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ARTICLE TYPE

Base-promoted dehydrogenative coupling of benzene derivatives with amides or ethers

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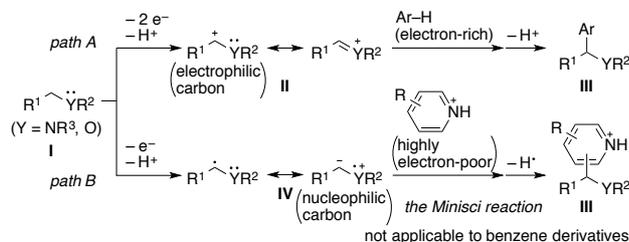
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Benzene derivatives are introduced into the dehydrogenative coupling via homolytic aromatic substitution (HAS) as arenes that couple with amides/ethers. NaOt-Bu is used as a critical promoter of HAS in combination with *t*-BuOO*t*-Bu as an oxidant.

Introduction

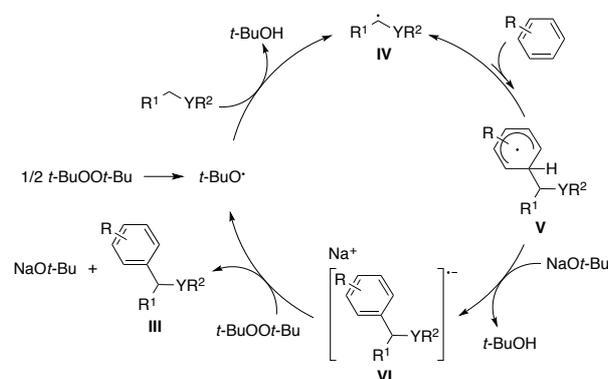
The dehydrogenative coupling between an aliphatic C–H bond and an aromatic C–H bond is a convenient method to introduce aliphatic substituents into aromatic rings because intricate introduction of reactive functional groups are not required.¹ The dehydrogenative coupling by use of an oxidant is convenient especially when amides, amines or ethers are employed as aliphatic compounds since they are readily oxidized merely at α -positions of the heteroatom to be converted into active species that react with arenes. This type of reactions is divided into two types according to the oxidation sequence (Scheme 1). In the first type (*path A*), two electron oxidation of R¹CH₂YR² (I: Y = NR³, O) gives heteroatom-stabilized cation II, which undergoes electrophilic aromatic substitution (S_EAr) leading to dehydrogenative coupling product III but only with electron-rich arenes.^{2,3} In the second type (*path B*), one electron oxidation of I gives *sp*³-carbon radical IV, which is transformed into III through homolytic aromatic substitution (HAS) consisting of radical addition and one electron oxidation (H[•] abstraction). This type, called as the Minisci reaction,⁴ is applicable only to protonated pyridine derivatives, where loss of aromaticity upon addition of heteroatom-stabilized radical IV is compensated with "polar effect" between electron-rich radical IV and a highly electron-poor arene. In contrast, such a strong driving force is not available in the case of benzene derivatives, even those having electron-withdrawing substituents, and thus the corresponding dehydrogenative coupling has never been reported. Here we



Scheme 1 Two pathways of the dehydrogenative coupling between an aliphatic C–H bond and an aromatic C–H bond.

report that the dehydrogenative coupling between benzene derivatives and amides/ethers proceeds in moderate yields,⁵ utilizing a base as a critical promoter of HAS.^{6–8}

t-BuOO*t*-Bu was chosen as an oxidant since its homolysis cleanly gives *t*-BuO[•], which should effectively abstract H[•] from heteroatom-containing aliphatic compounds. As a strong base compatible with the oxidant, we selected NaOt-Bu, expecting it to work as follows (Scheme 2). Thus, homolysis of *t*-BuOO*t*-Bu gives *t*-BuO[•], which abstracts H[•] from a C–H bond adjacent to the heteroatom. The resulting radical (IV) adds to a benzene derivative to give cyclohexadienyl radical V. Although this step is reversible and the equilibrium lies far to IV, deprotonation from V by NaOt-Bu shifts the equilibrium to V, converting it into the corresponding anion radical (VI). Single electron oxidation of VI with *t*-BuOO*t*-Bu gives dehydrogenative coupling product III and regenerates *t*-BuO[•] and NaOt-Bu.

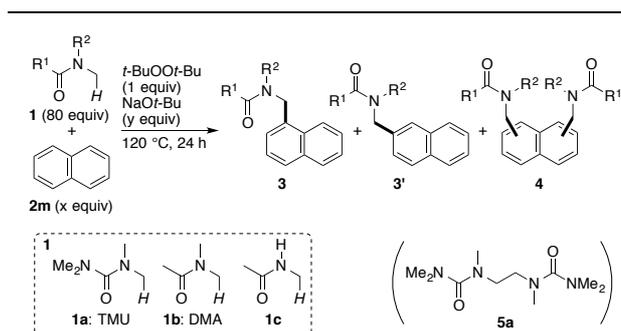


Scheme 2 Expected mechanism of the dehydrogenative coupling between an aliphatic C–H bond and a benzene C–H bond using a strong base.

Results and discussion

The reaction of naphthalene (**2m**: 3 equiv) with *N,N,N',N'*-tetramethylurea (TMU, **1a**: 80 equiv) in the presence of *t*-BuOO*t*-Bu (1 equiv) and NaO*t*-Bu (1 equiv) at 120 °C for 24 h gave *N,N,N',N'*-trimethyl-*N'*-(1-naphthylmethyl)urea (**3am**) and the 2-naphthyl isomer (**3'am**) in 70% combined yield based on *t*-BuOO*t*-Bu with a high regioselectivity (93:7) (Table 1, entry 1).^{9,10} In the absence of NaO*t*-Bu, the coupling products were obtained only in 2% yield, where a certain amount (38%) of *N,N'*-dimethyl-*N,N'*-bis(dimethylaminocarbonyl)ethylenediamine (**5a**) was produced (entry 2). Me₂NC(=O)NMeCH₂ (**IV** in Scheme 2), generated by H⁺ abstraction with *t*-BuO[•], is likely to undergo radical–radical homocoupling instead of HAS on **2m** in the absence of a base.¹¹ Both increase and decrease of the amount of NaO*t*-Bu from 1 equiv lowered the yield (entries 3 and 4). In the presence of 1 equiv of NaO*t*-Bu, *N,N*-dimethylacetamide (**1b**, DMA) also underwent the coupling with **2m** in a high regioselectivity on naphthalene for 1-position (entry 5). For the coupling of *N*-methylacetamide (**1c**), use of 2 equiv of NaO*t*-Bu was effective (entries 6–8). The existence of the acidic N–H bond in **1c** possibly weakens the net basicity, requiring a higher amount of the base. By use of 1:1 stoichiometry for **2m**:*t*-BuOO*t*-Bu instead of 3:1 in the coupling of **2m** with **1a–1c**, the combined yields of 1:1 coupling products **3/3'** and 1:2 coupling products **4** (a regioisomeric mixture) based on *t*-BuOO*t*-Bu, also on **2m** in this case, were 37–49%, which are slightly lower than those in

Table 1 Dehydrogenative coupling of naphthalene with amides^a

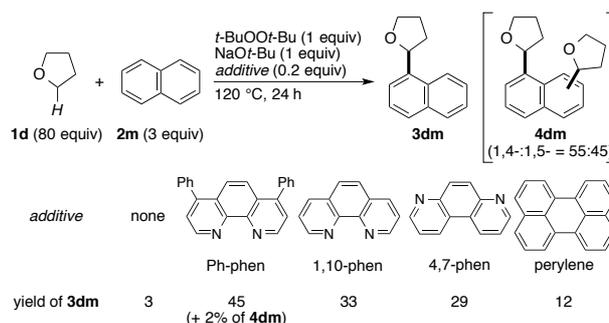


Entry	1	x	y	Yield ^b (%)	3:3':4^b
1	1a	3	1	70	93:7:<1
2	1a	3	0	2 ^c	90:10:<1
3	1a	3	0.5	68	95:5:<1
4	1a	3	2	53	94:6:<1
5	1b	3	1	54	96:4:<1
6	1c	3	1	41	97:3:<1
7	1c	3	2	59	98:2:<1
8	1c	3	3	48	97:3:<1
9	1a	1	1	49	80:4:16 ^d
10	1b	1	1	48	75:4:21 ^e
11	1c	1	2	38	96:4:<1

^a The reaction was carried out under a nitrogen atmosphere at 120 °C for 24 h using an amide (**1**: 17.8 mmol), naphthalene (**2m**: 0.223 or 0.669 mmol), *t*-BuOO*t*-Bu (0.223 mmol) and NaO*t*-Bu. ^b Determined by GC based on *t*-BuOO*t*-Bu. ^c Homocoupling product **5a** was observed (0.085 mmol, 38% yield based on *t*-BuOO*t*-Bu). ^d **4am**: 93:7 ratio of 1,5- and unidentified (1,3-, 1,6- or 1,7-) disubstituted naphthalenes. ^e **4bm**: 57:43 ratio of 1,5- and 1,4-disubstituted naphthalenes.

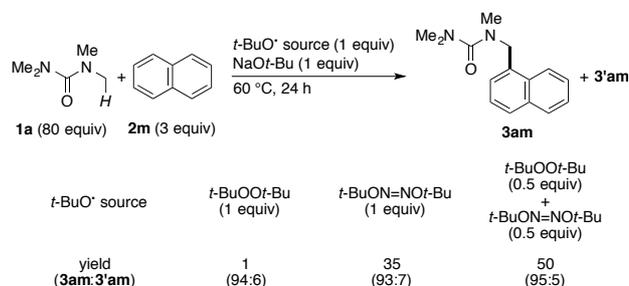
entries 1, 5 and 7 (entries 9–11). In order to avoid bothersome coproduction of 1:2 coupling products, we chose 3:1 stoichiometry for arene:*t*-BuOO*t*-Bu in the further investigation, though it looks rather unusual that the yield is not based on each of the substrates.

In contrast to amides **1a–1c**, tetrahydrofuran (**1d**, THF: 80 equiv) did not undergo efficient coupling with naphthalene (**2m**: 3 equiv) under similar conditions, giving just 3% yield of dehydrogenative coupling product **3dm**, where considerable amounts of polymeric compounds were produced (Scheme 3). We anticipated that the anion radical intermediate (**VI** in Scheme 2) is unstable, undergoing decomposition before being oxidized by *t*-BuOO*t*-Bu. Then, we added 4,7-diphenyl-1,10-phenanthroline (Ph-phen: 0.2 equiv) to the reaction mixture, expecting it to work as a single electron mediator that receives an electron from the anion radical and delivers it to *t*-BuOO*t*-Bu. As expected, the yield of **3dm** was increased to 47%.¹² Here a perfect regioselectivity for **3dm** over 2-isomer **3'dm** was observed but 1:2 coupling products **4dm** were produced in 2% yield. Other compounds, which should receive an electron at their relatively low-lying LUMO, also worked to some extents (12–33% yields). The result that 1,10- and 4,7-phen showed comparable efficiencies and even perylene, lacking heteroatoms, works implies that coordination on NaO*t*-Bu is not essential.



Scheme 3 Dehydrogenative coupling between naphthalene and THF with the aid of a single electron mediator.

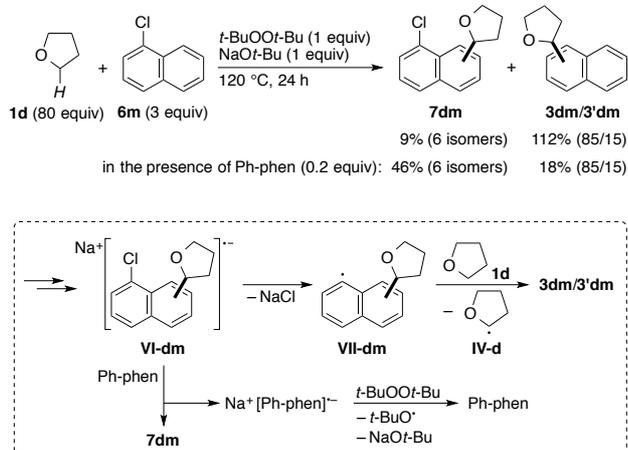
The reaction of **1a** with **2m** is sluggish at 60 °C (Scheme 4), probably because thermal homolysis of *t*-BuOO*t*-Bu is too slow to give a sufficient amount of *t*-BuO[•] to initiate the reaction. The same reaction proceeded in 35% yield at the same temperature by replacing *t*-BuOO*t*-Bu with *t*-BuON=NO*t*-Bu, which readily undergoes decomposition at the temperature to give *t*-BuO[•].¹³ The



Scheme 4 Effect of *t*-BuO[•] sources.

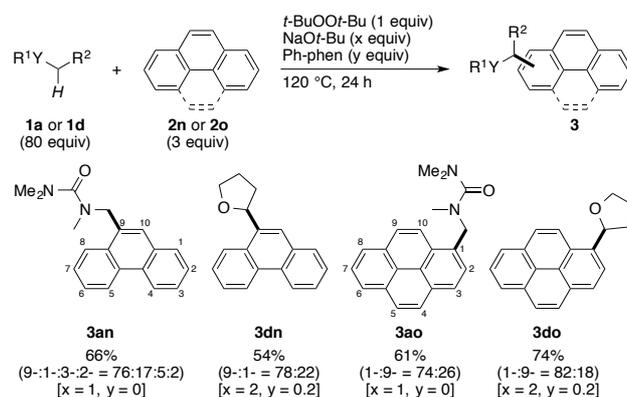
moderate yield is possibly ascribed to low oxidation ability of $t\text{-BuON}=\text{NO}t\text{-Bu}$ compared with $t\text{-BuOO}t\text{-Bu}$. The combination of $t\text{-BuON}=\text{NO}t\text{-Bu}$ (0.5 equiv) with $t\text{-BuOO}t\text{-Bu}$ (0.5 equiv) scored a higher yield, where $t\text{-BuO}^\bullet$ -releasing and oxidation abilities are likely to be well balanced. These results are consistent with the involvement of $t\text{-BuO}^\bullet$ in the coupling.

Aryl halides (Ar-X) are expected to work as anion radical probes since the corresponding anion radicals, $[\text{Ar-X}]^{\bullet-}$, are known to readily undergo decomposition into Ar^\bullet and X^- .¹⁴ The reaction of 1-chloronaphthalene (**6m**: 3 equiv) with THF (**1d**: 80 equiv) in the presence of $t\text{-BuOO}t\text{-Bu}$ (1 equiv) and $\text{NaO}t\text{-Bu}$ (1 equiv) gave dehydrochlorinative coupling products **3dm**/**3'dm** (83/17) rather than dehydrogenative coupling products **7dm** (6 regioisomers) (Scheme 5). This result strongly supports involvement of anion radical intermediates **VI** in Scheme 2 as **3dm** and **3'dm** are most likely to be produced through elimination of Cl^- from the anion radical intermediate (**VI-dm** in this case as shown in the bottom half of Scheme 5) and H^\bullet abstraction from THF by the resulting aryl radical (**VII-dm**). Generation of anion radical intermediate **VI-dm** as a regioisomeric mixture should be responsible for production of regioisomers in both the dehydrochlorination (**3dm**/**3'dm**) and the dehydrogenation (**7dm**).¹⁵ The overall yield of the carbon-carbon bond formation exceeded the amount of $t\text{-BuOO}t\text{-Bu}$ used because the Ar-Cl bond also works as an oxidant. The involvement of anion radical intermediates **VI** was further supported by the reversal of the selectivity between the dehydrochlorination and the dehydrogenation upon addition (0.2 equiv) of Ph-phen (*cf.* Scheme 3). SET from anion radical intermediate **VI-dm to Ph-phen is considered to be faster than elimination of Cl^- (the bottom half of Scheme 5). From these results in addition to indispensability of a base (*cf.* Table 1, entries 1 and 2) and $t\text{-BuO}^\bullet$ (*cf.* Scheme 4), the expected mechanism shown in Scheme 2 is most likely to be operative.**



Scheme 5 The reaction of 1-chloronaphthalene with THF.

In addition to the two ring-fused system, those with three or four underwent the coupling with TMU (**1a**) and THF (**1d**) respectively under the conditions of entry 1 of Table 1 and Scheme 3 utilizing Ph-phen¹⁶ (Scheme 6). The major regioisomers were 9- and 1-substituted ones for phenanthrene (**2n**) and pyrene (**2o**), respectively, where the regioselectivities



Scheme 6 Dehydrogenative coupling of polycyclic aromatic hydrocarbons with amides or ethers.

exceeded 70% in each case.

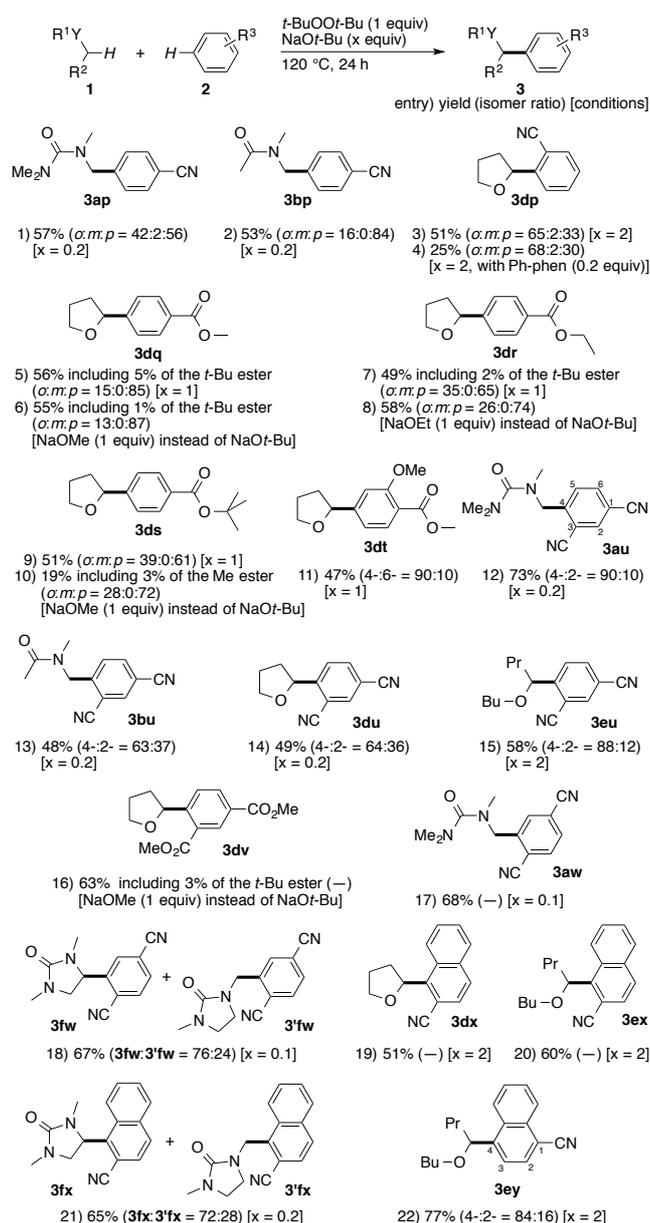
The dehydrogenative coupling is applicable also to benzene derivatives having electron-withdrawing substituents. The result is shown in Scheme 7, where the structures of major isomers are described with information on regioselectivities. As a whole, required amounts of $\text{NaO}t\text{-Bu}$ were smaller than those in the reaction of fused aromatic hydrocarbons, in particular with amides. Benzonitrile (**2p**) underwent the coupling with TMU (**1a**), DMA (**1b**) or THF (**1d**), where high ortho-para selectivities over meta were observed (entries 1–4). Ph-phen showed a negative effect even in the reaction of THF (entries 3 and 4; *cf.* Scheme 3). It is likely that the electron-withdrawing cyano-substituent stabilizes anion radical intermediate **VI** and a single electron mediator is no longer required. THF underwent the coupling with methyl (**2q**), ethyl (**2r**) and *tert*-butyl (**2s**) benzoates in relatively high para preferences (entries 5–11). Ester exchange giving *tert*-butyl esters were considerably prevented by choosing an appropriate alkoxide (NaOMe or NaOEt).¹⁷ Amides and ethers participated in the coupling with dicyano- and bis(methoxycarbonyl)benzenes (entries 12–18). In the reaction of cyclic urea **1f**, a new bond formed preferentially at a carbon on the ring (entry 18). 2-Cyanonaphthalene reacted exclusively at C1, which corresponds to ortho to cyano and α on naphthalene (entries 19–21). A high regioselectivity was observed also with 1-cyanonaphthalene (entry 22).¹⁸

Conclusions

In conclusion, we have disclosed that introduction of the base-promoted homolytic aromatic substitution into the dehydrogenative coupling enables us to conduct the coupling of amides/ethers with polycyclic aromatic hydrocarbons or benzene derivatives having electron-withdrawing groups.

Acknowledgements

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Scheme 7 Dehydrogenative coupling of benzene derivatives having electron-withdrawing groups with amides or ethers.

Notes and references

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 † Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and NMR spectra. See DOI: 10.1039/b000000x/

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- The reaction using 40 or 10 equiv of TMU (**1a**) gave 62% (94/6) or 35% (94/6) yield of **3am**/**3'am**, respectively. Low yields were observed in the reaction using a base other than NaOt-Bu: K_3PO_4 (5%, 94/6), DABCO (7%, 97/3), Et_3N (5%, 97/3).
- Although we used a glove box filled with nitrogen to mix the substrates and the reagents for operational simplicity, the dehydrogenative coupling can easily be conducted with a standard Schlenk technique as well. For details, see Supporting Information.

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- 15 The dehydrochlorination products (**3dm** and **3'dm**) are possibly produced by the dehydrogenative coupling of THF (**1d**) with naphthalene (**2m**), which ought to be generated through a sequence consisting of SET to **6m**, elimination of Cl⁻ from the resulting anion radical ([**6m**]^{-•}) and H[•] abstraction from THF by the resulting 1-naphthyl radical. However, the sequence is unlikely to be the main pathway as it should give **3dm** exclusively (*cf.* Scheme 3).
- 16 Slightly higher yields and selectivities resulted here in use of 2 equiv of NaO*t*-Bu than 1 equiv.
- 17 The methyl esters contaminated with the *tert*-butyl esters can be refined without loss by treatment with NaOMe in MeOH. For example, the product of entry 5 (Scheme 7) was converged into the methyl ester (**3dq**: 56% yield, *o/m/p* = 15/0/85). For details, see Supporting Information.
- 18 The minor regioisomer of entry 22 (Scheme 7) is most likely to have 1-butoxybutyl at 2-position but its structure could not be unambiguously determined. For details, see Supporting Information.