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Organocatalytic C−H/C−H′ Cross-Biaryl Coupling: C-Selective Arylation of Sulfonanilides with Aromatic Hydrocarbons

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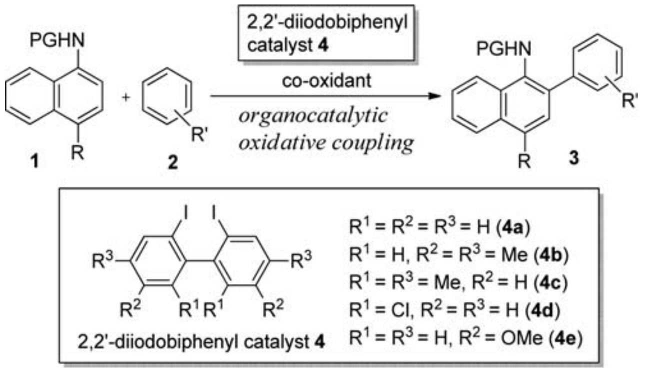
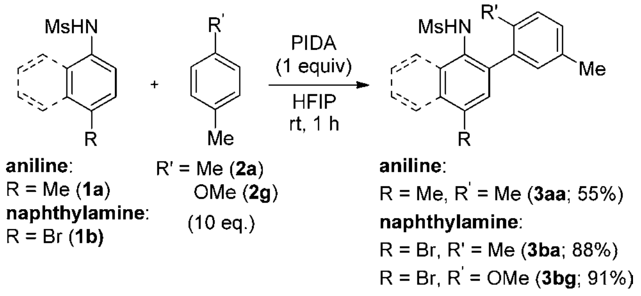
Supporting Information

ABSTRACT: The hypervalent iodine-mediated C−C selective coupling of *N*-methanesulfonyl anilides with aromatic hydrocarbons has been developed. The first organocatalytic oxidative cross-biaryl-coupling was achieved by the catalyst control in defining specific 2,2′-diiodobiphenyls for the direct C−C bond formations.

Scheme 1. 2,2′-Diiodobiphenyl Catalyzed Cross-Coupling of Anilides 1 with AHs 2



Scheme 2. Cross-Coupling of Anilides 1 with AHs 2 under Stoichiometric Conditions



Direct coupling between two aromatic substrates that accompanies the double C−H bond transformation, called oxidative cross-coupling or cross-dehydrogenative coupling (CDC), is now being extensively investigated as the short step and greener alternative to the well-established transition-metal-catalyzed coupling of metalated and halogenated arenes represented by Negishi and Suzuki−Miyaura coupling.[1−3] In general, the development of oxidative couplings has been severely hampered by various problematic side reactions, i.e., homocoupling, overoxidation, and polymerization, especially under catalytic conditions, while a significant advancement in transition-metal chemistry has realized a variety of controlled reactions in recent years.[1,2]

We have also devoted a great deal of effort to establish a green system for the synthesis of biaryls through the development of metal-free couplings using hypervalent iodine(III) reagents, such as $PhI(OAc)_2$ (PIDA) and $PhI(OCOCF_3)_2$ (PIFA), as the specific oxidants.[4] One of the important goals of this area is the development of organocatalytic oxidative cross-coupling, however, it has still remained as a big challenge, especially for the coupling of unfunctionalized aromatic hydrocarbons (AHs).

Here, we describe the discovery of a novel C−C selective cross-coupling of aniline derivatives with AHs under the first organocatalytic conditions (Scheme 1). The investigation of the protecting groups and AH (**2a**: *p*-xylene) as the nucleophile under stoichiometric conditions was initially studied in which the reaction of *N*-methanesulfonyl (Ms) anilide **1a** promptly afforded the biaryl product **3aa** by the C−C coupling under PIDA−HFIP (hexafluoroisopropanol)[5] reagent−solvent conditions (Scheme 2). The use of other protecting groups, such as Me, Ac, CF_3CO, Boc, and Tf groups, instead of the Ms group did not afford any of the desired coupling products.[6] Even the Ts group provided a significantly reduced yield (<30% yield) by forming undesired byproducts. On the other hand, the yield of the biaryl products **3** was dramatically improved by employing the 1-naphthylamine derivative **1b** as the substrate. Regarding the nucleophiles, the C−C coupling selectively occurred with the *para*-substituted phenyl ether **2g** as good as *p*-xylene **2a** to give a considerable yield of the corresponding biaryls, **3aa**, **3ba**, and **3bg**.

While the iodine(III)-mediated N-selective couplings of aniline derivatives with aromatic substrates have emerged in recent years,[7,8] at the outset of our studies, there were no reported examples of the C−C coupling with AH nucleophiles. AH nucleophiles, such as halobenzene and mesitylene, with *N*-acyl anilides were reported to predominantly provide diarylamines by the C−N bond formation over C−C coupling.[7] As an indirect example via formal [4 + 3] intermediates, Canesi and co-worker reported that the coupling of *N*-Ms anilides with thiophenes afforded biaryls through the C−N bond formation and successive cleavage for the fomation of the aromatics.[9a] More recently, an AH nucleophile, naphthalene, was demonstrated to provide a C−C coupling product through a similar

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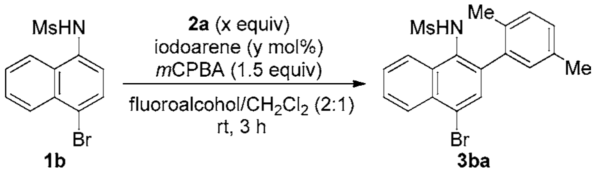
indirect way to that for thiophenes in utilizing our dearomatizing [2 + 3] cyclization[10]—isomerization process.[9b] These methods seem not to have a promising prospect for converting to a catalytic version due to the narrow reaction scope and rather low coupling productions.

Once the new coupling of the AHs was launched, we next envisioned extending the coupling to a catalytic version. Organoiodine compounds have been introduced as a unique class of organocatalysts for developing the oxidative bond-forming reactions by us[11e] and others.[11f] However, standard catalytic conditions using 10 mol % iodobenzene with *m*CPBA as the oxidant did not work well for the present oxidative cross-coupling and only afforded the biaryl **3ba** in a low yield. (Table 1, entry 1). However, the catalytic reactions might become realistic by some catalyst control. We have recently reported that 2,2′-diiodobiphenyls are efficient precursors of highly reactive iodine(III) species not aggregating with each other under mild oxidation conditions.[12] Therefore, we attempted to use the 2,2′-diiodobiphenyl catalysts **4a−d** and its new derivative **4e** for the coupling. To our delight, simple 2,2′-diiodobiphenyl **4a** showed an extremely high catalytic activity within a 5 mol % loading, which corresponds to a 10 mol % loading of the iodine moiety (entry 2). It should be emphasized that the catalytic amount of **4a** gave a result comparable to the stoichiometric use of the PIDA in HFIP, even in a more practical solvent, TFE (trifluoroethanol) (entry 3). Further tuning of the catalyst revealed the significant effect of the substituent. The yield slightly decreased with catalysts **4b** and **4c** by introducing alkyl substituents (entries 4 and 5).[13] While the lower catalytic activity was observed for the electron-withdrawing chlorine-substituted **4d** (entry 6), the introduction of an electron-donating methoxy group in the catalyst **4e** gave the best result (99% yield, entry 7).[14] Lowering the amount of **2a** to 5 equiv led to a decrease in product yield (entry 8).[15] The use of monoiodobiphenyl, which has a structure related to the diiodide catalyst **4a**, resulted in a sharp drop in the product yield (entry 9). This result indicated the importance of the second iodine moiety at the *ortho*-position of biaryl substructure in the catalyst. Nonetheless, the coupling did not proceed at all in the absence of the iodoarene catalysts (entry 10).

Table 1. Optimization of Conditions for the Catalytic Coupling of 1b with 2a

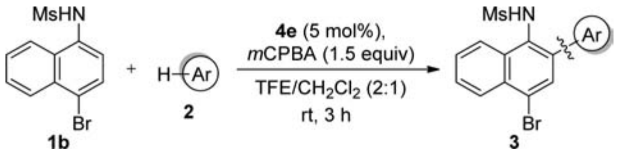


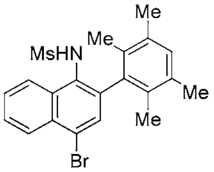
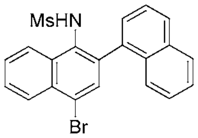
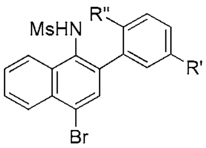
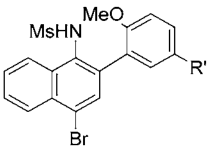
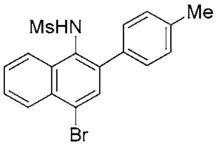
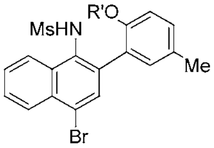
entry	**2a** (*x* equiv)	iodoarene (*y* mol %)	fluoroalcohol	yield[a]
1	10	PhI (10 mol %)	HFIP	38%
2	10	**4a** (5 mol %)	HFIP	94%
3	10	**4a** (5 mol %)	TFE	89%
4	10	**4b** (5 mol %)	TFE	78%
5	10	**4c** (5 mol %)	TFE	81%
6	10	**4d** (5 mol %)	TFE	81%
7	10	**4e** (5 mol %)	TFE	99%
8	5	**4e** (5 mol %)	TFE	76%
9	10	*o*-PhC$_6$H$_4$I (10 mol %)	HFIP	49%
10	10	none	HFIP	ND

[a] Isolated yield based on **1b**.

With the optimized catalyst **4e** in hand, we then examined the scope of the reaction with respect to the AH components (Table 2). The coupling of **1b** with AHs **2b−d** afforded the biaryl product **3bb−bd** in good to high yields (entries 1−3). The unsymmetrical **2c** reacted at the less hindered *ortho*-position of the methyl group with a high regioselectivity. Toluene **2e** was also applicable as a nucleophile (entry 4). The coupling with naphthalene **2f** exclusively occurred at the *α*-position (entry 5). *para*-Substituted phenyl ether **2g** afforded the biaryl **3bg** in quantitative yield by coupling at the *ortho*-position of the methoxy group (entry 6). The benzyl alcohol **2h** gave the desired biaryls **3bh** without any undesired oxidative side reactions (entry 7). For the electron-withdrawing bromine and ester substituted **2i** and **2j**, biaryls **3bi** and **3bj** were obtained in high yields, respectively, using HFIP as solvent (entries 8 and 9). The benzyl and silyl groups could also be used as protecting groups of the phenols (entries 10 and 11).

Table 2. Catalytic Coupling of 1b with Aromatic Hydrocarbons 2

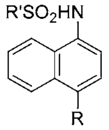
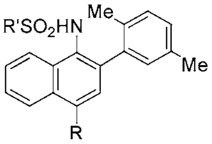
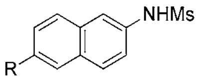
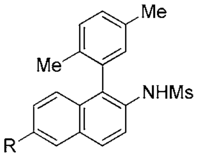
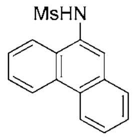
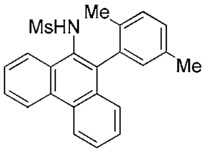


Entry	Biaryl **3**, Yield[a]	Entry	Biaryl **3**, Yield[a]
1	 **3bb**, 94%	5	 **3bf**, 82%
			
2	R‘ = *t*Bu, R“ = Me;	6	R‘ = Me; **3bg**, 99%
	3bc, 83%[b]	7	R‘ = CH$_2$OH; **3bh**, 67%
3	R‘ = R“ = *i*Pr;	8[c]	R‘ = Br; **3bi**, 92%
	3bd, 54%	9[c]	R‘ = CO$_2$Me; **3bj**, 74%
4	 **3be**, 66%		
		10	R’ = Bn; **3bk**, 99%
		11	R’ = TBDPS; **3bl**, 92%

[a] Isolated yield based on **1b**. [b] 9:1 mixture of regioisomeres. [c] HFIP was used instead of TFE.

We then investigated the scope of the anilides **1** in the coupling with AH **2a** (Table 3). The 1-naphthylamine derivatives **1c** and **1d** with protections by the benzylsulfonyl and cyclopropylsulfonyl groups produced the desired products

Table 3. Scope of Anilides 1 in the Coupling with 2a[a]

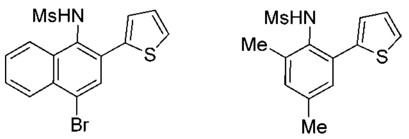
Entry	Anilide **1**	Biaryl **3**	Yield[b]
			
1	R = Br, R‘ = Bn (**1c**)	R = Br, R‘ = Bn (**3ca**)	76%
2	R = Br, R‘ = *c*-propyl (**1d**)	R = Br, R‘ = *c*-propyl (**3da**)	67%
			
3[c]	R = H (**1e**)	R = H (**3ea**)	62%
4[c]	R = Br (**1f**)	R = Br (**3fa**)	50%
5[c]	R = CH$_2$OAc (**1g**)	R = CH$_2$OAc (**3ga**)	54%
6[c]	 (**1h**)	 (**3ha**)	71%

[a] Reactions were performed by using the catalyst **4e** (5 mol %) with dry *m*CPBA (1.5 equiv) in TFE-CH$_2$Cl$_2$ (2:1) at room temperature for 3 h. [b] Isolated yield based on **1**. [c] HFIP was used instead of TFE.

3ca and **3da** in good yields (entries 1 and 2). The 2-naphthylamine derivative **1e** was also applicable as a substrate by using HFIP instead of TFE and the coupling occurred only at the 1-position of **1e** (entry 3). The introduction of bromine and acetoxymethyl groups at the 6-position of **1e** slightly affected the yields (entries 4 and 5). The more electron-rich phenanthrene **1h** afforded the biaryl **3ha** without causing any undesired oxidation (entry 6).

Furthermore, our new catalytic system is applicable for the coupling of **1b** with thiophene **5** to afford the biaryl product **6a** in high yield (Scheme 3). The coupling product **6b** was obtained from 2,4-dimethylanilide **1i** in higher yield by the catalyst **4e** than that reported with the use of stoichiometric PIDA in HFIP.[9a]

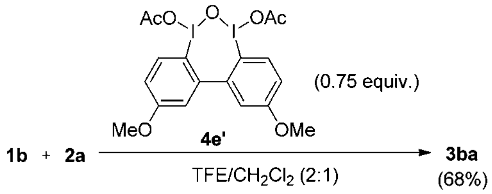
Scheme 3. Catalytic Coupling of Anilides 1 and Thiophene 5



6a; 80%

6b; 74%
(PIDA : 69%)[9a]

The more activated intermediate than the catalyst **4e′** itself might be generated during the catalytic cycle. Thus, the reaction with a stoichiometric amount of the isolated hypervalent iodine **4e′** provided the same product **3ba** in a slightly lower yield (68%, see eq 1) than that under catalytic conditions. We also ascertained the comparably faster consumption of anilides **1** with the 2,2′-diiodobiphenyl catalyst **4e** than **4e′** even though the loading of the iodine content in the catalyst is 15× lower (10 mol % for the catalyst **4e** vs 150 mol % I(III) for **4e′**). The substitution of the electron-donating methoxy groups in the catalyst **4e** seems to contribute to the acceleration of the reoxidation step for regeneration of the catalytic active species with *m*CPBA.

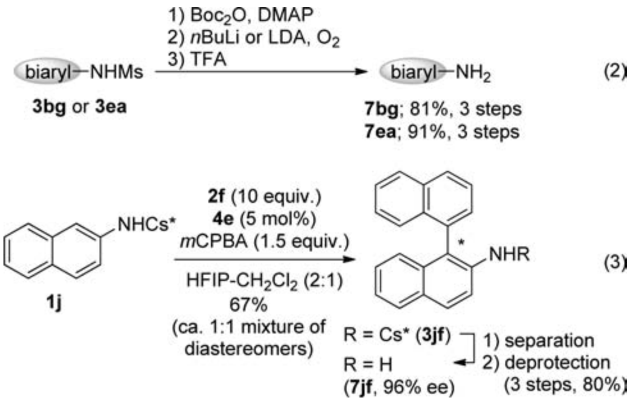


(1)

It is worth mentioning that our metal-free method provides mild conditions of tempearture compared to the recently reported Pd-catalyzed oxidative coupling of aniline derivatives within the same level of the loading of catalyst and substrates.[16]

Amino-substituted arenes often serve as organocatalysts, ligands, functionalized materials, and their precursors.[17] To apply the synthesized *N*-Ms biaryls as precursors of these compounds, a mild and high-yielding deprotection method of the Ms group is required due to the rare removal of the Ms group.[18] We achieved deprotection of the Ms group under *n*BuLi or LDA-mediated conditions, which were originally reported by Carreira and Urabe,[19] by utilizing the Boc group as a proxy protecting group of the sulfonamide N−H group (Scheme 4, eq 2). The (*R*)-(+)-camphorsulfonyl (Cs*) group was also deprotected by this three-step protocol. As a result, the synthesis of a useful chiral 2-aminobinaphthyl **7jf**[17d−f] becomes possible after separation of a 1:1 diastereomixture of the produced **3jf**, which was obtained by our coupling of **1j** and **2f** by the usual SiO$_2$ chromatography (Scheme 4, eq 3).

Scheme 4. Deprotection of *N*-Sulfonylamino Biaryls 3



In summary, by defining unique 2,2′-diiodobiphenyls **4** as a specific catalyst, we have developed for the first time the novel iodine(III)-mediated coupling of anilides **1** with AHs **2** by catalysis of the organoiodine. This is the first report of the organocatalytic intermolecular oxidative cross-biaryl coupling, and thus the catalyst-controlled methodology would provide a new opportunity for developing greener synthetic methods of the valuable biaryl motifs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) We anticipate that the C−C coupling proceeds via generation of nitrenium intermediate or related cationic species. As a referee pointed out, the acidity and nucleophilicity of the nitrogen atom are suitable for the interaction with hypevalent iodine species. We confirmed that moderate steric size of Ms group prevents overoxidation of the products. In addition, a possible effect for stabilizing positively charged aromatic ring by σ-donation of Ms group is recently proposed by Canesi et al.; see ref 9b.

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(13) Antonchick et al. used our catalyst **4c** for the catalytic C−N couplings of acetoanilides with AHs. See ref 7b.

(14) A greener co-oxidant, AcOOH, could also be used, but the yields were substantially lower (up to 52% for **3ba**) than that using *m*CPBA; see ref 12a.

(15) In the absence of coupling partner **2a**, ~30% of dimeric species of naphthylamine **2b** were produced.

(16) In the Pd-catalyzed oxidative coupling of aniline derivatives with AHs, ~10 mol % of the catalyst and 4−37 equiv of AHs were used at 70−120 °C in the presence of a strong acid: (a) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (b) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (c) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci* **2010**, *1*, 331.

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