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Selective Synthesis of *ortho*-Substituted Diarylsulfones by Using NHC-Au Catalysts under Mild Conditions

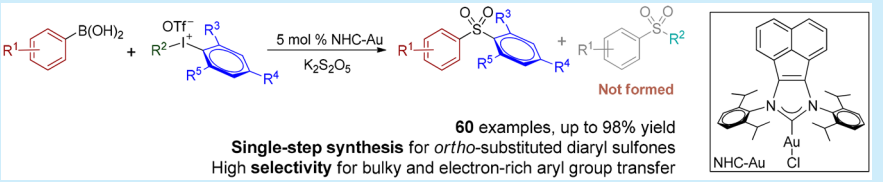
Haibo Zhu,[†,‡] Yajing Shen,[†] Daheng Wen,[†] Zhang-Gao Le,[‡] and Tao Tu*[,†,§]

[†]Shanghai Key Laboratory of Molecular Catalysis and Innovative Materials, Department of Chemistry, Fudan University, 2205 Songhu Road, Shanghai 200438, China

[‡]School of Chemistry, Biology and Material Science, East China University of Technology, Nanchang 330013, China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Supporting Information

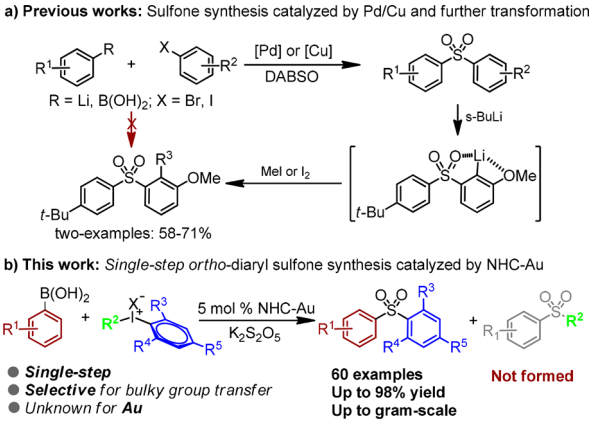


ABSTRACT: A single-step gold(I)-catalyzed chemoselective protocol to access *ortho*-substituted diarylsulfones has been established. Acenaphthoimidazolylidene gold complexes are effective catalysts for the arylsulfonylation of boronic acids by potassium metabisulfite ($K_2S_2O_5$) and diaryliodonium salts to access (poly-)*ortho*-substituted diarylsulfones even in gram scale. Unlike the transition metal-catalyzed two-component coupling systems, the sterically hindered aryl groups in diaryliodonium salts are preferentially transferred over less bulky ones to form synthetically difficult targets, including those of pharmaceutical importance.

Despite tremendous achievements in the transition-metal-mediated cross-coupling reactions,[1] the direct construction of highly sterically hindered carbon centers still constitutes a notorious challenge, especially, for syntheses of poly-*ortho*-substituted biaryls under mild reaction conditions.[2] With the aid of bulky electron-rich tertiary phosphines[3] or N-heterocyclic carbenes (NHCs),[4] several groups have demonstrated the possibility to access *ortho*-substituted biaryls[2] and diarylketones[5] by utilizing Pd-catalyzed cross-couplings of sterically hindered aryl halides or aryl boronic acids. Nevertheless, the efficient and practical protocols for *ortho*-substituted diaryl compounds syntheses are still in high demand.

Functional diarylsulfones are one type of privileged structural motif in various drugs and biologically active compounds.[6] As common sulfonylation agents, sodium sulfinates are often used to synthesize various functional sulfonamides[7] and sulfones.[8] However, the limited commercial sources of sodium sulfinates restrict the application in organic synthesis. Therefore, transition-metal-catalyzed three-component coupling reactions recently emerged as a promising strategy to prepare these compounds.[9,10] In 2013, Willis and co-workers pioneered Pd-catalyzed sulfonylative reactions with aryl lithium reagents, DABSO (1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide), a surrogate of SO_2) and aryl iodides (Scheme 1a).[9] To avoid the use of air-sensitive lithium reagents, and inconvenient two-step operation, they developed a more practical Cu(I)-catalyzed sulfonylative Suzuki−Miyaura coupling reaction.[10] However, a limitation for both protocols is difficulty in tolerating *ortho*-functional groups. The only example for direct *ortho*-substituted diarylsulfone synthesis is 1-methyl-2-(phenylsulfonyl)benzene in the Cu(I) catalytic system, where only a 49% yield was achieved with 10 mol % catalyst.[10] For bulky 1,2,3-trisubstituted aryl sulfones,

Scheme 1. Transition-Metal-Catalyzed Three-Component Sulfonylative Coupling Reactions for Diarylsulfone Synthesis



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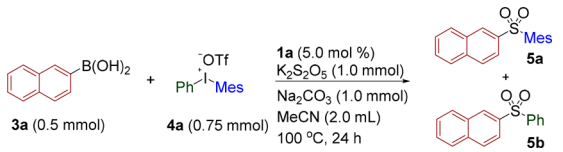
regioselective *ortho*-metalation with *s*-BuLi had to be applied (Scheme 1a).[9] Despite these achievements, the single-step synthesis of *ortho*-substituted diarylsulfones remains challenging.

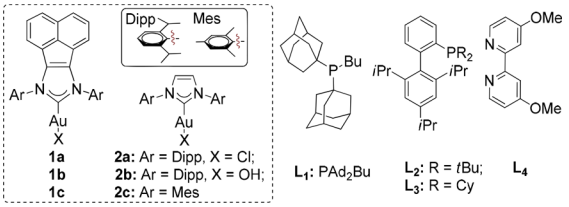
Gold(I) has the same d^{10} configuration as Pd(0), but gold(I)-complexes have rarely been employed for coupling reactions.[11] By using *t*-Bu_3P as a ligand, Toste and co-workers realized the first Au(I)-catalyzed alkylsulfonylation of aryl boronic acids.[12] Our group demonstrated the direct synthesis of alkyl-, vinyl-, and allylsulfones by utilizing NHC-Au(I) complexes at low catalyst loading.[13] However, no arylsulfonylation products were observed in the case of using aryl halides as reactants. The weak nucleophilicity and desulfitative Heck-type reactions of the possible intermediate, sodium sulfinate, may be responsible for this outcome.[14] Inspired by the high efficiency of diaryliodonium salts in arylation involving the formation of C−C, C−O, C−S, and C−N bonds,[15,16] we would like to explore the possibility of using diaryliodonium salts for the syntheses of diarylsulfones in three-component cross-coupling reactions.

Table 1. Optimization of the Reaction Conditions[a]



entry	variation from the standard conditions	5a (%)[b]
1	none	86
2	**1b** as a catalyst	65
3	**1c** as a ccatalyst	46
4	**2a** as a catalyst	68
5	**2b** as a catalyst	40
6	**2c** as a catalyst	35
7	$Pd(OAc)_2$ and $P^tBu_3{\cdot}HBF_4$	12
8	$Pd(OAc)_2$ and $\mathbf{L_1}$	<1
9	$Pd(MeCN)_2Cl_2$ and $\mathbf{L_2}$	45
10	$Cu(OAc)_2$ and $\mathbf{L_3}$	25
11	$Cu(MeCN)_4BF_4$ and $\mathbf{L_4}$	n.d.

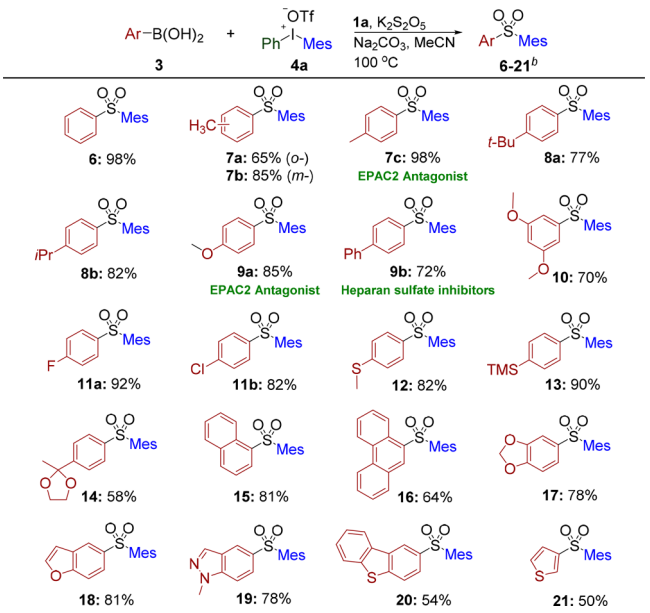
[a]Standard reaction conditions: under an atmosphere of N_2, NHC-Au(I) (5.0 mol %), 2-naphthaleneboronic acid **3a** (0.5 mmol), $K_2S_2O_5$ (1.0 mmol), **4a** (0.75 mmol), and Na_2CO_3 (1.0 mmol) were stirred in 2 mL of MeCN at 100 °C for 24 h. [b]Isolated yield. (Note: Mes = mesityl group, Dipp = di-isopropyl-phenyl group).



Initially, 2-naphthaleneboronic acid (**3a**), unsymmetrical diaryliodonium salts (**4a**), and potassium metabisulfite ($K_2S_2O_5$) were selected to test the three-component cross-coupling reactions (Table 1). After optimization of reaction conditions (see the Supporting Information, Table S1), the desired sulfone **5a** was obtained in 86% yield when the reaction was carried out with 5 mol % NHC-Au(I) **1a** and Na_2CO_3 in MeCN at 100 °C for 24 h (Table 1, entry 1). The chemoselectivity of the reaction was excellent, and no less-hindered sulfone **5b** was formed. This observation is quite different from the previous studies on the Pd-catalyzed $C-C_{Ar}$ bond formation reactions, in which the less bulky aryl groups are usually transferred.[17] The auxiliary ligand X (Scheme under Table 1) and the steric hindrance of the N−Ar group in NHC-Au(I) complexes obviously affected the reaction efficiency. Yields of 65% and 45% were obtained with NHC-Au **1b** and **1c** respectively (entries 2 and 3), indicating the bulkiness of the Ar groups is helpful in improving productivity. In the case of NHC-Au(I) analogues **2a−c**, derived from imidazolium salts, similar results were observed, but with lower yields (entries 4−6). These outcomes confirmed our previous conclusion that ylidenes derived from acenaphthoimidazolium salts with extended π-systems exhibited better catalytic activities.[4b,13,18] Other privileged catalysts in the literature derived from viable phosphines and palladium precursors in the sulfonylation reactions[8,19] were tested under our standard (entries 7−9, Table 1) or literature reaction conditions (entries 1−4, Table S2). Only a 45% yield was obtained when $Pd(MeCN)_2Cl_2$ and $\mathbf{L_2}$ were applied (entry 9). In the case of a copper catalyst, inferior yields were found (entries 10−11, Table 1). The use of the bulky and expensive Xphos $\mathbf{L_3}$ resulted in only 25% yield (entry 10, Table 1). When the catalyst was formed by $Cu(MeCN)_4BF_4$ and dipyridine $\mathbf{L_4}$, a privileged combination in the previous study,[8] no sulfone formation was observed (entry 11, Table 1).

With the optimal reaction conditions in hand, the feasibility and chemoselectivity of the protocol were then investigated, and the results were compiled in Scheme 2. Delightedly, whenever electron-rich and electron-deficient boronic acids were applied, the chemoselectivity was consistent: the bulky 2,4,6-trimethylphenyl ring was selectively transferred for the arylsulfonylation in the all cases to form sterically hindered poly-*ortho*-sulfones **6−11** in good to excellent yields (65%−98%, Scheme 2). The position of the methyl group of

Scheme 2. Chemoselective Arylsulfonylation of Boronic Acids[a]



[a]With NHC-Au **1a** (5.0 mol %), aryl boronic acid **3** (0.5 mmol), $K_2S_2O_5$ (1.0 mmol), **4a** (0.75 mmol), and Na_2CO_3 (1.0 mmol) in 2 mL MeCN at 100 °C for 24 h. [b]Isolated yield.

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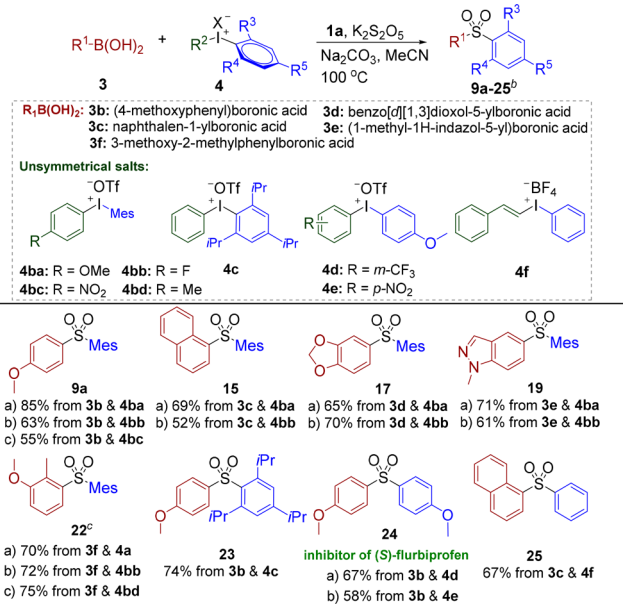
tolylboronic acid slightly affected the coupling efficiency. Sulfones **7a** and **7b** were produced in 65% and 85% yields, respectively. Sulfone **7c**, a potent and specific EPAC2 antagonist (commercially available, 5 mg/147 USD, Sigma-Aldrich),[20] was obtained in excellent yield (98%). Another EPAC2 antagonist, mesityl(4-methoxylphenyl)sulfone **9a**,[21] was also obtained in high yield (85%). A heparan sulfate inhibitor,[22] **9b**, was successfully prepared in 72% yield. These outcomes demonstrated the applicability of our protocol for the preparation of commercially valuable compounds. Besides *mono-* and *di*-electron-neutral, -rich, and -poor substituents (**8**–**11**), halo-substituted substrates were also suitable for the coupling. Sulfone **11b** was selectively produced in 82% yield with the chloro-group remaining unreacted, and no direct Suzuki-coupling products were detected, confirming the chemoselectivity of the protocol and the opportunity for further transformation.

The scope could also be further extended to boronic acid containing a thioether group (sulfone **12**), which is difficult to access by conventional oxidative protocols.[23] A yield of 82% was produced even though the sulfur donors have a strong affinity for gold centers. When 4-(trimethylsilyl)phenylboronic acid was used, sulfone **13** was also obtained in a good yield (90%). For aryl boronic acids containing a bulky and π-conjugated system, a 2,4,6-trimethylphenyl ring was still selectively transferred to form extremely hindered diarylsulfones in good yields (74–81%, **15**–**16**). Bulky heterocyclic boronic acids containing oxygen, nitrogen, or sulfur atoms were all well accommodated and resulted in sulfones **17**–**20** in moderate to good yields (54–81%). It should be noted that sulfone **21** is difficult to access by the known Pd-catalyzed arylsulfonylative reactions.[9]

Subsequently we turned our attention to the feasibility of other unsymmetrical salts (Scheme 3). When diaryliodonium salts **4b**–**4f** with different functional groups were selected as

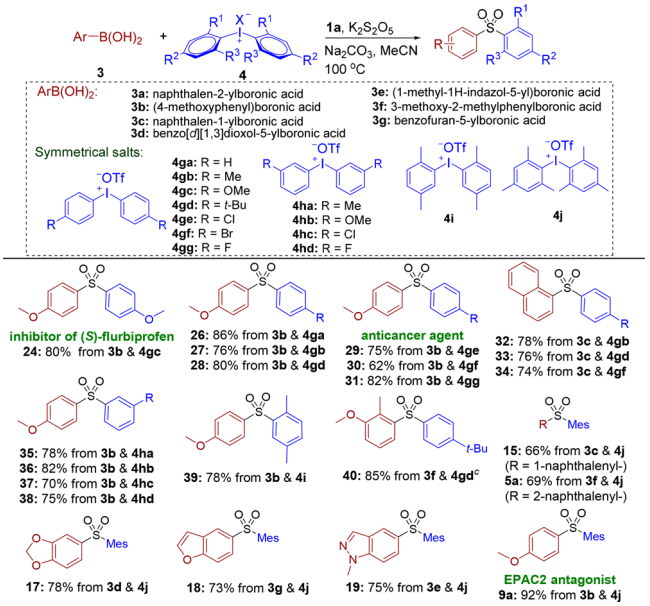
Scheme 3. Scope of Unsymmetrical Diaryliodonium Salts[a]



[a]Boronic acid (0.5 mmol), $K_2S_2O_5$ (1.0 mmol), Na_2CO_3 (1.0 mmol), **1a** (5.0 mol %) and triflate (0.75 mmol) were stirred in MeCN at 100 °C for 24 h. [b]Isolated yields. [c]10 mol % of **1a**, 48 h.

electrophiles, the bulky 2,4,6-trimethylphenyl ring was readily transferred in all the cases to generate corresponding sulfones in good to excellent yields (**9a**, **15**, **17**, **19**, and **22**, Scheme 3), regardless whether electron-rich, electron-poor, bulky, or heterocyclic aryl boronic acids were involved. The extremely sterically hindered *ortho-i*Pr group was also readily transferred to produce extremely bulky product **23** in good yield with excellent chemoselectivity (74%, Scheme 3). In contrast to electron-poor aryl groups, electron-rich ones were selectively transferred to produce, for example, sulfone **24**, an inhibitor to alter the rate of (*S*)-flurbiprofen metabolism *in vitro*,[24] in good yields (58–67%, Scheme 3). In the case of a salt containing both aryl and alkenyl groups, the aryl group was selectively transferred affording sulfone **25** in good yield (67%, Scheme 3). The selective synthesis of less bulky and/or electron-poor sulfones may be accessed with symmetrical diaryliodonium salts (Scheme 4), which further expanded the substrate scope.

Scheme 4. Scope of Symmetrical Diaryliodonium Salts[a]



[a]Boronic acid (0.5 mmol), $K_2S_2O_5$ (1.0 mmol), Na_2CO_3 (1.0 mmol), **1a** (5.0 mol %), and diaryliodonium triflate (0.75 mmol) were stirred in 2.0 mL of MeCN about 24 h at 100 °C. [b]Isolated yields. [c]10 mol % of **1a**, 48 h.

All tested symmetrical salts **4g**, **4h**, **4i**, and **4j** were readily coupled with various (hetero)aryl boronic acids to afford corresponding diarylsulfones in good yields (62–92%, Scheme 4). Sulfone **29**, an anticancer/antimalarial agent,[25] was attained in good yield (75%, Scheme 4). Sulfone **40**, prepared via *ortho*-lithiation in literature (Scheme 1a),[9] could be directly obtained in 85% yield by our developed protocol.

In order to further explore the potential of our protocol to access *ortho*-substituted pharmaceutical diarylsulfones, a concise gram-scale synthesis of bioactive sulfone **41**, an inhibitor of farnesyl-protein transferase,[26] was then carried out (Scheme 5). The selectivity of our protocol was relatively good even with halogen substrates where, except for diarylsulfones formation, no corresponding Suzuki-coupling product was observed. With (4-bromo-2-methyl-phenyl)-boronic acid and commercially available diphenyl-iodonium triflate as the coupling partner, sulfone **42** was formed in 75%

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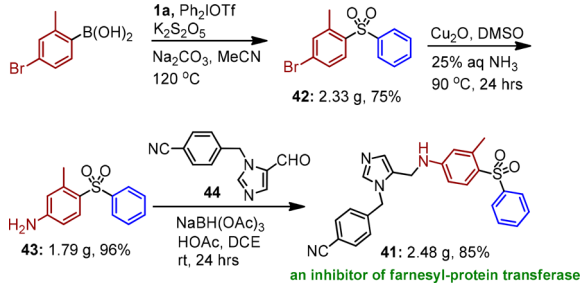
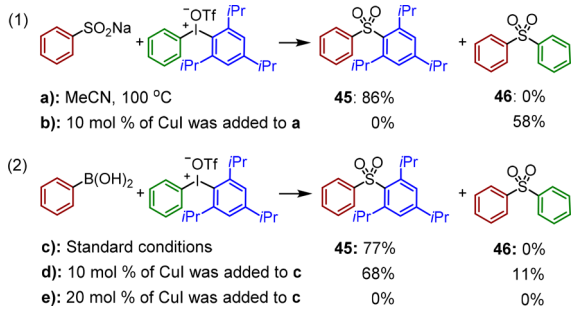
Scheme 5. Gram-Scale Synthesis of Diarylsulfone 41, an Inhibitor of Farnesyl-Protein Transferase



yield under our standard reaction conditions. After conversion of the bromo-group to an amine, diarylsulfone **43** was further condensed with aldehyde **44** and reduced into final product **41** in 85% yield. These results clearly demonstrate versatility and applicability of our newly developed protocol.

According to our previous study,[13] sulfinate might be the possible intermediate in NHC-Au(I) catalyzed sulfonylative reactions.[13a] In order to clarify the chemoselectivity and transfer inclination of bulky aryl groups in diaryliodonium salts, triflate **4c** was selected for the control tests (eqs 1 and 2, Scheme 6). When **4c** reacted with sodium benzenesulfinate in

Scheme 6. Control Experiments for Mechanism Investigation

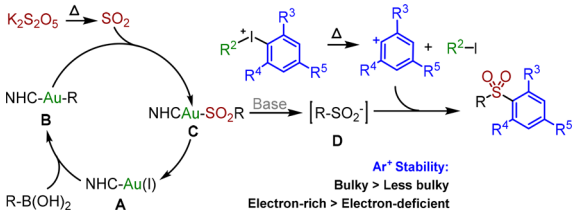


MeCN at 100 °C for 24 h, the bulky 2,4,6-triisopropylphenyl group was transferred preferentially to form the sterically hindered diarylsulfone **45** in a good isolated yield, without the formation of the less bulky sulfone **46** (eq 1a, Scheme 6). However, in the presence of 10 mol % CuI as an additive, the chemoselectivity of the reaction was completely opposite with only less bulky product **46** generated (eq 1b, Scheme 6). This observation is in agreement with previous reports that a bulky/*ortho*-substituted aryl group is favored for the transfer over a less bulky one in metal-free conditions.[8,27] However, even in the presence of transition metal Au, the bulky aryl groups are still transferred in our case.

With these outcomes, we conceived the chemoselectivity might be tuned by the addition of copper(I) salts. When 10 mol % CuI was added to the reaction under our standard reaction conditions (eq 2c, Scheme 6), the bulky group was still favorably transferred and only a small amount of sulfone **46** was formed (11% yield, eq 2d, Scheme 6). When more than 20 mol % CuI was added to the reaction, the transformation was completely suppressed. And most starting materials were recovered (eq 2e, Scheme 6), which could be attributed to the formation of a NHC-Cu intermediate. When NHC-Cu complexes **1d** and **2d** were applied as catalysts, no product formation was observed (see Supporting Information, Table S2).

With this information in hand, we proposed that the intermediate Ar^+ formed *in situ* from bulky and electron-rich aryl groups are more stable than that formed by less bulky and electron-poor aryl groups,[28] which may further explain the chemoselectivity of our newly developed protocol. Subsequently, a combination of control experiments and previous studies[13,29] led to the plausible mechanism illustrated in Scheme 7. After initial trans-metalation of the NHC-Au(I)

Scheme 7. Plausible Mechanism of Chemoselective Arylsulfonylation



species **A** with aryl boronic acid, intermediate **B** (NHC-Au-Ar) is generated.[30] Sulfur dioxide, generated *in situ* from heating $K_2S_2O_5$, is inserted into the Au−C_{Ar} bond to afford a sterically congested sulfonyl Au(I) complex **C** (NHC-Au-SO_2-Ar).[31] In the presence of a suitable base, NHC-Au(I) species **A** is regenerated, and a crucial intermediate **D** is produced, which can react with the more stable bulky Ar^+ formed by diaryliodonium salts. Sterically hindered diarylsulfone is thus favorably obtained.

In summary, a robust NHC-Au(I) complex **1a** exhibits high catalytic activity in a single-step arylsulfonylation of boronic acids by $K_2S_2O_5$ and diverse symmetrical and unsymmetrical diaryliodonium salts, which is a chemoselective and efficient protocol to access (poly-)*ortho-substituted* diarylsulfones even in gram scale under mild reaction conditions. The transformation can tolerate a broad range of functional groups with different electronic properties, bulkiness, and a heterocycle on both sides of the substrates to access various bioactive diarylsulfones. Unlike the two-component transition-metal-catalyzed coupling reactions with unsymmetrical diaryliodonium salts,[17] our protocol exhibits excellent chemoselectivity, where sterically hindered and electron-rich aryl groups in diaryliodonium salts are preferentially transferred to form otherwise synthetically difficult targets, including those of pharmaceutical importance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03957.

Exploratory investigation, experimental procedures, and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: taotu@fudan.edu.cn.

ORCID

Haibo Zhu: 0000-0002-9141-8204

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Tao Tu: 0000-0003-3420-7889

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yang, Y.; Lan, J.; You, J. Palladium-Catalyzed Transformations of Alkyl C-H Bonds. *Chem. Rev.* **2017**, *117*, 8787−8863. (b) Liu, L.; Zhang, J. Gold-Catalyzed Transformations of α-Diazocarbonyl Compounds: Selectivity and Diversity. *Chem. Soc. Rev.* **2016**, *45*, 506−516. (c) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. *Chem. Rev.* **2011**, *111*, 1780−1824.

(2) (a) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. A Highly Active Suzuki Catalyst for the Synthesis of Sterically Hindered Biaryls: Novel Ligand Coordination. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163. (b) Dai, C.; Fu, G. C. The First General Method for Palladium-Catalyzed Negishi Cross-Coupling of Aryl and Vinyl Chlorides: Use of Commercially Available $Pd(P(t\text{-}Bu)_3)_2$ as a Catalyst. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(3) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. A Rationally Designed Universal Catalyst for Suzuki-Miyaura Coupling Processes. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876.

(4) (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. Sterically Demanding, Bioxazoline-Derived N-Heterocyclic Carbene Ligands with Restricted Flexibility for Catalysis. *J. Am. Chem. Soc.* **2004**, *126*, 15195−15201. (b) Tu, T.; Sun, Z.; Fang, W.; Xu, M.; Zhou, Y. Robust Acenaphthoimidazolylidene Palladium Complexes: Highly Efficient Catalysts for Suzuki-Miyaura Couplings with Sterically Hindered Substrates. *Org. Lett.* **2012**, *14*, 4250−4253.

(5) (a) Dong, K.; Wu, X.-F. Carbonylations with CO_2 as the CO Source and Reactivity Modifier. *Angew. Chem., Int. Ed.* **2017**, *56*, 5399−5401. (b) Lian, Z.; Nielsen, D. U.; Lindhardt, A. T.; Daasbjerg, K.; Skrydstrup, T. Cooperative Redox Activation for Carbon Dioxide Conversion. *Nat. Commun.* **2016**, *7*, 13782−13788. (c) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. The Development and Application of Two-Chamber Reactors and Carbon Monoxide Precursors for Safe Carbonylation Reactions. *Acc. Chem. Res.* **2016**, *49*, 594−605. (d) Fang, W.; Zhu, H.; Deng, Q.; Liu, S.; Liu, X.; Shen, Y.; Tu, T. Design and Development of Ligands for Palladium-Catalyzed Carbonylation Reactions. *Synthesis* **2014**, *46*, 1689−1708.

(6) Ma, Y.; Liu, R.; Gong, X.; Li, Z.; Huang, Q.; Wang, H.; Song, G. Synthesis and Herbicidal Activity of N,N-Diethyl-3-(arylselenonyl)-1H-1,2,4-triazole-1-carboxamide. *J. Agric. Food Chem.* **2006**, *54*, 7724−7728.

(7) Zhu, H.; Shen, Y.; Deng, Q.; Tu, T. Copper-catalyzed Electrophilic Amination of Sodium Sulfinates at Room Temperature. *Chem. Commun.* **2015**, *51*, 16573−16576.

(8) Umierski, N.; Manolikakes, G. Metal-Free Synthesis of Diaryl Sulfones from Arylsulfinic Acid Salts and Diaryliodonium Salts. *Org. Lett.* **2013**, *15*, 188−191.

(9) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Palladium-Catalyzed Three-Component Diaryl Sulfone Synthesis Exploiting the Sulfur Dioxide Surrogate DABSO. *Angew. Chem., Int. Ed.* **2013**, *52*, 12679−12683.

(10) Chen, Y.; Willis, M. C. Copper(I)-Catalyzed Sulfonylative Suzuki−Miyaura Cross-Coupling. *Chem. Sci.* **2017**, *8*, 3249−3253.

(11) (a) Cai, R.; Lu, M.; Aguilera, E. Y.; Xi, Y.; Akhmedov, N. G.; Petersen, J. L.; Chen, H.; Shi, X. Ligand-Assisted Gold-Catalyzed Cross-Coupling with Aryldiazonium Salts: Redox Gold Catalysis without an External Oxidant. *Angew. Chem., Int. Ed.* **2015**, *54*, 8772−8776. (b) Levin, M. D.; Toste, F. D. Gold-Catalyzed Allylation of Aryl Boronic Acids: Accessing Cross-Coupling Reactivity with Gold. *Angew. Chem., Int. Ed.* **2014**, *53*, 6211−6215. (c) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; De Becker, J. D.; Rudolph, M.; Scholz, C.; Rominger, F. On Homogeneous Gold/Palladium Catalytic Systems. *Adv. Synth. Catal.* **2012**, *354*, 133−147. (d) Witzel, S.; Xie, J.; Rudolph, M.; Hashmi, A. S. K. Photosensitizer-Free, Gold-Catalyzed C-C Cross-Coupling of Boronic Acids and Diazonium Salts Enabled by Visible Light. *Adv. Synth. Catal.* **2017**, *359*, 1522−1528.

(12) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. Application of Fundamental Organometallic Chemistry to the Development of a Gold-Catalyzed Synthesis of Sulfinate Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 4404−4407.

(13) (a) Zhu, H.; Shen, Y.; Deng, Q.; Chen, J.; Tu, T. Acenaphthoimidazolylidene Gold Complex-Catalyzed Alkylsulfonylation of Boronic Acids by Potassium Metabisulfite and Alkyl Halides: A Direct and Robust Protocol to Access Sulfones. *ACS Catal.* **2017**, *7*, 4655−4659. (b) Zhu, H.; Shen, Y.; Deng, Q.; Chen, J.; Tu, T. Pd(NHC)-Catalyzed Alkylsulfonylation of Boronic Acids: A General and Efficient Approach for Sulfone Synthesis. *Chem. Commun.* **2017**, *53*, 12473−12476.

(14) (a) Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. Sulfinate Derivatives: Dual and Versatile Partners in Organic Synthesis. *Org. Biomol. Chem.* **2014**, *12*, 9743−9759. (b) Zhao, F.; Tan, Q.; Xiao, F.; Zhang, S.; Deng, G.-J. Palladium-Catalyzed Desulfitative Cross-Coupling Reaction of Sodium Sulfinates with Benzyl Chlorides. *Org. Lett.* **2013**, *15*, 1520−1523.

(15) Merritt, E. A.; Olofsson, B. Diaryliodonium Salts: A Journey from Obscurity to Fame. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070.

(16) (a) Deprez, N. R.; Sanford, M. S. Synthetic and Mechanistic Studies of Pd-Catalyzed C-H Arylation with Diaryliodonium Salts: Evidence for a Bimetallic High Oxidation State Pd Intermediate. *J. Am. Chem. Soc.* **2009**, *131*, 11234−11241. (b) Jalalian, N.; Ishikawa, E. E.; Silva, L. F. J.; Olofsson, B. Room Temperature, Metal-Free Synthesis of Diaryl Ethers with Use of Diaryliodonium Salts. *Org. Lett.* **2011**, *13*, 1552−1555. (c) Wang, M.; Fan, Q.; Jiang, X. Nitrogen-Iodine Exchange of Diaryliodonium Salts: Access to Acridine and Carbazole. *Org. Lett.* **2018**, *20*, 216−219. (d) Purkait, N.; Kervefors, G.; Linde, E.; Olofsson, B. Regiospecific N-Arylation of Aliphatic Amines under Mild and Metal-Free Reaction Conditions. *Angew. Chem., Int. Ed.* **2018**, *57*, 11427−11431.

(17) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. Oxidative C-H Activation/C-C Bond Forming Reactions: Synthetic Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2005**, *127*, 7330−7331.

(18) (a) Jiang, J.; Zhu, H.; Shen, Y.; Tu, T. Acenaphthoimidazolium Chloride-Enabled Nickel-Catalyzed Amination of Bulky Aryl Tosylates. *Org. Chem. Front.* **2014**, *1*, 1172−1175. (b) Liu, Z.; Dong, N.; Xu, M.; Sun, Z.; Tu, T. Mild Negishi Cross-Coupling Reactions Catalyzed by Acenaphthoimidazolylidene Palladium Complexes at Low Catalyst Loadings. *J. Org. Chem.* **2013**, *78*, 7436−7444. (c) Tu, T.; Fang, W.; Jiang, J. A Highly Efficient Precatalyst for Amination of Aryl Chlorides: Synthesis, Structure and Application of a Robust Acenaphthoimidazolylidene Palladium Complex. *Chem. Commun.* **2011**, *47*, 12358−12360.

(19) (a) Nguyen, B.; Emmett, E. J.; Willis, M. C. Palladium-Catalyzed Aminosulfonylation of Aryl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 16372−16373. (b) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Palladium-Catalyzed Synthesis of Ammonium Sulfinates from Aryl Halides and a Sulfur Dioxide Surrogate: A Gas- and Reductant-Free Process. *Angew. Chem., Int. Ed.* **2014**, *53*, 10204−10208. (c) Shavnya, A.; Hesp, K. D.; Mascitti, V.; Smith, A. C. Palladium-Catalyzed Synthesis of (Hetero)Aryl Alkyl Sulfones from (Hetero)Aryl Boronic Acids, Unactivated Alkyl Halides, and Potassium Metabisulfite. *Angew. Chem., Int. Ed.* **2015**, *54*, 13571−13575. (d) Wang, X.; Xue, L.; Wang, Z. A Copper-Catalyzed Three-Component Reaction of Triethox-

DOI: 10.1021/acs.orglett.8b03957
Org. Lett. XXXX, XXX, XXX−XXX

ysilanes, Sulfur Dioxide, and Hydrazines. *Org. Lett.* **2014**, *16*, 4056−4058.
(20) (a) Chen, H.; Tsalkova, T.; Chepurny, O. G.; Mei, F. C.; Holz, G. G.; Cheng, X.; Zhou, J. Identification and Characterization of Small Molecules as Potent and Specific EPAC2 Antagonists. *J. Med. Chem.* **2013**, *56*, 952−962.
(21) Kim, D. H.; Lee, J.; Lee, A. Visible-Light-Driven Silver-Catalyzed One-Pot Approach: A Selective Synthesis of Diaryl Sulfoxides and Diaryl Sulfones. *Org. Lett.* **2018**, *20*, 764−767.
(22) Crawford, B. E.; Glass, C. A.; Brown, J. R.; Witt, R. G.; Vollrath, B.; Lichter, J. Heparan Sulfate Inhibitors. *PCT Int. Appl.* 2010, WO2010003023, A2, 20100107.
(23) (a) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469−2476. (b) Trost, B. M.; Braslau, R. Tetra-n-Butylammonium Oxone. Oxidations under Anhydrous Conditions. *J. Org. Chem.* **1988**, *53*, 532−537.
(24) Locuson, C. W.; Gannett, P. M.; Ayscue, R.; Tracy, T. S. Use of Simple Docking Methods To Screen a Virtual Library for Heteroactivators of Cytochrome P450 2C9. *J. Med. Chem.* **2007**, *50*, 1158−1165.
(25) Langler, R. F.; Paddock, R. L.; Thompson, D. B.; Crandall, I.; Ciach, M.; Kain, K. C. Selected Sulfonyl Compounds as Anticancer/Antimalarial Agents. *Aust. J. Chem.* **2003**, *56*, 1127−1133.
(26) Dinsmore, C. J.; Williams, T. M.; O' Neill, T. J.; Liu, D.; Rands, E.; Culberson, J. C.; Lobell, R. B.; Koblan, K. S.; Kohl, N. E.; Gibbs, J. B. Imidazole-Containing Diarylether and Diarylsulfone Inhibitors of Farnesyl-Protein Transferase. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3301−3306.
(27) Allen, A. E.; MacMillan, D. W. C. Enantioselective α-Arylation of Aldehydes via the Productive Merger of Iodonium Salts and Organocatalysis. *J. Am. Chem. Soc.* **2011**, *133*, 4260−4263.
(28) (a) *Hypervalent Iodine Chemistry*; Topics in Current Chemistry 224; Wirth, T., Ed.; Springer: Berlin, 2003. (b) Lancer, K. M.; Wiegand, G. H. The ortho Effect in the Pyrolysis of Iodonium Halides. A Case for a Sterically Controlled Nucleophilic Aromatic (SN) Substitution Reaction. *J. Org. Chem.* **1976**, *41*, 3360−3364.
(29) Hashmi, A. S. K. Homogeneous Gold Catalysis Beyond Assumptions and Proposals-Characterized Intermediates. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232−5241.
(30) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.
(31) Gates, D. P.; White, P. S.; Brookhart, M. The Insertion of Sulfur Dioxide into Palladium-Methyl Bonds: The Synthesis and X-ray Crystal Structure of an Unusual $[(dppp)PdOS(Me)O]_2[BAr'_4]_2$ Dimer. *Chem. Commun.* **2000**, 47−48.

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