A general gold-catalyzed direct oxidative coupling of non-activated arenes†

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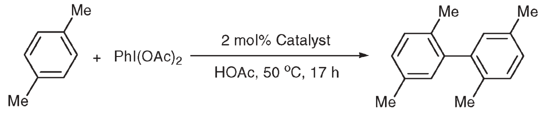
A gold-catalyzed mild and general oxidative homo-coupling of arenes using $PhI(OAc)_2$ as the oxidant is described (13 examples, 31–81% yield).

Biaryls constitute an important structural component in natural products, pharmaceuticals, agrochemicals and materials.[1] In recent decades there have been rapid advances in $C(sp^2)$–$C(sp^2)$ bond formation reactions to construct biaryls. Traditionally, the arene being coupled needs to be 'pre-activated', such as by halogenation, prior to metal-mediated coupling reactions.[2] Alternatively, halogenated arenes are converted to organometallic reagents and homo- or hetero-coupling reactions are performed in the next step. Transition metal-catalyzed cross-coupling reactions are undoubtedly the most versatile protocols to connect electrophilic reagents (ArX) with nucleophilic organometallic derivatives (ArM).[3] One drawback of these reactions is the necessity for an activating group on both the coupling partners. Though elegant C–H bond functionalization methods to obtain the organometallic reagents save one synthetic step,[4] direct metal (*e.g.* Pd, Rh, Ru *etc.*) catalyzed regioselective C–H bond activation with subsequent C–C bond formation with ArX or ArM has a better atom efficiency.[5] Very recently, significant advances have been made in the development of arylation of arenes, such as indole, benzofuran and naphthalene, with benzenes in metal-catalyzed reactions in the presence of oxidants.[6] Light mediated Ar–H substitution[7] and Lewis acid[8] mediated oxidative coupling of arenes are also impressive. However, these reactions typically take place under an inert atmosphere or drastic conditions and have limited substrate scope. Hence, the improvement of C–H bond transformations to biaryls through direct oxidation under practical and mild conditions is highly desired.

Gold has been under the spotlight of the chemistry stage as a catalyst in recent years.[9] Both heterogeneous and homogeneous gold catalysts showed excellent results in diversified reactivities. With regard to homogeneous catalysis, on the one hand gold shows reactivity as a 'soft' Lewis acid to perform C–C,[10] C–N,[11] C–O[12] and C–F[13] bond formation reactions with multiple bonds. On the other hand redox-type reactions such as reduction,[14] oxidation,[15] diboration,[16] homo-coupling of boronic acids,[17] cross-coupling reactions[18] and coupling of alkyl triflates with electron-rich arenes[19] have been demonstrated. Novel structures have been made smoothly with gold catalysts *via* cascade reactions.[20]

Notably, gold has a rich organometallic chemistry.[21] Its aryl complexes have been synthesized from Au(I)/(III) complexes.[22] Alternatively, C–H bond activation of arenes with Au(III) complexes to form gold aryl complexes is possible[23] and these gold aryl complexes can produce aryl acetylenes with concomitant formation of Au(I) species.[21a] Though the catalytic version of this interesting transformation has been attempted, it gave only the hydroarylation of alkynes.[24] Coupling of the ligands on gold complexes was also reported.[25] Thus, gold is a good candidate to act as a catalyst for biaryl synthesis from arenes with a suitable oxidant.[26] Based on our experience with C–H functionalization of arenes[27] and oxidation reactions,[28] here we report the first general gold-catalyzed oxidative coupling of arenes to yield biaryls.

Our screening started with a model reaction, using *p*-xylene to form 2,2′,5,5′-tetramethylbiphenyl catalyzed by various catalysts using $PhI(OAc)_2$ as the oxidant. 2 mol% of catalyst was employed in our primary investigations (eqn (1)). To our delight, $HAuCl_4$ catalyzed the reaction smoothly to yield the biphenyl in 74% yield at 55 °C (Table 1, entry 1). Other gold catalysts such as $Au(OAc)_3$ and $AuCl(PPh_3)$ also showed significant activity (39 and 76% yield respectively). Although Lewis acid mediated oxidative coupling of electron-rich arenes in an overstoichiometric amount has been reported, typical Lewis acids like $FeCl_3$ and $BF_3{\cdot}OEt_2$ did not work under our catalytic reaction conditions. Further solvent screening revealed that acetic acid is a good solvent for this reaction. Non-coordinative solvents like 1,2-dichloroethane (42% yield) and the substrate, *p*-xylene (58% yield), can also be used as the reaction medium (see ESI†).



(1)

Even though a slightly higher concentration (10 equiv. to the oxidant) of arene is used to get an optimized yield, the excess starting material can be recovered and reused. It should be noted that strong acids [*e.g.* TFA (>1% yield)] gave inferior results, possibly due to the formation of polymers. It is noteworthy that our protocol can be easily managed in ambient conditions. It is not necessary to use inert conditions and no pre-treatment of solvent or substrate is needed. When acetic anhydride was used (71% yield) instead of HOAc, no improvement was observed. This result implies that water in the reaction mixture does not affect our system very much. Among the several oxidants used ($K_2S_2O_8$,

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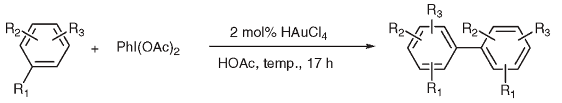
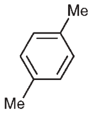
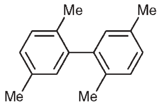
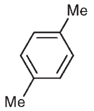
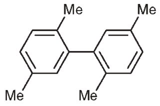
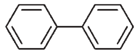
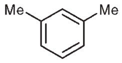
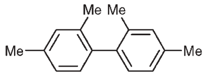
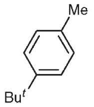
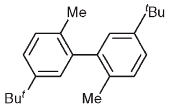
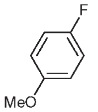
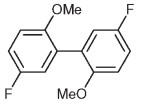
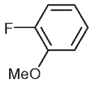
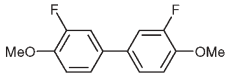
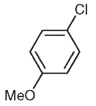
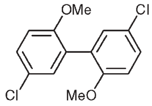
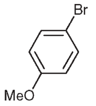
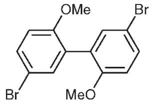
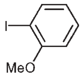
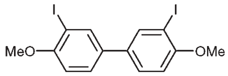
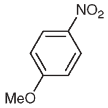
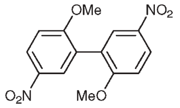
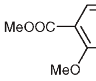
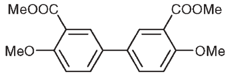
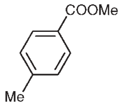
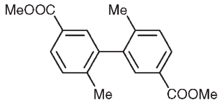
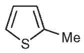
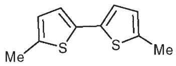
† Electronic supplementary information (ESI) available: Effect of solvent, oxidant and catalyst in oxidative homo-coupling of *p*-xylene and spectral data of compounds synthesized. See DOI: 10.1039/b714928j

Table 1 Au-catalyzed oxidative homo-coupling of arenes[a]



Entry	ArH	Major product	Temp./°C	Yield (%)[b]
1			55	74[c]
2[d]			55	81[c]
3[d]			95	71[c]
4			55	75[e]
5			95	62
6			95	68[c]
7[c]			55	63[f]
8			95	68
9			95	56
10			95	79[g]
11			95	38
12			95	74[h]
13			95	78
14			95	31

[a] Reaction conditions: oxidant (1.0 mmol), *p*-xylene (10.0 mmol), dodecane (55 μL, internal standard) and $HAuCl_4$ (0.02 mmol, 2.0 mol%) were heated in the appropriate solvent (1.0 mL) at 55 °C in air for 17 h. [b] Isolated yields based on the oxidant used. [c] GC yields; trimers were observed. [d] 2 mL of solvent were used. [e] An isomer mixture was isolated; product ratio = 89 : 11 by GC-FID. [f] 54% of *para–para* coupled product and 9% of *para–ortho* coupled product were isolated. [g] 69% of *para–para* coupled product and 10% of *para–ortho* coupled product were isolated. [h] 74% of *para–para* coupled product was isolated and the *para–ortho* coupled product was observed.

Oxone®, 35% CH_3CO_3H, $Cu(OAc)_2$, see ESI†), $PhI(OAc)_2$ proved to be the best oxidant for this reaction.

$PhI(OCOCF_3)_2$ is a suitable reagent for Lewis acid mediated biaryl formation reactions, however it gives slightly lower productivity in our model reaction (69% yield).

To test the effectiveness of the gold catalytic system, a range of arenes was examined using the preliminary optimized reaction conditions (Table 1). In general, the reaction shows a typical electrophilic aromatic substitution pattern. Notably, a variety of arenes work comparably well (Table 1). Even 4-nitroanisole, which gave no product in Lewis acid mediated oxidative coupling,[8g] furnished the corresponding biaryl in moderate yield (Table 1, entry 11).

The reaction protocol tolerates a wide range of functional groups. All halogens survive after the reaction. To the best of our knowledge, neither palladium- nor Lewis acid-catalyzed reactions can maintain the reactivity with tolerance to all halogens. Only a few C–H functionalization reactions exhibit such high halogen group preservation (Table 1, entries 7–10).[4b–e] Other functional groups such as methoxide and esters work equally well in our reaction conditions (Table 1, entries 12 and 13). It is worth mentioning that electron-rich heterocycles, such as thiophene, also gave the corresponding products in moderate yield.

Interestingly, a decrease of reactivity from $HAuCl_4$ to $Au(OAc)_3$ was observed. It suggests that some chloride ions may still coordinate to the catalytic center. As a trace amount of chlorinated product was detected by GC-MS, it is likely that the gold reaction center contains both acetate and chloride ions. Though arene cationic radical has been observed in Lewis acid mediated oxidative coupling reactions of electron-rich arenes at −78 °C,[8e] no biaryl was observed with 2 mol% $BF_3{\cdot}OEt_2$ in the present system. Moreover, nitro-substituted anisole did not work in the Lewis acid systems while it worked moderately in our case. Since $AuCl(PPh_3)$ worked as well as $HAuCl_3$ under our oxidative conditions, Au(III) is suggested as the CH-functionalization catalyst.[29] The substrate with the weakest carbon–halogen bond (C–I) coupled smoothly in our conditions (Table 1, entry 10). It further implies that high valent Au(III) is the major catalyst.[18,30] A typical electrophilic aromatic substitution pattern has been observed in our reaction conditions. Hence, participation of a free cationic radical is not likely, but the possibility of an auration reaction, a Friedel–Crafts type substitution or the participation of a coordinated cationic radical cannot be ruled out.

In summary, a new general gold-catalyzed oxidative homo-coupling of arenes is reported. It can be simply handled in air and no pre-treatment of substrate and solvent is necessary. Interestingly, our reaction protocol does not require any Ag salt to enhance the reactivity.[31] Remarkable functional group tolerance has been shown in our reaction conditions. The results shown represent the first successful example of Au-catalyzed oxidative homo-coupling of simple arenes. In principle the double CH-functionalization is the most efficient process for the synthesis of biaryls. Improved systems for direct cross-coupling of arenes are under investigation and mechanistic studies of this reaction are in progress in our laboratory.

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