

Annulations

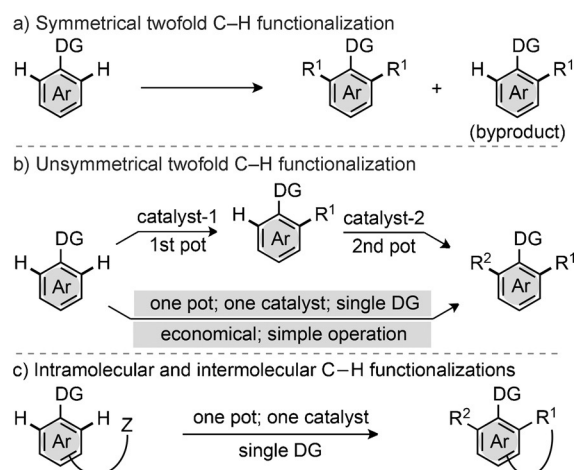
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Ruthenium-Catalyzed Hydroarylation and One-Pot Twofold Unsymmetrical C–H Functionalization of Arenes

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Abstract: A methyl phenyl sulfoximine (MPS) is used as a directing group in the ruthenium-catalyzed intramolecular hydroarylation of alkene-tethered benzoic acid derivatives to afford dihydrobenzofurans and indolines in good to excellent yields. A one-pot, unsymmetrical, twofold C–H functionalization involving intramolecular C–C and intermolecular C–C/C–N bond formations is successfully demonstrated by using a single set of catalytic reaction conditions, which is unprecedented thus far. A novel isoquinolone-bearing dihydrobenzofuran is constructed through an unsymmetrical twofold C–H functionalization.

Transition metal (TM) catalyzed directing group (DG)-aided functionalization of inert C–H bonds is a promising method for the step- and atom-efficient construction of versatile molecular structures from readily accessible starting materials.^[1–3] Despite the growth and success of C–H activation, synthetically useful DG-promoted multiple functionalizations of arene C–H bonds are less explored, yet exceedingly attractive. In general, the steric/electronic/coordinating effect of the *ortho*-monofunctionalized product, obtained from the DG-coupled arene, hampers the efficient introduction of other functional groups to the second *ortho* C–H bond on the arene. Consequently, effective twofold C–H bond functionalization of arenes remains challenging.^[4] Furthermore, the DG and catalytic conditions are highly selective for the respective bond formations, and as a consequence, unsymmetrical functionalization of C–H bonds in the presence of one catalyst is mostly unsuccessful. Moreover, the formation of numerous by-products and an incomplete reaction profile involved in each step of the transformation makes the overall process cumbersome and unproductive.^[5] Notably, single DG-enabled, symmetrical double *ortho*-C–H functionalization of arenes has been thoroughly investigated (Scheme 1a).^[6,7] Recently, the groups of Yu and Gevorgyan have independently disclosed elegant two-step unsymmetrical *ortho*-C–H functionalizations of arenes. The reactions proceeded well in the presence of two different catalytic systems and one DG (Scheme 1b).^[5,8,9] The realization of a one-pot, unsymmetrical, twofold C–H functionalization of arenes in the presence of a single DG and single catalyst would essentially lead to highly functionalized arene derivatives in a step-efficient and byproduct-free fashion, and would therefore be considered

Scheme 1. Unsymmetrical twofold *ortho*-C–H functionalization.

ideal (Scheme 1b). To the best of our knowledge, no such transformations are known.

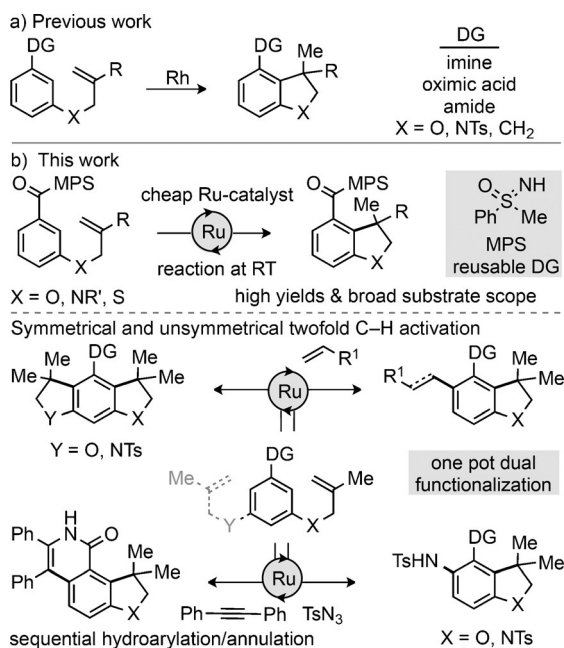
Dihydrobenzofuran skeletons are widely found in many biologically active compounds and potential drug candidates.^[10] The groups of Ellman and Bergman, Rovis, Cramer, and Yoshikai have independently demonstrated the rhodium- and cobalt-catalyzed intramolecular hydroarylation of O-bearing olefin-tethered arenes for the synthesis of dihydrobenzofurans (Scheme 2a).^[11–13] However, the use of air-stable and low-cost ruthenium catalysts for intramolecular hydroarylation with unactivated alkenes remains underdeveloped.^[14]

We therefore devised a one-pot, unsymmetrical, twofold C–H functionalization using a rationally designed olefin-tethered substrate (Scheme 1c). The reaction involves an intramolecular *ortho*-C–H hydroarylation and intermolecular functionalization of a second *ortho*-C–H bond. Herein, we discuss the methyl phenyl sulfoximine (MPS; **1**) directed^[15,16] ruthenium-catalyzed intramolecular hydroarylation of an O-tethered olefin bearing benzoic acid derivatives for the synthesis of a wide array of dihydrobenzofurans at room temperature (Scheme 2b). One-pot, symmetrical and unsymmetrical, twofold C–H functionalizations in the presence of a single catalyst were successfully investigated (Scheme 2b). A sequential hydroarylation and annulation with alkynes, through two C–H functionalizations, is also reported.

To realize the feasibility of the envisioned process sketched in Scheme 2b, the ruthenium-catalyzed intramolecular hydroarylation was explored with [3-(2-methylallyloxy)-benzoyl]methylphenyl sulfoximine (**2a**). Screening of the catalysts, additives, and bases led to the optimized reaction

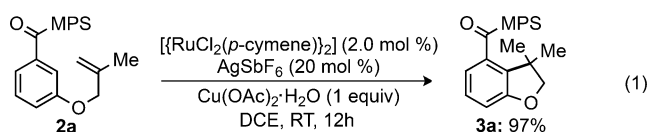
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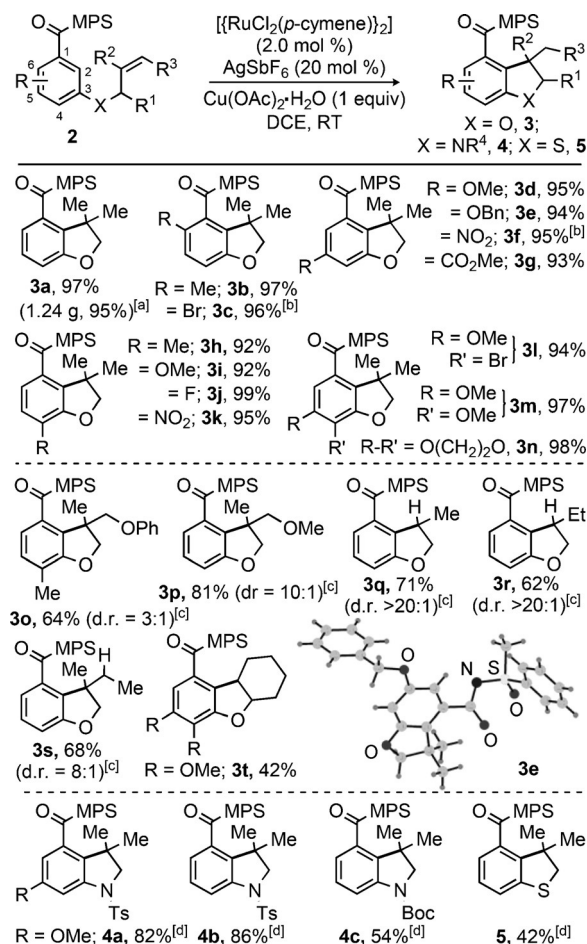


Scheme 2. Unsymmetrical twofold C–H functionalization.
Ts = 4-toluenesulfonyl.

conditions, $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.0 mol %), AgSbF_6 (20 mol %), and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.0 equiv) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ (DCE) at room temperature for 12 h, to access **3a** (97%) from **2a** [Eq. (1)].^[17]



The generality of this novel ruthenium-catalyzed DG-assisted intramolecular hydroarylation is showcased in Scheme 3. The reaction of **2a** (1.3 g) with 0.5 mol % of the ruthenium catalyst at 35 °C for 6 hours furnished **3a** (1.24 g), thus the reaction is scalable. The 6-methyl- (**2b**) and 6-bromo (**2c**) bearing sterically encumbered substrates smoothly underwent hydroarylation to produce **3b** and **3c**, respectively, in excellent yields. The electron-donating and electron-withdrawing (NO_2 , ester) functional groups at the 5-position of aryl moiety did not affect the reaction efficiency, thus yielding **3d–g** in excellent yields. X-ray crystallographic studies established the structure of **3e**.^[18] Excellent yield of the products **3h–k** were obtained from the 4-substituted benzoic acid derivatives **2h–k**, and electronically biased (OMe/NO_2) groups did not affect the yields. Construction of the highly substituted dihydrobenzofurans **3l–n** were readily obtained. The current transformation conveniently resulted in the phenoxy-methyl- and methoxymethyl-bearing (all-carbon quaternary stereocenter enabled) products **3o** (64%, 3:1) and **3p** (81%, 10:1), respectively.^[17] The O-allyl substrate **2q** successfully underwent hydroarylation, thus delivering 71% of **3q**.^[17] Internal alkenes also participated and the dihydro-

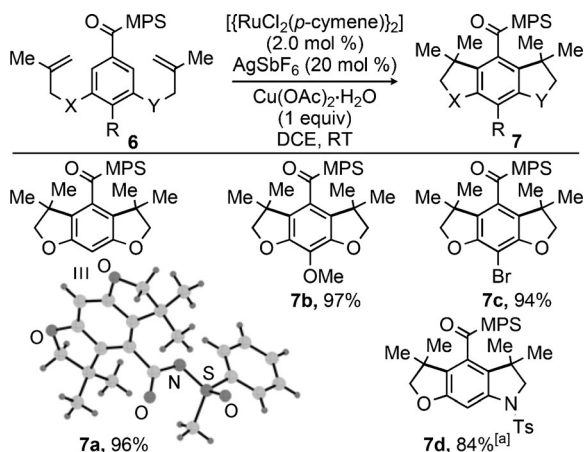


Scheme 3. Scope of the hydroarylation reaction. Reaction conditions: **2** (0.5 mmol), Ru catalyst (2.0 mol %), AgSbF_6 (20 mol %), and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.5 mmol) in DCE (2.0 mL) at RT for 8–16 h. [a] 0.5 mol % the Ru catalyst (at 35 °C). [b] At 50 °C. [c] Based on NMR/HPLC analysis. [d] 4.0 mol % Ru catalyst (at 65 °C). Boc = *tert*-butoxycarbonyl.

benzofuran derivatives **3r–t** were synthesized in appreciable yields.^[17] The identical reactions with the N- and S-tethered substrates were facile, thus resulting the N-Tosyl/Boc-protected indolines **4a–c** (54–86% yield) and dihydrobenzothio-**5** (Scheme 3).

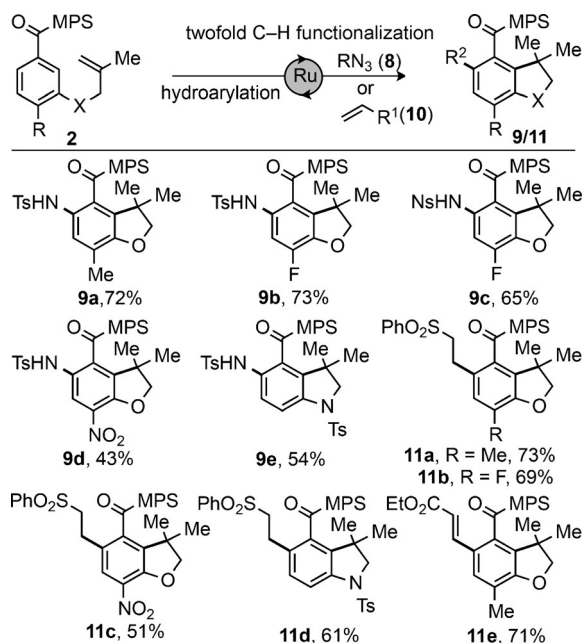
We next examined the twofold hydroarylation of the *ortho* C–H bonds with the appended olefins. Pleasingly, the dicyclization product **7a** (96%) was exclusively formed when **6a** was exposed to the optimized reaction conditions in (Scheme 4).^[18] This twofold hydroarylation with a low catalyst loading at room temperature is a distinct advantage over the rhodium-catalyzed transformations.^[11b] Likewise, 4-methoxy- and 4-bromo-substituted **7b** and **7c**, respectively, were achieved in the corresponding yields of 97% and 94%. The dihydroarylation of **6d** proceeded smoothly to exclusively produce 84% of **7d**. Collectively, these data reveal the potential of the MPS DG for the incorporation of two heterocycles into an arene moiety by a twofold hydroarylation.

Unsymmetrical functionalization of multiple C–H bonds creates densely functionalized scaffolds with the introduction



Scheme 4. Twofold hydroarylation reaction. Reaction conditions: **6** (0.5 mmol), Ru catalyst (2.0 mol %), AgSbF₆ (20 mol %), and Cu(OAc)₂·H₂O (0.5 mmol) in DCE (2.0 mL) for 10–16 h. [a] 4.0 mol % Ru catalyst (at 60 °C).

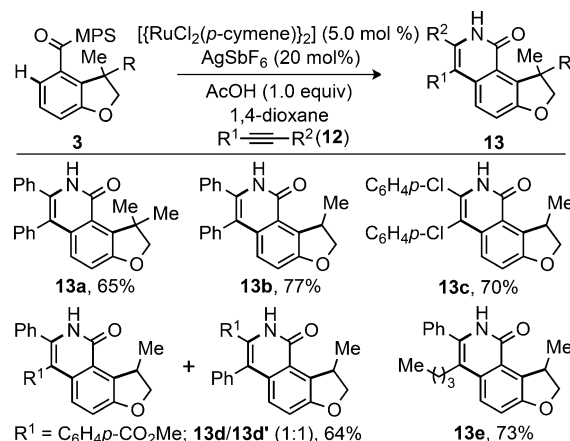
of diverse substituents. Thus, ruthenium-catalyzed intramolecular hydroarylation followed by intermolecular amidation with sulfonylazides under one set of catalytic conditions is envisioned (Scheme 5).^[15a,19] Gratifyingly, the compound **9a** (72 %) was isolated when **2h** was exposed to the ruthenium-catalyzed conditions in the presence of TsN₃ at room temperature, then with heating at 120 °C. Likewise, the dihydrobenzofurans **9b–d** were successfully constructed. The same reaction sequences were also applied to construct the N-tethered indoline derivative **9e**.



Scheme 5. One-pot hydroarylation-amidation/alkylation/alkenylation. Reaction conditions: **2** (0.5 mmol), Ru catalyst (5.0 mol %), AgSbF₆ (20 mol %), Cu(OAc)₂·H₂O (0.5 mmol), and either sulfonyl azide (1.0 mmol) or alkene (1.0 mmol) in DCE (4.0 mL) at RT for 12–16 h and then heated to 120 °C for 24 h.

The success of the one-pot hydroarylation amidation reaction led us to explore the unsymmetrical twofold C–C bond formations at the two *ortho* positions (Scheme 5). To our delight, the reaction of **2h** with phenyl vinyl sulfone (**10a**) under the optimized reaction conditions led directly to the 5-alkyl-substituted dihydrobenzofuran **11a** in 73 % yield in a single operation.^[15b,20] The presence of 4-fluoro and 4-nitro groups on the arene did not hamper the reaction, thus delivering **11b** (69 %) and **11c** (51 %), respectively. The steric strain of the quaternary group at the 3-position of the dihydrobenzofuran in the transition state suppresses the β -hydride elimination over proto-demetalation, and is presumably responsible for alkylation product formation.^[21] The N-tethered **2v** was also effectively reacted, thus leading to the indoline derivative **11d** (61 %). In contrast, the reaction of **2h** with ethyl acrylate (**10b**) gave the alkenylation product **11e**. To the best of our knowledge, the one-pot unsymmetrical functionalizations of arenes [hydroarylation/amidation, hydroarylation/olefination] under one set of catalytic conditions has not been reported previously.

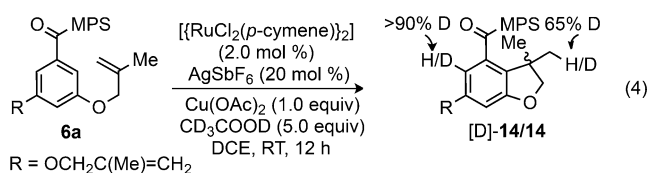
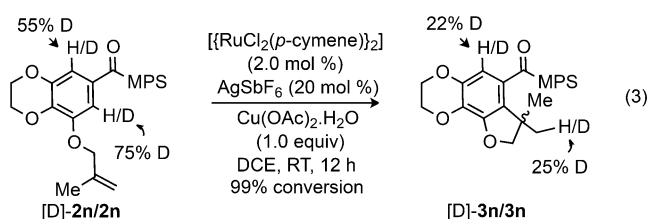
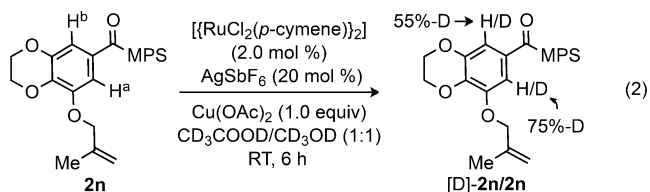
Development of a synthetic manifold for the introduction of isoquinolone motifs into (hetero)arenes is appealing, as they are widely found in the molecules of biological importance.^[22] We thus envisaged the introduction of an isoquinolone scaffold into the dihydrobenzofuran skeleton (Scheme 6).^[23] Gratifyingly, the reaction of **3a** and diphenyl-



Scheme 6. Sequential hydroarylation and annulation. Reaction conditions: **3** (0.5 mmol), Ru catalyst (5.0 mol %), AgSbF₆ (20 mol %), and AcOH (0.5 mmol) in 1,4-dioxane (4.0 mL) at 120 °C for 24 h.

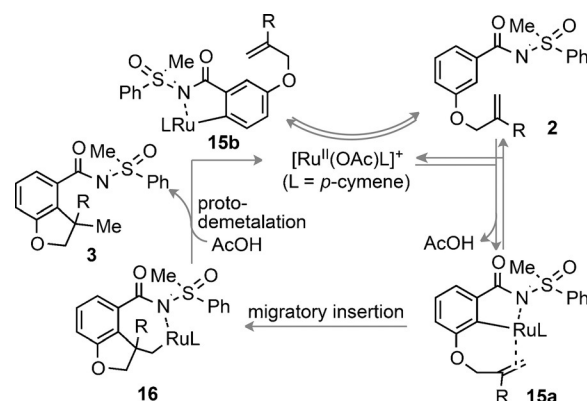
acetylene (**12a**) under the catalytic ruthenium conditions delivered the dihydrofuran-fused isoquinolone **13a** in 65 % yield. Likewise, annulation between **3q** and **12a** and **12b** led to **13b** (77 %) and **13c** (70 %), respectively. The use of the unsymmetrical diarylacetylene **12c** provided a mixture of regioisomers, **13d** and **13d'** (1:1; 64 %). Whereas the reaction of **3q** with the alkyl-aryl alkyne **12d** yielded **13e**, for which NOESY studies were used to establish the structure.^[17] Notably, the unsymmetrical twofold functionalization of inert C–H bonds, proceeding by hydroarylation and annulation, leads to novel N- and O-bearing heterocycles.

To gain some mechanistic insights, deuterium-labeling studies were performed. At first, the hydroarylation of **2n** in $\text{CD}_3\text{CO}_2\text{D}$ and CD_3OD (1:1) explicitly provided H/D scrambled products [D]-**2n/2n** [Eq. (2)]. The incorporation of D into the *ortho* C–H^a bond (75%), which is sandwiched between the DG and the O-allyl moiety, over the *ortho* C–H^b bond (55%) reveals that the tethered olefin moiety helps in the activation of the *ortho* C–H^a bond in **2n**. Interestingly, hydroarylation of [D]-**2n/3n** under the optimized reaction conditions resulted in [D]-**3n/3n** [Eq. (3)]. To our surprise, a significant decrease in the deuterium population at the arene *ortho* C–H bond (22%) and incorporation of only 25% of D into the 3-methyl in [D]-**3n/3n** is observed [Eq. (3)]. Thus, cleavage of the *ortho* C–H bond, which generally involves a concerted metalation-deprotonation (CMD) pathway, is reversible.^[24] Furthermore, ruthenium-catalyzed hydroarylation of **6a** in the presence of $\text{Cu}(\text{OAc})_2$ (1.0 equiv) and $\text{CD}_3\text{CO}_2\text{D}$ (5.0 equiv) afforded [D]-**14/14** with 65% deuterium incorporation in the 3-methyl moiety [Eq. (4)], thus indicating the involvement of protodemetalation.^[12a]



A plausible reaction pathway is outlined in Scheme 7. The active catalyst, generated from $[\text{RuCl}_2(\text{p-cymene})]_2$, AgSbF_6 , and $\text{Cu}(\text{OAc})_2$, coordinates to MPS and activates the *ortho* C–H bonds to produce the cyclometalated complex **15a/15b**. The additional interaction of the tethered olefin to the metal probably facilitates the activation of sterically encumbered proximal C–H bond to provide **15a** over **15b**. The migratory insertion of **15a** then leads to **16**, which upon proto-demetalation produces the desired product **3** with the regeneration of active catalyst.^[12a]

In summary, a novel and efficient DG-promoted ruthenium-catalyzed hydroarylation of benzoic acid derivatives at



Scheme 7. Possible mechanistic pathway.

room temperature was demonstrated for the first time. The reaction exhibits broad scope for synthesizing dihydrobenzofuran, indoline, and dihydro-benzothiophene derivatives. The unprecedented one-pot, unsymmetrical, twofold C–H functionalization of arene derivatives through hydroarylation-amidation and hydroarylation-alkylation/ alkenylation creates novel molecular scaffolds. The unsymmetrical twofold functionalization of unactivated C–H bonds involves hydroarylation and annulation (with alkynes) and leads to novel N- and O-bearing heterocycles by incorporating dihydrobenzofuran and isoquinolone motifs in a single molecule for the first time. The cleavage and recovery of the MPS group from the products makes this strategy synthetically viable.^[17]

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Keywords: annulations · C–H activation · heterocycles · reaction mechanisms · ruthenium

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