ACES Asian Chemical Editorial Society

doi.org/10.1002/ajoc.202500537

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

www.asianjoc.org

Cross-Dehydrogenative Coupling Reaction of 4-Aminophenols with 2-Naphthols Catalyzed by a Mesoporous Silica-Supported Oxovanadium Catalyst

Yutaro Ito,[a] Kengo Kasama,[b] Jihoon Moon,[a] Yui Kanzaki,[a] Tomoya Nishio,[a, c] Koichiro Masuda,[c] Kwihwan Kobayashi,[c] Atsushi Kimishima,[a] Hiroshi Aoyama,[a, d] Kyohei Kanomata,*[a] and Shuji Akai*[a, e]

Cross-dehydrogenative coupling (CDC) reactions offer an atom-economical approach for synthesizing biaryl compounds by directly forming C—C bonds from the C—H bonds of two aromatic molecules. In this study, the CDC reaction between 4-aminophenols and 2-naphthols was successfully catalyzed using a mesoporous silica-supported oxovanadium catalyst. This reaction involved the catalytic, chemo- and regio-selective oxidation of 4-aminophenols, with molecular oxygen as the terminal oxidant, eliminating the need for stoichiometric chemical oxidants, thereby making the reaction more environmentally friendly.

1. Introduction

Aminophenols are valuable starting materials for synthesizing highly functionalized aromatic compounds. They can be easily oxidized to quinone monoimines (QMIs), which subsequently undergo various transformations such as nucleophilic addition and annulation reactions, yielding products such as polycyclic compounds and biaryls.[1,2] Traditionally, QMIs are prepared from aminophenols using a stoichiometric amount of oxidants, followed by isolation before being used in subsequent reactions (Scheme 1a). Recently, methods involving the in situ generation of QMIs via electrochemical oxidation have been developed, enabling one-pot processes for subsequent transformations.[3–5] Moreover, transition-metal-catalyzed direct transformations of aminophenols using peroxides as terminal oxidants have also been reported.[6,7]

On the other hand, cross-dehydrogenative coupling (CDC) reactions, in which C—C bonds are formed directly from the C—H bonds of two different aromatic molecules, have recently gained significant attention from a green chemistry perspective because of their atom-economical nature and efficiency in accessing diverse biaryl compounds.[8–10] However, CDC reactions often involve side reactions, such as homocoupling and the formation of regioisomers. CDC reactions involving hydroxycarbazoles have been extensively studied[11–15] because of their high reactivity and potential for the development of bioactive molecules and functional materials.[16] Oxovanadium catalysts have been intensively studied in CDC reactions of 3-hydroxycarbazoles, including asymmetric catalysis.[17–19] We previously developed a heterogeneous oxovanadium catalyst supported on the inner surface of mesoporous silica with a pore diameter of 4 nm (V-MPS4).[20–24] This catalyst was successfully utilized in the CDC reaction between 3-hydroxycarbazoles and 2-naphthols (Scheme 1b).[14] Notably, the V-MPS4-catalyzed CDC reaction proceeded efficiently using molecular oxygen as the terminal oxidant.

Considering the importance of aminophenol derivatives in synthesizing functionalized molecules and the structural similarity between 3-hydroxycarbazoles and *N*-phenyl-4-aminophenols **1**, we envisioned a CDC reaction of **1** catalyzed by V-MPS4, which enables the direct transformation of **1** without isolating the QMI intermediate (Scheme 1c). Very recently, an electrochemical CDC reaction of *N*-tosyl-4-aminophenols with 2-naphthols was reported.[4] In contrast, our approach employs a heterogeneous catalytic system that simplifies both operation and product purification and uses molecular oxygen as the terminal oxidant.

[a] Y. Ito, J. Moon, Y. Kanzaki, Dr. T. Nishio, Dr. A. Kimishima, Prof. Dr. H. Aoyama, Dr. K. Kanomata, Prof. Dr. S. Akai
Graduate School of Pharmaceutical Sciences, The University of Osaka, 1–6 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: kanomata@phs.osaka-u.ac.jp
akai@phs.osaka-u.ac.jp

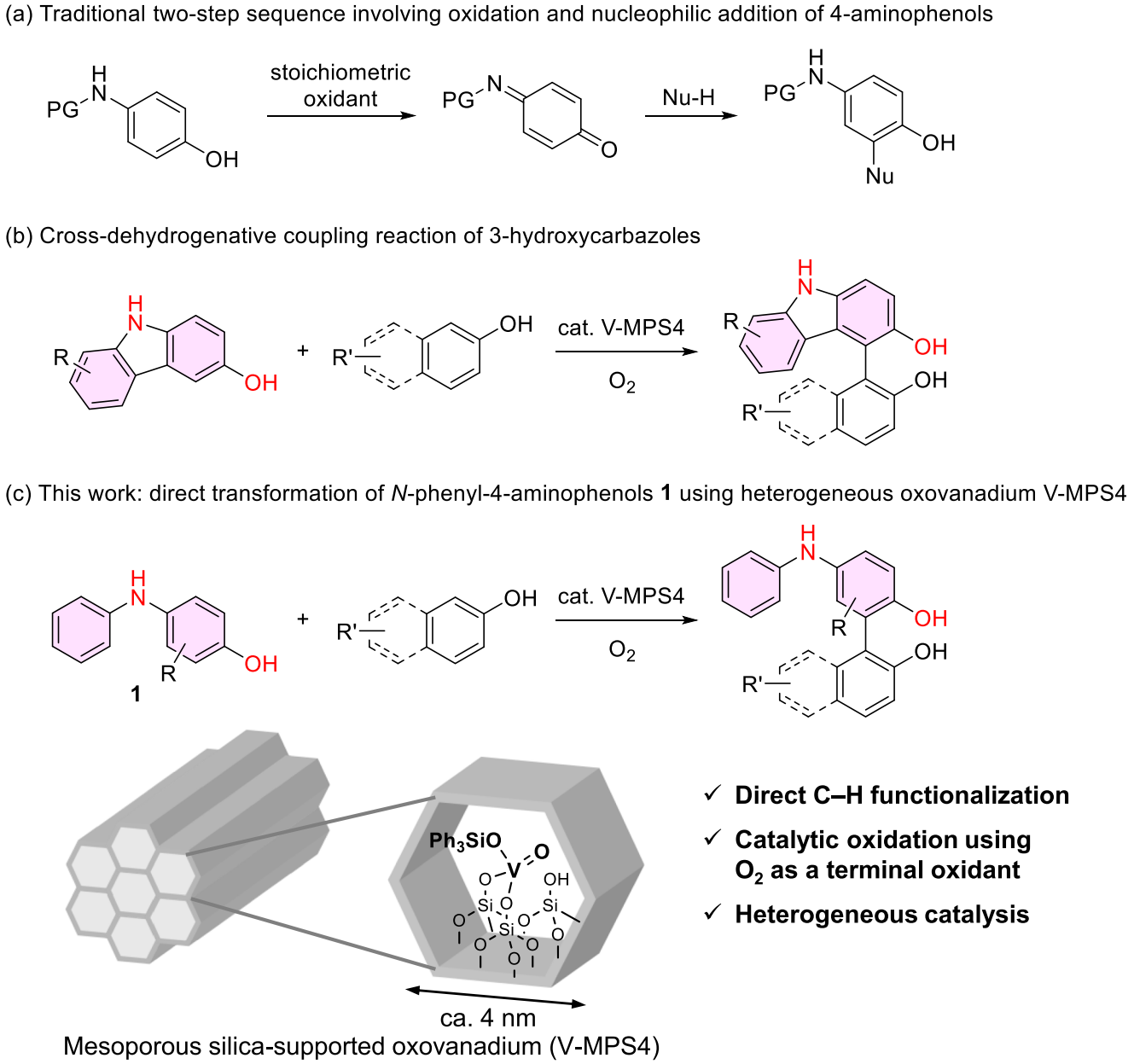
[b] Dr. K. Kasama
Faculty of Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan

[c] Dr. T. Nishio, Dr. K. Masuda, Dr. K. Kobayashi
Catalytic Chemistry Research Institute, Department of Materials and Chemistry, National Institute of Advanced Industrial Science and Technology, Central 5, Higashi 1-1-1, Tsukuba, Ibaraki 305-8565, Japan

[d] Prof. Dr. H. Aoyama
Faculty of Pharmacy, Juntendo University, Hinode, Urayasu, Chiba 279-0013, Japan

[e] Prof. Dr. S. Akai
SANKEN, The University of Osaka, 8-1 Mihogaoka, Ibaraki, Osaka 567-0047, Japan

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202500537



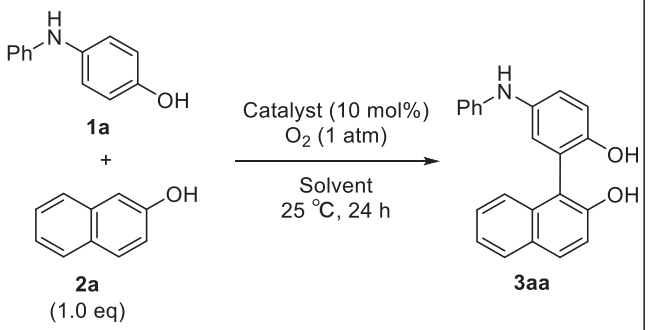
Scheme 1. Oxidative transformation of 4-aminophenols and 3-hydroxycarbazoles: a) traditional two-step sequence involving oxidation and nucleophilic addition of 4-aminophenols; b) direct cross-dehydrogenative coupling of 3-hydroxycarbaozles; c) direct transformation of *N*-phenyl-4-aminophenols **1** using V-MPS4.

Herein, we report a V-MPS4-catalyzed CDC reaction between *N*-phenyl-4-aminophenols and 2-naphthols to provide biaryl compounds.

2. Results and Discussion

The CDC reaction of 4-(phenylamino)phenol (**1a**) with 2-naphthol (**2a**) was investigated under the optimized conditions previously developed for the reaction of 3-hydroxycarbazole with **2a**.[14] Specifically, the reaction was performed using one equivalent of **2a** and a catalytic amount (10 mol%) of V-MPS4 relative to **1a** in CH_2Cl_2 under ambient oxygen at 25 °C for 24 h (Table 1, entry 1). Consequently, the cross-coupling product **3aa** was obtained in 59% NMR yield, with remaining **1a** and **2a** in 19% and 18% yields, respectively. Notably, no regioisomers or homo-coupling products were detected. The structure of **3aa** was confirmed by NMR and single-crystal X-ray analysis (CCDC 2443982; see Figure S1 and Table S1 for details). The choice of solvent had a notable impact on the reaction outcome. MeCN and toluene exhibited minimal effects on the reaction rate (entries 2 and 3); however, halogenated aromatic solvents, namely chlorobenzene and trifluorotoluene, significantly improved the yield, affording **3aa** in 67% and 71% NMR yields, respectively (entries 4 and 5). Further improvement was achieved by increasing the amount of **2a** to two equivalents, resulting in an 88% NMR yield

Table 1. Optimization of reaction conditions.[a)]



Entry	Catalyst	Solvent	%Yield (3aa)[b)]
1	V-MPS4	CH_2Cl_2	59
2	V-MPS4	MeCN	57
3	V-MPS4	toluene	60
4	V-MPS4	PhCl	67
5	V-MPS4	$PhCF_3$	71 (67)
6[c)]	V-MPS4	$PhCF_3$	88 (76)
7[d)]	V-MPS4	$PhCF_3$	decomp.
8[e)]	V-MPS4	$PhCF_3$	43
9	V-SilicaGel	$PhCF_3$	39
10	$VO(OSiPh_3)_3$	$PhCF_3$	11
11	MPS4	$PhCF_3$	10
12	–	$PhCF_3$	N.D.

[a)] Unless otherwise noted, the reaction was conducted using **1a** (0.10 mmol), **2a** (0.10 mmol), and V-MPS4 (10 mol% based on vanadium) in the indicated solvent (1.0 mL) at 25 °C under an oxygen atmosphere; [b)] Determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. Isolated yields are shown in parentheses; [c)] Two equiv. of **2a** was used; [d)] Reaction at 60 °C; [e)] Under air. N.D.: Not Detected.

(76% isolated yield) of **3aa** (entry 6). In contrast, increasing the reaction temperature led to the decomposition of **3aa** and formation of a complex mixture (entry 7). Considering that the oxidation potentials of **3aa** were comparable to those of **1a** (Figure 1), overoxidation of **3aa** was likely to proceed under elevated temperature. The reaction also proceeded under aerobic conditions, albeit more slowly, yielding **3aa** in 43% NMR yield (entry 8). Among the evaluated oxovanadium catalysts, V-MPS4 demonstrated superior catalytic activity compared to the oxovanadium catalyst immobilized on a commercial silica gel (V-SilicaGel, particle size: 40–50 μm)[24] and a homogenous catalyst $VO(OSiPh_3)_3$ (precursor for V-MPS4) under the same reaction conditions (entries 9 and 10). Although the precise effects of the catalyst support remain unclear, the mesoporous environment of V-MPS4 could play a critical role in accelerating the reaction.[21] The reaction using MPS4, the catalyst support without immobilized oxovanadium species, instead of V-MPS4 also afforded **3aa** whereas the yield was far lower compared to that using V-MPS4 catalyst (entry 11 versus 6). In contrast, no product formation was observed when **1a** and **2a** were mixed under an oxygen atmosphere in the absence of any catalyst (entry 12).

With the optimized reaction conditions in hand (Table 1, entry 6), the scope and limitations of the CDC reactions were explored (Scheme 2). The introduction of a methoxy group at either the 6- or 7-position of 2-naphthol **2** was well tolerated, yielding products **3ab** and **3ac** in 64% and 77% isolated yields, respectively. Similarly, bromine-substituted 2-naphthols at the 6- and 7-positions provided the cross-coupling products **3ad** and **3ae** in 57% and 46% yields, respectively. Notably, the reaction of 3-bromo-2-naphthol (**2f**) afforded **3af** in 50% yield, which is in sharp contrast to the previously reported CDC reaction of **2f** with 3-hydroxycarbazole that afforded the corresponding coupling product in only 12% yield.[14] The electron-withdrawing ethoxycarbonyl group on **2** was also tolerated, though the yield of **3ag** decreased to 39%. However, the reaction with resorcinol (**2h**) resulted in a modest 11% yield of **3ah** due to poor substrate conversion (<50%) and the formation of unidentified side products.

Next, the effects of substituents on aminophenol **1** were examined. The reaction of the fluorinated aminophenol **1b** with **2a** yielded **3ba** in 58% yield. The nature of the substituent on the amino groups significantly influenced the reaction outcome. Specifically, *N*,*N*-diphenyl-4-aminophenol provided **3ca** in 35% yield, whereas the *N*,*N*-dialkyl derivative **1d** showed low conversion, although product **3da** was detected in the reaction mixture. In contrast, the electron-withdrawing Cbz-protected aminophenol did not afford the desired product **3ea**, and the starting materials were recovered quantitatively. The reaction of *N*-Bn substituted aminophenol also did not afford any products, and the starting materials were recovered. On the other hand,

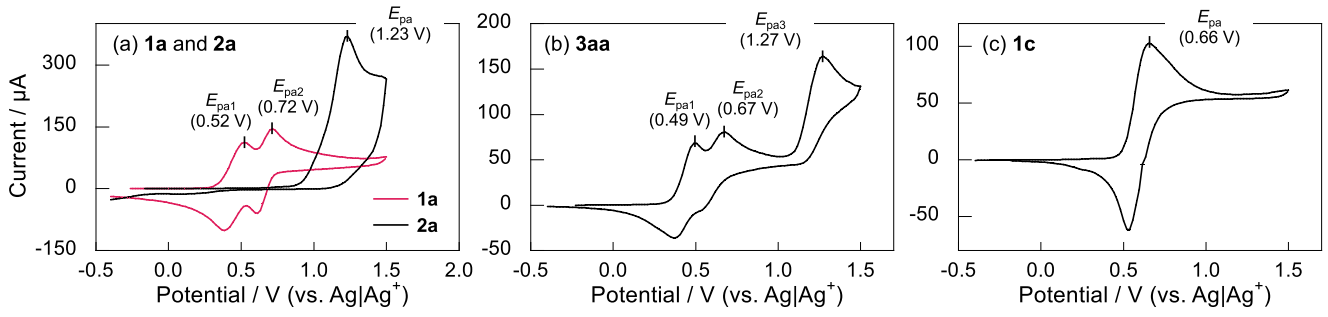
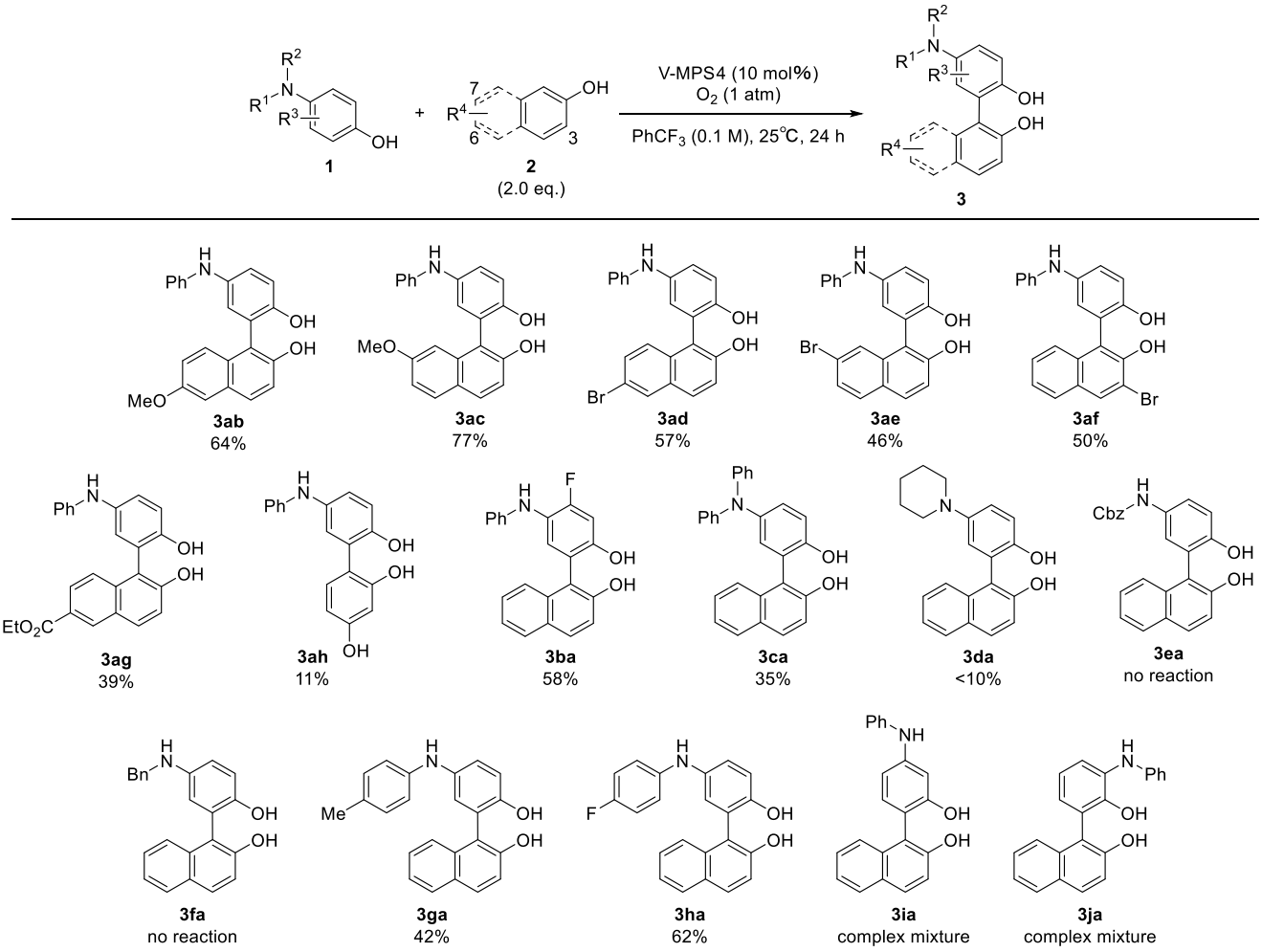


Figure 1. Cyclic voltammograms of a) **1a** and **2a**, b) **3aa**, and c) **1c**.



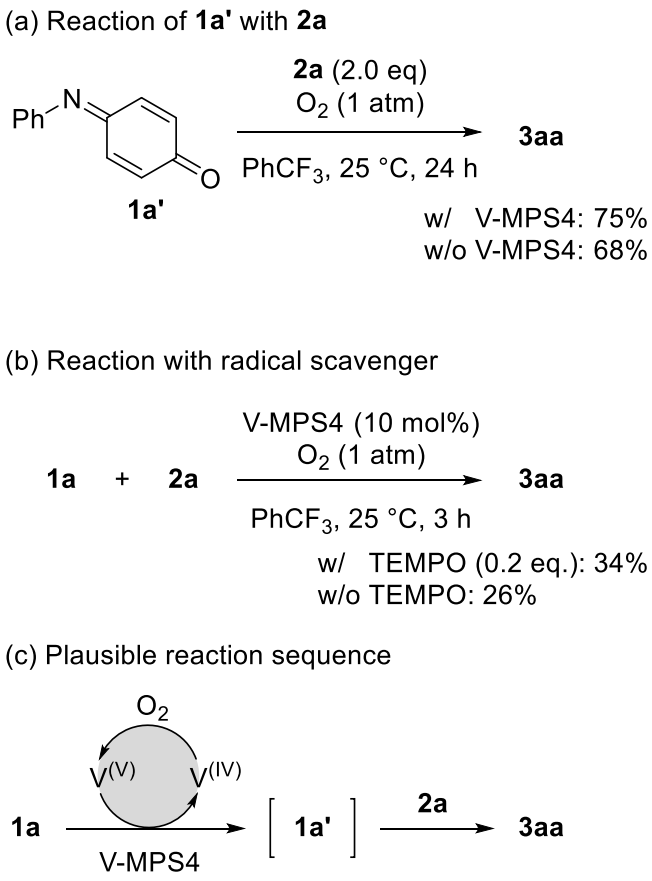
Scheme 2. Substrate scope. The reaction was conducted using **1** (0.10 mmol), **2** (0.20 mmol), and V-MPS4 (10 mol% based on vanadium) in $PhCF_3$ (1.0 mL) at 25 °C for 24 h under an oxygen atmosphere. The isolated yield of product **3** is shown.

introducing substituents on the *N*-Ph group did not affect the reactivity, and the reactions of 4-(*p*-tolylamino)phenol (**1g**) and 4-((4-fluorophenyl)amino)phenol (**1h**) afforded the corresponding products **3ga** and **3ha** in 42% and 62% yields, respectively. In contrast, *ortho*- and *meta*-substituted aminophenols led to complex mixtures.

In all cases where the desired products were obtained, aminophenols **1** were either completely consumed or only trace amounts were recovered after 24 h of reaction, and unidentified side products were formed along with the cross-coupling product **3**. As the oxidation potentials of **3** were comparable to those of **1** (Figure 1), overoxidation of **3** may occur under the reaction conditions, leading to a decrease in product yield.

To gain insight into the reaction mechanism, the oxidation potentials of **1a** and **2a** were examined by cyclic voltammetry and compared with that of 3-hydroxycarbazole (Figures 1 and S2). The analysis revealed that **1a** had two oxidation peaks (E_{pa1}[**1a**] = 0.52 V and E_{pa2}[**1a**] = 0.72 V versus Ag|Ag^+), both of which were lower than that of **2a** (E_{pa}[**2a**] = 1.23 V versus Ag|Ag^+), whereas 3-hydroxycarbazole showed a single oxidation peak at 0.77 V versus Ag||Ag^+ (Figure S2). These results suggest that the CDC reaction was initiated by the oxidation of **1a** in the presence of V-MPS4, forming a QMI intermediate via a two-electron oxidation process. On the other hand, *N*,*N*-disubstituted aminophenol **1c** exhibited a single pair of oxidation and reduction peaks, indicating a reversible redox process and the formation of a radical cation under oxidation conditions. Accordingly, the reaction between **1c** and **2a** is likely to proceed via nucleophilic addition of **2a** to the radical cation intermediate derived from **1c**, similar to the mechanism previously proposed for the reaction of 3-hydroxycarbazoles with **2a**.[14] The formation of **3da** could also proceed via a similar radical cation pathway, although only a trace amount of **3da** was detected in the reaction mixture. The redox nature of V-MPS4-catalyzed CDC reaction was further supported by the previously reported reaction of 3-hydroxycarbazoles with **2a**, in which an ESR measurement of V-MPS4 exhibited an octet signal characteristic of vanadium(IV) after the reaction, whereas no detectable signal was observed before the reaction.[14]

Control experiments were conducted to gain further insight into the reaction mechanism (Scheme 3). The QMI intermediate **1a**′ was synthesized by oxidation of **1a** with a stoichiometric



Scheme 3. Mechanism investigations.

amount of Ag_2O (see Supporting Information). This intermediate was isolated and reacted with **2a** under the optimized conditions (Scheme 3a). The reaction proceeded efficiently without the V-MPS4 catalyst, affording **3aa** in 68% yield, which was comparable to the 75% yield obtained with V-MPS4. These results suggest a non-catalytic reaction between **1a**′ with **2a**. Additionally, the radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) did not affect the outcome, with **3aa** obtained in comparable yields after 3 h both with and without TEMPO (Scheme 3b). The slightly higher yield obtained in the presence of TEMPO (34%) compared to the absence of TEMPO (26%) was attributed to a TEMPO-mediated background reaction between **1a** and **2a**, which was far less effective compared to V-MPS4-catalyzed process. Indeed, **3aa** was formed in 6% yield when TEMPO (0.2 eq.) was used in place of V-MPS4 under otherwise identical reaction conditions. These results indicate that the present CDC reaction proceeds via the V-MPS4-catalyzed two-electron oxidation of **1a** to generate **1a**′, which then undergoes a non-catalytic coupling with **2a** (Scheme 3c). Molecular oxygen serves as a terminal oxidant, regenerating the catalytically active oxovanadium(V) species.[14] The formation of **1a**′ from **1a** in the presence of V-MPS4 under an oxygen atmosphere was further confirmed experimentally (see Scheme S1). The reaction mechanism proposed herein for the V-MPS4-catalyzed CDC reaction of **1a** with **2a** contrasts sharply with that of 3-hydroxycarbazole with **2a**, which was significantly suppressed by TEMPO, suggesting the involvement of a radical intermediate.[14]

3. Conclusions

CDC reactions of *N*-phenyl-4-aminophenols **1** with 2-naphthols **2** were efficiently catalyzed using a mesoporous silica-supported oxovanadium catalyst (V-MPS4). The reaction proceeded smoothly under ambient oxygen at room temperature, yielding novel biaryl compounds. Mechanistic studies indicated that a quinone monoimine (QMI) intermediate generated from **1** through a two-electron oxidation was key intermediate in the reaction. Traditionally, aminophenols have been used as building blocks for functionalized aromatic compounds via stoichiometric oxidation to generate QMIs. In contrast, this study demonstrates a catalytic CDC method that uses molecular oxygen as the terminal oxidant. This environmentally friendly approach significantly reduces chemical waste, offering a more sustainable strategy for biaryl synthesis. Ongoing investigations of our group involve exploring the catalytic transformations of aminophenols and the application of V-MPS4 in CDC reactions, including continuous-flow processes.

Acknowledgments

The authors would like to appreciate Dr. Yuta Uetake (Graduate School of Engineering, The University of Osaka) for his kind support to cyclic voltammetry measurement and Dr. Naoki Oka (National Institute of Advanced Industrial Science and Technology) for the experimental supports. This work was supported by JSPS KAKENHI Grant Numbers 24K02148 (S.A.) and 24K08410 (K.K.), the Joint Usage/Research Center for Catalysis (23AY0215, 24AY0545) (K.K.), Amano Institute of Technology (K.K.), Tokuyama Science Foundation (K.K.), "Innovation inspired by Nature" Research Support Program, SEKISUI CHEMICAL CO., LTD. (K.K.), and Research Support Project for Life Science and Drug Discovery (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP24ama121054.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Crystallographic Data

Deposition Number 2443982 (for **3aa**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallo-

graphic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Keywords: Aminophenol · C—C bond formation · C—H functionalization · Heterogeneous catalyst · Quinone monoimine

[1] Z. H. Wang, X. H. Fu, Q. Li, Y. You, L. Yang, J. Q. Zhao, Y. P. Zhang, W. C. Yuan, *Molecules* **2024**, *29*, 2481, 1–27.
[2] J. Z. Wang, J. Zhou, C. Xu, H. Sun, L. Kürti, Q. L. Xu, *J. Am. Chem. Soc.* **2016**, *138*, 5202–5205.
[3] K. L. Jensen, P. T. Franke, L. T. Nielsen, K. Daasbjerg, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2010**, *49*, 129–133.
[4] Z. Zhu, Y. Li, S. Ma, X. Zhou, Y. Huang, J. Sun, W. Y. Ding, *J. Org. Chem.* **2024**, *89*, 16185–16194.
[5] Y. Li, L. Li, F. Li, S. Hu, R. Zhu, J. Sun, *Eur. J. Org. Chem.* **2025**, *28*, e202401126.
[6] Q. Yu, Y. Fu, J. Huang, J. Qin, H. Zuo, Y. Wu, F. Zhong, *ACS Catal.* **2019**, *9*, 7285–7291.
[7] M. A. Bashir, H. Zuo, X. Lu, Y. Wu, F. Zhong, *Chem. Commun.* **2020**, *56*, 5965–5968.
[8] C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292.
[9] T. Tian, Z. Li, C. J. Li, *Green Chem.* **2021**, *23*, 6789–6862.
[10] M. C. Carson, M. C. Kozlowski, *Nat. Prod. Rep.* **2024**, *41*, 208–227.
[11] L. Liu, P. J. Carroll, M. C. Kozlowski, *Org. Lett.* **2015**, *17*, 508–511.
[12] H. Kang, Y. E. Lee, P. V. G. Reddy, S. Dey, S. E. Allen, K. A. Niederer, P. Sung, K. Hewitt, C. Torruellas, M. R. Herling, M. C. Kozlowski, *Org. Lett.* **2017**, *19*, 5505–5508.
[13] M. Sako, K. Higashida, G. T. Kamble, K. Kaut, A. Kumar, Y. Hirose, D. Y. Zhou, T. Suzuki, M. Rueping, T. Maegawa, S. Takizawa, H. Sasai, *Org. Chem. Front.* **2021**, *8*, 4878–4885.
[14] K. Kasama, K. Kanomata, Y. Hinami, K. Mizuno, Y. Uetake, T. Amaya, M. Sako, S. Takizawa, H. Sasai, S. Akai, *RSC Adv.* **2021**, *11*, 35342–35350.
[15] K. Kasama, Y. Koike, H. Dai, T. Yakura, *Org. Lett.* **2023**, *25*, 6501–6505.
[16] A. W. Schmidt, K. R. Reddy, H. J. Knölker, *Chem. Rev.* **2012**, *112*, 3193–3328.
[17] M. Sako, S. Takizawa, H. Sasai, *Tetrahedron* **2020**, *76*, 131645.
[18] A. Kumar, H. Sasai, S. Takizawa, *Acc. Chem. Res.* **2022**, *55*, 2949–2965.
[19] H. Kang, M. R. Herling, K. A. Niederer, Y. E. Lee, P. Vasu Govardhana Reddy, S. Dey, S. E. Allen, P. Sung, K. Hewitt, C. Torruellas, G. J. Kim, M. C. Kozlowski, *J. Org. Chem.* **2018**, *83*, 14362–14384.
[20] M. Egi, K. Sugiyama, M. Saneto, R. Hanada, K. Kato, S. Akai, *Angew. Chem., Int. Ed.* **2013**, *52*, 3654–3658.
[21] K. Sugiyama, Y. Oki, S. Kawanishi, K. Kato, T. Ikawa, M. Egi, S. Akai, *Catal. Sci. Technol.* **2016**, *6*, 5023–5030.
[22] T. Nishio, S. Yoshioka, K. Hasegawa, K. Yahata, K. Kanomata, S. Akai, *Eur. J. Org. Chem.* **2021**, *2021*, 4417–4422.
[23] R. Ikeda, T. Nishio, K. Kanomata, S. Akai, *Chem. Pharm. Bull.* **2024**, *72*, 213–219.
[24] T. Nishio, H. Shigemitsu, T. Kida, S. Akai, K. Kanomata, *Bull. Chem. Soc. Jpn.* **2025**, *98*, uoae144.

Manuscript received: May 8, 2025
Revised manuscript received: August 14, 2025
Version of record online: ■■, ■■