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# Synthesis of 2-bromo-1*H*-indenes via copper-catalyzed intramolecular cross-coupling of *gem*-dibromoolefins

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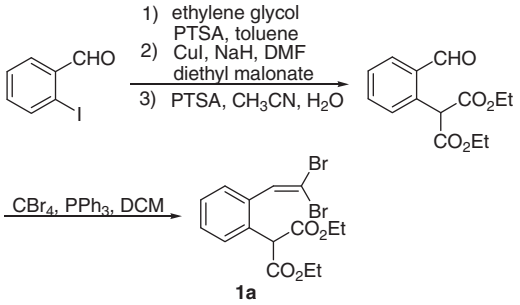
ABSTRACT

A novel copper-catalyzed intramolecular C–C coupling reaction of activated methylene aromatic compounds with *gem*-dibromoolefins is described. The reaction can tolerate various functional groups and lead to efficient formation of 2-bromo-1*H*-indenes.



Indene scaffolds are valuable synthetic targets as they exist in many molecules with diverse bioactivities[1] and are also present in various metallocene complexes used for the catalysis of olefin polymerizations.[2] In addition, indene derivatives are also of interest in the field of material science.[3] As a result, a number of synthetic methods for the construction of indene ring systems have been developed.[4] However, less attention has been paid to the synthesis of haloindenes which can be easily transformed into functionalized indene derivatives through subsequent coupling reactions. The preparation of haloindenes usually involves the bromination of indanes or indenes[5] and HI-mediated cyclization of *o*-(alkynyl)styrenes.[6] These traditional approaches to haloindenes often suffer from either long reaction sequences or strong acidic conditions under which many functional groups cannot be tolerated. Recently, several protocols for the synthesis of the haloindenes have been developed. These methods include Lewis-acid catalyzed cyclization of iodinated allylic alcohols,[7] iodonium-promoted carbocyclization of 2-substituted ethynylmalonates,[8] Pd-catalyzed carbocyclization of 2-alkenylphenylacetylenes in the presence of copper halide[9] and halocyclization of *o*-(alkynyl)styrenes.[10] Very recently, an efficient strategy for the synthesis of substituted *N*-(2-haloinden-1-yl)arenesulfobnamides from propargylic alcohols and sulfonamides has been reported.[11]

The chemistry of *gem*-dihaloolefins,[12] once limited mainly to the synthesis of terminal alkynes, has made remarkable progress in organic synthesis especially in transition metal-catalyzed reactions. A number of novel and elegant reactions using *gem*-dihaloolefins as building blocks have been developed and compounds such as dienes,[13] enynes,[14] heterocycles[15], and carbocycles[16] are prepared efficiently from various *gem*-dihaloolefins. In conjunction with our study of *gem*-dibromoolefins for the synthesis of heterocycles,[17] we have developed a straightforward and efficient method for the synthesis of 2-bromo-1*H*-indenes via copper-catalyzed intramolecular C–C cross-coupling reaction of activated methylene aromatic compounds bearing *gem*-dibromoolefins, and herein we report these results.




**1a**

**Scheme 1.** Preparation of diethyl 2-(2-(2,2-dibromovinyl)phenylmalonate **1a**.

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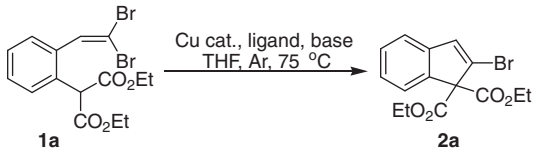
**Table 1**
Reaction condition screening for the synthesis of **2a** from **1a**[a]



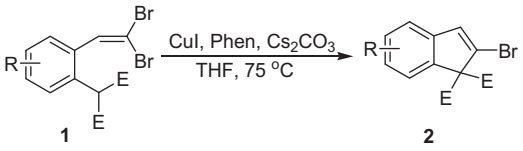

| Entry | Cat. | Ligand[b] | Base | Time (h) | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 | CuI | None | $Cs_2CO_3$ | 17 | 68 |
| 2 | CuI | None | $Cs_2CO_3$ | 17 | 37[d] |
| 3 | CuI | None | $Cs_2CO_3$ | 17 | 41[e] |
| 4 | CuI | None | $K_2CO_3$ | 17 | Trace |
| 5 | CuI | None | $K_3PO_4$ | 17 | Trace |
| 6 | CuCl | None | $Cs_2CO_3$ | 17 | 43 |
| 7 | CuBr | None | $Cs_2CO_3$ | 17 | 42 |
| 8 | None | None | $Cs_2CO_3$ | 24 | 38 |
| 9 | None | None | DBU | 12 | 0 |
| 10 | CuI | **L1** | $Cs_2CO_3$ | 24 | 48[f] |
| 11 | CuI | **L2** | $Cs_2CO_3$ | 24 | 52 |
| 12 | CuI | **L3** | $Cs_2CO_3$ | 12 | 63 |
| 13 | CuI | **L4** | $Cs_2CO_3$ | 12 | 79 |
| 14 | CuI | **L4** | $Cs_2CO_3$ | 12 | 79[f] |
| 15 | CuI | **L5** | $Cs_2CO_3$ | 12 | 54[f] |

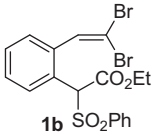
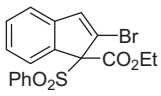
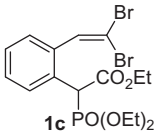
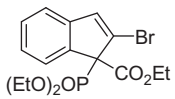
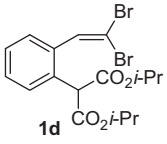
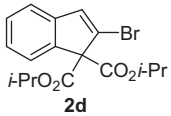
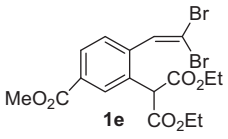
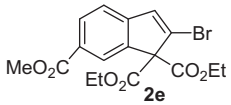
[a] Reaction condition: **1a** (0.5 mmol), catalyst (20 mol %), ligand (40 mol %), base (3 equiv), THF (5 mL), 75 °C under an argon atmosphere.
[b] **L1** = L-proline, **L2** = *N*,*N*-dimethylglycine, **L3** = 2-picolinic acid, **L4** = 1,10-phenanthroline, **L5** = 2-acetylcyclohexanone.
[c] Isolated yield.
[d] DMSO as the solvent.
[e] 10 mol % of CuI was used.
[f] 10 mol % of CuI and 20 mol % of ligand were used.

Diethyl 2-(2-(2,2-dibromovinyl)phenylmalonate **1a**, readily prepared from 2-iodobenzaldehyde through α-arylation of malonate[18] and subsequent *gem*-dibromoolefination of the aldehyde (Scheme 1),[19] was chosen as the model substrate to optimize the reaction conditions. The results are shown in Table 1. The substrate **1a** was first subjected to the following reaction conditions: CuI (20 mol %), $Cs_2CO_3$ (3 equiv) in THF at 75 °C under an argon atmosphere without any ligand. The desired cyclized product **2a** was obtained in a 68% yield (entry 1), while other reaction conditions gave lower yields (entries 2–7). Treating substrate **1a** with $Cs_2CO_3$ in the absence of the catalyst led to a lower yield of the desired product **2a** (entry 8). In addition, treating substrate **1a** with DBU gave the elimination product diethyl 2-(2-(bromoethynyl)phenyl) malonate exclusively, while the desired product **2a** was not observed even after a prolonged reaction time (entry 9). To further optimize the reaction conditions, we then investigated the reaction in the presence of various ligands including L-proline (**L1**), *N*,*N*-dimethylglucine (**L2**), 2-picolinic acid (**L3**), 1,10-phenanthroline (**L4**), and 2-acetylcyclohexanone (**L5**) (entries 10–15). Ligand 1,10-phenanthroline (**L4**) was found to be the most suitable additive for this coupling reaction (entries 13 and 14). Reduction of **L4** and CuI loading gave very similar results (entry 14). Thus, the optimized conditions included the use 10 mol % CuI as the catalyst, 20 mol % of 1,10-phenanthroline (**L4**) as the ligand, and 3 equiv of $Cs_2CO_3$ as the base in THF at 75 °C under an argon atmosphere.

With the optimal reaction conditions in hand, we set to investigate the generality of this coupling reaction. As shown in Table 2,[20] a broad range of substrates underwent this coupling reaction smoothly to afford the corresponding desired products in moderate to good yields. For example, substrates bearing different acti-

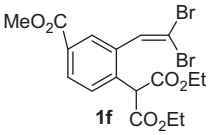
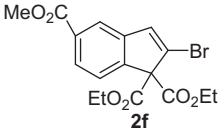
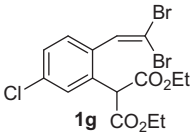
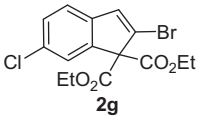
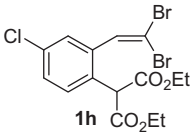
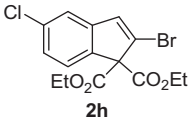
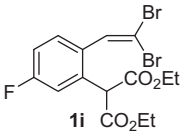
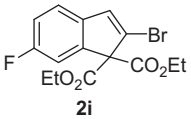
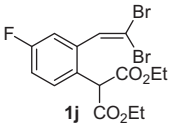
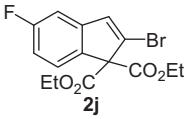
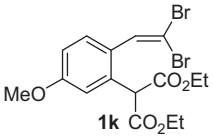
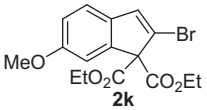
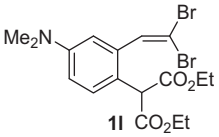
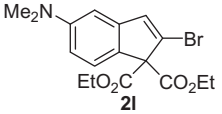
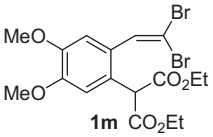
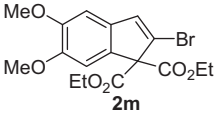
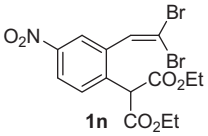
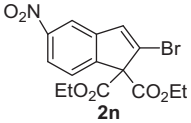
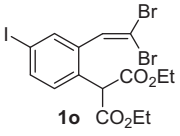
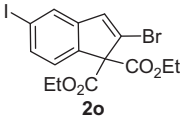
**Table 2**
Copper-catalyzed synthesis of 2-bromo-1*H*-indenes[a,b]




| Entry | Substrate | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  **1b** |  **2b** | 16 | 80 |
| 2 |  **1c** |  **2c** | 16 | 72 |
| 3 |  **1d** |  **2d** | 16 | 62 |
| 4 |  **1e** |  **2e** | 15 | 73 |

(*continued on next page*)

**Table 2** (*continued*)

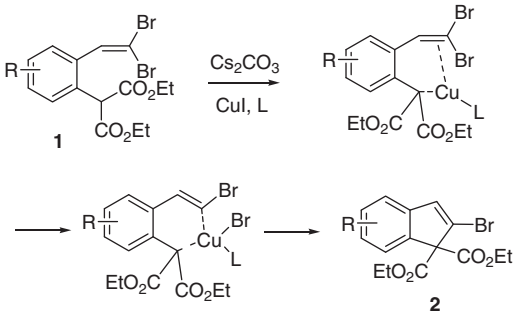
| Entry | Substrate | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 5 |  **1f** |  **2f** | 11 | 72 |
| 6 |  **1g** |  **2g** | 14 | 75 |
| 7 |  **1h** |  **2h** | 16 | 64 |
| 8 |  **1i** |  **2i** | 16 | 74 |
| 9 |  **1j** |  **2j** | 16 | 60 |
| 10 |  **1k** |  **2k** | 15 | 77 |
| 11 |  **1l** |  **2l** | 15 | 67 |
| 12 |  **1m** |  **2m** | 15 | 56 |
| 13 |  **1n** |  **2n** | 24 | 44 |
| 14 |  **1o** |  **2o** | 24 | 59 |

[a] Reactions were carried out using 0.5 mmol of substrate **1**, 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, and 3 equiv of $Cs_2CO_3$ in THF (5 mL) at 75 °C under an argon atmosphere.

[b] Isolated yield.

vated methylenes at 2-position of the aromatic ring smoothly proceeded to furnish the corresponding indenes (entries 1–3). Among these results, the substrate **1b** gave the highest yield (entry 1). The presence of a more sterically hindered isopropyl malonate led to a lower yield for the cyclized product (entry 3). Meanwhile, substrate bearing a nitro substituent on the aromatic ring gave a poor result (entry 13). Interestingly, while chloro and fluoro substituents on the aromatic ring were well tolerated (entries 6–9), a reactive iodo derivative (**2o**) also afforded the desired product with high chemoselectivity (entry 14).[21] No iodo reduction was detected from the reaction mixture.

A possible mechanism of the reaction is depicted in Scheme 2. It is likely that the malonate is deprotonated transiently under the reaction conditions. The anion is then coordinated with copper,




**Scheme 2.** Possible mechanism for the formation of **2** from compound **1**.

directing Cu insertion into the '*cis*'-Br, and leading to the desired product. This mechanism explains the high selectivity over the distal iodo substitution (Table 2, entry 14).

In conclusion, we have developed an efficient method for the synthesis of 2-bromo-1*H*-indenes via copper-catalyzed intramolecular C–C cross-coupling reaction. A variety of 2-bromo-1*H*-indenes were obtained in moderate to good yields. This method may provide a new way for the synthesis of highly functionalized indenes.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.102.

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19. *Typical procedure for the synthesis of diethyl 2-(2-(2,2-dibromovinyl) phenylmalonate* (**1a**): To a well-stirred mixture of ethyl 2-(2-formylphenyl) malonate (2.60 g, 9.85 mmol), $CBr_4$ (6.60 g, 19.90 mmol) in DCM (100 mL) was added dropwise a solution of $PPh_3$ (10.40 g, 39.65 mmol) in DCM (50 mL) over 0.5 h at 0 °C. At the end of addition, the reaction mixture was further stirred at 0 °C for 0.5 h, and then allowed to warm to room temperature. After 2 h stirring, hexane was added to precipitate as much $Ph_3PO$ as possible, and the suspension was filtered through silica (washed with EtOAc). The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether–EtOAc = 15:1) to give **1a** as a clear, colorless oil (2.96 g, 72%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (s, 1H), 7.50 (d, $J$ = 6.8 Hz, 1H), 7.35–7.40 (m, 3H), 4.76 (s, 1H), 4.17–4.29 (m, 4H), 1.28 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.7, 136.2, 136.0, 130.9, 129.5, 129.3, 128.7, 128.2, 94.2, 61.9, 55.0, 14.0; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}Br_2O_4$) requires $m/z$ 420.9473, found $m/z$ 420.9469.
20. *Typical procedure for the synthesis of diethyl 2-bromo-1H-indene-1,1-dicarboxylate* (**2a**): A mixture of **1a** (210 mg, 0.5 mmol), CuI (9 mg, 0.05 mmol, 10 mol %), 1,10-phenanthroline(18 mg, 0.10 mmol, 20 mol %), and $Cs_2CO_3$ (489 mg, 1.50 mmol) in THF (5 mL) was stirred for 12 h under an argon atmosphere at 75 °C. The resultant mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether–EtOAc = 15:1) to afford **2a** as a clear, yellow oil (134 mg, 79%).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (d, $J$ = 7.4 Hz, 1H), 7.30–7.34 (m, 1H), 7.23–7.27 (m, 2H), 7.08 (s, 1H), 4.19–4.32 (m, 4H), 1.27 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.2, 142.6, 140.5, 137.3, 128.9, 126.4, 124.8, 123.8, 120.8, 72.3, 62.4, 13.9; HRMS (ESI) exact mass calculated for $[M+H]^+$ ($C_{15}H_{16}BrO_4$) requires $m/z$ 339.0232, found $m/z$ 339.0232.
21. Similarly, iodo is tolerated in the analogous indole preparation: Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416–11417.