% yield (103 mg, 0.44 mmol): mp 44–46 °C (lit.[5b] 45–47 °C).

*4.4.9. Ethyl 2-propyl-4H-chromene-3-carboxylate (**3i**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl) benzene (**1a**) (170 mg, 0.5 mmol) and ethyl 3-oxohexanoate (**2i**) (161 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3i** as a pale yellow oil in 59% yield (72 mg, 0.29 mmol).

*4.4.10. Methyl 2-isoropyl-4H-chromene-3-carboxylate (**3j**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and methyl 4-methyl-3-oxopentanoate (**2j**) (144 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3j** as a colourless oil in 82% yield (95 mg, 0.41 mmol).

*4.4.11. Ethyl 2-isopropyl-4H-chromene-3-carboxylate (**3k**).*[5b] According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and ethyl 4-methyl-3-oxopentanoate (**2k**) (158 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (cyclohexane/Et_2O=15:1) gave **3k** as a pale yellow oil in 78% yield (95 mg, 0.39 mmol).

*4.4.12. Methyl 2-methyl-6-fluoro-4H-chromene-3-carboxylate (**3l**).* According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**) (179 mg, 0.5 mmol) and methyl acetoacetate (**2a**) (116 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (petroleum ether/EtOAc=20:1) gave **3l** as a colourless oil in 75% yield (83 mg, 0.37 mmol): R_f 0.41 (petroleum ether/EtOAc=5:1); IR (ATR) $\tilde{\nu}$ 3345, 1717, 1685, 1376, 1212, 1093, 955, 775 cm^{-1}; UV (MeCN) λ_{max} (log ε) 273 (3.93) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (t, ^2J (1′-H, 1′-H)=1.2 Hz, 3H, 1′-H), 3.60 (br s, 2H, 4-H), 3.76 (s, 3H, 2″-H), 6.78 (brdd, ^3J (6-F, 5-H)=8.2 Hz, ^4J (5-H, 7-H)=2.0 Hz, 1H, 5-H), 6.78 (overlapped, 2H, 7-H and 8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2 (C-1′), 25.0 (C-4), 51.4 (C-2″), 99.7 (C-3), 114.2 (d, ^2J (C–F)=23.8 Hz, C-7), 114.7 (d, ^2J (C–F)=23.8 Hz, C-5), 117.2 (d, ^3J (C–F)=8.8 Hz, C-8), 122.0 (d, ^3J (C–F)=7.5 Hz, C-4a), 146.1 (d, ^4J (C–F)=1.9 Hz, C-8a), 157.3 (C-2), 160.7 (d, ^1J (C–F)=28.8 Hz, C-6), 167.8 (C-1″); MS (EI, 70 eV) *m*/*z* (%) 222 (18) $[M]^+$, 207 (100) $[M-CH_3]^+$, 189 (58), 163 (16) $[M-COOCH_3]^+$, 133 (36), 115 (10); HRMS (EI) Calculated for $C_{12}H_{11}FO_3$ 222.0692, found 222.0680.

*4.4.13. Ethyl 2-methyl-6-fluoro-4H-chromene-3-carboxylate (**3m**).* According to general procedure II, a mixture of CuBr (7 mg, 0.05 mmol), K_3PO_4 (424 mg, 2 mmol), 2-bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**) (179 mg, 0.5 mmol) and ethyl acetoacetate (**2b**) (130 mg, 1 mmol) was reacted in dry CH_3CN (2 mL) in a sealed vial at 90 °C for 24 h. Flash chromatography over silica gel (petroleum ether/EtOAc=20:1) gave **3m** as a colourless oil in 68% yield (80 mg, 0.34 mmol): R_f 0.42 (petroleum ether/EtOAc=5:1); IR (ATR) $\tilde{\nu}$ 3267, 2947, 1707, 1409, 1289, 1239, 1084, 1054, 762 cm^{-1}; UV (MeCN) λ_{max} (log ε) 276 (4.66) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, ^3J (2″-H, 3″-H)=7.2 Hz, 3H, 3″-H), 2.36 (t, ^2J (1′-H, 1′-H)=1.2 Hz, 3H, 1′-H), 3.58 (br s, 2H, 4-H), 3.58 (s, 3H, 2″-H), 4.22 (q, ^3J (2″-H, 3″-H)=7.2 Hz, 2H, 2″-H), 6.79 (brdd, ^3J (6-F, 5-H)=8.0 Hz, ^4J (5-H, 7-H)=2.7 Hz, 1H, 5-H), 6.84 (overlapped, 2H, 7-H and 8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C-3″), 19.2 (C-1′), 25.1 (C-4), 60.2 (C-2″), 100.0 (C-3), 114.2 (d, ^2J (C–F)=23.5 Hz, C-7), 114.7 (d, ^2J (C–F)=23.5 Hz, C-5), 117.2 (d, ^3J (C–F)=8.7 Hz, C-8), 122.1 (d, ^3J (C–F)=7.8 Hz, C-4a), 146.2 (d, ^4J (C–F)=2.3 Hz, C-8a), 157.3 (C-2), 160.5 (d, ^1J (C–F)=9.9 Hz, C-6), 167.4 (C-1″); MS (EI, 70 eV) *m*/*z* (%) 236 (8) $[M]^+$, 207 (100) $[M-CH_2CH_3]^+$, 189 (54), 163 (16) $[M-COOCH_2CH_3]^+$, 133 (26), 115 (10); HRMS (EI) Calculated for $C_{13}H_{14}FO_3$ 236.0849, found 236.0835.

4.5. Ethyl 2-acetyl-3-(2-bromophenyl)propionate (4a)[5b]

In an oven dried round-bottomed flask ethyl acetoacetate (**2b**) (520 mg, 4 mmol) was dissolved in dry THF (5 mL) under argon. After cooling to 0 °C, NaH (60%) (80 mg, 2 mmol) was added in several portions within 15 min. The reaction mixture was allowed to warm to room temperature and 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (681 mg, 2 mmol) was added dropwise. After stirring at room temperature for 12 h the reaction mixture was poured into saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash column chromatography over silica gel (petroleum ether/EtOAc=20:1) to afford ethyl 2-acetyl-3-(2-bromophenyl)propionate (**4a**) as a colourless oil in 73% yield (435 mg, 1.4 mmol).

4.6. General procedure III for the Cu(I)-catalyzed synthesis of imidazobenzothiazines 6a–e

An oven-dried 10 mL vial was equipped with a magnetic stir bar and charged with CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), a 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene derivative **1** (0.5 mmol) and a 2-mercaptoimidazole derivative **5** (0.5 mmol) under air. After sealing the vial, dry DMSO (2 mL) was added by syringe and the reaction mixture was stirred at 110 °C (oil bath temperature) for 20 h. After cooling to room temperature, the vial was opened and the reaction mixture was partitioned between CH_2Cl_2 (30 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

*4.6.1. Benzimidazo[1,2-a][3,1]benzothiazine (**6a**).*[6a] According to general procedure III, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), 2-bromo-1-(4-methylbenzenesulfonate methyl)benzene (**1a**) (170 mg, 0.5 mmol) and 2-mercapto-benzimidazole (**5a**) (77 mg, 0.5 mmol) was reacted in dry DMSO (2 mL)

in a sealed vial at 110 °C for 20 h. Flash chromatography over silica gel (petroleum ether/EtOAc=2:1) gave **6a** as a colourless solid in 82% yield (97 mg, 0.40 mmol): mp 118–119 °C (lit. [6a] 112–113 °C).

*4.6.2. 9-Fluorobenzimidazo[1,2-a][3,1]benzothiazine (**6b**).* According to general procedure III, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), 2-bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**) (179 mg, 0.5 mmol) and 2-mercaptobenzimidazole (**5a**) (77 mg, 0.5 mmol) was reacted in dry DMSO (2 mL) in a sealed vial at 110 °C for 20 h. Flash chromatography over silica gel (petroleum ether/EtOAc=2:1) gave **6b** as a colourless solid in 78% yield (99 mg, 0.40 mmol): mp 146–148 °C; R_f 0.32 (petroleum ether/EtOAc=3:1); IR (ATR) $\tilde{\nu}$ 3123, 2984, 1499, 1434, 1319, 1239, 1124, 843, 710, 673 cm^{-1}; UV (MeCN) λ_{max} (log ε) 282 (3.97), 262 (4.57) nm; ^1H NMR (300 MHz, CD_3COCD_3) δ 4.31 (s, 2H, CH_2), 7.28–7.31 (overlapped, 1H, 3-H), 7.32–7.34 (overlapped, 1H, 2-H), 7.35 (overlapped, 1H, 10-H), 7.45 (dd, ^3J (F-9, 8-H)=8.7 Hz, ^4J (8-H, 10-H)=2.7 Hz, 1H, 8-H), 7.62–7.67 (m, 1H, 4-H), 7.89–7.94 (m, 1H, 1-H), 7.99 (dd, ^3J (10-H, 11-H)=8.8 Hz, ^4J (F-9, 8-H)=4.7 Hz, 1H, 11-H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 29.8 (C-7), 112.4 (C-1), 116.0 (d, ^2J (C–F)=23.8 Hz, C-8), 116.1 (d, ^2J (C–F)=22.8 Hz, C-10), 119.9 (d, C-4), 120.7 (d, ^3J (C–F)=8.7 Hz, C-11), 123.8 (C-2), 124.1 (C-3), 129.7 (d, ^3J (C–F)=7.9 Hz, C-7a), 132.7 (d, ^4J (C–F)=2.6 Hz C-11a), 133.5 (C-12a), 144 (C-4a), 150.9 (C-5a), 160.7 (d, ^1J (C–F)=244.0 Hz, C-9); MS (EI, 70 eV) *m/z* (%) 256 (20) $[M]^+$, 198 (12); HRMS (EI) Calculated for $C_{14}H_9FN_2S$ 256.0470, found 256.0475.

*4.6.3. 9-Chlorobenzimidazo[1,2-a][3,1]benzothiazine (**6c**).*[6a] According to general procedure III, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), 2-bromo-5-chloro-1-(4-methylbenzenesulfonatemethyl)benzene (**1e**) (187 mg, 0.5 mmol) and 2-mercaptobenzimidazole (**5a**) (77 mg, 0.5 mmol) was reacted in dry DMSO (2 mL) in a sealed vial at 110 °C for 20 h. Flash chromatography over silica gel (petroleum ether/EtOAc=2:1) gave **6c** as a colourless solid in 81% yield (111 mg, 0.40 mmol): mp 178–179 °C (lit.[6a] 175–177 °C).

*4.6.4. 7-Fluoroimidazo[1,2-a][3,1]benzothiazine (**6d**).* According to general procedure III, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), 2-bromo-5-fluoro-1-(4-methylbenzene sulfonatemethyl)benzene (**1d**) (179 mg, 0.5 mmol) and 2-mercaptoimidazole (**5b**) (51 mg, 0.5 mmol) was reacted in dry DMSO (2 mL) in a sealed vial at 110 °C for 20 h. Flash chromatography over silica gel (petroleum ether/EtOAc=1:1) gave **6d** as a colourless solid in 79% yield (81 mg, 0.39 mmol): mp 98–99 °C; R_f 0.26 (petroleum ether/EtOAc=2:1); IR (ATR) $\tilde{\nu}$ 3123, 2984, 1499, 1434, 1319, 1239, 1124, 843, 710, 673 cm^{-1}; UV (MeCN) λ_{max} (log ε) 278 (3.97), 248 (4.02), 203 (4.56) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 2H, CH_2), 7.04 (brdd, ^3J (F, 6-H)=6.1 Hz, ^4J (6-H, 8-H)=2.7 Hz, 1H, 6-H), 7.10 (brdd, ^3J (F, 8-H)=8.0 Hz, ^3J (8-H, 9-H)=8.0 Hz, ^4J (6-H, 8-H)=2.7 Hz, 1H, 8-H), 7.14 (d, ^3J (1-H, 2-H)=1.5 Hz, 1H, 2-H), 7.24 (brdd, ^3J (8-H, 9-H)=8.0 Hz, ^4J (F, 9-H)=4.7 Hz, 1H, 9-H), 7.45 (d, ^3J (1-H, 2-H)=1.5 Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7 (C-5), 115.2 (d, ^2J (C–F)=23.5 Hz, C-6), 115.6 (d, ^2J (C–F)=23.0 Hz, C-8), 116.0 (C-1), 119.3 (d, ^3J (C–F)=8.5 Hz, C-9), 126.2 (d, ^3J (C–F)=7.7 Hz, C-5a), 129.8 (C-2), 131.29 (d, ^4J (C–F)=3.0 Hz, C-9a), 140.1 (C-3a), 160.1 (d, ^1J (C–F)=248.2 Hz, C-7); MS (EI, 70 eV) *m/z* (%) 206 (100) $[M]^+$, 148 (64); HRMS (EI) Calculated for $C_{10}H_7FN_2S$ 206.0314, found 206.0305.

*4.6.5. 7-Chloroimidazo[1,2-a][3,1]benzothiazine (**6e**).*[6a] According to general procedure III, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), 2-bromo-5-chloro-1-(4-methylbenzene sulfonatemethyl)benzene (**1e**) (187 mg, 0.5 mmol) and 2-mercaptoimidazole (**5b**) (51 mg, 0.5 mmol) was reacted in dry DMSO (2 mL) in a sealed vial at 110 °C for 20 h. Flash chromatography over silica gel (petroleum ether/EtOAc=1:1) gave **6e** as a colourless solid in 73% yield (80 mg, 0.36 mmol): mp 114–115 °C (lit.[6a] 108–110 °C).

4.7. 2-(2-Bromobenzylsulfonyl)-1*H*-benzimidazole (7)[42]

A mixture of K_3PO_4 (318 mg, 1.5 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (179 mg, 0.5 mmol) and 2-mercaptobenzimidazole (**5a**) (77 mg, 0.5 mmol) was reacted in dry DMSO (2 mL) in a sealed vial at 110 °C for 20 h. Flash chromatography over silica gel (petroleum ether/EtOAc=4:1) gave **7** as a colourless solid in 62% yield (99 mg, 0.31 mmol): mp 185–186 °C (lit.[42] 195–198 °C).

4.8. General procedure IV for the copper-catalyzed synthesis of quinazolines 9a–f

An oven-dried 10 mL vial was equipped with a magnetic stir bar and charged with CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), a 2-bromo-1-(4-methylbenzene sulfonatemethyl)benzene derivative **1** (0.5 mmol) and an amidinium salt **8** (0.5 mmol) under air. After sealing the vial, dry 1,2-dichlorobenzene (3 mL) was added by syringe and the reaction mixture was stirred at 110 °C (oil bath temperature) for 18 h. After cooling to room temperature, the vial was opened and the reaction mixture was partitioned between CH_2Cl_2 (30 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

*4.8.1. 2-Phenylquinazoline (**9a**).*[36a] According to general procedure IV, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), 2-bromo-1-(4-methylbenzene sulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and benzamidine hydrochloride (**8a**) (78 mg, 0.5 mmol) was reacted in dry 1,2-dichlorobenzene (3 mL) in a sealed vial at 110 °C for 18 h. Flash chromatography over silica gel (petroleum ether/EtOAc=10:1) gave **9a** as a colourless solid in 63% yield (64 mg, 0.31 mmol): mp 100–102 °C (lit.[36a] 101–103 °C).

*4.8.2. 2-(4-Chlorophenyl)quinazoline (**9b**).*[36a] According to general procedure IV, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and 4-chlorobenzamidine hydrochloride (**8b**) (147 mg, 0.5 mmol) was reacted in dry 1,2-dichlorobenzene (3 mL) in a sealed vial at 110 °C for 18 h. Flash chromatography over silica gel (petroleum ether/EtOAc=10:1) gave **9b** as a colourless solid in 79% yield (95 mg, 0.39 mmol): mp 137–138 °C (lit.[36a] 139–141 °C).

*4.8.3. 2-(3-Methylphenyl)quinazoline (**9c**).*[33b] According to general procedure IV, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), 2-bromo-1-(4-methylbenzenesulfonatemethyl)benzene (**1a**) (170 mg, 0.5 mmol) and 3-methylbenzamidine hydrochloride (**8c**) (90 mg, 0.5 mmol) was reacted in dry 1,2-dichlorobenzene (3 mL) in a sealed vial at 110 °C for 18 h. Flash chromatography over silica gel (petroleum ether/EtOAc=10:1) gave **9c** as a colourless solid in 58% yield (63 mg, 0.28 mmol): mp 101–102 °C.

*4.8.4. 6-Fluoro-2-phenylquinazoline (**9d**).*[36a] According to general procedure IV, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), 2-bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**) (101 mg, 0.5 mmol) and benzamidine hydrochloride (**8a**) (78 mg, 0.5 mmol) was

Please cite this article in press as: Omar, M. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.071

reacted in dry 1,2-dichlorobenzene (3 mL) in a sealed vial at 110 °C for 18 h. Flash chromatography over silica gel (petroleum ether/EtOAc=10:1) gave **9d** as a colourless solid in 51% yield (57 mg, 0.25 mmol): mp 149–150 °C (lit.[36a] 150–151 °C).

*4.8.5. 6-Fluoro-2-(4-chlorophenyl)quinazoline (**9e**).*[36a] According to general procedure IV, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), 2-bromo-5-fluoro-1-(4-methylbenzenesulfonatemethyl)benzene (**1d**) (179 mg, 0.5 mmol) and 4-chlorobenzamidine hydrochloride (**8b**) (147 mg, 0.5 mmol) was reacted in dry 1,2-dichlorobenzene (3 mL) in a sealed vial at 110 °C for 18 h. Flash chromatography over silica gel (petroleum ether/EtOAc=10:1) gave **9e** as a colourless solid in 69% yield (89 mg, 0.34 mmol): mp 182–183 °C (lit.[36a] 185–187 °C).

*4.8.6. 6-Chloro-2-phenylquinazoline (**9f**).*[35d] According to general procedure IV, a mixture of CuI (9 mg, 0.05 mmol), K_3PO_4 (318 mg, 1.5 mmol), pivalic acid (20 mg, 0.2 mmol), 2-bromo-5-chloro-1-(4-methylbenzenesulfonatemethyl)benzene (**1e**) (187 mg, 0.5 mmol) and benzamidine hydrochloride (**8a**) (78 mg, 0.5 mmol) was reacted in dry 1,2-dichlorobenzene (3 mL) in a sealed vial at 110 °C for 18 h. Flash chromatography over silica gel (petroleum ether/EtOAc=10:1) gave **9f** as a colourless solid in 53% yield (63 mg, 0.26 mmol): mp 159–160 °C (lit.[35d] 157–159 °C).

Acknowledgements

We thank Ms. S. Mika and Mr. M. Wolf for recording of NMR spectra and Dr. A. Baskakova for recording of mass spectra. M.A.O. is grateful to Deutscher Akademischer Austauschdienst (DAAD) for financial support.

Supplementary data

Analytical and spectroscopic data of selected known compounds; ^1H NMR and ^{13}C NMR spectra of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.071.

References and notes

1. (a) Lui, Y.; Wan, J.-P. *Chem.—Asian J.* **2012**, *7*, 1488; (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954; (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054; (d) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450; (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5400.
2. Beletskaya, I. P.; Chepravov, A. V. *Organometallics* **2012**, *31*, 7753.
3. Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley VCH: Weinheim, Germany, 2006.
4. (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084; (b) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805; (c) Liu, Y.; Wan, J.-P. *Org. Biomol. Chem.* **2011**, *9*, 6873; (d) Sadig, J. E. R.; Willis, M. C. *Synthesis* **2011**, 1.
5. (a) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. *Chem.—Eur. J.* **2012**, *18*, 8882; (b) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *132*, 1971.
6. (a) Wang, R.; Qian, W.; Bao, W. *Tetrahedron Lett.* **2012**, *53*, 442; (b) Zhang, X. Y.; Fang, L. L.; Liu, N.; Wu, H. Y.; Fan, X. S. *Chin. Chem. Lett.* **2012**, *23*, 1129; (c) Maity, A.; Mondal, S.; Paira, R.; Hazra, A.; Naskar, S.; Sahu, K. B.; Saha, P.; Banerjee, S.; Mondal, N. B. *Tetrahedron Lett.* **2011**, *52*, 3033.
7. (a) Yoshimi, Y.; Maeda, H.; Hatanaka, M.; Mizuno, K. *Tetrahedron* **2004**, *60*, 9425; (b) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762.
8. (a) Yeung, K.; Schmid, K. M.; Phillips, S. T. *Chem. Commun.* **2013**, 394; (b) Joseph, K. M.; Larraza-Sanchez, I. *Tetrahedron Lett.* **2011**, *52*, 13.
9. (a) Lewis, R. J.; *Sax's Dangerous Properties of Industrial Materials*, 9th ed.; Van Nostrand Reinhold: New York, NY, 1996, Vols. 1–3; p 373; (b) Prager, J. C. *Environmental Contaminant Reference Databook* Vol. 2; Van Nostrand Reinhold: New York, NY, 1996, Vol. 2; p 1021.
10. (a) Dakas, P.-Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Wissinger, N. *Chem.—Eur. J.* **2009**, *15*, 11490; (b) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586; (c) Cox, M.; Wirth, T. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 659; (d) Duffault, J.-M.; Tellier, F. *Synth. Commun.* **1998**, *28*, 2467; (e) Mease, A. D.; Strauss, M. J.; Horman, I.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1968**, *90*, 1797.
11. For reviews, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939; (b) Keay, B. A.; Dibble, P. W. Furans and Their Benzo Derivatives: Applications In *Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds. Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, UK, 1996; Vol. 2, p 395.
12. (a) Patil, S. A.; Wang, J.; Li, X. S.; Chen, J.; Jones, T. S.; Hosni-Ahmed, A.; Patil, R.; Seibel, W. L.; Li, W.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4458; (b) Khoshneviszadeh, M.; Edraki, N.; Miri, R.; Foroumadi, A.; Hemmateenejad, B. *Chem. Biol. Drug Des.* **2012**, *79*, 442; (c) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Crogan-Grundy, C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2008**, *51*, 417; (d) Kidawai, M.; Saxena, S.; Khan, K. R.; Thukral, S. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4295; (e) Wang, J.-L.; Liu, D.; Zhang, Z.-J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. *PNAS* **2000**, *97*, 7124.
13. Salni, D.; Sargent, M. V.; Skelton, B. W.; Soediro, I.; Sutisna, M.; White, A. H.; Yulinah, E. *Aust. J. Chem.* **2002**, *55*, 229.
14. Shaheen, F.; Ahmad, M.; Khan, S. N.; Hussain, S. S.; Anjum, S.; Tashkhodjaev, B.; Turgunov, K.; Sultankhodzhaev, M. N.; Choudhary, M. I.; Rahman, A.-U. *Eur. J. Org. Chem.* **2006**, 2371.
15. Tian, D.; Das, S. G.; Doshi, J. M.; Peng, J.; Lin, J.; Xing, C. *Cancer Lett.* **2008**, *259*, 198.
16. (a) Wang, F.; Qu, M.; Chen, F.; Li, L.; Shi, M. *Chem. Commun.* **2012**, 437; (b) Dong, Z.; Liu, X.; Feng, J.; Wang, M.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* **2011**, 137; (c) Bunce, R. A.; Rogers, D.; Nago, T.; Bryant, S. *J. Heterocycl. Chem.* **2008**, *45*, 547; (d) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427; (e) Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. *Org. Lett.* **2006**, *8*, 3853.
17. Raddatz, S.; Bartel, S.; Guarnieri, W.; Rosentreter, U.; Ruppelt, M.; Wild, H.; Endermann, R.; Kroll, H.-P. WO Patent 9940094 A1, 1999; *Chem. Abstr.* **1999**, *131*, 144608.
18. Ichijima, Y.; Ono, M.; Sasaki, N. JP Patent 60233649 A, 1985; *Chem. Abstr.* **1985**, *104*, 196909.
19. Gauthier, J.; Duceppe, J. S. *J. Heterocycl. Chem.* **1984**, *21*, 1081.
20. Dolbier, W. R.; Burkholder, C.; Abboud, K. A.; Loehle, D. *J. Org. Chem.* **1994**, *59*, 7688.
21. For reviews, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166; (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787; (c) D'yakonov, A. L.; Telezhenetskaya, M. V. *Chem. Nat. Compd.* **1997**, *33*, 221.
22. (a) Lin, Z.-Y.; Chuang, W.-L. *Biomed. Pharmacother.* **2012**, *66*, 583; (b) da Silva, J. F. M.; Walters, M.; Al-Damluji, S.; Ganellin, C. R. *Bioorg. Med. Chem.* **2008**, *16*, 7254; (c) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49.
23. (a) Lange, F.; Rateitschak, K.; Kossow, C.; Wolkenhauer, O.; Jaster, R. *World J. Gastroenterol.* **2012**, *18*, 6226; (b) Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2008**, *51*, 3367; (c) Pao, W.; Miller, V.; Zakowski, M.; Doherty, J.; Politi, K.; Sarkaria, I.; Singh, B.; Heelan, R.; Rusch, V.; Fulton, L.; Mardis, E.; Kupfer, D.; Wilson, R.; Kris, M.; Varmus, H. *PNAS* **2004**, *101*, 13306.
24. (a) Mitsudomi, T.; Morita, S.; Yatabe, Y.; Negoro, S.; Okamoto, I.; Tsurutani, J.; Seto, T.; Satouchi, M.; Tada, H.; Hirashima, T.; Asami, K.; Katakami, N.; Takada, M.; Yoshioka, H.; Shibata, K.; Kudoh, S.; Shimizu, E.; Saito, H.; Toyooka, S.; Nakagawa, K.; Fukuoka, M. *Lancet Oncol.* **2010**, *11*, 121; (b) Mok, T. S.; Wu, Y.-L.; Thongprasert, S.; Yang, C.-H.; Chu, D.-T.; Saijo, N.; Sunpaweravong, P.; Han, B.; Margono, B.; Ichinose, Y.; Nishiwaki, Y.; Ohe, Y.; Yang, J.-J.; Chewaskulyong, B.; Jiang, H.; Duffield, E. L.; Watkins, C. L.; Armour, A. A.; Fukuoka, M. *N. Engl. J. Med.* **2009**, *361*, 947; (c) Azzoli, C. G.; Baker, S., Jr.; Temin, S.; Pao, W.; Aliff, T.; Brahmer, J.; Johnson, D. H.; Laskin, J. L.; Masters, G.; Milton, D.; Nordquist, L.; Pfister, D. G.; Piantadosi, S.; Schiller, J. H.; Smith, R.; Smith, T. J.; Strawn, J. R.; Trent, D.; Giaccone, G. *J. Clin. Oncol.* **2009**, *27*, 6251.
25. (a) Cameron, D.; Casey, M.; Press, M.; Linquist, D.; Pienkowski, T.; Romieu, C. , G.; Chan, S.; Jagiello-Gruszfeld, A.; Kaufman, B.; Crown, J.; Chan, A.; Campone, M.; Viens, P.; Davidson, N.; Gorbounova, V.; Raats, J. I.; Skarlos, D.; Newstat, B.; Roychowdhury, D.; Paoletti, P.; Oliva, C.; Rubin, S.; Stein, S.; Geyer, C. E. *Breast Cancer Res. Treat.* **2008**, *112*, 533; (b) Nelson, M. H.; Dolder, C. R. *Ann. Pharmacother.* **2006**, *40*, 261; (c) Burris, H. A., III. *Oncologist* **2004**, *9*, 10.
26. (a) Short, C.-E. S.; Gilleece, Y. C.; Fisher, M. J.; Churchill, D. R. *AIDS* **2009**, *23*, 1287; (b) Queener, S. F.; Bartlett, M. S.; Jay, M. A.; Durkin, M. M.; Smith, J. W. *Antimicrob. Agents Chemother.* **1987**, *31*, 1323; (c) Allegra, C. J.; Kovacs, J. A.; Drake, J. C.; Swan, J. C.; Chabner, B. A.; Masur, H. *J. Exp. Med.* **1987**, *165*, 926.
27. (a) Chien, T.-C.; Chen, C.-S.; Yu, F.-H.; Chern, J.-W. *Chem. Pharm. Bull.* **2004**, *52*, 1422; (b) Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M. *Antimicrob. Agents Chemother.* **2004**, *48*, 4154.
28. (a) Rohini, R.; Shanker, K.; Reddy, P. M.; Ravinder, V. *J. Braz. Chem. Soc.* **2010**, *21*, 49; (b) Rohini, R.; Shanker, K.; Reddy, P. M.; Ho, Y.-P.; Ravinder, V. *Eur. J. Med. Chem.* **2009**, *44*, 3330; (c) Bedi, P. M. S.; Kumar, V.; Mahajan, M. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5211.
29. (a) Madapa, S.; Tusi, Z.; Mishra, A.; Srivastava, K.; Pandey, S. K.; Tripathi, R.; Puri, S. K.; Batra, S. *Bioorg. Med. Chem.* **2009**, *17*, 222; (b) Guan, J.; Zhang, Q.; O'Neil, M.; Obaldia, N., III; Ager, A.; Gerena, L.; Lin, A. J. *Antimicrob. Agents Chemother.* **2005**, *49*, 4928; (c) Ashton, W. T.; Hynes, J. B. *J. Med. Chem.* **1973**, *16*, 1233.
30. (a) Noolvi, M. N.; Patel, H. M.; Bhardwaj, V.; Chauhan, A. *Eur. J. Med. Chem.* **2011**, *46*, 2327; (b) El-Azab, A. S.; Al-Omar, M. A.; Abdel-Aziz, A. A.-M.; Abdel-Aziz, N. I.; El-Sayed, M. A.-A.; Aleisa, A. M.; Sayed-Ahmed, M. M.; Abdel-Hamide, S. G. *Eur. J. Med. Chem.* **2010**, *45*, 4188; (c) Sirisoma, N.; Pervin, A.; Zhang, H.; Jiang, S.; Willardsen, J. A.; Anderson, M. B.; Mather, G.; Pleiman, C. M.; Kasibhatla, S.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2009**, *52*, 2341; (d) Foster, B. A.; Coffey, H. A.; Morin, M. J.; Rastinejad, F. *Science* **1999**, *286*, 2507.

31. (a) Srivastav, M. K.; Shantakumar, S. M. *Chem. Sci. Trans.* **2013**, *2*, 1056; (b) Kuneš, J.; Bažant, J.; Pour, M.; Waisser, K.; Šlosárek, M.; Janota, J. *Il Farm.* **2000**, *55*, 725.
32. For reviews, see: (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153; (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491; (c) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849; (d) Undheim, K.; Benneche, T. Pyrimidines and Their Benzo Derivatives In *Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds. Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, UK, 1996; Vol. 6, pp 93–231; (e) Brown, D. J. Fused Pyrimidines, Part 1: Quinazolines In *Armarego, W. L. F., Ed. Chemistry of Heterocyclic Compounds*; John Wiley & Sons: Sydney, Australia, 1967; Vol. 24, pp 11–38.
33. (a) Vypolzov, A. V.; Dar'in, D. V.; Ryazanov, S. G.; Lobanov, P. S. *Chem. Heterocycl. Compd.* **2011**, *46*, 1481; (b) Truong, V. L.; Morrow, M. *Tetrahedron Lett.* **2010**, *51*, 758.
34. (a) Ju, J.; Hua, R.; Su, J. *Tetrahedron* **2012**, *68*, 9364; (b) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, 6333.
35. (a) Zhang, Z.-H.; Zhang, X.-N.; Mo, L.-P.; Li, Y.-X.; Ma, F.-P. *Green Chem.* **2012**, *14*, 1502; (b) Han, B.; Wang, C.; Han, R.-F.; Yu, W.; Duan, X.-Y.; Fang, R.; Yang, X.-L. *Chem. Commun.* **2011**, 7818; (c) Zhang, J.; Zhu, D.; Yu, C.; Wan, C.; Wang, Z. *Org. Lett.* **2010**, *12*, 2841; (d) Zhang, J.; Yu, C.; Wang, S.; Wan, C.; Wang, Z. *Chem. Commun.* **2010**, 5244; (e) Ferrini, S.; Ponticelli, F.; Taddei, M. *Org. Lett.* **2007**, *9*, 69.
36. (a) Omar, M. A.; Conrad, J.; Beifuss, U. *Tetrahedron* **2014**, *70*, 3061; (b) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936.
37. Chen, Z.; Chen, J.; Liu, M.; Ding, J.; Gao, W.; Huang, X.; Wu, H. *J. Org. Chem.* **2013**, *78*, 11342.
38. Sheldrake, H. M.; Wallace, T. W. *Tetrahedron Lett.* **2007**, *48*, 4407.
39. For a review on transition metal-catalyzed N-arylations of amidines and guanidines, see: Rauws, T. R. M.; Maes, B. U. W. *Chem. Soc. Rev.* **2012**, *41*, 2463.
40. (a) Elyashberg, M.; Blinov, K.; Smurnyy, Y.; Churanova, T.; Williams, A. *Magn. Reson. Chem.* **2010**, *48*, 219; (b) Blinov, K. A.; Smurnyy, Y. D.; Churanova, T. S.; Elyashberg, M. E.; Williams, A. J. *Chemom. Intell. Lab. Syst.* **2009**, *97*, 91; (c) Thomas, S.; Brühl, I.; Heilmann, D.; Kleinpeter, E. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 726; (d) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03 (Revision E.01)*; Gaussian: Wallingford, CT, 2004; (e) Sarotti, A. M.; Pellegrinet, S. C. *J. Org. Chem.* **2009**, *74*, 7254.
41. Chem3D Pro, Version 12; Cambridge Soft: Cambridge, MA, 2009.
42. Kumar, R. V.; Gopal, K. R.; Kumar, K. V. S. R. S. *J. Heterocycl. Chem.* **2005**, *7*, 1405.

Please cite this article in press as: Omar, M. A.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.06.071