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Cu(I)-Catalyzed Domino Reactions: Efficient and Selective Synthesis of 4*H*-Chromenes and Naphthalenes

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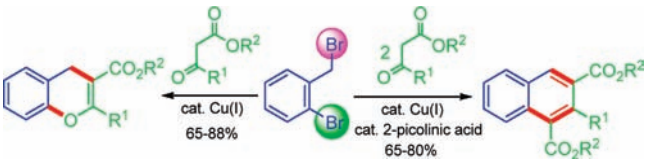
ABSTRACT



Depending on the ratio of the substrates and the reaction conditions, the Cu(I)-catalyzed domino reaction between bromobenzyl bromides and β-ketoesters exclusively yields either 4*H*-chromenes or naphthalenes.

Over the past years remarkable progress has been achieved in the field of Cu(I)-catalyzed C-, N-, O-, and S-arylations.[1] In contrast, few examples of the combination of such arylations with other transformations into new domino processes have been developed.[1,2] Predictably, these domino processes will be more and more important for the synthesis of carbocycles and heterocycles. Most known examples are related to the synthesis of *N*-heterocycles such as indoles,[3] isoindoles,[4] benzimidazoles,[5] and isoquinolines.[6] In addition, benzofurans,[7] benzothiazoles,[8] benzoxazoles,[9] and phenothiazines[10] can also be obtained using this strategy.

Here we report on two new and efficient Cu(I)-catalyzed domino reactions between readily available and inexpensive 2-bromobenzyl bromides and β-ketoesters. Depending on the ratio of the substrates and the reaction conditions employed, either 4*H*-chromenes or naphthalenes are formed exclusively.

Due to their diverse biological activities, chromenes have attracted considerable attention.[11] Some prominent examples of biologically active 4*H*-chromenes are the antibiotic rhodomyrtone,[12a] the α-glucosidase inhibitor myrtucommolone-E,[12b] and the apoptosis inducing agent sHA 14-1.[12c]

(1) Reviews: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. Some examples: (e) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540. (f) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660. (g) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.

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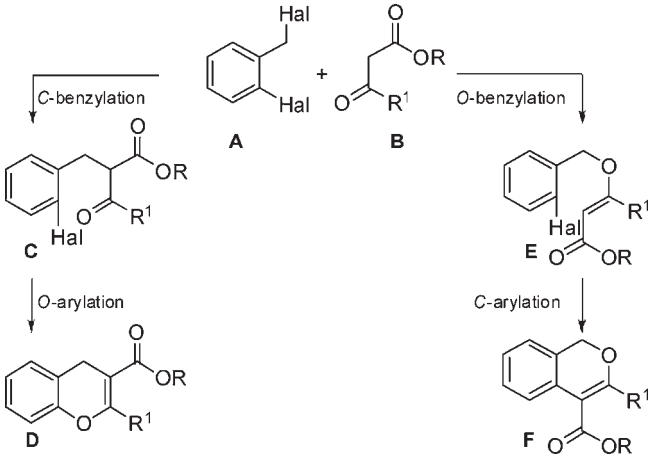
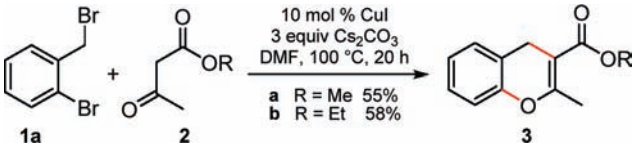
Considering the selective synthesis of 4*H*-chromenes **D** we assumed that a domino *C*-benzylation/*O*-arylation between a 2-halobenzyl halide **A** and a 1,3-dicarbonyl **B** could serve this purpose (Scheme 1). However, a domino *O*-benzylation/*C*-arylation with formation of 2*H*-chromenes **F** seemed to be possible, too.

Scheme 1. Possible Domino Processes upon Reaction of a 2-Halobenzyl Halide **A** and a 1,3-Dicarbonyl **B**



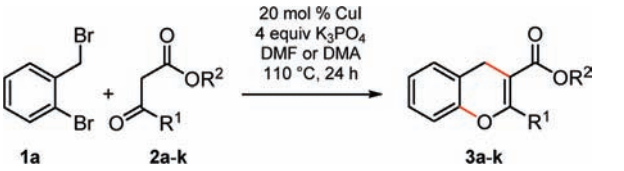
This is why it was a great pleasure when the reactions of 1 equiv 2-bromobenzyl bromide (**1a**) with 1 equiv of the *β*-keto esters **2a,b** in the presence of 10 mol % CuI and with 3 equiv of Cs_2CO_3 exclusively yielded the corresponding 4*H*-chromenes **3a** and **3b** in 55% and 58% yield, respectively (Scheme 2).[13] Not even traces of the corresponding 2*H*-chromenes were isolated. It seems that the *C*-benzylation/*O*-arylation is more favorable than the *O*-benzylation/*C*-arylation. It should be emphasized that the formation of 4*H*-chromenes **3** not only is highly selective but also can be performed under ligand-free conditions which are typical of many other Cu(I)-catalyzed transformations.[1]

Scheme 2. Initial Experiments for the Cu(I)-Catalyzed Synthesis of 4*H*-Chromenes



Optimizing the reaction conditions with regard to Cu source, base, additive, solvent, reaction temperature, and time revealed that the highest yield of **3b** was obtained when 1 equiv of **1a** and 2 equiv of **2b** were reacted with 20 mol % CuI and 4 equiv of K_3PO_4 in DMF or DMA at 110 °C for 24 h.[13] Control experiments verified that the reaction does not proceed in the absence of a Cu source. With optimized reaction conditions at hand it was demonstrated that **1a** could be reacted with numerous *β*-ketoesters **2** in DMF or DMA to produce the corresponding 4*H*-chromenes **3a**−**k** with yields ranging from 65% to 88% (Table 1). In no case did we observe the formation of a 2*H*-chromene.

Table 1. Cu(I)-Catalyzed Synthesis of 4*H*-Chromenes[a]



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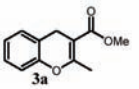
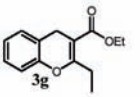
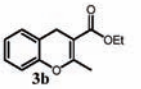
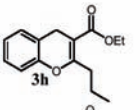
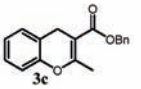
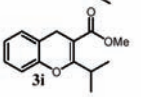
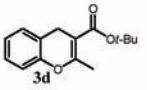
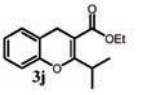
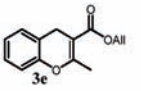
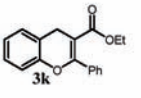
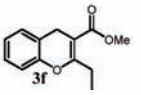
1		73/72	7		88/88
2		76/76	8		84/85
3		72/74	9		85/84
4		75/76	10		80/79
5		65/ –	11		79/81
6		78/83			

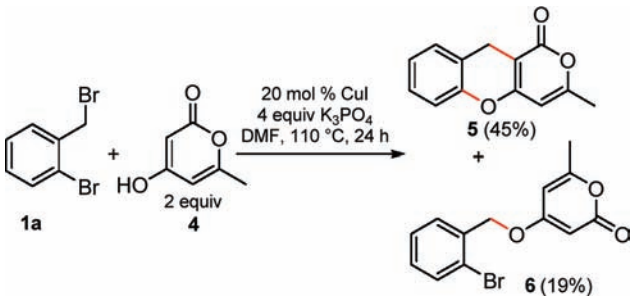
[a] All reactions were performed using 1 mmol of **1** and 2 mmol of **2** in a sealed vial.

Also, the 4-hydroxy-6-methyl-pyrone (**4**) was reacted with **1a** to afford the expected cyclization product **5** in 45% yield along with the benzyl ether **6** in 19% yield (Scheme 3). So far this has been the only example of the additional formation of an *O*-benzylated product.

Our experiments have clearly established that 4*H*-chromenes **3** and related skeletons can be synthesized in a highly efficient and selective one-pot process by reacting 2-bromobenzyl bromide (**1a**) and a *β*-ketoester **2**. Therefore, the new domino process is a valuable alternative to the intramolecular *O*-arylation of α-(2-bromobenzyl)-*β*-ketoesters of type **C** since it does not require the separate synthesis and isolation of the α-(2-bromobenzyl)-*β*-ketoesters.[14a] It is also a valuable supplement to the Fe(III)-catalyzed reaction between 2-(hydroxymethyl)

(13) For details see Supporting Information.
(14) (a) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427–6431. (b) Fan, J.; Wang, Z. *Chem. Commun.* **2008**, 5381–5383. (c) Bunce, R. A.; Rogers, D.; Nago, T.; Bryant, S. A. *J. Heterocycl. Chem.* **2008**, *45*, 547–550.

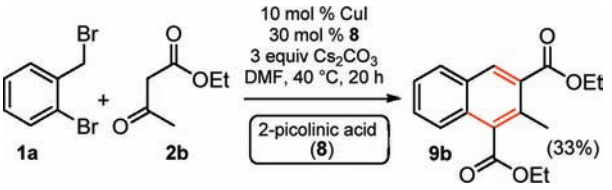
Scheme 3. Cu(I)-Catalyzed Reaction of Pyrone **4**



phenols and β-ketoesters[14b] and the synthesis of 4*H*-chromenes by a domino S_N2/S_NAr reaction.[14c]

After having successfully developed the domino *C*-benzylation/*O*-arylation, the question was whether the intramolecular *O*-arylation of **C** to **D** (Scheme 1) could be suppressed in favor of an intermolecular *C*-arylation of **C** with a second equivalent of a β-keto ester. To this purpose 1 equiv of 2-bromobenzyl bromide (**1a**) was reacted with 2 equiv of ethyl acetoacetate (**2b**) in the presence of 2-picolinic acid (**8**), an additive which has recently proven to be highly efficient for promoting the *C*-arylation of malonates with aryl iodides.[15] And indeed, 33% of the naphthalene **9b**, which can be regarded as a product resulting from a *C*-benzylation/*C*-arylation process, were isolated (Scheme 4). Under these conditions the corresponding 4*H*-chromene **3b** was formed in traces only.

Scheme 4. Cu(I)-Catalyzed Synthesis of Naphthalene **9b**[a]

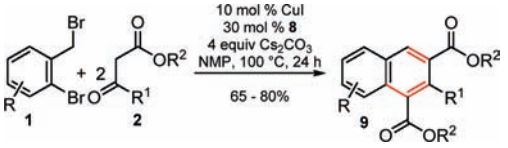


[a] In addition, traces of **3b** were observed.

We decided to study this transformation in more detail as it represents not only a new domino reaction but also a new method for the synthesis of polysubstituted naphthalenes.[16] Naphthalenes are important building blocks in organic synthesis; they occur in natural products and other bioactive products and play a significant role in the field of material sciences. Thus, the development of new and efficient synthetic approaches to polysubstituted naphthalenes is of general interest.[17] Optimizing the reaction conditions with regard to Cu source, base, additive, solvent, reaction temperature, and time[13] revealed that naphthalene **9b** could be isolated in 68% yield when 1 equiv of **1a** was reacted with 3 equiv of **2b** in the presence of 10 mol % of CuI, 30 mol % of 2-picolinic acid (**8**), and 4 equiv of Cs_2CO_3 in *N*-methyl pyrrolidine at 100 °C for 24 h. In the absence of CuI the naphthalene **9b** did not form.

The scope of the three-component reaction was then studied. It was found that numerous substituted

Table 2. Cu(I)-Catalyzed Synthesis of Naphthalenes **9**[a]



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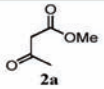
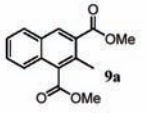
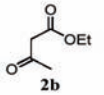
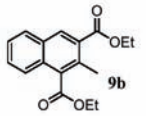
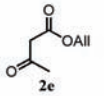
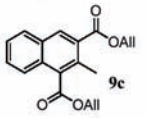
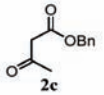
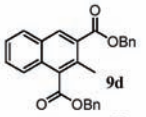
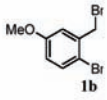
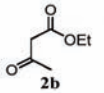
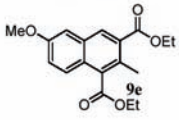
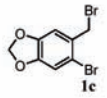
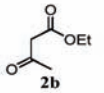
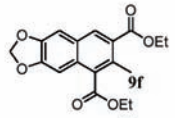
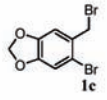
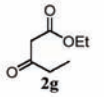
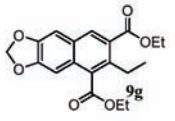
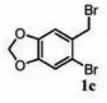
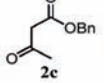
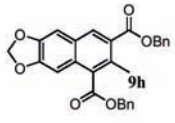
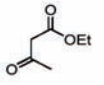
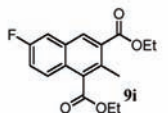
1				65
2				68
3				69
4				65
5				76
6				70
7				73
8				80
9				68

[a] All reactions were performed using 0.5 mmol of **1** and 1.5 mmol of **2**.

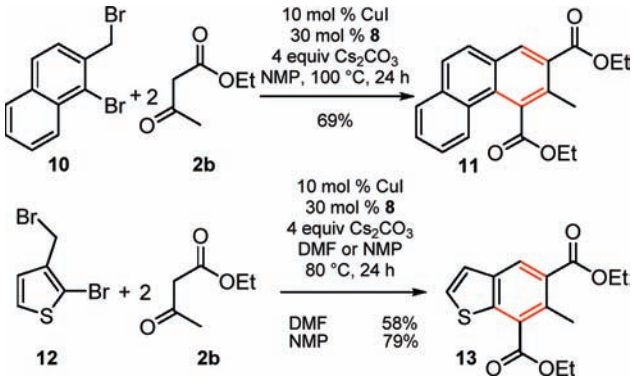
(15) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469–3472.

(16) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7–36.

(17) Mason, R. T.; Talukder, M.; Kates, C. R. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Kirk, R. E., Ed.; Wiley: New York, 1995; p 963.

2-bromobenzyl bromides **1** can be successfully reacted with a range of β-keto esters **2** (Table 2). It was also established that the annulation is not restricted to the synthesis of naphthalenes **9** but also allows for the synthesis of polycyclic aromatic hydrocarbons and heteroaromatics (Scheme 5).

Scheme 5. Cu(I)-Catalyzed Synthesis of Phenanthrene **11** and Benzo[*b*]thiophene **13**

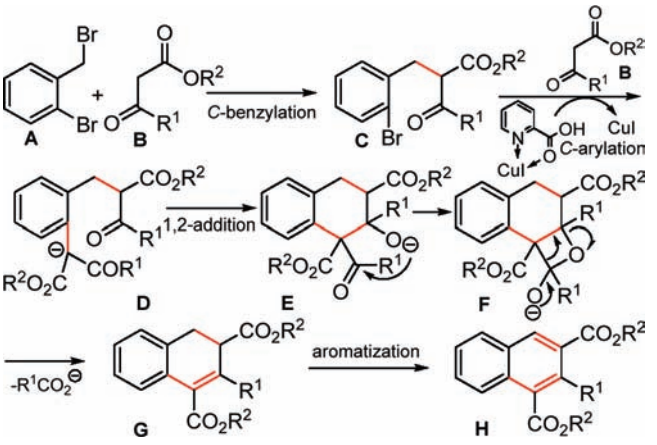


We assume that the annulation of aromatics starts with the intermolecular *C*-benzylation of a β-keto ester (**A** + **B** → **C**) (Scheme 6). After intermolecular *C*-arylation of a second β-keto ester moiety (**C** + **B** → **D**) an intramolecular 1,2-addition takes place (**D** → **E**). The final steps of the sequence including the cleavage of a carboxylic acid (**E** → **F** → **G**) and aromatization lead to the desired product (**G** → **H**).

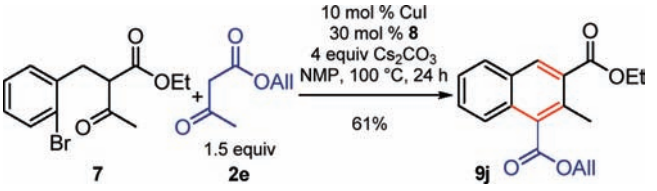
In accordance with this mechanistic proposal it was anticipated that the method would allow for the synthesis of naphthalenes with two different ester functionalities when an α-(2-halobenzyl)-β-ketoester **C** is reacted with a β-keto ester **B** carrying a different alcohol component. Thus, it was no surprise when the trisubstituted naphthalene **9j** with two different ester functionalities was formed upon reaction of **7** and **2e** (Scheme 7).

To conclude, two new, easy-to-perform, and efficient Cu(I)-catalyzed domino processes using readily available and cheap substrates are presented. Depending on the ratio of the substrates and the reaction conditions, the

Scheme 6. Possible Reaction Mechanism



Scheme 7. Differentiation of the Ester Functionalities[a]



[a] In addition, 5% of **3b** were isolated.

Cu(I)-catalyzed domino reaction between bromobenzyl bromides and β-ketoesters exclusively yields either 4*H*-chromenes or naphthalenes.

Acknowledgment. We thank S. Mika for NMR spectra and Dr. H. Leutbecher, Dipl.-Chem. H.-G. Imrich, Dipl. -Chem. C. Asta, and Dr. T. Tolasch (all affiliated with the University of Hohenheim) for mass spectra.

Supporting Information Available. Experimental details and spectra of all new compounds are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.