HETEROCYCLES, Vol. 103, No. 1, 2021, pp. 403 - 415. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 29th July, 2020, Accepted, 24th August, 2020, Published online, 23rd September, 2020
DOI: 10.3987/COM-20-S(K)27

DIRHODIUM(II)-CATALYZED *ORTHO* C–H AMINATION OF *N*-ALKYLDIARYLAMINES

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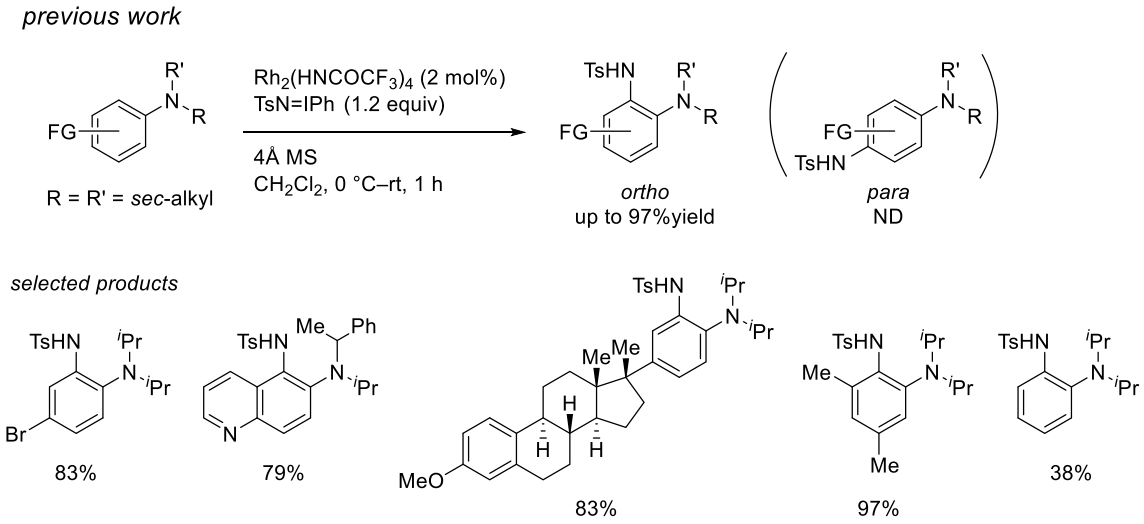
Abstract – Dirhodium(II)-catalyzed *ortho* C–H amination of *N*-alkyldiarylamines has been developed. The C(sp^2)–H amination proceeded with high preference over C(sp^3)–H amination to provide *N*-aryl-*o*-phenylenediamines in up to 80% yield. With the use of unsymmetric diarylamines as substrates, selective amination of one of two distinct aromatic rings was also achieved.

INTRODUCTION

Recently, metal-catalyzed C–H amination reactions have emerged as one of the most straightforward synthetic methods for both aliphatic and aromatic amines.[1] Aside from the great advancement based on the chelation-assisted C–H activation strategy, metal-catalyzed nitrene insertion provides an alternative method for C–H amination without the need for introducing directing groups.[2] Since the pioneering work by Du Bois and co-workers, the exceptional efficiency of C(sp^3)–H amination with Rh(II)-nitrene species in organic synthesis has been widely explored.[3] In stark contrast, there are still limited examples of C(sp^2)–H amination reactions.[4-7] With respect to intermolecular reactions, after early limited examples by Hashimoto and Anada in 2007,[4a] Falck and co-workers reported the first widely applicable aromatic C–H amination with Rh(II)-nitrene species using *O*-(arylsulfonyl)hydroxylamine as the nitrene precursor in the protic solvent CF_3CH_2OH.[4b] In 2018, Kawabata, Ueda, and co-workers reported the aromatic C–H amination of alkoxyarenes under aprotic conditions.[4c] These amination reactions proceeded with high to excellent selectivity at the *para* position of the electron-donating group, including at alkyl and alkoxy groups. Meanwhile, aromatic C–H amination of *para*-substituted substrates led to insufficient results in terms of both regioselectivity on the benzene rings or chemoselectivity over benzylic C(sp^3)–H amination. Thus, there were no successful examples of *ortho* C–H amination until we reported the reaction using

This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

N,*N*-dialkylanilines as substrates in 2018 (Scheme 1).[5] A notable feature of our process is that aromatic substrates bearing the extremely bulky di(*sec*-alkyl)amino group underwent C–H amination at the *ortho* position with virtually perfect regioselectivity regardless of whether the *para* position is substituted or not. This transformation enabled easy and rapid access to a range of *o*-phenylenediamine derivatives with high yields and broad functional group tolerance.



Scheme 1. Rh(II)-Catalyzed *ortho* C–H amination of *N*,*N*-dialkylanilines

Of the *o*-phenylenediamine derivatives, *N*-aryl-*o*-phenylenediamines are important synthetic targets because they are found in a large number of pharmaceuticals[8a–c] as well as functional materials, including dyes[8e] and optoelectric materials.[8f] For example, the pharmaceuticals shown in Figure 1 exhibit a variety of biological activities, including antipsychotic, and antitumor activities. Additionally, the structure is contained as a part of fused heteroaromatic skeleton of (+)-staurosporine, a naturally occurring protein kinase inhibitor.[8d]

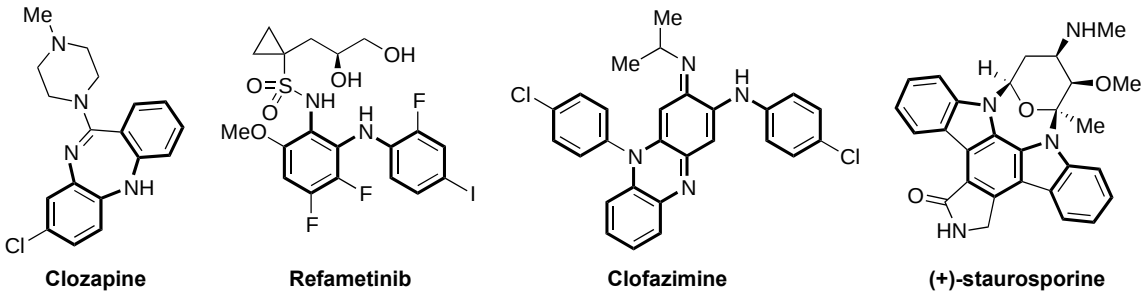
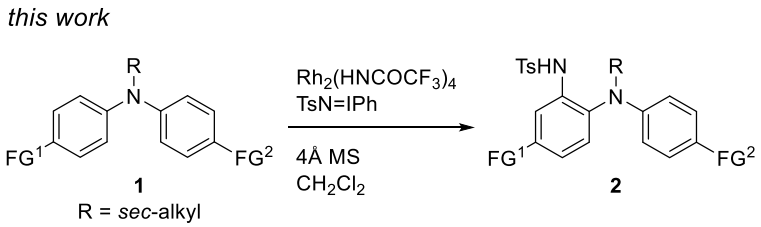


Figure 1. Bioactive compounds that include *N*-aryl-*o*-phenylenediamine skeletons

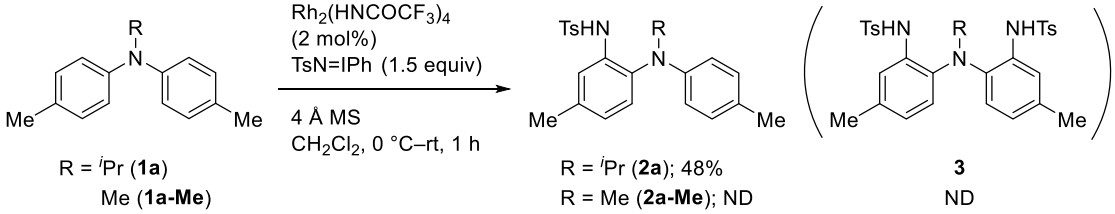
In this context, as a logical extension of our *ortho* C–H amination strategy, we herein report the synthesis of *N*-aryl-*o*-phenylenediamines by dirhodium(II)-catalyzed amination using *N*-alkyldiarylamines as substrates (Scheme 2).



Scheme 2. Rh(II)-Catalyzed *ortho* C–H amination of *N*-alkyldiarylamines

RESULTS AND DISCUSSION

Based on our previous work,[5] we initially examined the reaction of *N*-isopropyl-*N*,*N*-di(*p*-tolyl)amine (**1a**) with 1.5 equiv of (tosylimino)phenyliodinane (TsN=IPh) in CH_2Cl_2 using $Rh_2(HNCOCF_3)_4$ (2 mol%) as the catalyst (Scheme 3). The reaction proceeded smoothly to completion below room temperature in less than 1 h and afforded the expected diamine **2a** in 48% yield. Similar to *N*,*N*-dialkylanilines, a virtually complete preference for aromatic C–H amination over benzylic C(sp^3)–H amination was observed. It is also noteworthy that no signs of the formation of diamination product **3** were observed, even though a slight excess amount of TsN=IPh was used. In contrast, the substrate **1a-Me**, which bears the *N*-methyl group instead of the *N*-isopropyl group, did not provide the desired amination product **2a-Me**.[9] Thus, the choice of alkyl group on the nitrogen atom is crucial for aromatic C–H amination.

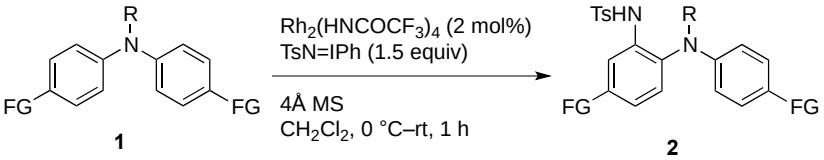


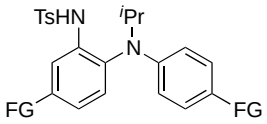
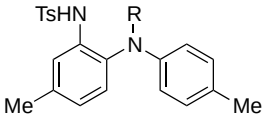
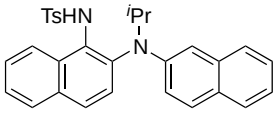
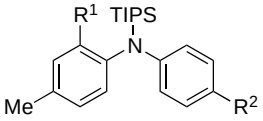
Scheme 3. Rh(II)-Catalyzed *ortho* C–H amination of *N*-alkyl-*N*,*N*-di(*p*-tolyl)amine (**1a**)

We then explored reactions using various *N*-alkyldiarylamines **1b**–**f** as substrates (Table 1). While amine **1b**, which bears electron-donating methoxy groups, provided a higher yield than that obtained with **1a**,[10] the use of bromo-substituted amine **1c** slightly diminished the yield (entries 1 and 2). The amination of di(2-naphthyl)amine **1d** proceeded exclusively at the α position in 42% yield (entry 3). With respect to the substituent on the nitrogen atom of the substrates, the cyclohexyl group provided a comparable result

to the isopropyl group (entry 4). Unfortunately, the readily removable α-methylbenzyl group led to a considerable drop in the product yield (entry 5). We also investigated the substrate bearing the triisopropylsilyl (TIPS) group as the *N*-protecting group instead of other alkyl groups. *N*-TIPS-*N*,*N*-di(*p*-tolyl)amine (**1g**) did not provide the aromatic C–H amination product **2g**. Instead, imine **4** was obtained in 23% yield via benzylic C(sp^3)–H amination followed by oxidation. Thus, the significant dependence of chemoselectivity between aromatic C–H amination and C(sp^3)–H amination on the *N*-protecting groups was again demonstrated.

Table 1. Rh(II)-Catalyzed *ortho* C–H amination of diarylamines **1**[a]

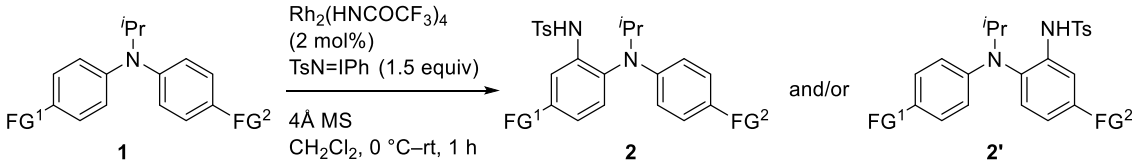


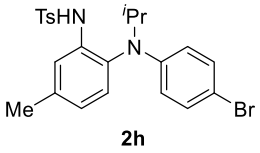
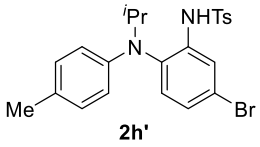
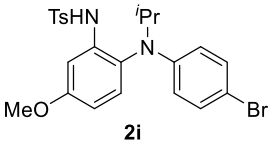
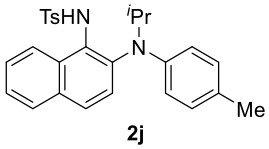
entry	product	yield (%)[b]	entry	product	yield (%)[b]
					
1	FG = OMe (**2b**)	54	4	R = ^{c}Hex (**2e**)	59
2	Br (**2c**)	33	5	CH(Me)Ph (**2f**)	19
3	 **2d**	42	7	 R^1 = NHTs, R^2 = Me; **2g** R^1 = H, R^2 = CH=NTs; **4**	**2g**; ND, **4**; 23

[a] Reaction conditions: **1** (0.100 mmol), $Rh_2(HNCOCF_3)_4$ (2.00×10^{-3} mmol, 2 mol%), TsN=IPh (0.150 mmol), and 4Å MS (powder, 40 mg) in CH_2Cl_2 (1 mL). [b] Yields of isolated products. Ts = Tosyl.

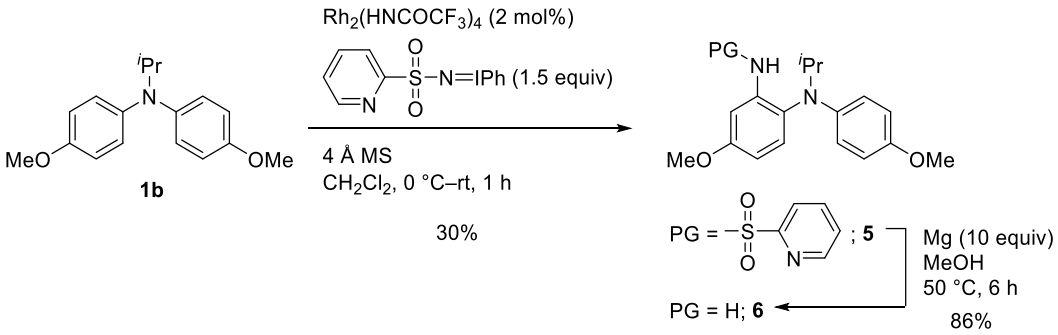
We then examined the reactions of diarylamines that bear two distinct aromatic rings (Table 2). *N*-(4-Bromophenyl)-*N*-(*p*-tolyl)amine **1h** provided a 59:41 mixture of regioisomers **2h** and **2h'** (entry 1). The C–H amination of substrate **1i** displayed strong preference for the highly nucleophilic 4-methoxyphenyl ring over the 4-bromophenyl ring (entry 2). In addition to complete regioselectivity, a high product yield was obtained with amine **1j** that bears 2-naphthyl group (entry 3).

Table 2. Rh(II)-Catalyzed *ortho* C–H amination of unsymmetrical diarylamines **1**



entry	product	yield (%)
1	 **2h** +  **2h'**	33 (59:41 mixture)
2	 **2i**	43
3	 **2j**	80

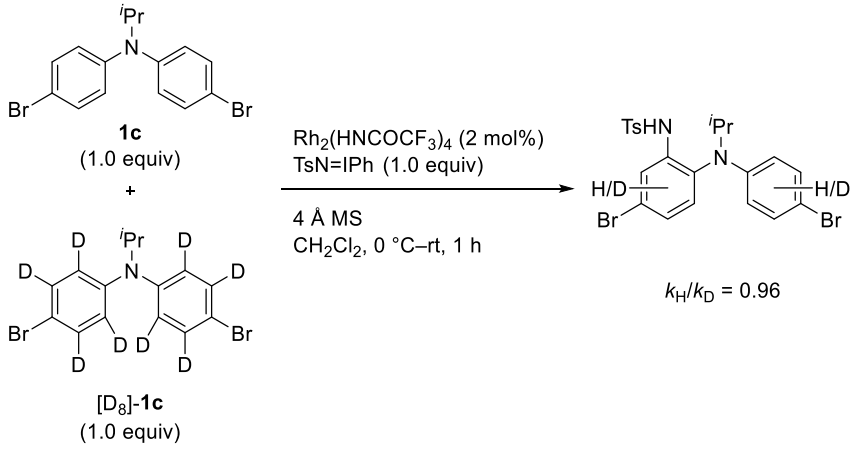
With a view to remove a sulfonyl group from the C–H amination product, we then tested the performance of an iminoiodinane bearing 2-pyridylsulfonyl group in place of the tosyl group (Scheme 4).[11] The reaction of **1b** with the iminoiodinane provided the desired C–H amination product **5** in 30% yield. Removal of the 2-pyridylsulfonyl group was uneventfully achieved by treatment with Mg in methanol to provide primary amine **6** in 86% yield.



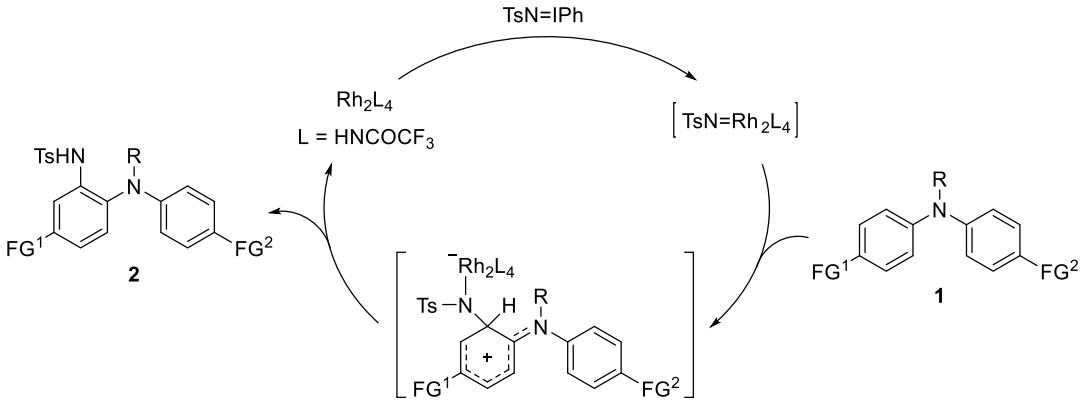
Scheme 4. C–H Amination using (2-pyridylsulfonylimino)phenyliodinane and removal of a sulfonyl group

To gain insight into the reaction mechanism, we performed a kinetic isotope effect (KIE) experiment using deuterated di(4-bromophenyl)amine [D_8]-**1c** (Scheme 5). Similar to our previous work,[5] an inverse

secondary isotope effect was observed (k_H/k_D = 0.96). Thus, a pathway that includes direct C(sp^2)–H insertion of the Rh(II)-nitrene intermediate was ruled out, and the result indicated that a stepwise pathway that involves electrophilic addition of the Rh(II)-nitrene intermediate to the benzene ring followed by elimination is plausible (Scheme 6). The reaction pathway is also consistent with the selectivity observed with unsymmetrical amines **1i** and **1j**; that is, strong preference of the C–H amination for electron-rich aromatic rings was observed (see, Table 2, entries 2 and 3).



Scheme 5. KIE experiment of deuterated di(2-naphthyl)amine [D]-**1c**



Scheme 6. Plausible reaction mechanism

In conclusion, we developed dirhodium(II)-catalyzed aromatic C–H amination of *N*-alkyldiarylamines, providing *N*-aryl-*o*-phenylenediamines in up to 80% yield. The reaction proceeded with high preference over C(sp^3)–H amination, and selective amination of one of the two distinct aromatic rings of unsymmetric diarylamine was achieved. Further studies on the extension of the substrate scope as well as theoretical studies are currently in progress.

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro melting point apparatus. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on a JEOL JNM-AL 300 (300 MHz) spectrometer or a JEOL JNM-ECA 400 (400 MHz) spectrometer or JEOL JNM-ECZ 500 (500 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00, $CDCl_3$ at δ_H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 400 (100 MHz) spectrometer or JEOL JNM-ECZ 500 (125 MHz) spectrometer. Chemical shifts are reported relative to internal standard ($CDCl_3$ at δ 77.00). Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system. Column chromatography was carried out on Kanto silica gel 60 N (40–50 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. All non-aqueous reactions were carried out in flame-dried glassware under Ar atmosphere unless otherwise noted. Reagents and solvents were used without purification. 4Å MS (powder) from nacalai tesque was used after drying. Dirhodium(II) complex catalysts $Rh_2(HNCOCF_3)_4$ was prepared according to a literature.[12] Iminoiodinanes were prepared according to literatures.[13,14]

Starting Materials. *N*-Isopropyldiarylamines **1a**, **1b**, **1d**, and **1j** were prepared from corresponding diarylamines by reductive amination with 2-methoxypropene in high yields (>90%).[15] *N*-Cyclohexyl derivative **1e** was synthesized by reductive amination using cyclohexanone dimethyl acetal instead of 2-methoxypropene under otherwise identical conditions. *N*-α-Methylbenzyl derivative **1f** was prepared by the reaction of di(*p*-tolyl)amine and 1-(bromoethyl)benzene.[5] Diarylamine **1c**, **1h** and **1i** bearing 4-bromophenyl rings were synthesized by bromination of corresponding *N*-aryl-*N*-phenylamines using NBS (2.1 equiv for **1c** or 1.05 equiv for **1h** and **1i**) in DMF.[16] *N*-Triisopropylsilyl derivative **1g** was prepared according to a literature.[17]

Typical procedure for Rh(II)-catalyzed *ortho* C−H amination of *N*-alkyldialkylamines: Preparation of *N*-isopropyl-4-methyl-*N*-(*p*-tolyl)-2-(tosylamido)aniline (2a). TsN=IPh (56.0 mg, 0.150 mmol) was added to a stirred mixture of *N*-isopropyl-di(*p*-tolyl)amine (**1a**) (23.9 mg, 0.100 mmol), $Rh_2(HNCOCF_3)_4$ (1.3 mg, 2.00×10^{-3} mmol, 2 mol%) and 4Å MS (powder, 40 mg) in CH_2Cl_2 (1.0 mL) at 0 °C under Ar atmosphere. After stirring at room temperature for 1 h, the whole mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 8:1 *n*-hexane/AcOEt) to give aromatic C–H amination product **2a** (19.5 mg, 48%) as a colorless solid: mp 166−168 °C; IR (KBr) *ν* 3239, 2973, 1509, 1381, 1167, 1091,

809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 2.23 (s, 3H, ArC*H*$_3$), 2.35 (s, 3H, ArC*H*$_3$), 2.39 (s, 3H, ArC*H*$_3$), 4.24 (septet, *J* = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$), 6.18 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.80 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.83–6.87 (m, 2H, Ar*H*), 7.16 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.45 (brs, 1H, N*H*), 7.56 (s, 1H, Ar*H*), 7.60 (d, *J* = 8.5 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (CH_3), 20.3 (CH_3), 21.5 (CH_3), 21.6 (CH_3), 48.9 (CH), 115.0 (CH), 117.6 (CH), 124.8 (CH), 127.3 (CH), 127.4 (C), 129.4 (CH), 129.5 (CH), 129.6 (C), 130.6 (CH), 136.2 (C), 137.0 (C), 138.1 (C), 143.7 (C), 145.6 (C); HRMS (EI) calcd for $C_{24}H_{28}N_2O_2S$ $[M]^+$ 408.1871, found 408.1874.

***N*-Isopropyl-4-methoxy-*N*-(4-methoxyphenyl)-2-(tosylamido)aniline (2b).** Yield 54%; purified by column chromatography (silica gel, 4:1 *n*-hexane/AcOEt); colorless solid; mp 145−146 °C; IR (KBr) *v* 3236, 2971, 1507, 1380, 1334, 1242, 1039, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.0 Hz, 6H, CH(C*H*$_3$)$_2$), 2.39 (s, 3H, ArC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 4.18 (septet, *J* = 6.0 Hz, 1H, C*H*(CH$_3$)$_2$), 6.24 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.55 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 6.59 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.89 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.17 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.32 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.59 (brs, 1H, N*H*), 7.61 (d, *J* = 8.0 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (CH_3), 21.5 (CH_3), 49.4 (CH), 55.4 (CH_3), 55.6 (CH_3), 102.5 (CH), 109.6 (CH), 114.4 (CH), 116.5 (CH), 125.3 (C), 127.4 (CH), 129.5 (CH), 131.4 (CH), 136.0 (C), 138.1 (C), 142.2 (C), 143.8 (C), 152.5 (C), 158.8 (C); HRMS (EI) calcd for $C_{24}H_{28}N_2O_4S$ $[M]^+$ 440.1770, found 440.1767.

***N*-Isopropyl-4-bromo-*N*-(4-bromophenyl)-2-(tosylamido)aniline (2c).** Yield 33%; purified by column chromatography (silica gel, 10:1 *n*-hexane/AcOEt); light yellow solid; mp 162 °C (decomp.); IR (KBr) *v* 3231, 2973, 1490, 1165, 929, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 2.43 (s, 3H, ArC*H*$_3$), 4.25 (septet, *J* = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$), 6.08 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.02 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.18–7.20 (m, 3H, Ar*H*), 7.33 (brs, 1H, N*H*), 7.56 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.99 (d, *J* = 2.5 Hz, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.9 (CH_3), 21.6 (CH_3), 49.1 (CH), 110.8 (C), 116.2 (CH), 120.7 (CH), 122.2 (C), 127.2 (CH), 127.5 (CH), 129.8 (CH), 130.2 (C), 131.8 (CH), 132.3 (CH), 135.7 (C), 138.5 (C), 144.5 (C), 146.9 (C); HRMS (EI) calcd for $C_{22}H_{22}Br_2N_2O_2S$ $[M]^+$ 535.9769, found 535.9771.

***N*-Isopropyl-*N*-(naphthalen-2-yl)-1-(tosylamido)naphthalen-2-amine (2d).** Yield 42%; purified by column chromatography (silica gel, 8:1 to 4:1 *n*-hexane/AcOEt); colorless solid; mp 133–135 °C; IR (KBr) *v* 3271, 2973, 1627, 1594, 1507, 1469, 1389, 1304, 1159, 909, 811, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.8 Hz, 6H, CH(C*H*$_3$)$_2$), 2.22 (s, 3H, ArC*H*$_3$), 4.26 (septet, *J* = 6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 6.70–6.76 (m, 3H, Ar*H*), 6.96 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.25–7.28 (m, 1H, Ar*H*), 7.30 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.36 (t, *J* = 6.8 Hz, 1H, Ar*H*), 7.46–7.54 (m, 6H, Ar*H* and N*H*), 7.68 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.81 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H, Ar*H*), 8.24 (d, *J* = 8.0 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (CH_3), 21.4 (CH_3), 50.5 (CH), 111.5 (CH), 118.8 (CH), 123.1 (CH),

125.6 (CH), 126.2 (CH), 126.3 (CH), 126.4 (CH), 126.6 (CH), 127.1 (CH), 127.4 (CH), 127.7 (CH), 127.8 (C), 127.9 (CH), 128.2 (CH), 128.8 (CH), 129.2 (CH), 130.9 (C), 131.8 (C), 133.0 (C), 134.5 (C), 137.1 (C), 137.7 (C), 143.4 (C), 145.2 (C); HRMS (EI) calcd for $C_{30}H_{28}N_2O_2S$ $[M]^+$ 480.1871, found 480.1874.

***N*-Cyclohexyl-4-methyl-*N*-(*p*-tolyl)-2-(tosylamido)aniline (2e).** Yield 59%; purified by column chromatography (silica gel, 8:1 to 6:1 *n*-hexane/AcOEt); colorless solid; mp 184−186 °C; IR (KBr) *v* 3244, 2932, 1508, 1375, 1333, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.95–1.03 (m, 3H, *c*Hex), 1.32 (tq, *J* = 13.0, 3.5 Hz, 2H, *c*Hex), 1.60 (d, *J* = 13.0 Hz, 1H, *c*Hex), 1.7 (d, *J* = 13.0 Hz, 2H, *c*Hex), 1.91 (d, *J* = 11.5 Hz, 2H, *c*Hex), 2.22 (s, 3H, ArC*H*$_3$), 2.35 (s, 3H, ArC*H*$_3$), 2.38 (s, 3H, ArC*H*$_3$), 3.75 (tt, *J* = 11.5, 3.0 Hz, 1H, *c*Hex), 6.17 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.79 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.82 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 6.86 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.15 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.44 (brs, 1H, N*H*), 7.57 (d, *J* = 1.5 Hz, 1H, Ar*H*), 7.60 (d, *J* = 8.0 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2 (CH_3), 21.5 (CH_3), 21.6 (CH_3), 25.7 (CH_2), 25.9 (CH_2), 30.5 (CH_2), 57.8 (CH), 114.7 (CH), 117.6 (CH), 124.8 (CH), 127.2 (C), 127.3 (CH), 129.4 (CH), 129.5 (CH), 129.9 (C), 131.0 (CH), 136.2 (C), 137.0 (C), 138.1 (C), 143.7 (C), 145.4 (C); HRMS (EI) calcd for $C_{27}H_{32}N_2O_2S$ $[M]^+$ 448.2184, found 448.2188.

4-Methyl-*N*-(1-phenylethyl)-*N*-(*p*-tolyl)-2-(tosylamido)aniline (2f). Yield 19%; purified by column chromatography (silica gel, 10:1 *n*-hexane/AcOEt); colorless solid; mp 150−153 °C; IR (KBr) *v* 3301, 2943, 1509, 1378, 1334, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)Ph), 2.21 (s, 3H, ArC*H*$_3$), 2.31 (s, 3H, ArC*H*$_3$), 2.37 (s, 3H, ArC*H*$_3$), 5.10 (q, *J* = 6.8 Hz, 1H, C*H*(CH_3)Ph), 6.30 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.77–7.80 (m, 3H, Ar*H*), 6.87 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.13 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.19–7.30 (m, 6H, Ar*H* and N*H*), 7.42 (s, 1H, Ar*H*), 7.51 (d, *J* = 8.4 Hz, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9 (CH_3), 20.3 (CH_3), 21.5 (CH_3×2), 58.4 (CH), 116.6 (CH), 118.1 (CH), 124.8 (CH), 127.0 (CH), 127.2 (CH), 127.3 (CH), 128.4 (C), 128.6 (CH), 129.4 (CH), 129.5 (CH), 130.7 (CH), 131.1 (C), 136.3 (C), 136.4 (C), 137.9 (C), 142.8 (C), 143.6 (C), 145.7 (C); HRMS (EI) calcd for $C_{29}H_{30}N_2O_2S$ $[M]^+$ 470.2028, found 470.2029.

4-Methyl-*N*-{4-[*p*-tolyl(triisopropylsilyl)amino]benzylidene}benzenesulfonamide (4). Yield 23%; purified by column chromatography (silica gel, 6:1 *n*-hexane/AcOEt); light yellow amorphous; IR (KBr) *v* 2946, 2867, 1578, 1504, 1280, 1155, 1088 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.04 (d, *J* = 7.5 Hz, 18H, CH(C*H*$_3$)$_2$), 1.41 (septet, *J* = 7.5 Hz, 3H, C*H*(CH_3)$_2$), 2.39 (s, 3H, ArC*H*$_3$), 2.40 (s, 3H, ArC*H*$_3$), 6.59 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.01 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.21 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.29 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.63 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.83 (d, *J* = 8.0 Hz, 2H, Ar*H*), 8.81 (s, 1H, ArC*H*=N); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9 (CH), 18.6 (CH_3), 21.1 (CH_3), 21.5 (CH_3), 117.2 (CH), 122.1 (C),

127.6 (CH), 129.5 (CH), 130.3 (CH), 130.4 (CH), 132.9 (CH), 136.5 (C), 136.7 (C), 141.6 (C), 143.7 (C), 158.6 (C), 169.0 (CH=N); HRMS (EI) calcd for $C_{30}H_{40}N_2O_2SSi$ $[M]^+$ 520.2580, found 520.2577.

***N*-(4-Bromophenyl)-*N*-isopropyl-4-methyl-2-(tosylamido)aniline (2h) and 4-bromo-*N*-isopropyl-*N*-(*p*-tolyl)-2-(tosylamido)aniline (2h').** Yield 33% (59:41 mixture); purified by column chromatography (silica gel, 6:1 *n*-hexane/AcOEt); colorless solid; IR (KBr) *v* 3241, 2972, 1509, 1489, 1380, 1334, 1166, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$ for major product and 6H, CH(C*H*$_3$)$_2$ for minor product), 2.24 (s, 3H, ArC*H*$_3$ for major product), 2.37 (s, 3H, ArC*H*$_3$ for minor product), 2.41 (s, 3H, ArC*H*$_3$ for major product and 3H, ArC*H*$_3$ for minor product), 4.24 (septet, *J* = 6.3 Hz, 1H, C*H*(CH$_3$)$_2$ for major product and 1H, C*H*(CH$_3$)$_2$ for minor product), 6.08 (d, *J* = 8.7 Hz, 2H, Ar*H* for minor product), 6.19 (d, *J* = 8.7 Hz, 2H, Ar*H* for major product), 6.81–6.88 (m, 3H, Ar*H* for major product and 2H, Ar*H* for minor product), 7.00 (d, *J* = 8.7 Hz, 2H, Ar*H* for minor product), 7.15–7.23 (m, 3H, Ar*H* for major product and 3H, Ar*H* and N*H* for minor product), 7.50–7.63 (m, 3H, Ar*H* and N*H* for major product and 3H, Ar*H* for minor product), 7.91 (d, *J* = 1.8 Hz, 1H, Ar*H* for major product); HRMS (EI) calcd for $C_{23}H_{25}BrN_2O_2S$ $[M]^+$ 472.0820, found 472.0822.

***N*-(4-Bromophenyl)-*N*-isopropyl-4-methoxy-2-(tosylamido)aniline (2i).** Yield 43%; purified by column chromatography (silica gel, 6:1 *n*-hexane/AcOEt); colorless solid; mp 142−144 °C; IR (KBr) *v* 3241, 2972, 1587, 1489, 1381, 1336, 1289, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C): δ 1.08 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 2.40 (s, 3H, ArC*H*$_3$), 3.82 (s, 3H, OC*H*$_3$), 4.22 (septet, *J* = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$), 6.12 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.58 (dd, *J* = 8.5, 3.0 Hz, 1H, Ar*H*), 6.86 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.02 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.15–7.17 (m, 3H, Ar*H* and N*H*), 7.37 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.57 (d, *J* = 8.0 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8 (CH_3), 21.6 (CH_3), 48.9 (CH), 55.5 (CH_3), 103.0 (CH), 109.9 (C), 110.0 (CH), 115.9 (CH), 123.5 (C), 127.2 (CH), 129.6 (CH), 131.5 (CH), 131.6 (CH), 136.0 (C), 138.0 (C), 144.1 (C), 147.0 (C), 159.3 (C); HRMS (EI) calcd for $C_{23}H_{25}BrN_2O_3S$ $[M]^+$ 488.0769, found 488.0769.

***N*-Isopropyl-*N*-(*p*-tolyl)-1-(tosylamido)naphthalen-2-amine (2j).** Yield 80%; purified by column chromatography (silica gel, 8:1 *n*-hexane/AcOEt); light yellow solid; mp 148−150 °C; IR (KBr) *v* 3303, 2972, 1508, 1386, 1322, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 2.25 (s, 3H, ArC*H*$_3$), 2.38 (s, 3H, ArC*H*$_3$), 4.02 (septet, *J* = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$), 6.43 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.59 (s, 1H, N*H*), 6.93 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.14 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.28 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.40–7.46 (m, 2H, Ar*H*), 7.52 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.75 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.79 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar*H*), 8.17 (dd, *J* = 8.0, 2.0 Hz, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4 (CH_3), 21.0 (CH_3), 21.5 (CH_3), 50.5 (CH), 118.3 (CH), 125.5 (CH), 125.8 (CH), 126.1 (CH), 126.8 (CH), 127.3 (CH), 127.5 (CH), 128.0 (CH), 129.1 (C), 129.2 (CH), 129.4 (C), 129.9 (CH), 131.9 (C),

132.4 (C), 137.9 (C), 138.4 (C), 143.4 (C), 144.7 (C); HRMS (EI) calcd for $C_{27}H_{28}N_2O_2S$ $[M]^+$ 444.1871, found 444.1872.

***N*-Isopropyl-4-methoxy-*N*-(4-methoxyphenyl)-2-[(2-pyridylsulfonyl)amido]aniline (5).**

[(2-Pyridylsulfonyl)imino]phenyliodinane (108 mg, 0.300 mmol) was added to a stirred mixture of *N*-isopropyl-di(4-methoxyphenyl)amine (**1b**) (54.3 mg, 0.200 mmol), $Rh_2(HNCOCF_3)_4$ (2.6 mg, 4.00×10^{-3} mmol, 2 mol%) and 4Å MS (powder, 80 mg) in CH_2Cl_2 (2.0 mL) at 0 °C under Ar atmosphere. After stirring at room temperature for 1 h, the whole mixture was filtered through a pad of Celite, and the filtrate was evaporated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 3:1 *n*-hexane/AcOEt) to give N–H amination product **5** (25.9 mg, 30%) as a colorless amorphous: IR (KBr) *v* 3244, 2970, 1508, 1383, 1337, 1242, 1180, 1118, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 3.74 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 4.20 (septet, *J* = 6.4 Hz, 1H, C*H*(CH$_3$)$_2$), 6.56 (d, *J* = 9.2 Hz, 2H, Ar*H*), 6.56 (dd, *J* = 8.8, 3.2 Hz, 1H, Ar*H*), 6.64 (d, *J* = 9.2 Hz, 2H, Ar*H*), 6.92 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.39 (d, *J* = 3.2 Hz, 1H, Ar*H*), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, Ar*H*), 7.83 (dt, *J* = 7.6, 1.6 Hz, 1H, Ar*H*), 7.96–7.99 (m, 2H, Ar*H* and N*H*), 8.50–8.51 (m, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (CH_3), 49.5 (CH), 55.4 (CH_3), 55.6 (CH_3), 102.7 (CH), 109.8 (CH), 114.3 (CH), 116.8 (CH), 122.6 (CH), 125.8 (C), 126.9 (CH), 131.4 (CH), 137.7 (CH), 137.8 (C), 142.4 (C), 150.1 (CH), 152.5 (C), 156.3 (C), 158.7 (C); HRMS (EI) calcd for $C_{22}H_{25}N_3O_4S$ $[M]^+$ 427.1566, found 427.1568.

***N*^{1}-Isopropyl-4-methoxy-*N*^{1}-(4-methoxyphenyl)benzene-1,2-diamine (6).**

A suspension of (2-pyridylsulfonyl)amide **5** (22.3 mg, 5.20×10^{-2} mmol) and magnesium (powder, 12.0 mg, 0.520 mmol) in MeOH (1.0 mL) was stirred at 50 °C for 6 h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with AcOEt. The organic extract was successively washed with brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 6:1 *n*-hexane/AcOEt) to give primary amine **6** (12.8 mg, 86%) as a colorless oil: IR (KBr) *v* 3472, 3371, 2969, 1617, 1506, 1240, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 3.73 (s, 3H, OC*H*$_3$), 3.79 (s, 3H, OC*H*$_3$), 3.86 (brs, 2H, N*H*), 4.22 (septet, *J* = 6.4 Hz, 1H, C*H*(CH$_3$)$_2$), 6.32 (dd, *J* = 8.4, 2.8 Hz, 1H, Ar*H*), 6.36 (d, *J* = 2.8 Hz, 1H, Ar*H*), 6.53 (d, *J* = 9.2 Hz, 2H, Ar*H*), 6.75 (d, *J* = 9.2 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.4 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4 (CH_3), 48.6 (CH), 55.2 (CH_3), 55.8 (CH_3), 100.8 (CH), 104.2 (CH), 114.4 (CH), 114.7 (CH), 122.5 (C), 132.3 (CH), 142.8 (C), 147.3 (C), 151.3 (C), 159.2 (C); HRMS (EI) calcd for $C_{17}H_{22}N_2O_2$ $[M]^+$ 286.1681, found 286.1678.

KIE experiment between 1c and [D$_8$]-1c (Scheme 5).

[D$_8$]-**1c** was synthesized from commercially available diphenylamine-d_{10} by reductive amination with 2-methoxypropene[15] followed by treatment with NBS in DMF.[16]

TsN=IPh (37.3 mg, 0.100 mmol) was added to a stirred mixture of **1c** (36.9 mg, 0.100 mmol), [D_8]-**1c** (37.7 mg, 0.100 mmol), $Rh_2(HNCOCF_3)_4$ (1.3 mg, 2.00×10^{-3} mmol, 2 mol%) and 4Å MS (powder, 40 mg) in CH_2Cl_2 (1.0 mL) at 0 °C under Ar atmosphere. After stirring at room temperature for 1 h, the whole mixture was filtered through a pad of Celite, and the filtrate was evaporated in vacuo to furnish the crude product, which was purified by column chromatography (silica gel, 10:1 *n*-hexane/AcOEt) to give a mixture of **2c** and [D_7]-**2c** (21.6 mg) with recovery of a mixture of starting materials (50.6 mg). The k_H/k_D value was determined to be 0.96 by ^{1}H NMR analysis of the mixture of products (**2c**:[D_7]-**2c** = 49:51). Ratio of the recovered starting materials **1c** and [D_8]-**1c** was also determined to be 51:49.

ACKNOWLEDGEMENTS

This work is financially supported by a Grant-in-Aid for Young Scientists (B) (No. 17K15428) from JSPS, Japan. We thank T. Koseki of the Analytical Center of Meiji Pharmaceutical University for mass spectral measurements.

REFERENCES AND NOTES

1. Reviews, see: (a) J. Jiao, K. Murakami, and K. Itami, *ACS Catal.*, 2016, **6**, 610; (b) Y. Zhou, J. Yuan, Q. Yang, Q. Xiao, and Y. Peng, *ChemCatChem*, 2016, **8**, 2178; (c) Y. Park, Y. Kim, and S. Chang, *Chem. Rev.*, 2017, **117**, 9247.
2. Reviews, see: (a) P. Müller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905; (b) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439; (c) J. L. Roizen, M. E. Harvey, and J. Du Bois, *Acc. Chem. Res.*, 2012, **45**, 911; (d) J. Buendia, G. Grelier, and P. Dauban, *Adv. Organomet. Chem.*, 2015, **64**, 77; (e) B. Darses, R. Rodrigues, L. Neuville, M. Mazurais, and P. Dauban, *Chem. Commun.*, 2017, **53**, 493.
3. (a) C. G. Espino, K. W. Fiori, M. Kim, and J. Du Bois, *J. Am. Chem. Soc.*, 2004, **126**, 15378; (b) K. W. Fiori and J. Du Bois, *J. Am. Chem. Soc.*, 2007, **129**, 562.
4. (a) M. Tanaka, Y. Kurosaki, T. Washio, M. Anada, and S. Hashimoto, *Tetrahedron Lett.*, 2007, **48**, 8799; (b) M. P. Paudyal, A. M. Adebesin, S. R. Burt, D. H. Ess, Z Ma, L. Kürti, and J. R. Falck, *Science*, 2016, **353**, 1144; (c) K. Arai, Y. Ueda, K. Morisaki, T. Furuta, T. Sasamori, N. Tokitoh, and T. Kawabata, *Chem. Commun.*, 2018, **54**, 2264; (d) L. He, P. W. H. Chan, W.-M. Tsui, W.-Y. Yu, and C.-M. Che, *Org. Lett.*, 2004, **6**, 2405.
5. M. Ito, T. Nakagawa, K. Higuchi, and S. Sugiyama, *Org. Biomol. Chem.*, 2018, **16**, 6876.
6. For examples of Rh(II)-catalyzed intramolecular C(sp^2)−H amination, see: (a) S. Chiba, G. Hattori, and K. Narasaka, *Chem. Lett.*, 2007, **36**, 52; (b) B. J. Stokes, B. Jovanović, H. Dong, K. J. Richert, R. D. Riell, and T. G. Driver, *J. Org. Chem.*, 2009, **74**, 3225; (c) R. Singh, K. Nagesh, and M.

Parameshwar, *ACS Catal*., 2016, **6**, 6520.

7. For intermorecular C(sp^2)−H amination with metal-nitrenes derived from Cu, Au and Fe catalysts, see: (a) M. M. Díaz-Requejo, T. R. Belderraín, M. C. Nicasio, S. Trofimenko, and P. J. Pérez, *J. Am. Chem. Soc*., 2003, **125**, 12078; (b) C. W. Hamilton, D. S. Laitar, and J. P. Sadighi, *Chem. Commun*., 2004, 1628; (c) M. R. Fructos, S. Trofimenko, M. Mar Díaz-Requejo, and P. J. Pérez, *J. Am. Chem. Soc*., 2006, **128**, 11784; (d) Z. Li, D. A. Capretto, R. O. Rahaman, and C. He, *J. Am. Chem. Soc*., 2007, **129**, 12058; (e) S. Liang and M. P. Jensen, *Organometallics*, 2012, **31**, 8055; (f) A. John, J. Byun, and K. M. Nicholas, *Chem. Commun*., 2013, **49**, 10965.
8. (a) R. A. Smits, H. D. Lim, B. Stegink, R. A. Bakker, I. J. P. de Esch, and R. Leurs, *J. Med. Chem.*, 2006, **49**, 4512; (b) M. B. Said, T. Baramov, T. Herrmann, M. Gottfried, J. Hassfeld, and S. Roggan, *Org. Process Res. Dev*., 2017, **21**, 705; (c) D. Zhang, Y. Lu, K. Liu, B. Liu, J. Wang, G. Zhang, H. Zhang, Y. Liu, B. Wang, M. Zheng, L. Fu, Y. Hou, N. Gong, Y. Lv, C. Li, C. B. Cooper, A. M. Upton, D. Yin, Z. Ma, and H. Huang, *J. Med. Chem*., 2012, **55**, 8409; (d) J. T. Link, S. Raghavan, and S. J. Danishefsky, *J. Am. Chem. Soc*., 1995, **117**, 552; (e) J. Sun, J. Zhao, L. Wang, H. Li, F. Yang, and X. Yang, *ACS Sensors*, 2018, **3**, 183; (f) F. Chen, S. Wang, Y. Xiao, F. Peng, N. Zhou, L. Ying, and X. Li, *Chem. Asian J.*, 2018, **13**, 1335.
9. We previously reported that *N*,*N*-dialkylanilines bearing methyl or primary alkyl groups underwent *N*-dealkylation with preference over aromatic C–H amination (see, reference 5). See also, V. Bagchi, P. Paraskevopoulou, P. Das, L. Chi, Q. Wang. A. Choudhury, J. S. Mathieson, L. Cronin, D. B. Pardue, T. R. Cundari, G. Mitrikas, Y. Sanakis, and P. Stavropoulos, *J. Am. Chem. Soc*., 2014, **136**, 11362.
10. We previously reported that an *N*,*N*-dialkylaniline derived from *p*-anisidine underwent C–H amination at the *ortho*-position of amino group with a virtually perfect regioselectivity, and the structure of the product was unambiguously defined by X-ray crystallography. See reference 5.
11. C. S. Pak and D. S. Lim, *Synth. Commun*., 2001, **31**, 2209.
12. (a) K. Guthikonda and J. Du Bois, *J. Am. Chem. Soc*., 2002, **124**, 13672; (b) E. Martinand-Lurin, R. Gruber, P. Retailleau, P. Fleurat-Lessard, and P. Dauban, *J. Org. Chem*., 2015, **80**, 1414.
13. A. K. Mishra, M. M. Olmstead, J. J. Ellison, and P. P. Power, *Inorg. Chem*., 1995, **34**, 3210.
14. M. Ito, A. Tanaka, K. Higuchi, and S. Sugiyama, *Eur. J. Org. Chem.*, 2017, 1272.
15. T. J. Reddy, M. Leclair, and M. Proulx, *Synlett*, 2005, 583.
16. T. Ishi-i, K. Ikeda, M. Ogawa, and Y. Kusakaki, *RSC Adv*., 2015, **5**, 89171.
17. T. vom Stein, M, Peréz, R. Dobrovetsky, D. Winkelhaus, C. B. Caputo, and D. W. Stephan, *Angew. Chem. Int. Ed*., 2015, **54**, 10178.