C–H Functionalization

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Aldimine-Directed Branched-Selective Hydroarylation of Styrenes**

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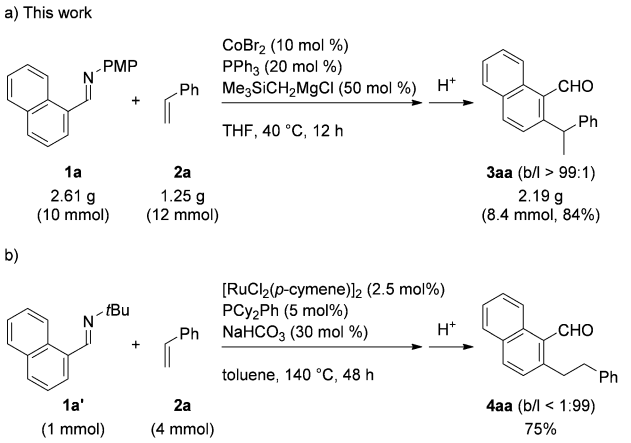
Efficient and selective construction of a 1,1-diarylethane core structure has received considerable attention because of its occurrence in a variety of pharmacologically active compounds.[1] Among various synthetic approaches to 1,1-diarylethanes, hydroarylation of styrene derivatives with branched regioselectivity is attractive for the inherently perfect atom economy.[2–6] Such transformations can be achieved through two mechanistically distinct modes of substrate activation: activation of the styrene C=C bond with a Lewis acid followed by a Friedel–Crafts-type aromatic alkylation,[2,3] and activation of the aromatic C–H bond with a low-valent transition-metal catalyst and subsequent insertion of styrene.[4,5,7] The former type of reaction is applicable to electron-rich arenes with exclusive branched selectivity, but is often accompanied by imperfect regioselectivity with respect to the arene substrate. In contrast, the latter type of reaction typically leads to 1,2-diarylethanes rather than 1,1-diarylethanes as the major products.[7] Some exceptions to this trend include the ruthenium-catalyzed reaction of the *ortho* position of *N*-methylaniline[4] and the nickel-catalyzed reaction of the C2 position of electron-deficient heteroarenes such as azole derivatives.[5a–c] As such, significant limitations remain in the synthetic scope of the hydroarylation approach to 1,1-diarylethanes.[8]

Recently, we reported that cobalt/tricyclohexylphosphine (PCy_3) and cobalt/N-heterocyclic carbene (NHC) catalysts promote the addition of 2-arylpyridine to styrene in branched-selective and linear-selective manners, respectively.[9a] The former case represents a rare example of branched-selective styrene hydroarylation by chelation-assisted C–H activation.[4] However, the utility of the hydroarylation products was severely limited by the pyridyl directing group, which is not amenable to further transformations. Herein we report that a simple cobalt/triarylphosphine catalyst[10,11] allows aldimine-directed, branched-selective hydroarylation of styrene derivatives under mild reaction conditions. The *ortho*-formyl group of the 1,1-diarylethane products can either be utilized as a synthetic handle to construct polycyclic aromatic hydrocarbons (PAHs) by Lewis acid catalyzed dehydrative cyclization or can be removed by catalytic decarbonylation to afford 1,1-diarylethanes with substitution patterns not accessible by the Friedel–Crafts alkylation.

The addition of the aldimine **1a**, derived from 1-naphthaldehyde and *p*-anisidine, to styrene (**2a**) serves as an illustrative example showing the efficiency, selectivity, and scalability of the cobalt catalysis (Scheme 1a). A catalytic system consisting of $CoBr_2$ (10 mol%), PPh_3 (20 mol%), and Me_3SiCH_2MgCl (50 mol%) promoted this transformation on a 10 mmol scale at 40 °C, and subsequent acidic hydrolysis afforded the adduct **3aa** in 84% yield with exclusive branched selectivity, which was in sharp contrast to the linear selectivity observed by Darses et al. for the ruthenium-catalyzed reaction of a similar aldimine (**1a′**) with **2a** (Scheme 1b).[7h] Comparable reaction efficiencies were achieved using triarylphosphine ligands bearing *p*-methyl and *p*-methoxy substituents, whereas the use of triarylphosphines with electron-withdrawing substituents (e.g., F, Cl) and PCy_3 led to lower catalytic activities. In contrast to our previous study on the reaction of 2-arylpyridines,[9a] NHC preligands such as IMes·HCl (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride) were not very effective, thus affording no adducts or a mixture of the branched and linear adducts in a low yield (see Table S1 in the Supporting Information).



Scheme 1. Contrasting regioselectivity of cobalt- and ruthenium-catalyzed aldimine-directed hydroarylation reactions of styrene. a) Cobalt catalysis: branched selectivity. b) Ruthenium catalysis: linear selectivity (Ref. [7h]). PMP = *p*-methoxyphenyl, THF = tetrahydrofuran.

A variety of aromatic aldimines participated in the addition reaction to styrene under the Co/P(*p*-Tol)$_3$ catalytic system,[12] thereby affording the corresponding 1,1-diarylethanes with high branched selectivity (Scheme 2). The *ortho*-substituted aromatic aldimines, including those having an electron-donating amino group and a pyrene skeleton, afforded the corresponding adducts **3ba**–**3ga** in moderate to

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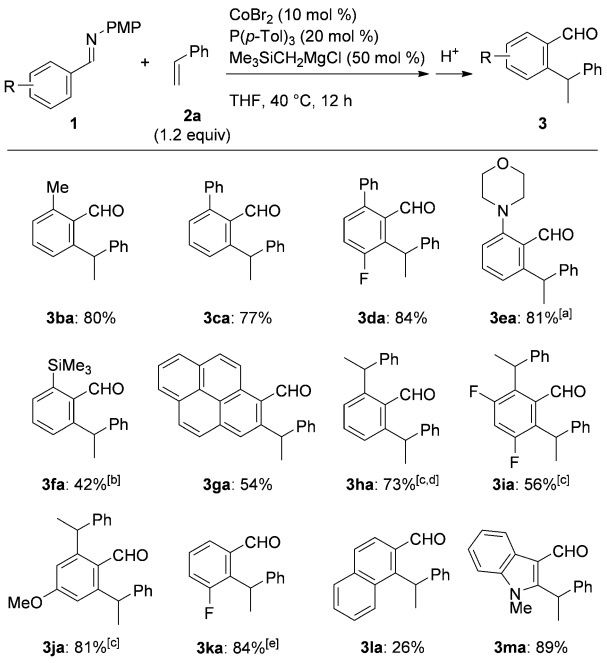
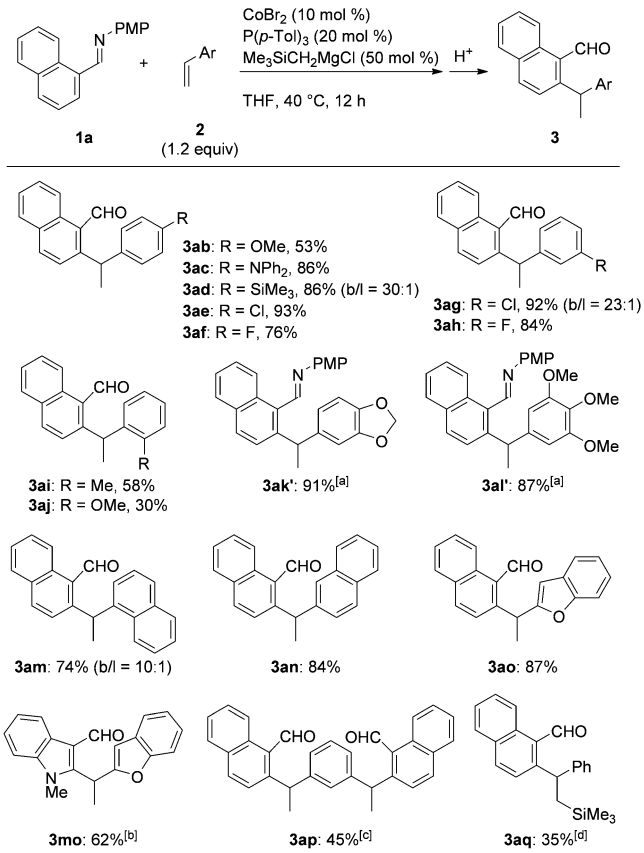


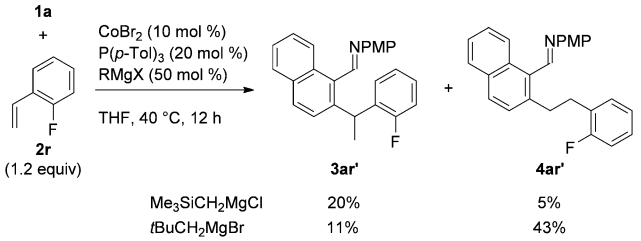
Scheme 2. Addition of various aromatic aldimines to styrene (0.3 mmol scale). The branched/linear ratio was greater than 50:1. Unless otherwise stated the yields are those of the isolated products. [a] A 0.9 mmol scale. [b] The yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c] The reaction was performed using 2.4 equiv of styrene. The product was obtained as an approximately 1:1 mixture of diastereomers. [d] The product obtained as a mixture with the monoadduct (7%). [e] The reaction was performed using 0.3 mmol of aldimine and 0.12 mmol of styrene. The yield was based on styrene.



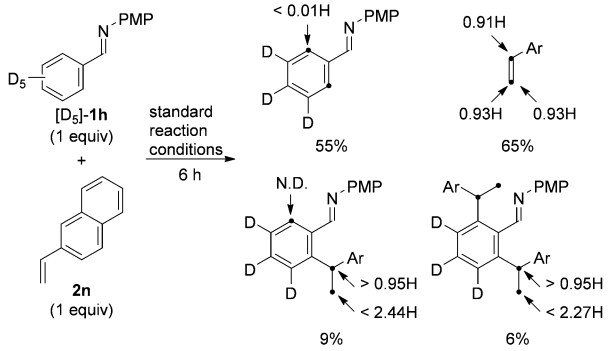
Scheme 3. Addition of **1a** to various styrene derivatives (0.3 mmol scale). The branched/linear ratio was greater than 50:1 unless otherwise noted. The yields are those of the isolated products. [a] The product was obtained without acidic hydrolysis. [b] The aldimine derived from indole-3-carboxaldehyde (**1l**) was used instead of **1a**. [c] The reaction was performed using 3 mmol of **1a**, 1.2 mmol of 1,3-divinylbenzene, 20 mol% of $CoBr_2$, 40 mol% of $P(p\text{-Tol})_3$, and 100 mol% of Me_3SiCH_2MgCl. The product was obtained as an approxiamtely 1:1 mixture of diastereomers. [d] The reaction was performed using (*Z*)-trimethyl(styryl)silane.

good yields. The reaction of aldimines, having no *ortho* substitutent, that is, aldimines derived from benzaldehyde, 3,5-difluorobenzaldehyde, and *p*-anisaldehyde, with 1.2 equivalents of styrene resulted in the formation of a mixture of mono- and dialkylation products, with the latter being the major product. In the presence of an excess amount of styrene (2.4 equiv), these aldimines afforded the corresponding adducts **3ha**, **3ia**, and **3ja** in moderate to good yields. When the amount of styrene was limited to 0.4 equivalents, an aldimine derived from *m*-fluorobenzaldehyde reacted regioselectively at the C–H bond proximal to the fluorine atom, thus affording the adduct **3ka** in 84% yield. Such regioselectivity has been frequently observed in aromatic C–H functionalization reactions using cobalt and other transition-metal catalysts.[10a,13–15] An aldimine derived from 2-naphthaldehyde reacted regioselectively at the more hindered position, thus affording the adduct **3la**, albeit in a modest yield. The reaction on the C2 position of the indole proceeded efficiently (see **3ma**). Aldimines bearing electron-withdrawing groups (p-CF_3 and p-CN) did not participate in the reaction.

We next explored the scope of styrene derivatives using **1a** as the reaction partner (Scheme 3). A variety of styrene derivatives bearing electron-donating (alkoxy, amino, and silyl) and electron-withdrawing (chloro and fluoro) substituents participated in the reaction, thereby affording the branched adducts **3ab**–**aj**, **3ak′**, and **3al′** in moderate to good yields with high branched selectivity, and bromo and iodo substituents were not tolerable because of hydrodehalogenation. The products **3ak′** and **3al′** were isolated as aldimine derivatives because the acidic hydrolysis resulted in intramolecular Friedel–Crafts cyclization (see below). An *ortho* substituent, especially the methoxy group, slowed the reaction (see **3ai** and **3aj**). The reaction was also applicable to 1- and 2-vinylnaphthalenes and 2-vinylbenzofuran, as demonstrated by the formation of the adducts **3am**–**3ao** in good yields. The latter olefin also afforded the adduct **3mo** with indole in 62% yield. Twofold addition of **1a** to 1,3-divinylbenzene took place to afford the adduct **3ap** as a 1:1 mixture of diastereomers in 45% overall yield. (*Z*)-Trimethylsilyl(styryl)silane was also amenable to the present hydroarylation, thus affording the 1,1-diarylalkane **3aq**, albeit in a modest yield. Note that the reaction of the *E* isomer of this vinylsilane was more sluggish under identical reaction conditions (7% yield). α-Methylstyrene did not participate in the reaction.



Scheme 4. Influence of Grignard reagent on the branched/linear selectivity of the addition of **1a** to 2-fluorostyrene (**2r**). The yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

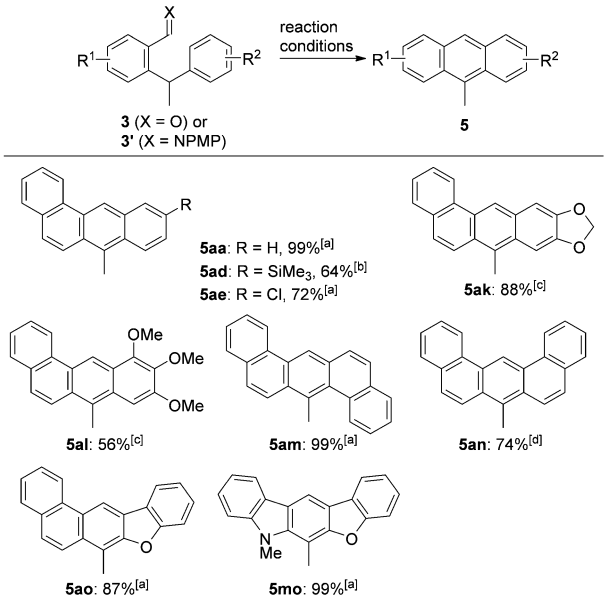


Scheme 5. Deuterium-labeling experiment. The yields refer to the isolated yields. The content of protons on each carbon atom was determined by ^{1}H NMR analysis. Ar = 2-naphthyl. N.D. = Not determined.

During the exploration of styrene derivatives, we observed an interesting effect of Grignard reagents on the branched/linear selectivity (Scheme 4). Whereas the reaction of **1a** and 2-fluorostyrene (**2r**) preferentially afforded the expected branched adduct **3ar′** under the standard reaction conditions employing Me_3SiCH_2MgCl, the use of *t*$BuCH_2MgBr$ instead resulted in selective formation of the linear adduct **4ar′**, albeit in modest overall yields for both cases. Though not as drastic as this case, the reaction of other styrenes using *t*$BuCH_2MgBr$ also resulted in considerable formation of linear adducts (see Table S2 in the Supporting Information). These observations may suggest that the Grignard reagent not only serves as a reducing agent for the cobalt precatalyst but also is intimately associated with the catalytically active species to influence the product-determining step.[9,10a]

In our previous study on the cobalt-catalyzed reaction of 2-arylpyridine with styrene, we proposed a catalytic cycle consisting of C–H oxidative addition, styrene insertion leading to either a branched or linear alkylcobalt intermediate, and reductive elimination (see Scheme S1 in the Supporting Information), where the former two steps are reversible and the last step is rate- and regioselectivity-determining.[9] Given this background, we were surprised to find that the pentadeuterated benzaldimine [D_5]-**1h** failed to react with parent and substituted styrenes including **2a**, **2c**, **2k**, and 4-*tert*-butylstyrene under the standard reaction conditions. Only the reaction with 2-vinylnaphthalene (**2n**) afforded the mono- and dialkylation products in low yields (Scheme 5). The distribution of the deuterium atoms in the recovered starting materials and the products was in contrast to the extensive deuterium scrambling observed in the Co/PCy_3-catalyzed reaction of 2-(pentadeuteriophenyl)pyridine.[9a] The deuterium content at the *ortho* position of [D_5]-**1h** did not decrease at all, and the α and β positions of **2n** were only slightly deuterated. The products had a significant deuterium content at the methyl groups, while no apparent deuteration was observed at the methine groups. While we speculate that the present and previous reactions share the same mechanistic framework, the above observations suggest that there is a significant difference in terms of the relative rates of the elementary steps. Thus, the most rate-influencing steps of the present reaction is likely the C–H oxidative addition rather than reductive elimination.

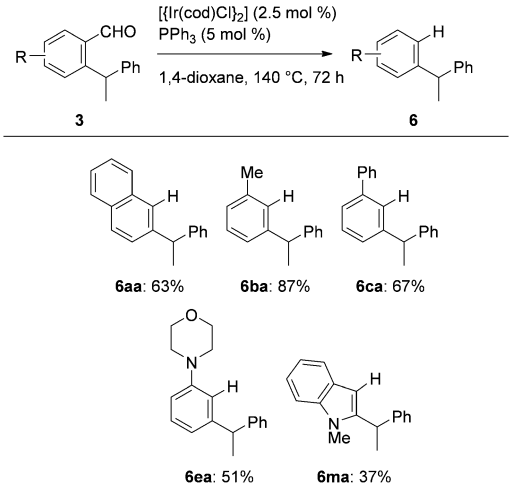
The *ortho*-formyl functionality in the present 1,1-diarylethane products serves as a versatile synthetic handle for additional transformations. Given the importance of linearly fused PAHs as building blocks for optoelectronic applications,[16] an attractive transformation of the diarylethane products would be the construction of linearly fused PAHs through Lewis or Brønsted acid mediated cyclization (Scheme 6). Thus, the tetraphene derivatives **5aa**, **5ad**, and **5ae** were obtained in good yields by In$(OTf)_3$-catalyzed dehydrative cyclization[17] or BF_3-catalyzed, sulfonamide-mediated deaminative cyclization.[18] Because of the electron-rich 3,4-methylenedioxyphenyl and 3,4,5-trimethoxyphenyl groups, the hydroarylation products **3ak′** and **3al′**



Scheme 6. Transformation of the hydroarylation products into polycyclic aromatic hydrocarbons. The yields are those of the isolated products. [a] Reaction conditions: In$(OTf)_3$ (5 mol%), DCE, 115 °C. [b] Reaction conditions: *p*-toluenesulfonamide (1.1 equiv), $BF_3{\cdot}OEt_2$ (30 mol%), toluene, RT. [c] Reaction conditions: 3 N HCl, EtOAc, RT. [d] Reaction conditions: 3 N HCl, EtOAc, 70 °C.

smoothly underwent cyclization to the tetraphenes **5ak** and **5al**, respectively, upon treatment with aqueous HCl at room temperature. Benzo[*k*]tetraphene **5am**, benzo[*m*]tetraphene **5an**, and heteroacenes **5ao** and **5mo** were also obtained in good yields.

Another notable transformation of the 1,1-diarylethane products is catalytic decarbonylation (Scheme 7). With the aid of the [{Ir(cod)Cl}$_2$]/PPh$_3$ catalytic system,[19] the formyl groups on the hydroarylation products **3aa**–**3ca**, **3ea**, and **3ma** were removed to afford the corresponding 1,1-diarylethanes **6aa**–**6ca**, **6ea**, and **6ma** in moderate to good yields, and thus featuring substitution patterns that are not accessible by the Friedel–Crafts-type alkylation.



Scheme 7. Removal of the *ortho*-formyl group of the 1,1-diarylethane products by iridium-catalyzed decarbonylation. The yields are those of the isolated products. cod = cyclo-1,5-octadiene.

In summary, we have developed a mild and highly branched-selective addition reaction of aromatic aldimines to styrenes using a simple cobalt/triarylphosphine catalyst, which has significantly expanded the synthetic scope of the hydroarylation approach to 1,1-diarylethanes. Furthermore, the use of the aldimine directing group has enabled the facile preparation of linearly fused PAHs through the hydroarylation/cyclization sequence, which may complement existing synthetic methods such as those based on Diels–Alder reactions and metal-catalyzed annulation reactions involving alkynes.[20] Further studies on the mechanism, development, and application of regio- and stereoselective olefin hydroarylation by C–H activation are currently underway.

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