Reaction of Benzyne with Formamides and Acetylimidazole

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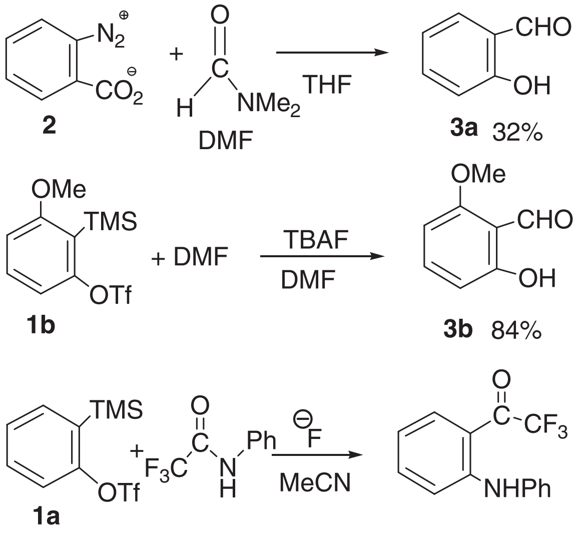
The reaction of DMF with *o*-trimethylsilylphenyl triflate in the presence of CsF afforded dimethyldiphenylammonium triflate, xanthene, and xanthone in 62%, 16%, and 24% yields, respectively. On the other hand, the reaction of dimethylthioformamide with triflate and CsF resulted in diphenyl sulfide, xanthene, and xanthone in 62%, 10%, and 12% yields, respectively. The reaction of acetylimidazole with benzyne gave 9-*N*,*N*-diphenylaminoanthracene in 85% yield.

Arynes are highly reactive intermediates that have found numerous applications in organic synthesis.[1] The dienophilic nature of benzyne has been exploited in [2 + 2] and [4 + 2] cycloaddition reactions with enes and dienes.[2] Our ongoing interest in the utility of reacting benzyne with thiones for the synthesis of functionalized *S*-heterocycles has led to our investigation of the synthesis of benzothietes, benzothianes, and 1,3-dithiols.[3] Following reports in the early 70s of the reaction of aldehydes with benzyne to give C=O bond insertion products (ca. 20%),[4] Yoshida et al. reported the formation of 9-arylxanthenes via the novel insertion reaction of benzyne derived from *o*-trimethylsilylphenyl triflate (**1a**) with aromatic aldehydes (22–70%).[5] Recently, we have reported the reaction of salicylaldehydes with benzyne generated from triflate and CsF to give xanthenes and xanthones.[6] The reaction of benzyne derived from benzenediazonium 2-carboxylate (**2**) with *N*,*N*-dimethylformamide (DMF) was reported by Yaroslavsky.[7] In that case, the sole product was salicylaldehyde (**3a**) in 32% yield, but the precise reaction mechanism was not reported. Very recently, Yoshioka et al. reported that the reaction of 3-methoxy-2-(trimethylsilyl)phenyl triflate (**1b**) with DMF and tetrabutylammonium triflate (TBAF) gave 2-hydroxy-6-methoxybenzaldehyde (**3b**) in 84% yield.[8] The benzyne-[2 + 2] cycloaddition reaction with enamides was recently reported as well.[9] A survey of the literature, nevertheless, revealed few general methods for the insertion reaction of benzyne with benzamides (Scheme 1).[10] This prompted us to reinvestigate the reaction of DMF with benzyne. Herein, we report the reactions of triflate **1** with DMF, dimethylthioformamide, and acetylimidazole, which afforded xanthenes, xanthones, diphenyl sulfide, and 9-*N*,*N*-diphenylaminoanthracene.

Results and Discussion

We first tried to perform the reaction of excess benzenediazonium carboxylate **2** with DMF to investigate whether salicylaldehyde would be formed or not. Treatment of DMF with **2** in refluxing chloroform resulted in the formation of **3a** (31%) and 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**4**) (21%). The result is similar to that of Yaroslavsky[7] except for the formation of triazene **4**. The reaction might have proceeded as follows: the [2 + 2] cycloaddition reaction of benzyne with DMF gave benzoxete and the ring opening of benzoxete produced a betaine intermediate. Hydration furnished salicylaldehyde and dimethylamine, the latter of which reacted with diazonium carboxylate to give triazine (Scheme 2). The independent reaction of dimethylamine with carboxylate **2** to give triazene **4**[11] in almost quantitative yield confirmed this mechanism.



Scheme 1.

Although Yoshioka et al. reported the synthesis of **3b** via the reaction of **1b** with DMF,[8] they did not mention the formation of salicylaldehyde by the reaction of **1a** with DMF. Thus, we tried to perform the reaction of triflate **1a** with DMF. Treatment of **1** with DMF in the presence of CsF for 13 h at rt resulted in the formation of xanthene (**5**), xanthone (**6**), and dimethyldiphenylammonium triflate (**7a**) in 16%, 24%, and 62% yields, respectively. The reaction of *N*-formylmorpholine with **1a** and CsF also afforded *N*,*N*-diphenylmorpholinium triflate (**7b**), **5**, and **6** in 62%, 15%, and 23% yields, respectively (Scheme 3). When dried CsF, acetonitrile, and DMF was used, the reaction afforded only trace amount of

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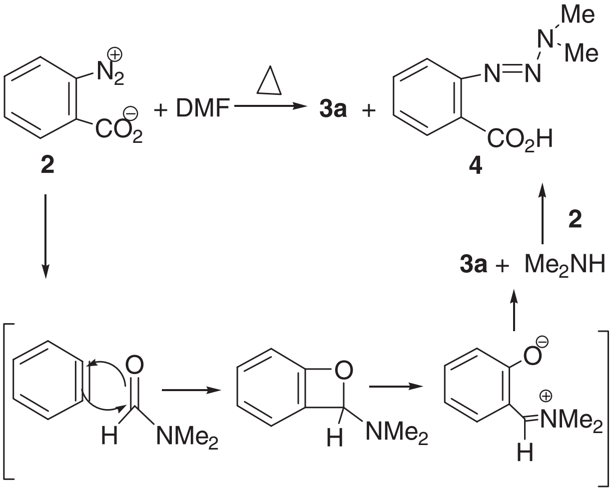
xanthene and xanthone along with unidentified products, indicating that a trace amount of water played very important role in the present reaction.

Although it is well known that primary and secondary amines react with benzyne to afford phenylated tertiary amines,[1,12] the formation of quaternary ammonium salts from secondary amines rarely occurs. The reaction of triethylamine with benzyne to afford triethylanilinium salt (46%) and the reaction of triethylamine or alkylimidazoles with benzyne to give *N*-phenylimidazolium triflate (33–59%) were reported by Wittig et al.[13] and Yoshida et al., respectively.[14] To confirm the phenylation of tertiary amine, the reaction of *N*,*N*-dimethylaniline with triflate **1a** was carried out and ammonium triflate **7a** was obtained in 86% yield (Scheme 4).

As the acid- and metal-catalyzed disproportionation of 9-hydroxyxanthene (**8**) was already reported,[15] we investigated the present reaction under basic conditions to isolate **8**. When CsF was added to a suspension of triflate **1a**, DMF, and K_2CO_3 in acetonitrile, compound **8** was obtained in 52% yield (Scheme 5).

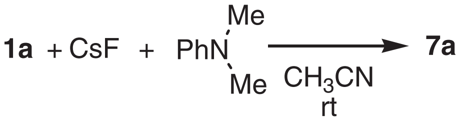
The reaction might have proceeded as follows: benzyne reacted with DMF to afford betaine intermediate **9** via the 2*H*-benzoxete intermediate, and **9** was hydrolyzed to give salicylaldehyde and dimethylamine. Excess benzyne further reacted with salicylaldehyde to give **8**, which disproportionated to give **5** and **6**. Dimethylamine also reacted with benzyne to afford ammonium triflate **7a** (Scheme 6).



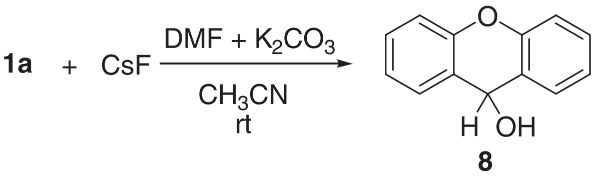
Scheme 2.

We then examined the reaction of *N*,*N*-dimethylthioformamide (**10**) with benzyne, to see whether electronically stabilized thiones, such as dimethylthioformamide, would produce benzothietes or not. Treatment of dimethylthioformamide with triflate and CsF resulted in the formation of diphenyl sulfide, **5**, **6**, and **7a** in 60%, 10%, 12%, and 60% yields, respectively. This shows that the initially formed betaine was further hydrolyzed to afford benzenethiol and DMF, which further reacted with another benzyne to afford diphenyl sulfide, **5**, and **6** (Scheme 7).

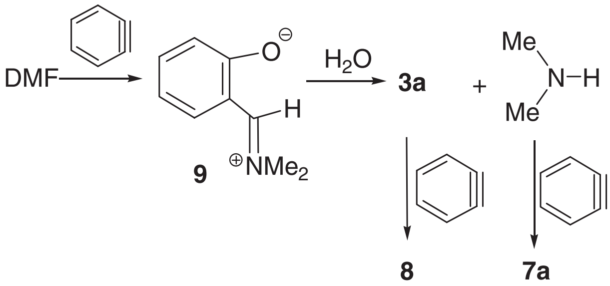
Larock et al. reported that the reaction of imidazole with triflate gave phenylimidazole.[16] Meanwhile, Yoshida et al. reported that the reaction of methylimidazole with triflate gave *N*-methyl-*N*′-phenylimidazolium triflate.[14] These results prompted us to investigate whether or not the reaction of *N*,*N*-dimethylacetamide (**11**) with benzyne would produce ammonium salts. Treatment of **11** with triflate **1a** and CsF resulted in the recovery of acetamide **11** (60%), indicating that the acetyl



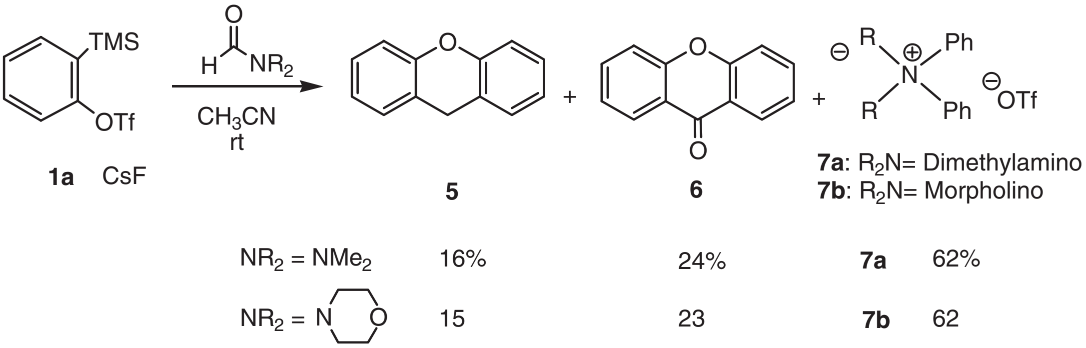
Scheme 4.



Scheme 5.



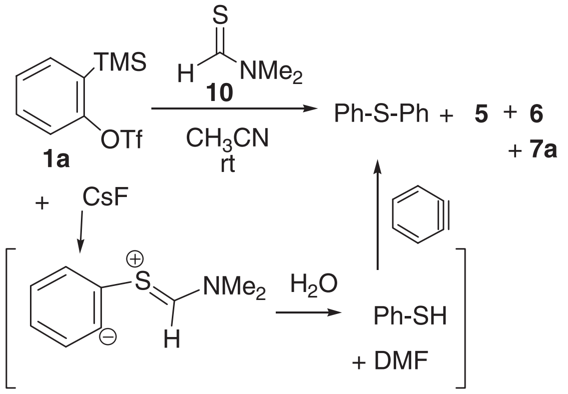
Scheme 6.



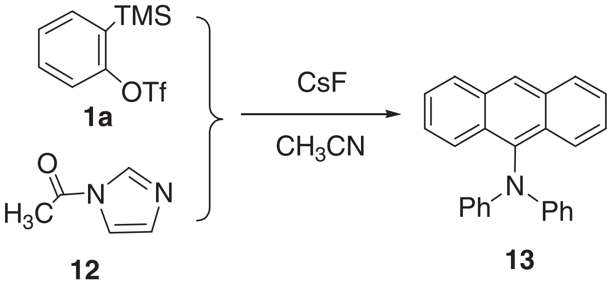
Scheme 3.

substituent is less reactive than the formyl group. However, when *N*-acetylimidazole (**12**) was used as the acetamide, a completely different product was obtained. Treatment of triflate (1 equiv) with **12** in the presence of CsF at rt resulted in the formation of 9-*N*,*N*-diphenylaminoanthracene (**13**) in 23% yield. When 4 equiv of triflate **1a** was used, anthracene **13** was obtained in 85% yield (Scheme 8).

Xie and Zhang have reported that the reaction of alkylimidazoles with triflate **1** gave *N*-alkyl-*N*-phenylaminoanthracenes.[17] The reaction might have proceeded as follows: acetylimidazole **12** reacted with benzyne to give *N*-phenylimidazolium triflate, and deacetylation gave *N*-phenylimidazole (**14**), which further reacted with benzyne to give a Diels–Alder adduct. Retro Diels–Alder reaction of the adduct gave *N*-phenylisoindole (**15**), which further reacted with another benzyne to yield a Diels–Alder adduct. Ring opening reaction of the adduct with another benzyne gave the final product (Scheme 9).



Scheme 7.



Scheme 8.

Actually, when the reaction of triflate **1a** (0.3 equiv) with **12** was carried out in CD$_3$CN, acetic acid and **14** were detected.

Conclusion

In conclusion, the present method provides a novel approach to the synthesis of 9-hydroxyxanthene, xanthene, xanthone, and *N*,*N*-diphenylaminoanthracene by reacting benzyne with DMF or *N*-acetylimidazole. Further studies on the synthetic application of this procedure are under way.

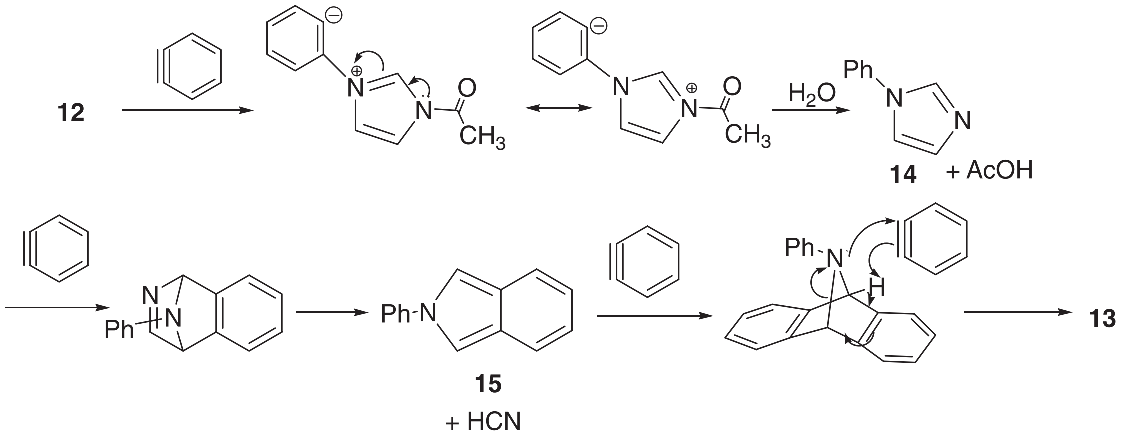
Experimental

General. All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70–230 mesh). NMR spectra (^{1}H at 400 MHz; ^{13}C at 100 MHz) were recorded in CDCl$_3$, and chemical shifts are expressed in ppm relative to internal TMS for ^{1}H- and ^{13}C NMR. Melting points were uncorrected.

Material. All reagents were purchased from TCI or Aldrich. Authentic samples (**5**, **6**, **8**, and **14**) were purchased from Aldrich or TCI. Triflate **1a** and carboxylate **2** were synthesized by a method in the literature.[18,19]

Reaction of Benzenediazonium Carboxylate 2 with DMF. To a solution of DMF (0.146 g, 2.0 mmol) in THF (6 mL) was added benzenediazonium carboxylate **2** (0.59 g, 4.0 mmol) in one portion. After refluxing for 2 h, the reaction mixture was evaporated to give pale brown oil, which was chromatographed over silica gel by elution with hexane:dichloromethane (2:1) to afford **3a** (0.078 g, 0.062 mmol) and **4** (0.079 g, 0.41 mmol). Compound **4**: pale yellow crystals; mp 120–122 °C (lit.[20] mp 122–126 °C). ^{1}H NMR (CDCl$_3$): δ 3.31 (s, 3H, CH$_3$), 3.70 (s, 3H, CH$_3$), 7.27 (t, $J = 8.0$ Hz, 1H, Ar), 7.50 (t, 1H, $J = 8.0$ Hz, Ar), 7.70 (d, 1H, $J = 8.0$ Hz, Ar), 8.24 (d, 1H, $J = 8.0$ Hz, Ar). Compound **4** was independently synthesized by the reaction of carboxylate **2** with dimethylamine in refluxing THF solution.

Reaction of DMF with Triflate 1a. To a suspension of CsF (0.339 g, 2.2 mmol) and triflate **1a** (0.33 g, 1.1 mmol) in acetonitrile (6 mL) was added DMF (0.037 g, 0.50 mmol). After



Scheme 9.

being stirred for 13 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown oily solid, which was chromatographed over silica gel by elution with hexane:ethyl acetate (10:1) to give **5** (0.014 g, 0.08 mmol) and **6** (0.023 g, 0.12 mmol) then eluted with ethyl acetate to afford **7a** (0.107 g, 0.31 mmol). Compound **5**: ^{1}H NMR ($CDCl_3$): δ 4.05 (s, 2H, CH_2), 6.95–7.07 (m, 4H, Ar), 7.14–7.22 (m, 4H, Ar). Compound **6**: ^{1}H NMR ($CDCl_3$): δ 7.38 (t, 2H, $J = 8.0$ Hz, Ar), 7.50 (d, 2H, $J = 8.0$ Hz, Ar), 7.72 (t, 2H, $J = 8.0$ Hz, Ar), 8.35 (d, 2H, $J = 8.0$ Hz, Ar).

Compound **7a**: Pale yellow oil: ^{1}H NMR ($CDCl_3$): δ 4.04 (s, 6H, CH_3), 7.59 (br s, 8H, Ph). ^{13}C NMR ($CDCl_3$): δ 58.81 (CH_3), 120.95 (q, $J = 320$ Hz, CF_3), 121.40, 130.87, 130.97, 148.79 (Ar). Elemental analysis was carried out as its tetraphenylborate: Anal. Found: C, 85.12; H, 7.18; N, 2.63%. Calcd for $C_{38}H_{38}BNO$: C, 85.23; H, 7.15; N, 2.62%.

Reaction of Formylmorpholine with Triflate 1a. To a suspension of CsF (0.339 g, 2.2 mmol) and triflate **1a** (0.360 g, 1.2 mmol) in acetonitrile (8 mL) was added formylmorpholine (0.058 g, 0.50 mmol). After being stirred for 14 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown oily solid, which was chromatographed over silica gel by elution with hexane:ethyl acetate (10:1) to give **5** (0.013 g, 0.08 mmol) and **6** (0.022 g, 0.12 mmol) then eluted with ethyl acetate to afford **7b** (0.121 g, 0.31 mmol). Compound **7b**: ^{1}H NMR ($CDCl_3$): δ 4.10 (m, 4H, CH_2), 4.77 (m, 4H, CH_2), 7.44 (t, 2H, $J = 7.6$ Hz, Ar), 7.56 (t, 4H, $J = 7.6$ Hz, Ar), 7.81 (d, 4H, $J = 7.6$ Hz, Ar). ^{13}C NMR ($CDCl_3$): δ 62.48 (CH_2), 63.74 (CH_2), 120.85 (q, $J = 330$ Hz, CF_3), 121.77, 130.74, 131.58, 146.33. Elemental analysis was carried out as its tetraphenylborate. Anal. Found: C, 83.51; H, 6.58; N, 2.33%. Calcd for $C_{40}H_{38}BNO$ (+H_2O): C, 83.18; H, 6.98; N, 2.43%.

Reaction of *N*,*N*-Dimethylaniline with Triflate 1a. To a suspension of CsF (0.339 g, 2.2 mmol) and triflate **1a** (0.360 g, 1.2 mmol) in acetonitrile (8 mL) was added *N*,*N*-dimethylaniline (0.061 g, 0.50 mmol). After being stirred for 13 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown oil, which was chromatographed over silica gel by elution with ethyl acetate to give ammonium triflate **7a** (0.149 g, 0.43 mmol).

Reaction of DMF with Triflate 1a in the Presence of K_2CO_3. To a suspension of CsF (0.339 g, 2.2 mmol), triflate **1a** (0.360 g, 1.2 mmol), and K_2CO_3 (0.42 g, 3.0 mmol) in acetonitrile (6 mL) was added DMF (0.037 g, 0.50 mmol). After being stirred for 14 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown oily solid, which was chromatographed over alumina by elution with hexane:ethyl acetate (10:1) to give **8** (0.051 g, 0.26 mmol). Colorless crystals: mp 127–128 °C. ^{1}H NMR spectral data and mp were identical with the authentic sample (mp 127–128 °C). ^{1}H NMR ($CDCl_3$): δ 2.00 (d, $J = 8.4$ Hz, OH), 5.85 (d, 1H, $J = 8.4$ Hz, CH), 7.08–7.24 (m, 4H, Ar), 7.36 (dd, 2H, $J = 6.8$ and 7.6 Hz, Ar), 7.61 (d, 2H, $J = 7.6$ Hz, Ar). MS: Calcd for $C_{13}H_{10}O_2$: 198.02. Found: 198.06 (M^+).

Reaction of *N*,*N*-Dimethylthioformamide (10) with Triflate 1a. To a suspension of CsF (0.339 g, 2.2 mmol) and triflate **1a** (0.360 g, 1.2 mmol) in acetonitrile (15 mL) was added **10** (0.045 g, 0.50 mmol). After being stirred for 13 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give brown oil. A small amount of DMF was detected by ^{1}H NMR in the reaction mixture. This mixture was chromatographed over silica gel by elution with hexane:ethyl acetate (10:1) to give diphenyl sulfide (0.056 g, 0.30 mmol), ^{1}H NMR data of which was identical with the authentic sample. Further elution gave **5** (0.009 g, 0.05 mmol), **6** (0.012 g, 0.06 mmol), and ammonium triflate **7a** (0.105 g, 0.30 mmol).

Reaction of *N*,*N*-Dimethylacetamide (11) with Triflate 1a. To a solution of CsF (0.352 g, 2.3 mmol) and triflate **1a** (0.360 g, 1.2 mmol) in acetonitrile (10 mL) was added **11** (0.044 g, 0.50 mmol). After being stirred for 15 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give pale brown oil. ^{1}H NMR of the mixture showed mainly the peaks of **11** and biphenylene. Careful separation of silica gel chromatography by elution with hexane:ethyl acetate (10:1) resulted in the isolation of **11** (0.026 g, 0.30 mmol) and biphenylene (0.015 g, 0.10 mmol).

Reaction of *N*-Acetylimidazole (12) with Triflate 1a. To a suspension of CsF (0.26 g, 1.7 mmol) and triflate **1a** (0.274 g, 0.92 mmol) in acetonitrile (10 mL) was added **12** (0.023 g, 0.21 mmol). After being stirred for 16 h at rt, sat. aq. NaCl solution (10 mL) was added to this suspension, and extracted with dichloromethane (7 mL × 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to pale give brown oil, which was subjected to PTLC to afford **13** (0.062 g, 0.18 mmol). Greenish yellow crystals; mp 232–234 °C (lit.[21] mp 233–234 °C). ^{1}H NMR ($CDCl_3$): δ 6.87 (t, $J = 7.2$ Hz, 1H), 7.53 (t, $J = 3.2$ Hz, 2H), 7.69 (t, $J = 3.6$ Hz, 2H), 8.05 (d, $J = 8.4$ Hz, 2H), 8.10 (d, $J = 8.0$ Hz, 2H), 8.50 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 120.40, 121.41, 124.53, 125.76, 126.92, 127.15, 129.16, 129.45, 130.91, 133.03, 137.41, 147.94. IR (ν): 3053, 2921, 1723, 1589, 1489, 1325, 1288, 1180, 1030, 892, 734, 687 cm^{-1}. HRMS Calcd for $C_{26}H_{19}N$: $[M]^+$ 345.1517; Found, 345.1510.

Reaction of *N*-Acetylimidazole (12) with Triflate 1a in CD_3CN. To a suspension of CsF (0.015 g, 0.10 mmol) and triflate (0.010 g, 0.033 mmol) in CD_3CN (0.4 mL) was added imidazole **12** (0.011 g, 0.10 mmol) in CD_3CN (0.2 mL). The reaction was monitored by ^{1}H NMR. After standing for 15 h, acetic acid (28%) and **14** (20%) was formed. Imidazole **12** (60%) remained unreacted. Acetic acid: ^{1}H NMR (CD_3CN): δ 1.91 (s, 3H). Compound **14**: ^{1}H NMR (CD_3CN): δ 7.11 (s, 1H, imidazole), 7.35–7.42 (m, 1H, Ph), 7.42–7.54 (m, 4H, Ph), 7.45 (s, 1H, imidazole), 7.92 (s, 1H, imidazole).

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