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Intermolecular Cross-Coupling of Simple Arenes via C−H Activation by Tuning Concentrations of Arenes and TFA

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Summary: Formation of unsymmetrical biaryls from simple arenes has been achieved successfully in a catalytic system of $Pd(OAc)_2/CF_3CO_2H(TFA)/K_2S_2O_8$ just by tuning the concentrations of arenes and TFA under mild conditions. A proposed mechanism containing two-step aromatic C−H activation on this novel intermolecular cross-coupling of arenes is also suggested and partly supported by experiments.

Formation of biaryls, especially unsymmetrical biaryls, is a very useful method in organic synthesis, which normally involves an aryl halide coupling with another organometallic fragment such as in the Suzuki, Stille, and Negishi reactions.[1−2] Recently, some progress has been made in the coupling of aryl halides with simple arenes through aromatic C−H activation to produce biaryls.[3] However, only a few examples of intermolecular homocouplings of simple arenes have been reported since VanHelden and Verberg disclosed the formation of biphenyl from benzene by using a stoichiometric amount of $PdCl_2$.[4−5] Herein, we describe a novel method to form unsymmetrical biaryls by a palladium-catalyzed intermolecular cross-coupling reaction of simple arenes via aromatic C−H activations.

Initially, we focused on Pd(II)-catalyzed homocoupling of benzene in an oxidative system on the basis of those previous efforts.[6] After screening a variety of palladium catalysts, oxidants, and solvents, we found that the optimum catalytic system for the formation of biphenyl was $Pd(OAc)_2/CF_3CO_2H$ (TFA)/$K_2S_2O_8$, which is the same system for the Pd(II)-catalyzed carboxylation of arenes.[6d,e] In the testing of homocoupling of benzene at room temperature, no product was detected by GC or TLC when the catalyst was $PdCl_2$, Pd/C, or $PtCl_2$, respectively, or TFA was replaced by AcOH.

Subsequently, we tried the cross-coupling of benzene (**1a**) with anisole (**1b**) in the same catalytic system (Scheme 1). In the reaction, with a high concentration of TFA and excess **1a**, the major product normally was biphenyl **2a**. Unexpectedly, just by decreasing the amount of TFA to 0.63 mmol under the same conditions, we found that major products could be these unsymmetrical biaryls **2b**,**c** generated from **1a** with **1b**. Meanwhile, neither homocoupling products from **1b** nor *m*-methoxy biphenyls were detected by GC in this case. In contrast, if the concentration ratio of **1a** to **1b** was less than 10, the homocoupling product from **1b** could be detected by GC. Thus, these results suggest that both the lower concentration of TFA and the higher concentration ratio of **1a** to **1b** are favorable to avoid producing homocoupling products from **1b** and enhance the yields of unsymmetrical biaryls as major products. Moreover, the coupling of **1a** with mesitylene (**1c**) to form the unsymmetrical biaryl **2d** was another example which displayed an analogous performance (Scheme 1). In the above processes, however, formation of biphenyls cannot be avoided just by tuning the concentrations of arenes and TFA.

For further investigations on the selectivity, TON, and yield of preparing unsymmetrical biaryls in the system of $Pd(OAc)_2$/TFA/$K_2S_2O_8$ by tuning concentrations of arenes and TFA, a more active arene, naphthalene (**1d**), was selected to undergo the cross-coupling with benzene (**1a**), anisole (**1b**), mesitylene (**1c**), *p*-xylene (**1e**), and chlorobenzene (**1f**) under the corresponding reaction conditions, respectively. These effects of catalyst, TFA, $K_2S_2O_8$, and concentration ratio of arenes on the cross-coupling of naphthalene with benzene have been screened, and details are given in the Supporting Information.

As given in Table 1, various unsymmetrical biaryls as major or sole products were produced by controlling the concentrations of arenes and TFA in the Pd(II)-catalyzed oxidative cross-coupling reactions of **1d** with a variety of arenes. No homocoupling products from ArH were obtained in the presence of **1d** in these reactions, except for entry 7 of Table 1; therefore,

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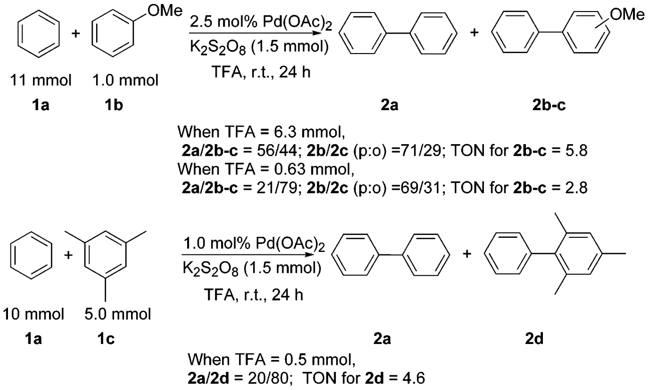
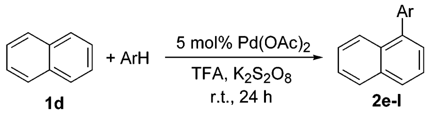
Scheme 1. Pd(II)-Catalyzed Oxidative Cross-Coupling of Benzene with Anisole or Mesitylene (GC Detection)

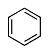
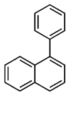
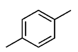
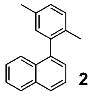
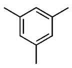
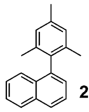
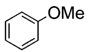
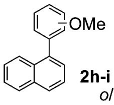
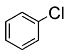
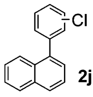


When TFA = 6.3 mmol,
2a/**2b-c** = 56/44; **2b**/**2c** (p:o) =71/29; TON for **2b-c** = 5.8
When TFA = 0.63 mmol,
2a/**2b-c** = 21/79; **2b**/**2c** (p:o) =69/31; TON for **2b-c** = 2.8

When TFA = 0.5 mmol,
2a/**2d** = 20/80; TON for **2d** = 4.6

Table 1. Pd(II)-Catalyzed Oxidative Cross-Coupling of Naphthalene with Various Arenes[a]

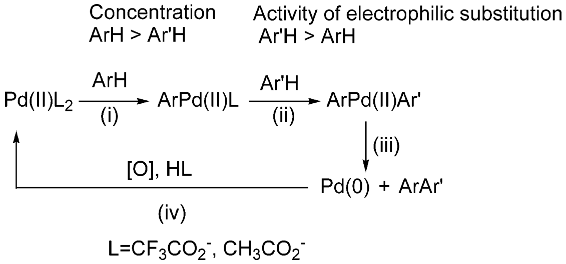


entry	ArH	ArH/**1d** (mol/mol)	TFA (mmol)	product	yield[b] (%)	selectivity[c] (mol%)	TON
1	 **1a**	25	0.5	 **2e**	15	93[d]	3.1[d]
2[e]		100	1.3		32	>99	3.2
3[f]		50	2.6		11	55	22.0
4	 **1e**	25	1.0	 **2f**	16	>99	3.3
5		25	2.6		50	77	10.0
6	 **1c**	15	0.5	 **2g**	25	>99	5.0
7[g]		15	1.0		21	>99	21.0
8	 **1b**	5	0.1	 **2h-i** *o*/*m*/*p*=29:0:71[h]	15	71[d]	3.0[d]
9[i]	 **1f**	60	1.0	 **2j-l** *o*/*m*/*p*=47:8:45	16	62[d]	3.3[d]

[a] Conditions: **1d**, 1.0 mmol; Pd(OAc)$_2$, 0.05 mmol; K$_2$S$_2$O$_8$, 1.5 mmol; room temperature; 24 h; GC analysis. [b] GC yield based on **1d**. [c] Selectivity = (cross-coupling products)/(all consumed **1d**). [d] Isolated products. [e] Conditions: **1d**, 0.5 mmol. [f] Conditions: Pd(OAc)$_2$, 0.01 mmol; 55 °C, 72 h. [g] Conditions: Pd(OAc)$_2$, 0.01 mmol; 2-(3,5-dimethylbenzyl)-1,3,5-trimethylbenzene (**2m**), 0.13 mmol produced. [h] ^{1}H NMR analysis. [i] Conditions: **1d**, 0.5 mmol; 55 °C.

the selectivity was only related to the consumed **1d** (selectivity = (unsymmetrical biaryl)/(all consumed **1d**)), in a range of 55−99%. Comparing **1f** with **1b**, we found that both higher concentrations of ArH and TFA were necessary for the electron-poor arene **1f** in these cross-coupling reactions (Table 1, entries 8 and 9), and *m*-chloro biaryl could even be produced by heating (Table 1, entry 9), which means more TFA and heating may enhance the activation of C−H bonds on electron-poor arenes in the presence of palladium catalyst. Without the catalyst Pd(OAc)$_2$ in these cases, however, no coupling reaction occurred. Although TON could be improved to over 20 by reducing the amount of catalyst with a longer reaction time (Table 1, entries 3 and 7), the yields of all unsymmetrical biaryls based on **1d** were still not high, just from 11% to 50%. One explanation is that the unsymmetrical biaryls produced in these reactions are more active in aromatic C−H activation than the starting arenes; hence, with the amount of the cross-coupling products accumulating, these biaryls easily undergo other further couplings which would seriously limit the yields and the efficient TONs for the unsymmetrical biaryls. Therefore, in order to get a high selectivity of this cross-coupling reaction, those factors related to the reaction rate, particularly the reaction time and temperature, must be restricted. Overall, these influences of the concentrations of arenes and TFA are remarkable in the formation of unsymmetrical biaryls, inspiring us to consider the mechanism of this cross-coupling of simple arenes.[7]

Scheme 2. Possible Mechanism of Cross-Coupling Reactions of Arenes



According to the previous mechanism of carboxylation of arenes via aromatic C−H activation in the same catalytic system of Pd(OAc)$_2$/TFA/K$_2$S$_2$O$_8$,[6d,e] it is possible that there is a catalytic cycle with four steps in the formation of unsymmetrical biaryl, as shown in Scheme 2: (i) the first electrophilic attack of Pd^{II}L$_2$ on ArH, which is in excess in the mixture, mainly produces an arylpalladium(II) species, ArPd^{II}L; (ii) the second electrophilic attack of ArPd^{II}L on the electron-rich arene Ar′H generates the species ArPd^{II}Ar′; (iii) after a reductive elimination, the unsymmetrical biaryl ArAr′ is produced, and Pd(0) is formed as well; (iv) finally, Pd(0) is reoxidized by an oxidant in the presence of HL to give Pd^{II}L$_2$ again and the catalytic cycle is complete.

In order to avoid the homocoupling of the more active arene Ar′H, generally the relative electron-poor arene ArH should be in excess in the coupling reaction. In step i, the formation of ArPd^{II}L is mainly dependent on the concentrations of arenes; that is, the relatively electron-poor arene with higher concentration is preferred to be attacked by a Pd(II) catalyst. Otherwise, if Pd^{II}L$_2$ attacks the electron-rich arene Ar′H with lower concentration in the mixture to produce Ar′Pd^{II}L at the same time, then it also tends to attack the more active arene Ar′H and finally the homocoupling product Ar′Ar′ is generated. However, for example, we have not found any binaphthyl products by GC detection in the reactions of naphthalene with excess benzene, *p*-xylene, or mesitylene, respectively (Table 1, entries 2, 4, and 6), which indicates that the selectivity of forming ArPd^{II}L in step i is very high in our cases.

TFA, in comparison with AcOH, can improve the reactivity of Pd(II) catalysts strongly, as mentioned before.[6] In contrast, decreasing the amount of TFA mainly leads to the less electrophilic catalyst ArPd^{II}L, which displays preferential attack of the electron-rich arene in step ii. However, if the difference in arene activity between ArH and Ar′H is not large enough or the concentration of TFA is too high, the homocoupling product ArAr from the relatively electron-poor arene ArH will be produced in those reactions, such as in Scheme 1 and entry 7

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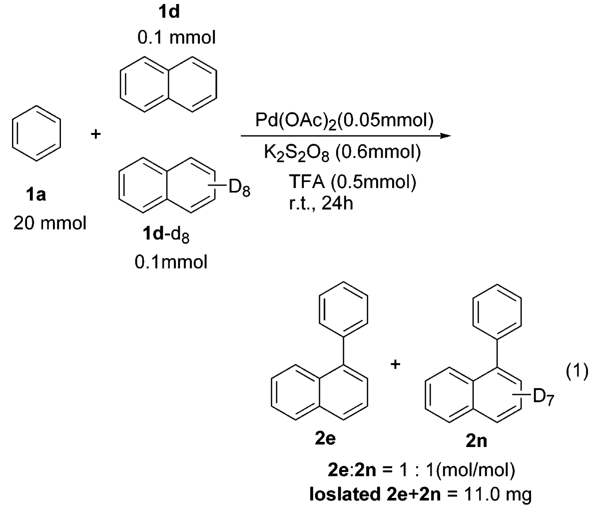

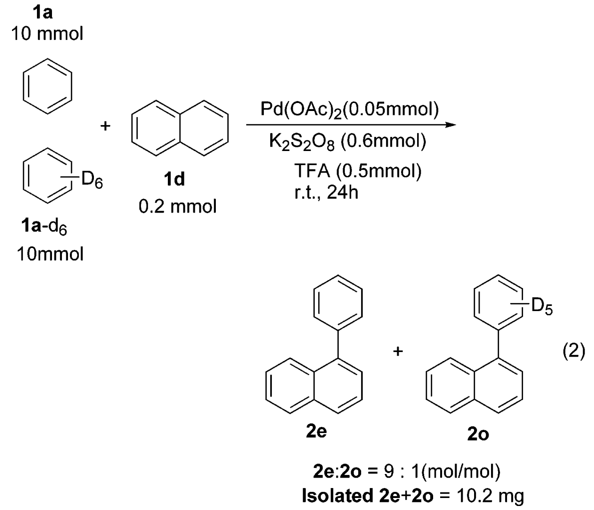

of Table 1. Therefore, through the concentration selection of step i and the activity selection of step ii, an unsymmetrical biaryl is obtained from this cross-coupling reaction.

This proposed mechanism involving two-step aromatic C−H activation is partly supported by the following reactions between **1a**/**1a**-*d*$_6$ and **1d**/**1d**-*d*$_8$. After product isolation, a kinetic isotope effect (KIE) was observed by using ^{1}H NMR spectroscopy only in the coupling reaction of **1a**/**1a**-*d*$_6$ with **1d** (eq 2), not in the reaction of **1a** with **1d**/**1d**-*d*$_8$ (eq 1).[8] This indicates that the activation of C−H bonds[9] on benzene has a significant effect on the entire reaction rate, and it seems that there are two-step aromatic C−H activations happening during the reaction. In addition, since homocoupling products have not been found in these reactions, it also indicates that the first step in the reaction is to form PhPd^{II}L from **1a**; then the attack of PhPd^{II}L on the more active **1d**, resulting in a cross-coupling with high selectivity, is favorable and reasonable.

In summary, preparation of unsymmetrical biaryls as the major or sole products via aromatic C−H activation is feasible and has been achieved just by tuning the concentrations of simple arenes and TFA in the system Pd(OAc)$_2$/TFA/K$_2$S$_2$O$_8$. Although this cross-coupling reaction is currently not a practical method because of its low yields and TONs, it provides some valuable information on potential catalytic systems in the synthesis of unsymmetrical biaryls from simple arenes and in aromatic C−H activations. The scope and the actual mechanism of this novel cross-coupling reaction will be explored further.

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Supporting Information Available: Text and figures giving experimental details and characterization data of cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] No H/D exchange was observed in the coupling of **1a** with **1d**-*d*$_8$. See the Supporting Information.

[9] Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440.