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Regioselective *Ortho* Amination of an Aromatic C−H Bond by Trifluoroacetic Acid via Electrochemistry

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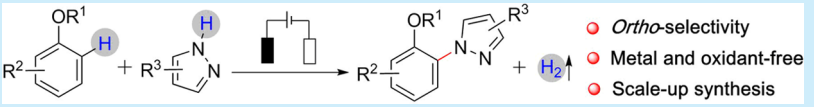
Supporting Information



ABSTRACT: A trifluoroacetic acid-facilitated *ortho* amination of alkoxyl arene has been established via anodic oxidation in an undivided cell. In the absence of any additional metal or oxidant reagents, a series of aromatic and heteroaromatic amine derivatives have been synthesized in good to excellent yields. Our findings reveal the possibility of achieving complete *ortho*-selective amination of a simple arene, which emerges as an efficient route for facile and large-scale organic synthesis.

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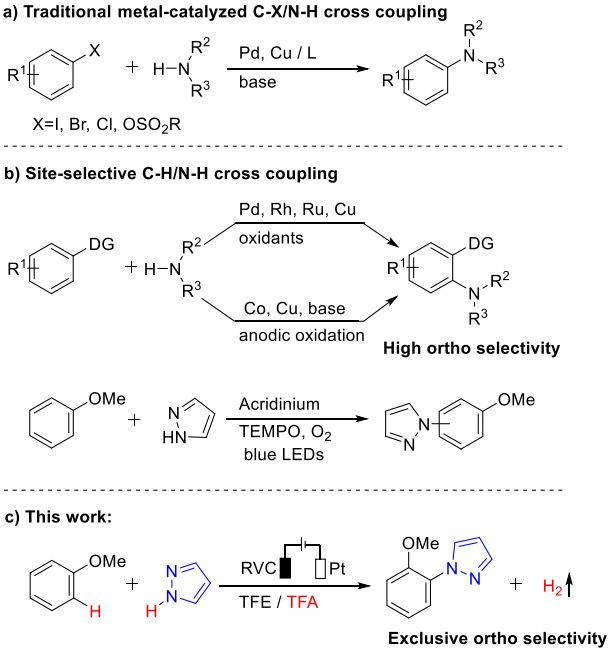
An aromatic amine derivative is a significant structural motif that widely exists in natural products, agrochemicals, pharmaceuticals, and medical compounds,[1] which leads to the hot topic of its construction in organic chemistry. Traditional methods using metal-catalyzed (e.g., Pd and Cu)[2,3] cross coupling of aromatic halide (or psudohalide) and nitrogen species has been regarded as the most significant way to realize selective C−N bond formation, but starting material prefunctionalization and ligand elaboration are needed (Scheme 1a). A more straightforward and atom-economical way would be direct C−N bond formation from C−H/N−H cross coupling. In this context, directing group-assisted selective C−H activation/amination processes by either transition metal (such as Pd,[4] Rh,[5] Ru,[6] Cu,[7] etc.) catalysis or electrocatalysis in which Co participates[8−10] achieved highly *ortho*-selective C−H amination. Other seminal methods like photocatalysis[11] or metalla-photocatalysis[12] also realized the amination, but they showed poor selectivity for the substituted substrate due to the weak control of the reaction site (Scheme 1b). To date, the site-selective amination of arene remains challenging to achieve with high selectivity for a simple arene without a strong directing group.

This work discloses that trifluoroacetic acid (TFA) can control the electrocatalytic amination of alkoxy arenes with unprecedented high *ortho* selectivity. As is known, electrocatalysis and photoelectrocatalysis are promising for the construction of C−C and C−N bonds in a series of cross-coupling reactions.[13−19] Herein, direct oxidative C−H/N−H cross coupling of arenes by employing pyrazole as the amination reagent has been realized with 2 equiv. of TFA. *Ortho*-selective aromatic amine derivatives have been synthesized in good to excellent yields (Scheme 1c). More significantly, the strong effect of TFA to control nearly the regiospecificity for the *ortho* isomer is uncovered for the first time, which shows great potential in practical organic synthesis.

Scheme 1. Amination of Arene



Initially, anisole **1** and pyrazole **2** were used as model substrates. The electrochemical reactions were carried out in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum plate cathode. When the solution

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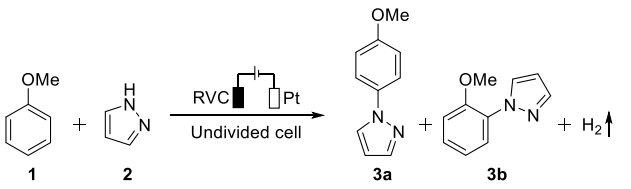
of **1**, **2**, and 0.1 M $^{n}Bu_4NOAc$ in 1,1,1-trifluoroethanol (TFE) was electrolyzed, an 83% yield of the amino product was observed with a moderate *ortho*/*para* ratio (64:19 **3b**:**3a**) (Table 1, entry 2). To our surprise, with the addition of TFA,

Table 1. Optimization of Conditions[a]



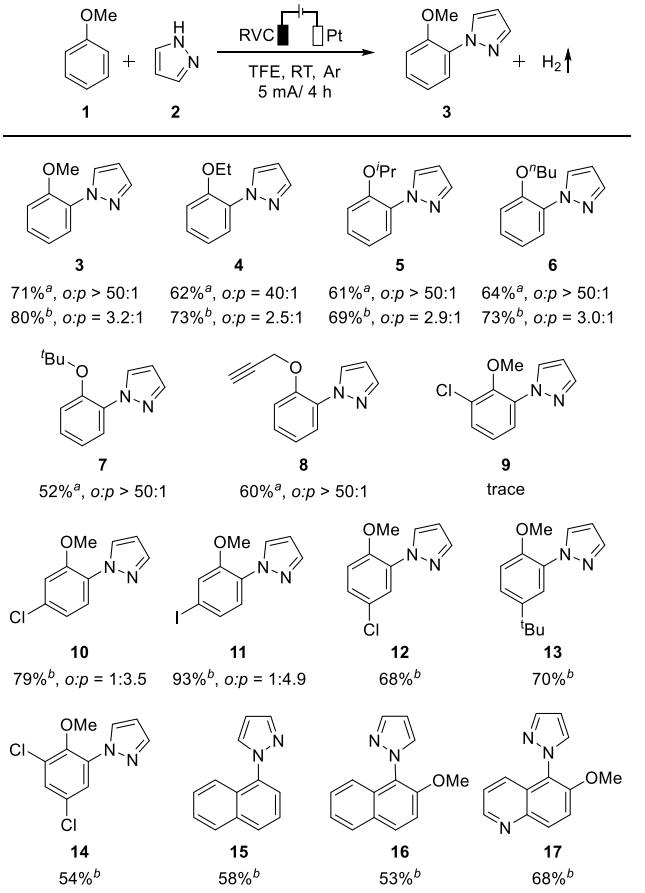
entry	electrolysis conditions	conversion of **1** (%)	yield (%) **3a**	**3b**	**3**
1	C(+)/Pt(−), 5 mA/4 h, TFE, TFA, rt, Ar	85	trace	75	75
2	no TFA	92	19	64	83
3	HFIP as the solvent	93	trace	56	56
4	DCE as the solvent	64		trace	
5	CH_3COOH as the additive	81	14	29	43
6	PivOH as the additive	73	17	25	42
7	TfOH as the additive	90	trace	72	72
8	$NaHCO_3$ as the additive	73	16	31	47
9	$^{n}Bu_4NBF_4$ as the electrolyte	62	trace	16	16
10	$^{n}Bu_4NClO_4$ as the electrolyte	78		trace	
11	RVC as the cathode	79	18	50	68
12	nickel foam as the cathode	92	21	63	84
13	Pt plate as the anode	79	5	26	31
14	under 10 mA and 2 h	89	trace	59	59
15	under air	88	trace	37	37
16	no electric current	0	not detected		

[a]Conditions: RVC anode (500 PPI, 1.0 cm × 1.0 cm × 0.5 cm), Pt plate as the cathode (0.5 cm × 1 cm), **1** (0.2 mmol), **2** (0.4 mmol), $^{n}Bu_4NOAc$ (0.1 M), 2 equiv. of TFA, TFE (4.0 mL), rt, Ar. Conversion and yield determined by GC analysis with tetradecane as the internal standard. The yield was based on **1** (0.2 mmol).

almost a single *ortho* isomer was formed with a yield of 75% (Table 1, entry 1). Further solvent screening demonstrated that 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as a solvent could also give the regioselectivity with a decreased 56% yield (Table 1, entry 3), and no desired product was obtained when TFE was replaced by 1,2-dichloroethane (DCE), methanol (MeOH), ethanol (EtOH), or acetonitrile (CH_3CN) (Table S1). Then, other different additives instead of TFA, including acetic acid (CH_3COOH), pivalic acid (PivOH), trifluoromethanesulfonic acid (TfOH), and $NaHCO_3$, were tested. The results showed that acetic acid, pivalic acid, and $NaHCO_3$ yielded product **3** in 43%, 42%, and 47% yields, respectively, with poor selectivities. Notably, TfOH exhibited similar activity with TFA, and a yield of 72% for the *ortho* product was obtained (Table 1, entries 5−8). In addition, the parameters of this electrolytic system were further optimized. Replacement of the electrolyte, cathode, or anode gave lower yields and poorer regioselectivity (Table 1, entries 9−13). Increasing the current density or reaction in the air atmosphere preserved the selectivity but decreased the yields (Table 1, entries 14 and 15). Finally, no product could be observed when the reaction was carried out in the absence of electricity, demonstrating the nature of electrocatalysis (Table 1, entry 16).

With the optimized reaction conditions in hand, we tried to explore the substrate generality of this electrochemical transformation (Scheme 2). Initially, a series of monosubstituted anisole derivatives were examined. For methyl, ethyl, *i*-Pr, and *n*-Bu substitutions, the absence of TFA delivered good yields but poor selectivities, providing mixtures of *ortho* and *para* amination products (**3**−**6**, <3.2:1 *o*:*p*). When the acid was added, almost pure *ortho* isomers were formed (≥40:1 *o*:*p*). These results further demonstrated the excellent regiocontrol by strong Bronsted acid TFA. Likewise, other monosubstituted anisole derivatives, such as *tert*-butyl phenyl ether and (prop-2-ynyloxy)benzene, selectively furnished the *ortho* amination in 52% (>50:1 *o*:*p*) and 60% (>50:1 *o*:*p*) yields, respectively, in the presence of TFA (**7** and **8**). Unfortunately, no corresponding products were formed for *ortho*-disubstituted arene (**9**), and *meta*-disubstituted arenes gave high *para* isomers (**10** and **11**). With respect to 1,4-disubstituted arenes, corresponding amination products with a single *ortho* isomer were afforded (**12** and **13**). Interestingly, 2,4-dichloroanisole, which has three substitutions, gave a single *ortho* product in a moderate yield (**14**). In addition, other aromatic compounds like naphthalene and 2-methoxynaphthalene were also investigated to selectively furnish C_1 amination products (**15** and **16**). Even 6-methoxyquinoline could be converted into a single isomer (**17**) in 68% yield.

Scheme 2. Substrate Scope of Anisole[a]



[a]Standard conditions: RVC anode (500 PPI, 1.0 cm × 1.0 cm × 0.5 cm), Pt plate as the cathode (0.5 cm × 1 cm), **1** (0.2 mmol), **2** (0.4 mmol), $^{n}Bu_4NOAc$ (0.1 M), 2 equiv. of TFA, TFE (4.0 mL), rt, Ar. Isolated yields were provided. [b]Reaction ran without TFA.

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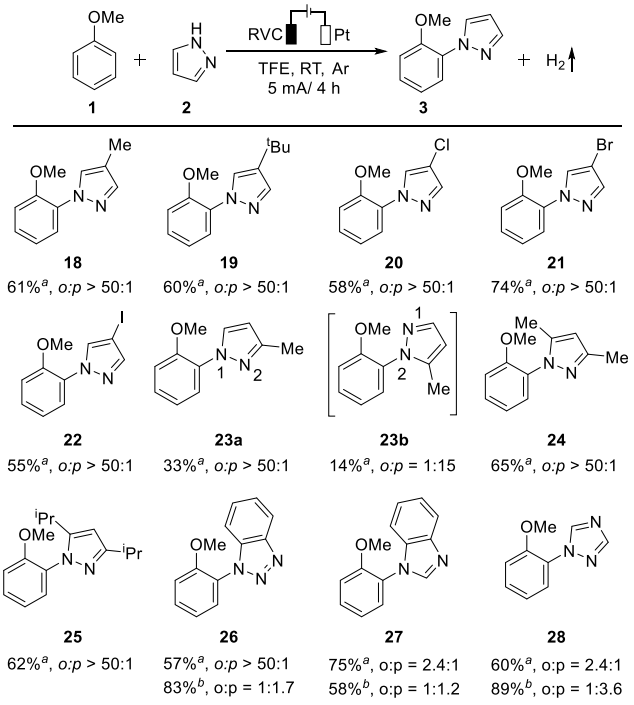
Subsequently, a series of heterocyclic amines as amination reagents were studied to expand the synthetic utility of this method (Scheme 3). In the presence of TFA, pyrazole with

Scheme 3. Substrate Scope of Amines[a]

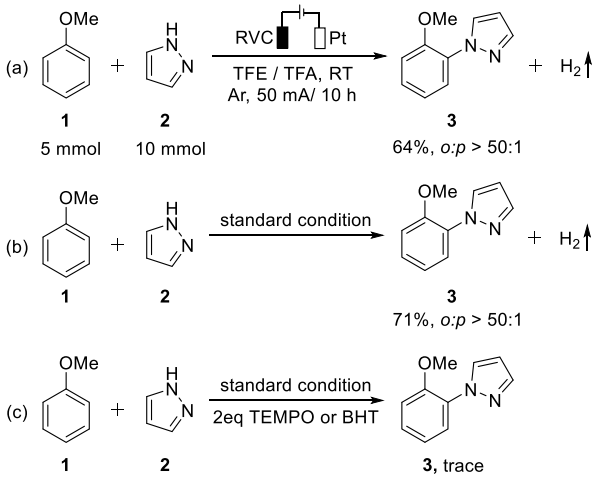


[a]Standard conditions: RVC anode (500 PPI, 1.0 cm × 1.0 cm × 0.5 cm), Pt plate as the cathode (0.5 cm × 1 cm), **1** (0.2 mmol), **2** (0.4 mmol), $^{n}Bu_4NOAc$ (0.1 M), 2 equiv. of TFA, TFE (4.0 mL), rt, Ar. Isolated yields were provided. [b]Reaction ran without TFA.

different groups worked smoothly and could be selectively transferred into its corresponding *ortho* products. For example, the pyrazole derivatives bearing a methyl, *tert*-butyl, or halogen group at 4-position showed good activities to form the *ortho* isomer with 55−74% yields and a >50:1 *o*:*p* ratio (**18**−**22**). 3-Methyl-1*H*-pyrazole mainly produced the N-1 product in 33% yield (>50:1 *o*:*p*), along with 14% N-2 product (1:15 *o*:*p*) (**23**). Moreover, disubstituted 3,5-dimethyl-1*H*-pyrazole and 3,5-diisopropyl-1*H*-pyrazole were well tolerated with good yields and *ortho* selectivity (**24** and **25**, >50:1 *o*:*p*). It should be noted that benzotriazole instead of pyrazole as the amination agent could give a 57% yield of the *ortho* product (>50:1 *o*:*p*) under the optimized condition, while a 83% yield of the mixture with a 1:1.7 *o*:*p* ratio was detected without TFA, further highlighting the importance of TFA for selective amination. Similarly, the method could also be applied to two other derivatives such as benzimidazole, 1,2,4-triazoles, which gave the corresponding C−N coupling products in good yields but low selectivities. Apparently, the TFA enabled us to adjust the regioselectivity for *ortho* priority (**27** and **28**). Finally, a scaled-up reaction of template in 5 mmol was carred out. After the reaction system was electrolyzed at 50 mA for 10 h, **3** was obtained in 64% yield and the selectivity remained >50:1 *o*:*p* (Scheme 4a), indicating the robustness of this strategy and its great potential for practical organic synthesis and industral application.

To understand this reaction, several control experiments were carried out. Under the optimized condition, the reaction

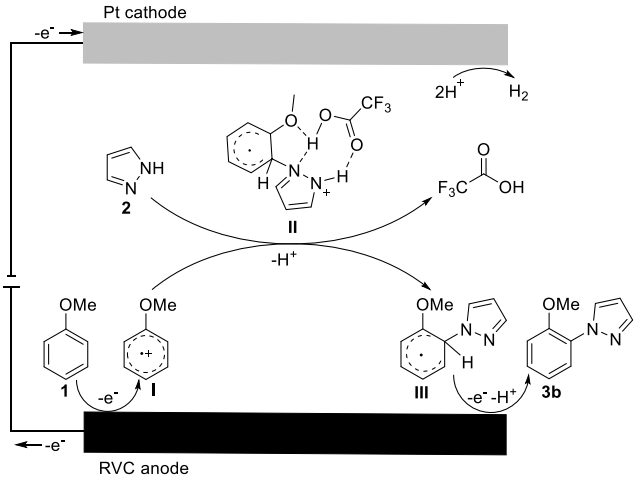
Scheme 4. Scale-Up Reaction and Control Experiment



of anisole **1** and pyrazole **2** could give a 71% isolated yield of the *ortho* isomer (>50:1 *o*:*p*) (Scheme 4b). However, when 2 equiv. of TEMPO or BHT was added for radical capture, no corresponding C−N coupling products were formed, demonstrating a possible radical pathway in this system (Scheme 4c). In addition, cyclic voltammetry of two substrates showed that the oxidation potentials of anisole **1** and pyrazole **2** were 1.67 and 2.10 V versus SCE, respectively (Figure S2). Clearly, anisole was oxidized first under electrolytic conditions.

On the basis of the aforementioned results, a possible mechanism for the electro-oxidative amination reaction is outlined in Scheme 5. Initially, anisole was oxidized to

Scheme 5. Proposed Mechanism



corresponding radical cation intermediate **I** on the anode surface through a single-electron transfer. The fluorinated solvent had the function of stabilizing radical cations.[20] Subsequently, pyrazole as a nucleophile attacked the radical cation to form intermediate **II** probably via TFA-assisted hydrogen bond interaction.[21] Then, intermediate **III** was afforded with the loss of one proton. Followed by the rearomatization, final product **3b** was formed.

In summary, we have developed an electrochemical oxidative C−H/N−H cross coupling, which realized the almost completely *ortho*-selective amination of arene. TFA plays an essential role in the control of regioselectivity. This protocol

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provides a straightforward approach for aryl-azole under mild and easy conditions, avoiding the insertion of strong directing groups, and no metals or oxidants were needed. Control experiments suggested that the arene radical cation intermediate was the key to successful conversion. Further exploration of acid-assisted regioselective conversions of arene is undergoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01910.

Materials and methods, condition optimization and general experimental procedures, scale-up reaction, control experiments, cyclic voltammetry experiments, characterization data for all products, references, and ^{1}H and ^{13}C spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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