Cationic iron-catalyzed intramolecular alkyne-hydroarylation with electron-deficient arenes†

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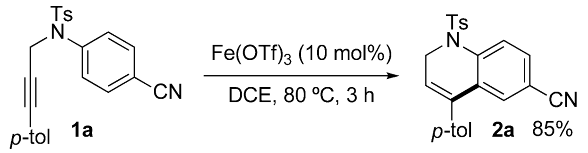
$Fe(OTf)_3$ effectively catalyzed intramolecular hydroarylation of aryl-substituted alkynes with electron-deficient arenes under mild conditions.

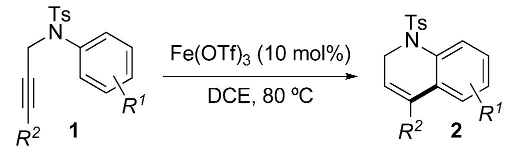
Transition metal-catalyzed hydroarylation of alkynes has attracted much attention in the pivotal areas of synthesis of conjugated aromatic compounds in an atom-economical manner.[1] Moreover, the importance of its intramolecular reaction has been widely recognized as a feasible approach to cyclic vinylarene frameworks. Although numerous examples have been reported,[2] a number of problems remain unresolved: (1) in some cases, expensive catalysts are necessary to promote the reaction; (2) a mixture of *exo-* and *endo*-cyclization products is contaminated;[2f] and (3) there are limitations in the types of performable substrates, especially, electron-rich aryl nucleophiles are crucial, electron-deficient ones do not participate, so far.[3] During our investigation on catalytic activities of iron complexes,[4] we found unprecedented reactivity in the cationic iron catalyst, $Fe(OTf)_3$, for hydroarylation of alkynes with electron-deficient arenes.



(1)

Treatment of 1-tol-3-(*N*-tosyl-4-cyanoanilino)prop-1-yne (**1a**) with $Fe(OTf)_3$ (10 mol%) afforded 1,2-dihydroquinoline **2a** in 85% yield through exclusive 6-*endo-dig* cyclization (eqn (1)). Although $Cu(OTf)_2$ was a slightly effective catalyst (22% yield), conventional catalysts such as $PtCl_2$, $Sc(OTf)_3$, $In(OTf)_3$, $GaCl_3$, $AlCl_3$, and $BF_3{\cdot}OEt_2$ in similar hydroarylation did not provide **2a**, and most of **1a** was recovered unchanged. Of iron catalysts, the high catalytic activity strongly depended on its counter anion, thus replacement of OTf with BF_4, ClO_4, CF_3CO_2, and Cl extremely decreased the activity.[5] 1,2-Dichloroethane (DCE) and nitromethane were the solvent of choice, whereas acetonitrile, toluene, and 1,4-dioxane were unfavorable.[6]

Table 1 Iron-catalyzed hydroarylation of *N*-proparlgylanilines **1**[a]



Entry	Substrate R^1	R^2	**1**	Time/h	Product **2**	Yield/%[b]
1	H	Ph	**1b**	8	**2b**	90
2	4-Br	Ph	**1c**	5	**2c**	81
3	2-Br	4-tol	**1d**	22	**2d**	67
4	4-F	Ph	**1e**	4	**2e**	76
5	$4\text{-}CO_2Me$	Ph	**1f**	20	**2f**	79
6	$4\text{-}NO_2$	4-tol	**1g**	10	**2g**	71
7	$3,5\text{-}F_2$	Ph	**1h**	12	**2h**	76
8[c]	4-Me	Ph	**1i**	14	**2i**	10
9[c]	4-Me	Ph	**1i**	24	**2i**	57
10[c]	4-MeO	Ph	**1j**	48	**2j**	19
11[c]	2-MeO	Ph	**1k**	48	**2k**	13
12[c]	$2\text{-}^i\text{Pr}$	Ph	**1l**	48	**2l**	46

[a] Conditions: substrate (0.15 mmol), $Fe(OTf)_3$ (15 μmol), DCE (0.5 mL). [b] Isolated yield. [c] 20 mol% $Fe(OTf)_3$.

With optimized conditions in hand, we examined the scope and limitation of aryl nucleophiles (Table 1). Similar to electron-neutral phenyl ring **1b** (entry 1), substrates bearing halogen, 4-Br **1c**, 2-Br **1d**, and 4-F **1e**, were also efficiently converted into 1,2-dihydroquinolines **2c**, **2d**, and **2e** in 81%, 67%, and 76% yields, respectively, without loss of halogen functions (entries 2–4). Many electron-poor arenes possessing $4\text{-}CO_2Me$, $4\text{-}NO_2$, and $3,5\text{-}F_2$ groups (**1f**, **1g**, and **1h**) took part in the reaction, giving rise to the desired products **2f**, **2g**, and **2h** in high yields (entries 4–6). In sharp contrast, electron-rich aryl rings depressed the transformation (entries 8–12) counter-intuitively. Thus, the reactions of substrates with 4-Me **1i**, 4-MeO **1j**, 2-MeO **1k**, and $2\text{-}^i\text{Pr}$ **1l** were very slow, even with twice the amounts of the catalyst and it was necessary to have longer reaction times to obtain the products in moderate yields (entries 8–12).

During the investigation, the important role of terminal attachments R^2 in the present hydroarylation was recognized (Table 2). When the terminal phenyl group of **1b** was replaced with electron-deficient aryl rings ($4\text{-}CF_3C_6H_4$ **1m**, $4\text{-}MeO_2CC_6H_4$ **1n**, and $2\text{-}MeO_2CC_6H_4$ **1o**), *n*-Bu **1p**, H **1q**, and Br **1r**, these substrates hardly produced the products (entries 1–6). On the other hand, electron-rich aryl substituents such as $4\text{-}MeC_6H_4$ **1s**, $4\text{-}(MeOCH_2)C_6H_4$ **1t**,[7] $4\text{-}MeOC_6H_4$ **1u**, and $2\text{-}MeOC_6H_4$ **1v**, $2,3,4\text{-}(MeO)_3C_6H_2$ **1w** drastically increased the reaction rate, leading to the corresponding

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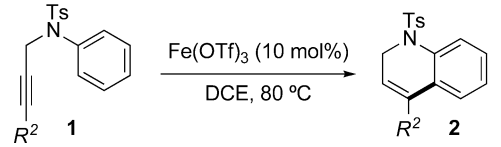
Table 2 Effect of terminal attachments R^2



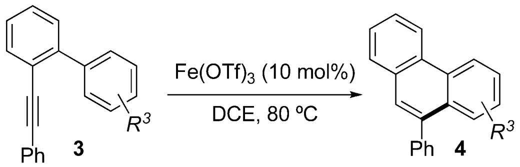
Entry	Substrate R^2	**1**	Time/h	Product **2**	Yield/%[a]
1	$4\text{-}CF_3C_6H_4$	**1m**	96	**2m**	Trace
2	$4\text{-}MeO_2CC_6H_4$	**1n**	96	**2n**	Trace
3	$2\text{-}MeO_2CC_6H_4$	**1o**	96	**2o**	Trace
4	*n*-Bu	**1p**	43	**2p**	7
5	H	**1q**	24	**2q**	0
6	Br	**1r**	24	**2r**	0
7	$4\text{-}MeC_6H_4$	**1s**	3	**2s**	83
8	$4\text{-}(MeOCH_2)C_6H_4$	**1t**	4	**2t**	65
9	$4\text{-}MeOC_6H_4$	**1u**	1	**2u**	75
10	$2\text{-}MeOC_6H_4$	**1v**	1	**2v**	72
11	$2,3,4\text{-}(MeO)_3C_6H_4$	**1w**	1	**2w**	77

[a] Isolated yield.

1,2-dihydroquinolines in good to high yields (65–83%) within 4 h (entries 7–11).

The $Fe(OTf)_3$-catalyzed hydroarylation could also be extended to the cyclization of *ortho*-alkynyl biaryls **3** (Table 3). Various electron-deficient aryl nucleophiles bearing CN, CO_2Me, NO_2, CF_3, and F, and an electron-neutral phenyl ring were perfectly tolerated to provide phenanthrene derivatives **4a–4f** in high yields *via* exclusive 6-*endo-dig* cyclization mode (entries 1–6).[8] Interestingly, electron-rich aryl nucleophile like 4-anisyl substrate **3g** also participated in the reaction, but, 5-*exo-dig* cyclization corporately occurred along with the 6-*endo-dig* reaction (entry 7). In addition, similar to Table 2, the lack of the electron density of terminal aryl rings of *o*-alkynyl biaryl also inhibited the reaction. That is, the transformation of 4′-nitro-2-[(4-nitrophenyl)ethynyl]-1,1′-biphenyl did not progress at all even though a longer reaction time (96 h) was used.

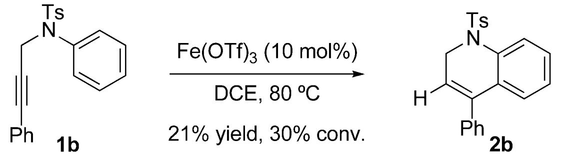
Table 3 Iron-catalyzed hydroarylation of *o*-alkynyl biaryls **3**



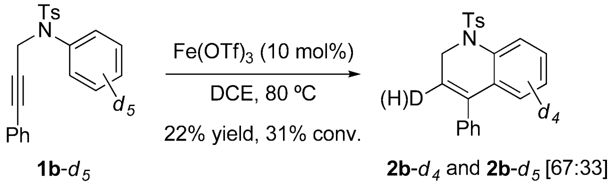
Entry	Substrate R^3	**3**	Time/h	Product **4**	Yield/%[a]
1	4-CN	**3a**	12	**4a**	87
2	$4\text{-}CO_2Me$	**3b**	2	**4b**	85
3	$4\text{-}NO_2$	**3c**	6	**4c**	79
4	$4\text{-}CF_3$	**3d**	7	**4d**	95
5	$3,5\text{-}F_2$	**3e**	2	**4e**	91
6	H	**3f**	1	**4f**	86
7[b]	4-MeO	**3g**	3	**4g**	68

[a] Isolated yield. [b] 9-Benzylidene-2-methoxyfluorene was obtained in 11% yield.

To gain an insight into the reaction mechanism, a kinetic isotope effect for the cyclization of **1b** and **1b**-d_5 was carefully investigated (eqn (2) and (3)). As a result, the reaction rates were found to be nearly equal (k_H/k_D = 0.95).[9]



(2)



(3)

This result indicates that the cyclization proceeds *via* a Friedel–Crafts type reaction, wherein the vinyl cation often works as a key intermediate.[2b–d] Although, it is known that various Lewis acids produce the vinyl cation from alkynyl arenes, the present reaction was efficiently promoted only by $Fe(OTf)_3$. Moreover, the progress of the iron-catalyzed hydroarylation strongly depended on the electronic characters of two aryl rings, that is, electron-deficiency of Ar^1 and electron-richness of Ar^2 drastically accelerated the reaction (Fig. 1). By considering these findings, we envisaged that the present hydroarylation might employ a cationic iron-arene intermediate as depicted in Scheme 1. Thus, the coordination of the electrophilic iron center to the aryl ring of **1** or **3** would afford two types of iron-arene complexes **A** and **B**.[10] When electronic density of the aryl ring Ar^2 is higher than that of Ar^1, generation of the arene complex **A** would be superior to that of **B**. **A** would efficiently produce the vinyl cation **C** due to π-electron delocalization between the arene and the conjugated alkyne as shown in the alkynyl chromium-arene complexes.[11] In contrast, the non-conjugated arene complex **B** would not be suitable for the vinyl cation formation. Arylation of **C** could produce the intermediate **D**, and then sequential deprotontion would yield the product **2** or **4** and the catalyst.

In conclusion, inexpensive and environmentally benign iron complex $Fe(OTf)_3$ has been proven to be an effective catalyst for intramolecular hydroarylation of aryl-substituted alkynes to form 1,2-dihydroquinolines and phenanthrenes in good to high yields.‡ Of special importance, the cationic iron-catalyst permits the participation of electron-deficient aryl nucleophiles, which provides unprecedented and valuable examples of hydroarylation. The definite role of the iron catalyst in the present reaction is not clear, but the unique reaction mode would most likely be induced by the generated cationic

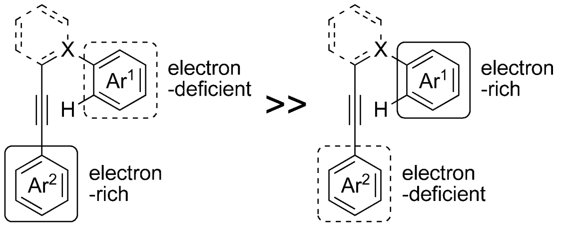
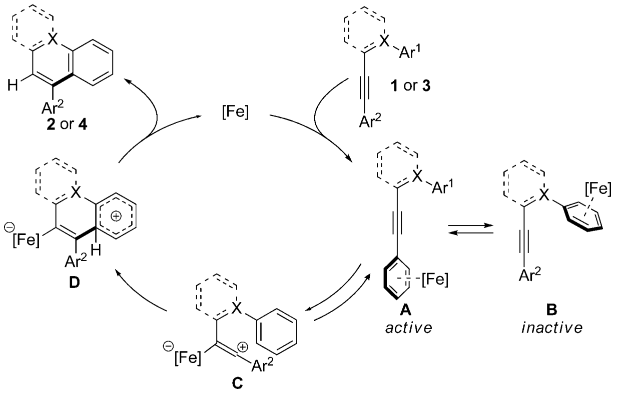


Fig. 1 Preferred electronic properties of the two arenes.



Scheme 1 Plausible reaction mechanism of cationic-iron catalyzed intramolecular alkyne-hydroarylation.

iron-arene complexes during the reaction. Studies on details of mechanistic aspects and extension of this protocol are in progress.

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. K.K. acknowledges financial supports from Kinki Invention Center and Furukawa technical foundation. Finally, we thank Dr H. Fukuoka for X-ray analysis of **4e**.

Notes and references

‡ *General procedure for hydroarylation of* **1a**: In a 20 mL Schlenk tube, a mixture of **1a** (60.0 mg, 0.15 mmol), $Fe(OTf)_3$ (7.5 mg, 15 μmol), and DCE (0.5 mL) was heated at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was passed through a short silica gel column with diethyl ether, and then concentrated *in vacuo*. The obtained crude product was purified by column chromatography with hexane/ethyl acetate (5 : 1) to afford 6-cyano-4-tolyl-1-tosyl-1,2-dihydroquinoline (**2a**) in 85% yield (51.0 mg). Isolated as a white solid (Mp. 162.0–163.0 °C); R_f (SiO_2, hexane:EtOAc = 5 : 1) = 0.28; ^1H NMR ($CDCl_3$, 270.05 MHz) δ 2.32 (3H, s), 2.36 (3H, s), 4.57 (2H, d, J = 4.5 Hz), 5.67 (1H, t, J = 4.5 Hz), 6.59 (2H, d, J = 7.9 Hz), 7.10 (4H, d, J = 8.0 Hz), 7.17 (1H, d, J = 2.0 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.58 (1H, dd, J = 8.2, 2.0 Hz), 7.89 (1H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 67.80 MHz) δ 21.2, 21.4, 45.3, 110.0, 123.1, 127.3, 127.9, 128.2, 129.1, 129.4, 129.8, 131.4, 131.9, 133.8, 135.8, 137.3, 138.2, 139.6, 144.1, 146.7; HRMS m/z (EI): M^+ calcd for $C_{24}H_{20}N_2O_2S$, 400.1245; found 400.1235.

Crystal Data: Chemical formula and formula weight (M): $C_{20}H_{12}F_2$. Unit-cell dimensions (angstrom or pm, degrees) and volume, with estimated standard deviations: a = 5.6736(8), b = 23.503(3), c = 10.7482(17), beta = 107.425(5). Temperature: 296.1. Crystal system: monoclinic. Space group symbol (if non-standard setting give related standard setting): $P121/n1$. No. of formula units in unit cell (Z): 4. Number of reflections measured: 13 109 and number of independent reflections: 3137. Rint: 0.036. Final R values (and whether quoted for all or observed data): 0.0335. CCDC no.: 750245.

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4 (*a*) K. Komeyama, T. Morimoto and K. Takaki, *Angew. Chem., Int. Ed.*, 2006, **45**, 2938; (*b*) K. Komeyama, T. Morimoto, Y. Nakayama and K. Takaki, *Tetrahedron Lett.*, 2007, **48**, 3259; (*c*) K. Komeyama, Y. Mieno, S. Yukawa, T. Morimoto and K. Takaki, *Chem. Lett.*, 2007, **36**, 752; (*d*) K. Komeyama, R. Igawa, T. Morimoto and K. Takaki, *Chem. Lett.*, 2009, **38**, 724.

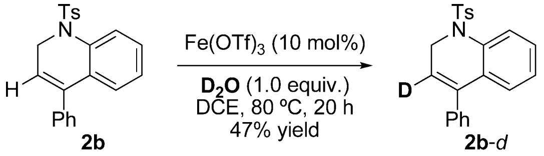
5 Reactivities of various iron catalysts (yield of **2a**, conversion of **1a**): $Fe(BF_4)_3$ (8%, 11%); $Fe(ClO_4)_3$ (2%, 45%); $Fe(CF_3CO_2)_3$ (0%, 11%); and $FeCl_3$ (4%, 30%). Lu and Campagne reported $FeCl_3$-catalyzed hydroarylation of alkynes with electron-rich arenes. See: (*a*) R. Li, S. R. Wang and W. Lu, *Org. Lett.*, 2007, **9**, 2219; (*b*) C. D. Zotto, J. Wehbe, D. Virieux and J.-M. Campagne, *Synlett*, 2008, 2033. TfOH also provided **2a** in only 20% yield with complete consumption of **1a**.

6 Yields of **2a** using various solvents: 1,2-dichloroethane (85%) > nitromethane (70%) ≫ toluene (11%) > acetonitrile (9%) > 1,4-dioxane (trace).

7 Treatment of **1t** with $FeCl_3$ (10 mol%) provided a complex mixture, in which a negligible amount of **2t** was formed (<5% yield).

8 Exact structure of **4e** was determined by X-ray analysis.

9 The vinyl proton of 1,2-dihydroquinoline **2b** was deuterated in the presence of D_2O (1 equiv.) under the similar conditions (eqn (4)). In eqn (3), 2b-d_4 could be afforded by the reaction of **2b**-d_5 and contaminated water



(4)

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