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Copper-Catalyzed Domino S_N2'/Coupling Reaction: A Versatile and Facile Synthesis of Cyclic Compounds from Baylis–Hillman Acetates

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Abstract: A variety of substituted quinoline/pyridine, thiochromene and naphthalene derivatives, which might be of biological and medicinal value, were synthesized by copper-catalyzed domino S_N2'/coupling, S_N2'/deacylation/coupling and S_N2'/coupling/elimination reactions. The method provides a general and convenient approach to the synthesis of various substituted cyclic compounds from the corresponding Baylis–Hillman (B-H) acetates and N-/S-/C-nucleophiles.

Keywords: copper; cross-coupling; cyclization; domino reactions; nucleophilic substitution

Introduction

Substituted quinoline,[1] pyridine,[2] thiochromene,[3] and naphthalene derivatives[4] exist in many useful natural products, synthetic drugs, agrochemicals and functional materials. The traditional approaches to these molecules may have some limitations with respect to the tedious procedures, harsh conditions, low selectivity and the limited scopes.[1d,2b,3a,4f] In contrast with the traditional stepwise methods, the domino reactions can conveniently and directly assemble complex molecules from simple starting materials.

In the last decade, copper-mediated coupling reactions have achieved remarkable progress.[5] And recently, Cu-mediated domino reactions with coupling as the key step have emerged as attractive approaches to structurally diversified molecules due to their low cost, convenience and efficiency.[6] Notably, although numerous Cu-catalyzed domino protocols for the assembly of cyclic compounds have been developed, most reports focused on the construction of one or two cyclic systems. And only a few examples have been reported to demonstrate that the versatility of the same Cu-catalyzed domino protocols can be applied for constructing three or more types of cyclic systems.[7]

Baylis–Hillman acetates (B-H acetates) can be facilely derived from the corresponding Baylis–Hillman adducts (B-H adducts), and their applications toward synthetically and medicinally valuable compounds have been intensely investigated.[8] It was reported that some quinoline, thiochromene and naphthalene derivatives could be generated from B-H adduct derivatives through one-pot approaches.[9–12] Kim et al. developed the synthesis of 3-quinolinecarboxylic acid esters[9a,b] and 2-substituted naphthalenes[9c] from *ortho*-fluoro and dihalo B-H adducts *via* S_N2'/S_NAr process. They also reported that 3-ethoxycarbonyl-4-hydroxyquinoline *N*-oxides could be prepared by the rearrangements of *ortho*-nitro B-H adducts.[9d] It was demonstrated that some *ortho*-halo B-H acetates reacted with primary amines to afford the dihydroquinolines.[10] Kaye and Nocanda found that the DBU-facilitated reaction of 2,2′-dithiodibenzaldehyde with activated alkenes gave 2*H*-1-benzothiopyrans in yields up to 67%.[11] Lee and co-workers synthesized 3-carbomethoxy-2*H*-thiochromene from *ortho*-halo/*ortho*-nitro aryl B-H acetates, but low yields (20–43%) were achieved.[12] Generally, the application of these methods may suffer from the limitations such as the poor availability of starting materials, excessive amount of the substrates, harsh conditions, unsatisfactory yields, and/or the narrow scopes. Therefore, there is still

a demand for novel domino approaches to these cyclic moieties with broad application scope and high efficiency.

On the other way, to the best of our knowledge, there is no report for the Cu-mediated domino synthesis of cyclic compounds from B-H adducts and their derivatives. Herein, to overcome the inherent problems of the previously reported protocols and develop a versatile and facile pathway to a wide variety of cyclic molecules that just depends on variation of the nucleophiles, we describe a domino synthesis of quinoline/pyridine, thiochromene and naphthalene derivatives from B-H acetates based on the Cu-catalyzed S_N2'/coupling process.

Results and Discussion

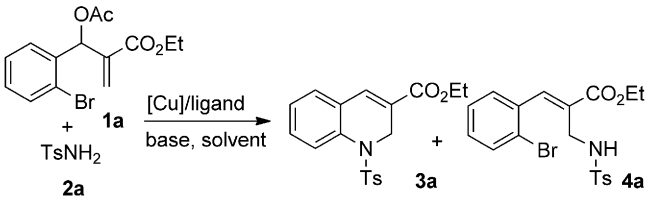
One-Pot Synthesis of Hydroquinoline Derivatives

Our studies commenced with the reaction of *ortho*-bromo B-H acetates **1a** and *para*-toluenesulfonamide ($TsNH_2$) **2a**. The initial attempt was performed in CH_3CN with CuI (5 mol%) as the catalyst and 1,10-phenanthroline (10 mol%) as the ligand in the presence of Cs_2CO_3 (3 equiv.) at 80 °C (Table 1, entry 1). To our delight, the anticipated *N*-sulfonyldihydroquinoline **3a** was obtained in a moderate yield after 12 h (entry 1). Several ligands were tested (entries 1–5), and 1,10-Phen was found to be the optimal ligand (entry 1). The ligand was essential for this transformation and a trace amount of the desired product was observed in a control experiment without the addition of ligand (entry 6, 86% yield of the intermediate **4a** was isolated). A slightly higher yield of the cyclized product was isolated when the base was replaced by K_2CO_3 (entry 7). Whereas K_3PO_4 only provided a poor yield (entry 8). Among the copper sources examined (CuI, CuBr, CuCl, and Cu_2O), CuCl showed the best effect (entries 7 and 9–11). When the reaction was carried out without any catalyst, only intermediate **4a** could be recovered in 85% yield and no desired product **3a** was detected, indicating that the Cu catalyst is indispensable for the cyclization process (entry 12). Different solvents were also screened (entries 10 and 13–15), and it was found that the reaction worked best in CH_3CN (entry 10). Increasing the amount of the base to 4 equiv. did not bring about any obvious improvement (entry 16). However, an inferior yield was obtained when the amount of the base was reduced to 2 equiv. (entry 17). A decrease of the yield was also observed at 70 °C (entry 18). Notably, ethyl quinoline-3-carboxylate **5a** generated from the elimination of *para*-toluenesulfinic acid (TsH) was not observed during these studies.

The effect of the leaving group on the transformation was also investigated. As shown in Scheme 1, *ortho*-bromo substrates bearing different leaving groups (OAc, OH and OBoc) were tested, and the substrate with an OAc proved to be the most active.

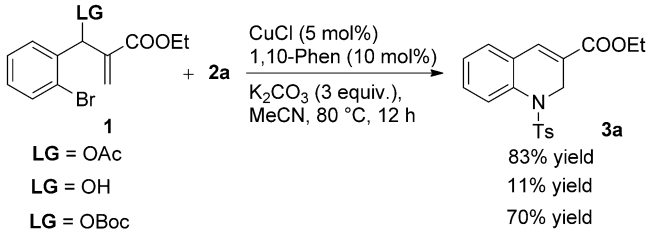
After the optimized conditions had been established, we then explored the generality and scope of the Cu-mediated domino reaction by using a variety of *ortho*-halo B-H acetates and benzsulfamides (Table 2). This transformation seems to be general, as

Table 1. Optimization of the reaction conditions.[a]



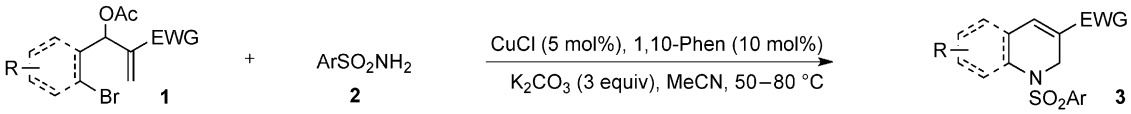
Entry	Cat.	Ligand	Base	Solvent	Yield of **3a**[b]
1	CuI	1,10-Phen	Cs_2CO_3	MeCN	60%
2	CuI	2,2'-Bipy	Cs_2CO_3	MeCN	45%
3	CuI	Picolinic acid	Cs_2CO_3	MeCN	48%
4	CuI	L-Proline	Cs_2CO_3	MeCN	38%
5	CuI	DMEDA	Cs_2CO_3	MeCN	25%
6	CuI	-	Cs_2CO_3	MeCN	trace
7	CuI	1,10-Phen	K_2CO_3	MeCN	65%
8	CuI	1,10-Phen	K_3PO_4	MeCN	12%
9	CuBr	1,10-Phen	K_2CO_3	MeCN	24%
10	CuCl	1,10-Phen	K_2CO_3	MeCN	83%
11	Cu_2O	1,10-Phen	K_2CO_3	MeCN	41%
12	-	1,10-Phen	K_2CO_3	MeCN	n.d.[c]
13	CuCl	1,10-Phen	K_2CO_3	dioxane	81%
14	CuCl	1,10-Phen	K_2CO_3	PhMe	33%
15	CuCl	1,10-Phen	K_2CO_3	DMF	66%
16	CuCl	1,10-Phen	K_2CO_3	MeCN	84%[d]
17	CuCl	1,10-Phen	K_2CO_3	MeCN	72%[e]
18	CuCl	1,10-Phen	K_2CO_3	MeCN	75%[f]

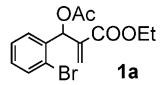
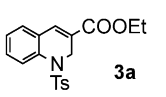
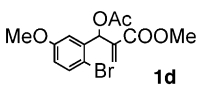
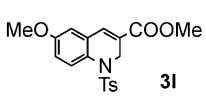
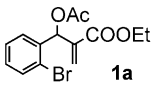
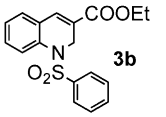
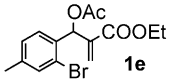
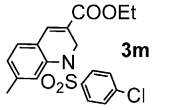
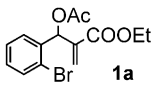
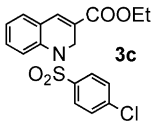
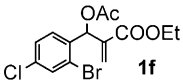
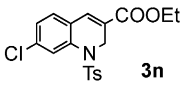
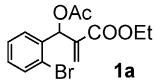
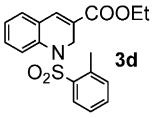
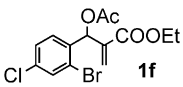
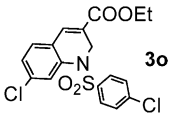
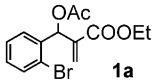
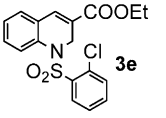
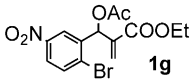
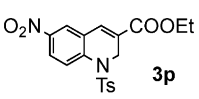
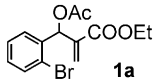
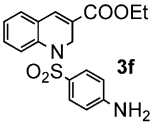
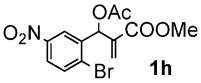
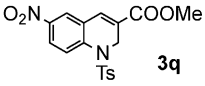
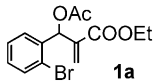
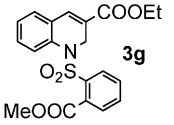
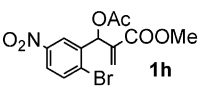
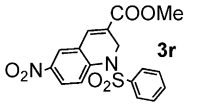
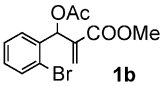
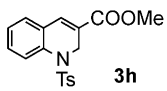
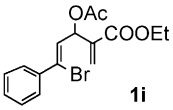
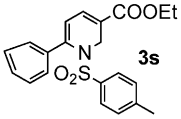
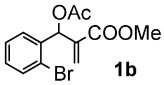
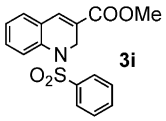
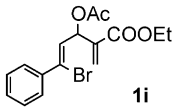
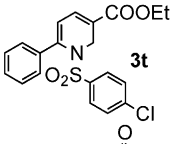
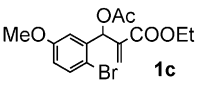
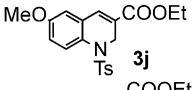
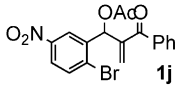
[a] *Reaction conditions:* substrate **1a** (1.0 mmol), N-nucleophile **2a** (1.2 mmol), Cu catalyst (0.05 mmol, 5 mol%), ligand (0.10 mmol, 10 mol%), base (3 equiv.), in solvent (4 mL), under N_2, at 80 °C for 12 h.
[b] Isolated yield.
[c] n.d. = not detected.
[d] K_2CO_3 (4 equiv.) was used as the base.
[e] K_2CO_3 (2 equiv.) was used as the base.
[f] At 70 °C.



Scheme 1. The effect of leaving group.

Table 2. Cu-catalyzed domino synthesis of *N*-sulfonyldihydroquinolines from B-H acetates.[a]



Entry	Substrate **1**	Product **3**	Time	Yield[b]	Entry	Substrate **1**	Product **3**	Time	Yield[b]
1	 **1a**	 **3a**	12 h	83%	12	 **1d**	 **3l**	12 h	81%
2	 **1a**	 **3b**	12 h	91%	13	 **1e**	 **3m**	14 h	65%
3	 **1a**	 **3c**	11 h	84%	14	 **1f**	 **3n**	12 h	86%
4	 **1a**	 **3d**	12 h	45%	15	 **1f**	 **3o**	12 h	90%
5	 **1a**	 **3e**	11 h	83%	16	 **1g**	 **3p**	10 h	75%[c]
6	 **1a**	 **3f**	12 h	64%	17	 **1h**	 **3q**	10 h	80%[c]
7	 **1a**	 **3g**	15 h	trace	18	 **1h**	 **3r**	11 h	72%[c]
8	 **1b**	 **3h**	12 h	82%	19	 **1i**	 **3s**	30 h	50%[d]
9	 **1b**	 **3i**	12 h	80%	20	 **1i**	 **3t**	30 h	52%[d]
10	 **1c**	 **3j**	12 h	76%	21	 **1j**	**3u**	10 h	37%
11	**1c**	**3k**	12 h	72%	22	**1k**	**3a**	15 h	10%

[a] *Reaction conditions:* substrate **1** (1.0 mmol), sulfamide **2** (1.2 mmol), CuCl (0.05 mmol, 5 mol%), 1,10-Phen (0.10 mmol, 10 mol%), K_2CO_3 (3 mmol, 3 equiv.), in MeCN (4 mL), under N_2, at 80 °C.

[b] Isolated yield.

[c] At 50 °C.

[d] The substrate was unstable under heating.

a range of *ortho*-bromo B-H acetates **1** derived from *ortho*-bromobenzaldehydes were converted into the corresponding *N*-sulfonyldihydroquinolines **3** (Table 2). And in most cases, moderate to excellent yields could be obtained within 12 h (entries 1–18).

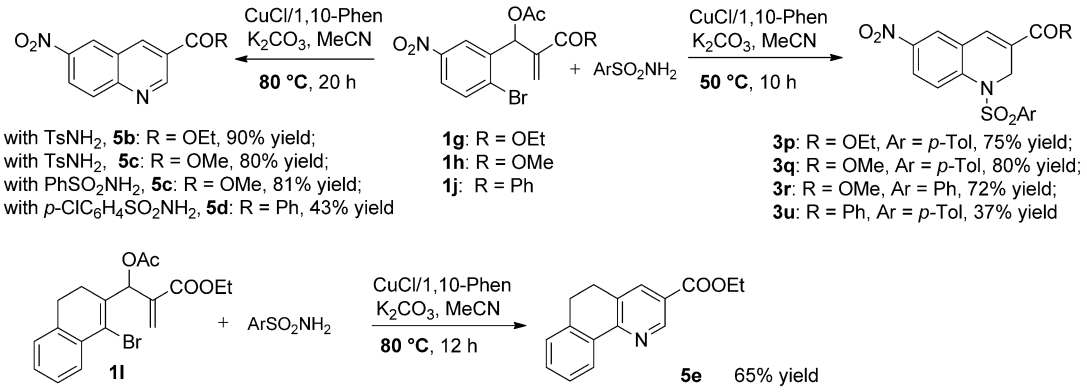
Both electron-donating and electron-withdrawing groups on the phenyl ring of the sulfamides (entries 1-3, 5 and 6) or *ortho*-bromo B-H acetates (entries 1 and 10–18) could be well tolerated. However, *ortho*-substituents such as *ortho*-methyl (entry 4) and *ortho*-ester group (entry 7) on the sulfamides have negative effects on the reactions. *ortho*-Methoxycarbonylbenzsulfamide afforded the desired cyclized product only in trace amount (entry 7), due probably to the *ortho*-steric hindrance of the *ortho*-ester group, as well as the weakening of the nucleophilicity of the amino group. Amazingly, *ortho*-chlorobenzsulfamide gave the desired dihydroquinoline in good yield (entry 5), maybe because of the relatively smaller chloro atom and its inductive effect on the amino group. It was noteworthy that ethyl 1-[(4-aminophenyl)sulfonyl]-1,2-dihydroquinoline-3-carboxylate **3f** could be selectively assembled from *para*-aminobenzsulfamide, and no product derived from the reaction initiated by the assault of the arylamino group was observed (entry 6). Various substituents including methoxy, nitro groups and chloro atom on the phenyl ring of the *ortho*-bromo B-H acetates are well tolerated (entries 1 and 10–18). To our surprise, *p*-tol B-H acetate **1e** proved to be less active and afforded the desired products only in moderate yields (entry 13). Interestingly, substrates with a nitro group showed higher activities and reacted smoothly with benzsulfamides to give the desired dihydroquinolines at a much lower temperature (50 °C) (entries 16–18). Different electron-withdrawing groups on the vinyl moiety of the B-H acetates were also studied. Both ethoxycarbonyl and methoxycarbonyl groups showed good performance (entries 1 and 8; 2 and 9; 10 and 12; 16 and 17). However, substrate **1j** bearing a benzoyl group gave the desired product in a low yield (entry 21). *ortho*-Bromovinyl B-H acetate **1i** derived from (*Z*)-3-bromo-3-phenylacrylaldehyde required longer reaction time to afford the corresponding dihydroquinoline with a moderate yield (entries 19–20). A chloride **1k** was also tested, and only a low yield of the desired product was isolated (entry 22).

Generally, the desulfonation process did not occur even at a higher temperature or after a longer reaction time. And the *N*-sulfonyldihydroquinolines were delivered as the sole cyclized products. But in a few cases, the eliminations could be observed under properly modified conditions (Scheme 2). Once higher temperature and longer reaction time were applied, the substrates bearing a nitro group (**1g**, **1h** and **1j**) underwent elimination selectively and afford products **5b–5d** as the sole products. It was noteworthy that a tricyclic eliminated derivative **5e** could be smoothly assembled from bicyclic *o*-bromovinyl B-H acetate **1l**, and no dihydroquinoline derivative was detected.

In order to achieve further desulfonation for the reactions of common substrates, we carried out representative experiments for tandem synthesis of 3-quinolinecarboxylic acid esters from B-H acetates (Table 3). When the S_N2'/coupling process was complete with CuCl/1,10-Phen/K_2CO_3 (12 h), DBU was then added and the desired desulfonated product **5a** could be isolated in good yield (81%) after about 3 h (entry 1).

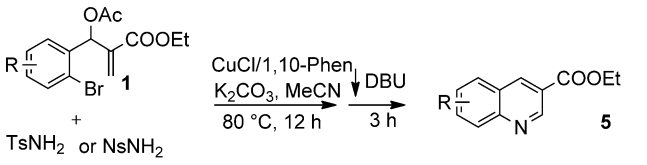
Considering that *para*-nitrobenzenesulfonyl (Ns) groups might be removed more easily, $NsNH_2$ was used instead of $TsNH_2$. However, the elimination of Ns also requires the presence of DBU. In this case, the yield of **5a** was improved to 85% (Table 3, entry 2).[13] Substrates **1c** and **1f** bearing either an electron-donating or electron-withdrawing group on the phenyl ring delivered good yields of the corresponding 3-quinolinecarboxylic acid esters in this tandem process (entries 3 and 4).

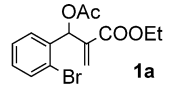
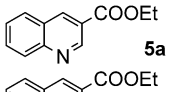
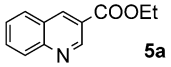
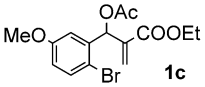
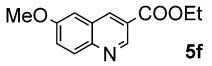
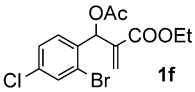
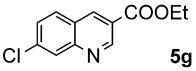
Therefore, the selective one-pot synthesis of dihydroquinoline- or quinoline-3-carboxylic acid esters could be conveniently and tunably achieved.



Scheme 2. Cu-catalyzed one-pot selective synthesis of *N*-sulfonyldihydroquinoline and 3-quinolinecarboxylic/3-picolinic acid ester derivatives from nitroaryl or vinyl B-H acetates.

Table 3. Typical examples for tandem synthesis of 3-quinolinecarboxylic acid esters from B-H acetates.[a]



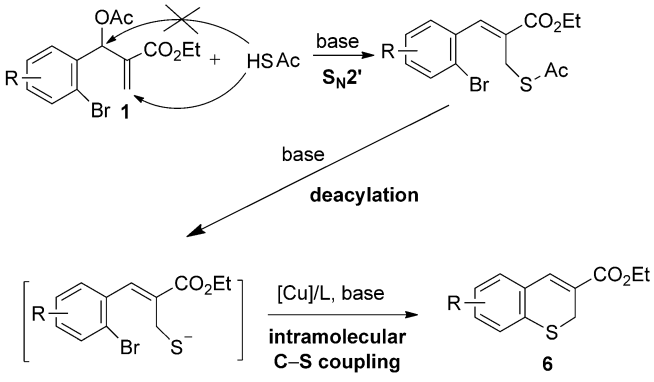
Entry	Substrate **1**	Sulfamide **2**	Product **5**	Yield[b]
1	 **1a**	$TsNH_2$	 **5a**	81%
2	**1a**	$NsNH_2$	 **5a**	85%
3	 **1c**	$NsNH_2$	 **5f**	80%
4	 **1f**	$NsNH_2$	 **5g**	86%

[a] *Reaction conditions:* substrate **1** (1.0 mmol), sulfamide **2** (1.2 mmol), CuCl (0.05 mmol, 5 mol%), 1,10-Phen (0.10 mmol, 10 mol%), K_2CO_3 (3 mmol, 3 equiv.), in MeCN (4 mL), under N_2, at 80 °C for 12 h; then DBU (3 mmol, 2 equiv.) was added, at 80 °C for 3 h.

[b] Isolated yield.

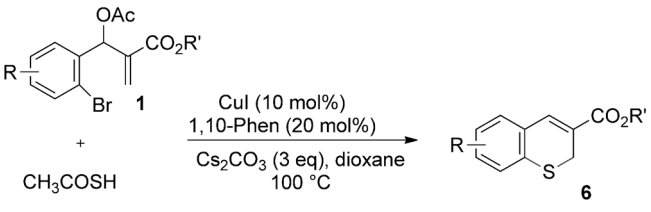
One-Pot Synthesis of Thiochromene Derivatives

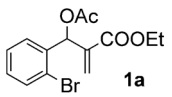
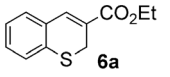
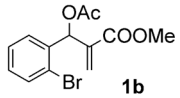
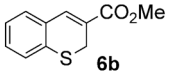
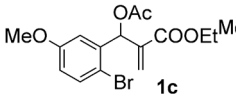
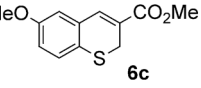
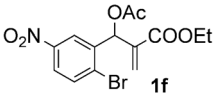
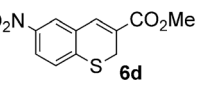
Having developed an efficient method for the assembly of quinoline/pyridine derivatives, we then sought to extend the method to synthesize 2*H*-thiochromenes. By using **1a** and Na_2S as the model substrates under the above optimized conditions, no desired thiochromene product **6a** was observed. When the S-nucleophile was replaced by thioacetic acid, the desired cyclized product **6a** could be obtained in a poor yield, probably *via* a S_N2'/deacylation[14]/coupling process (see Scheme 3). Shifting the solvent to dioxane and raising the reaction temperature to 100 °C provided **6a** in a moderate yield (57%). Further investigation



Scheme 3. A probable mechanism for the synthesis of 2*H*-thiochromene-3-carboxylic acid esters.

Table 4. Cu-catalyzed domino synthesis of 2*H*-thiochromene-3-carboxylic acid esters from B-H acetates.[a]



Entry	Substrate **1**	Product **6**	Time	Yield[b]
1	 **1a**	 **6a**	30 h	91%
2	 **1b**	 **6b**	30 h	86%
3	 **1c**	 **6c**	30 h	51%
4	 **1f**	 **6d**	28 h	80%

[a] *Reaction conditions:* substrate **1** (1.0 mmol), thioacetic acid **2** (1.5 mmol), CuI (0.10 mmol, 10 mol%), 1,10-Phen (0.20 mmol, 20 mol%), Cs_2CO_3 (3 mmol, 3 equiv.), in dioxane (4 mL), under N_2, at 100 °C.

[b] Isolated yield.

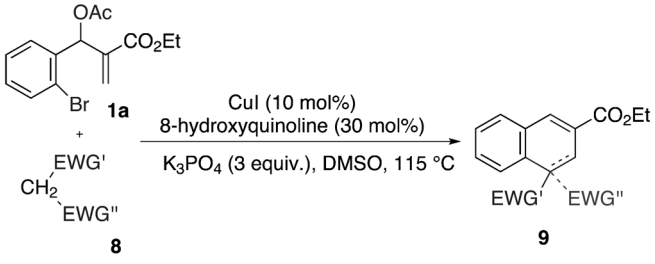
proved that CuI (10 mol%) was the best catalyst and Cs_2CO_3 was the optimal base for this domino process.

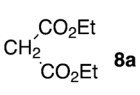
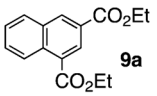
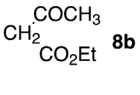
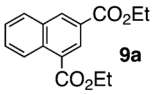
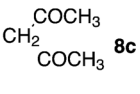
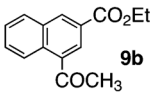
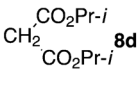
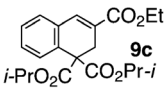
Then different substrates were employed to examine the scope of the reaction under the above modified conditions (Table 4). And generally, good to excellent yields were obtained.

One-Pot Synthesis of Naphthalene Derivatives

In order to further broaden the scope of our protocol, we then investigated the domino reaction with C-nucleophiles to assemble naphthalene derivatives. To our delight, the domino cyclization process with several active methylene compounds proceeded successfully although slightly modified conditions had to be applied (Table 5). Thus moderate to good yields of 3-naphthalenecarboxylic acid esters **9** were isolated under the promotion of CuI/8-hydroxyquinoline/K_3PO_4 in DMSO at 115 °C. And interestingly, when diethyl malonate, ethyl acetoacetate or acetylacetone were utilized as the nucleophile, further elimination processes including decarboxylation (or deacylation) and aromatization[15] led to the formation of disubstituted naphthalenes (Table 5, entries 1–3); while the reaction with diisopropyl malonate **8d** afforded trisub-

Table 5. Cu-catalyzed domino synthesis of 3-naphthalenecarboxylic acid esters from B-H acetates.[a]



Entry	Nucleophile **8**	Product **9**	Yield[b]
1	 **8a**	 **9a**	70%
2	 **8b**	 **9a**	56%
3	 **8c**	 **9b**	60%
4	 **8d**	 **9c**	78%

[a] *Reaction conditions:* substrate **1** (1.0 mmol), active methylene compound **8** (1.2 mmol), CuI (0.10 mmol, 10 mol%), 8-hydroxyquinoline (0.30 mmol, 30 mol%), K_3PO_4 (3 equiv.), in DMSO (4 mL), under N_2, at 115 °C for 15 h.

[b] Isolated yield.

stituted dihydronaphthalene **9c** as the sole cyclized product (entry 4), probably due to the bulky isopropyl groups.

Conclusions

In summary, we have described a versatile approach to various quinoline/pyridine, thiochromene, and naphthalene derivatives by Cu-catalyzed domino S_N2'/coupling, S_N2'/deacylation/coupling or S_N2'/coupling/elimination of *ortho*-bromo B-H acetates and the N-/S-/C-nucleophiles. The starting materials are readily available, the procedures are simple, and the cyclized products could be synthesized in moderate to excellent yields. The quinolines and dihydroquinolines were selectively assembled in one pot. Furthermore, this Cu-catalyzed domino method can be successfully applied for constructing three different types of cyclic moieties by varying the nucleophiles. Therefore, the Cu-catalyzed domino synthesis may be practical and useful for the assembly of various cyclic compounds of biological and pharmaceutical interests. Further investigations concerning exploration of this domino protocol in the assembly of other valuable molecules are underway.

Experimental Section

General Procedure for the Domino Synthesis of *N*-Sulfonyldihydroquinolines (Products 3)

An oven-dried Schlenk tube was charged with a magnetic stir bar, substrate **1** (1.0 mmol, 1 equiv.), benzsulfamide **2** (1.2 mmol, 1.2 equiv.), CuCl (0.05 mmol, 5 mol%), 1,10-Phen (0.10 mmol, 10 mol%), and K_2CO_3 (3.0 mmol, 3 equiv.). The Schlenk tube was capped, and then evacuated and backfilled with N_2 (3 times). Under a positive pressure of N_2, MeCN (4 mL) was added *via* syringe. The Schlenk tube was sealed and the mixture allowed to stir at 50–80 °C (monitored by TLC). After cooling to room temperature, additional 10 mL of EtOAc were added. The mixture was directly passed through a pad of silica gel and rinsed with additional 30 mL of EtOAc. The combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (160–200 mesh) using petrol/EtOAc (15:1→10:1, v:v) as eluent to give the corresponding product **3**.

General Procedure for the Tandem Synthesis of 3-Quinolinecarboxylic Acid Esters (Products 5)

An oven-dried Schlenk tube was charged with a magnetic stir bar, substrate **1** (1.0 mmol, 1 equiv.), benzsulfamide **2** (1.2 mmol, 1.2 equiv.), CuCl (0.05 mmol, 5 mol%), 1,10-Phen (0.10 mmol, 10 mol%), and K_2CO_3 (3.0 mmol, 3 equiv.). The Schlenk tube was capped, and then evacuated and backfilled with N_2 (3 times). Under a positive pressure of N_2, MeCN (4 mL) was added *via* syringe. The Schlenk tube was sealed and the mixture allowed to stir at 80 °C for 12 h. Then DBU (4.0 mmol, 4 equiv.) was added *via* syringe, and the mixture was stirred at 80 °C for another 3 h. After cooling to room temperature, additional 10 mL of EtOAc were added. The mixture was directly passed through a pad of silica gel and rinsed with additional 30 mL of EtOAc. The combined filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (160–200 mesh) using petrol/EtOAc (10:1, v:v) as eluent to give the corresponding product **5**.

General Procedure for the Domino Synthesis of 2*H*-Thiochromene-3-carboxylic Acid Esters (Products 6)

An oven-dried Schlenk tube was charged with a magnetic stir bar, substrate 1 (1.0 mmol, 1 equiv.), CuI (0.10 mmol, 10 mol%), 1,10-Phen (0.20 mmol, 20 mol%), and Cs_2CO_3 (3.0 mmol, 3 equiv.). The Schlenk tube was capped, and then evacuated and backfilled with N_2 (3 times). Under a positive pressure of N_2, thioacetic acid (1.5 mmol, 1.5 equiv.) and dioxane (4 mL) was added *via* syringe. The Schlenk tube was sealed and the mixture allowed to stir at 100 °C (monitored by TLC). After cooling to room temperature, an additional 10 mL of EtOAc was added. The mixture was directly passed through a pad of silica gel and rinsed with additional 30 mL of EtOAc. The combined filtrate was concentrated

under reduced pressure. The residue was purified by column chromatography on silica gel (160–200 mesh) using petrol/EtOAc (10:1 v:v) as eluent to give the corresponding product **6**.

General Procedure for the Domino Synthesis of 3-Naphthalenecarboxylic Acid Esters (Products 9)

An oven-dried Schlenk tube was charged with a magnetic stir bar, substrate **1** (1.0 mmol, 1 equiv.), active methylene compound **8** (1.2 mmol, 1.2 equiv.), CuI (0.10 mmol, 10 mol%), 8-hydroxyquinoline (0.30 mmol, 30 mol%), and K_3PO_4 (3.0 mmol, 3 equiv.). The Schlenk tube was capped, and then evacuated and backfilled with N_2 (3 times). Under a positive pressure of N_2, DMSO (4 mL) was added *via* syringe. The Schlenk tube was sealed and the mixture allowed to stir at 115 °C (monitored by TLC). After cooling to room temperature, additional 30 mL of EtOAc were added. The mixture was subsequently washed with brine (10 mL × 3). The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (160–200 mesh) using petrol/EtOAc (15:1, v:v) as eluent to give the corresponding product **9**.

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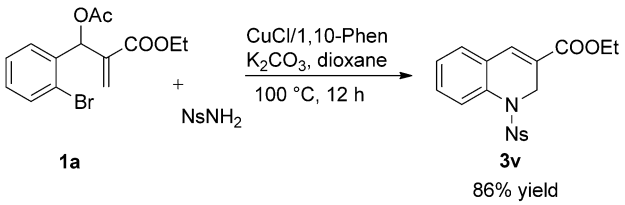

1a **3v** 86% yield

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