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Dirhodium(II)-Catalyzed *ortho* C–H Amination of Sterically Congested *N,N*-Dialkylanilines

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Dirhodium(II)-catalyzed ortho C–H amination of N,Ndialkylanilines has been developed. Sterically congested 1,2diaminobenzenes were obtained in high yields with excellent chemo- and regioselectivities from para-substituted anilines and even from para-unsubstituted anilines. The ortho selectivity observed was rationalized in terms of the interaction between the dialkylamino group and a Rh(II)-nitrene intermediate.

1,2-Diaminobenzenes constitute important structural motifs in pharmaceuticals as part of nitrogen-containing heterocycles.¹ In recent years, with remarkable progress in the field of transition metal-catalyzed C-H functionalization, *ortho* C-H amination of aniline derivatives has emerged as one of the most step- and atom-economical synthetic methods for 1,2diaminobenzenes.^{2,3} In this context, high-efficiency C-H metallation is achieved owing to chelation-assistance by coordinating groups (*e.g.*, acyl, sulfonyl, and nitrogencontaining heterocyclic groups), which facilitate predictable *ortho* amination via five- or six-membered metallacycle intermediates (Scheme 1a). However, the goal for *ortho* C-H amination of anilines without metallacycle intermediates remains elusive.⁴

Alternatively, it is known that highly reactive metal-nitrene species lead to C–H amination without any assistance by coordinating groups.⁵ Since the pioneering work by Du Bois and co-workers,⁶ Rh(II)-nitrenes, generated from dirhodium(II) complexes and (*N*-arylsulfonylimino)aryliodinanes, have been extensively used for both inter- and intramolecular $C(sp^3)$ –H amination reactions. In sharp contrast, there are very few reports of aromatic C–H amination in the literature.^{7–11} The first example of Rh(II)-catalyzed intermolecular $C(sp^2)$ –H amination of aromatic hydrocarbons was reported by Hashimoto, Anada and co-workers in 2007 during the course of their studies on the amination of silylketene acetals using

the chiral dirhodium(II) complex $Rh_2(S-TCPTTL)_4$.^{7a,9} Among the substrates reported, those bearing an *ortho*-substituted benzene ring did not undergo the expected aziridination of the ketene acetal moiety; instead, aromatic C–H amination occurred at the *para* position. Very recently, Falck and coworkers reported the aromatic C–H amination of alkyl- and alkoxybenzenes by exploiting *O*-(arylsulfonyl)hydroxylamine as a nitrene precursor in the protic solvent CF₃CH₂OH (Scheme 1b).^{7b} The reaction proceeded with an excellent preference over C(sp³)–H amination and aziridination, but the functional group tolerance was limited due to rather strong acidity of the conditions. As well as chemoselectivity, another issue in



(b) Rh(II)-catalyzed intermolecular aromatic C-H amination reported by Falck



selected example of products





(c) This work: ortho C-H amination of N,N-dialkylaniline



Scheme 1 Overview of transition metal-catalyzed aromatic C–H amination

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⁺ Electronic Supplementary Information (ESI) available: detailed experimental procedures, spectral data, X-ray crystallographic data for **2g** (CIF). See DOI: 10.1039/x0xx00000x

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aromatic C-H amination is regiocontrol. For example, amination of 4-ethylanisole provides a 3.6:1 mixture of regioisomers under Falck's conditions. Therefore, development of Rh(II)-catalyzed chemo- and regioselective aromatic C-H amination is a worthwhile challenge that remains unmet. In this context, as part of our continuing studies on the reactions of Rh(II)-nitrenes with anilines,¹² we herein report the ortho C-H amination of N,N-dialkylanilines using a combination of $Rh_2(HNCOCF_3)_4$ and (Nsulfonylimino)phenyliodinanes. This methodology enables extremely sterically synthesis of congested 1.2diaminobenzenes in high yield with excellent chemo- and regioselectiv-ity from para-substituted anilines and even from para-unsubstituted anilines (Scheme 1c).

We initially examined the reaction of *N*,*N*-dimethyl-4bromoaniline (**1a**) with (tosylimino)phenyliodinane (TsN=IPh) in CH₂Cl₂ using Rh₂(HNCOCF₃)₄ (2 mol%). However, no aromatic C–H amination was observed. Instead, undesired monodealkylation produced *N*-methyl-4-bromoaniline **3a** as the major product (Table 1, entry 1).¹³ Unexpectedly, the desired C–H amination products **2b** and **2c** were obtained upon switching the alkyl group from methyl to ethyl or benzyl group, but the yields were unsatisfactory (entries 2 and 3).



^{*a*} Reactions conditions: **1** (0.1 mmol), Rh(II) catalyst (0.002 mmol, 2 mol%), TsN=IPh (0.12 mmol), and 4Å MS (powder, 40 mg) in the indicated solvent (1 mL). ^{*b*} Isolated Yield. ^{*c*} Yields in parenthesis refer to yields of **3**. ^{*d*} Recovery of starting aniline **1**, Entry 1: 18%, Entry 2: 17%, Entry 3: 46%, Entry 12: 89%. ^{*e*} 2 equiv of TsN=IPh was used. ^{*f*} PhI(OAc)₂ (1.2 equiv), TsNH₂ (1.5 equiv), and MgO (2.3 equiv) was used instead of TsN=IPh. ^{*g*} TsN=IPh was added at 10 °C. ^{*h*} 3Å MS was used. Ts = tosyl. ^{*t*} Am = *tert*-amyl. esp

Encouraged by these results, we next examined the reaction of N,N-diisopropyl-4-bromoaniline (1d). The reaction proceeded smoothly to completion at room temperature in less than 1 h and afforded 1,2-diaminobenzene 2d in 83% yield with no trace of N-dealkylation (entry 4). It is known that tertiary amines, including aniline derivatives, likely to undergo N-N bond formation and C(sp³)–H amination at α -position of nitrogen.¹³⁻¹⁵ Thus, it is notable that the C-H amination proceeded with perfect chemo- and regioselectivity even at extremely sterically congested ortho position. Selective monoamination was observed even in the presence of 2 equiv of iminoiodinane (entry 5). In situ preparation of TsN=IPh from PhI(OAc)₂ and TsNH₂ was also applicable, but the yield of 2d was slightly decreased (entry 6).⁶ Switching the solvent from CH₂Cl₂ to benzene, benzotrifluoride, MeCN, or tert-amyl alcohol had little impact on product yields (entries 7-10). No reaction was observed in the absence of Rh(II) complex, and $Rh_2(OAc)_4$ barely worked as a catalyst (entries 11 and 12). Rh₂(esp)₂ having sterically bulky ligands was less effective than Rh₂(HNCOCF₃)₄ (entry 13).^{16,17}

Having established the optimal conditions, we then investigated the applicability of the reaction to a range of N,Ndialkylanilines 1 (Table 2).¹⁸ With respect to the substituents at the para position of the benzene ring, high product yields were maintained with alkyl, phenyl, methoxy and alkoxycarbonyl groups (entries 1-5). Among the products obtained, the structure of 2g was unambiguously established by X-ray crystallography (Table 2, top right).¹⁹ Secondary alkyl groups such as α -methylbenzyl and cyclohexyl groups were also the optimal substituents for the amino group (entries 6-8). Excellent functional group tolerance of the C-H amination conditions was displayed for substrates bearing acid- and oxidation-sensitive functional groups such as tertbutyldimethylsilyl (TBS), methoxymethyl (MOM), and pmethoxybenzyl (PMB) ethers (entries 9–11). Complete α selectivity was observed with 2-naphthylamine 1p and 6aminoquinoline 1q (entries 12 and 13). 3,4-Dimethylaniline 1r afforded a 70:30 mixture of regioisomers, and the structure of the major isomer was assigned as **2r** by ¹H NMR analysis of the mixture after removal of the α -methylbenzyl group (entry 14). In sharp contrast, the reaction of 3-methoxycarbonyl-4methylaniline 1s proceeded with virtually perfect preference for amination at the para position of the methoxycarbonyl group to give 2s' (entry 15), although the reasons for the reversal of regioselectivity are not clear at present. The present protocol was also applicable to aniline 1u derived from estrone, which provided product 2u in 83% yield without protection of the tertiary hydroxy group (entry 17). The use of range of (N-sulfonylimino)phenyliodinanes provided а comparable results to that obtained with TsN=IPh (entries 18-20).

While ortho C–H amination of para-substituted anilines is successfully accomplished using the system above, regioselective C–H amination of para-unsubstituted anilines still remains elusive. To address this issue, the reaction of *N*,*N*-diisopropylaniline (**1v**) was performed (Scheme 2a). Ortho C–H

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^a All reactions were performed on a 0.1 mmol scale unless otherwise noticed. ^a Yields of isolated products. ^a 0.5 mmol scale. ^d 1.5 equiv of PGN=IPh was used. ^e Structures of the products were determined after removal of α -methylbenzyl groups by hydrogenolysis using Pd(OH)₂/C. ^f 2.0 equiv of TsN=IPh was used. *p*Ns = 4-O₂NC₆H₄SO₂. Py = pyridyl. Tces = 2,2,2-trichloroethoxysulfonyl.

amination product 2v was obtained as the major product in 38% yield with 30% recovery of 1v. To our surprise, the para amination product 7 was not obtained. However, the formation of by-products 8 and 9 implied over-oxidation of nascent **7** under the reaction conditions.^{15,20} To avoid *para* amination, it should be reasonable to introduce a bulky substituent into the meta position of dialkylamino group. As expected, introduction of a tert-butyl group significantly increased the yield of ortho amination product to afford 2w as the sole product in 67% yield (Scheme 2b). A similarly good yield was also observed with aniline 1x derived from (3aminophenyl)- α , α -dimethylacetate. Surprisingly, 3,5dimethylaniline 1y afforded ortho amination product 2y in excellent yield, even though the para position was much less hindered than the ortho position. Selective ortho C-H amination was also achieved with 3,5-dimethoxybenzene 1z to provide 2z in 65% yield.

To gain insight into the reaction mechanism, we performed a kinetic isotope effect (KIE) experiment between **1d** and $[D_4]$ -**1d** (see Scheme S2 in ESI). The inverse secondary kinetic

isotope effect observed ($k_{\rm H}/k_{\rm D}$ = 0.96) indicates rehybridization of the deuterium labeled carbon atom from sp^2 to sp^3 , thus suggesting a pathway including electrophilic addition of Rh(II)nitrene intermediates to the benzene ring but not a pathway involving direct $C(sp^2)$ -H insertion.^{8,10c,21} Further mechanistic insights were gained by a series of competition experiments between 1d and phenylether 10 (Scheme 3). First, to obtain information about the reactivity of 1d and 10 under dirhodium(II)-complex catalyzed conditions, the reaction with a Rh(II)-carbene, a carbon analog of Rh(II)-nitrene, was investigated. In the reaction with ethyl diazoacetate under the catalysis of Rh₂(OAc)₄, 1d provided the aromatic cyclopropanation product 12 instead of the ortho C-H insertion product 11,²² while 10 gave the C-H insertion product 13. The ratio of 12 and 13 was 46:54 and a 51:49 mixture of starting 1d and 10 was recovered. Hence, these substrates were equally reactive under these conditions. Conversely, the reaction under Rh(II)-nitrene conditions provided a 91:9 mixture of C-H amination products 2d and 14 in 81% combined yield. These results indicated the interaction

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between the Rh(II)-nitrene and **1d** specifically accelerated the rate of reaction with **1d**. Recently, Dauban and co-workers reported that the electrophilic nitrogen atom of the Rh(II)-nitrenes coordinates to nitrogen atom of the substrates as a Lewis acid.^{14,23-25} Similarly, we postulated that coordination of Rh(II)-nitrenes to the amine nitrogen of **1** facilitated electrophilic addition to the sterically hindered *ortho* position of the dialkylamino group. This hypothesis was validated by performing competition experiments in several solvents. While



 $\label{eq:scheme 3} \begin{array}{l} \text{Scheme 3} \\ \text{and phenylether 10} \\ \end{array}$

the use of MeCN instead of CH_2Cl_2 had little impact on product distribution, protic *tert*-amyl alcohol resulted in a marked decrease in the relative reaction rate of **1d** to provide a 60:40 mixture of **2d** and **14**. These results can be explained in terms of disruption of the coordination of the Rh(II)-nitrene owing to the hydrogen bonding between **1d** and *tert*-amylalcohol.

On the basis of the above results, a plausible reaction mechanism is proposed, as illustrated in Scheme 4. Starting from anilines 1, the coordination of Rh(II)-nitrenes to the dialkylamino group generates intermediates I. The formation of I facilitates the electrophilic addition of Rh(II)-nitrene to the sterically hindered ortho position to form zwitterionic intermediates II,²⁶ which provide 1,2-diaminobenzenes 2 via proton transfer. Conversely, when the amino group has methyl or primary alkyl group, intermediates I undergoes Ndealkylation through C(sp³)-H amination at α -position of nitrogen atom.¹³ As with known Rh(II)-catalyzed C-H amination reactions,⁵ the reaction of anilines 1 and Rh(II)nitrene proceeds via an outer-sphere mechanism,^{5b,10c} in which the substrates attack the electrophilic nitrogen atom bound to Rh(II) atom but not the Rh(II) atom itself. Unlike the chelation-assisted mechanism (Scheme 1a), the outer-sphere mechanism does not involve the formation of metallacycle intermediates that endow predictable regiocontrol for C-H functionalization. Thus, regioselectivity in aromatic C-H functionalization via the outer- sphere mechanism relies mainly on the steric and electronic nature of the benzene ring.^{7b,8,11e,27} Conversely, in the present reaction, paraunsubstituted anilines 1w-z greatly favored ortho amination over para amination (Scheme 2b). These results are noteworthy because it seems that the regioselectivities are controlled by coordination of the Rh(II)-nitrene rather than the steric nature of the substrates.^{28,29} To the best of our knowledge, this is the first successful example of regiocontrol in intermolecular C-H functionalization by harnessing a noncovalent interaction between substrates and Rh(II)-nitrene intermediates.

In conclusion, we have developed dirhodium(II)-catalyzed aromatic C–H amination of *N*,*N*-dialkylanilines, providing 1,2-



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diaminobenzenes in high yields with excellent chemo- and regioselectivities. Bulky alkyl groups attached on the amino group plays a pivotal role in prevention of side-reactions such as dealkylation without compromising reactivity at the sterically congested *ortho* position. The *ortho* selectivity observed is rationalized in terms of the coordination of the dialkylamino group to the Lewis acidic nitrogen atom of the Rh(II)-nitrene intermediate. This method represents the first example of regiocontrol in Rh(II)-catalyzed C–H amination by harnessing non-covalent interaction between substrates and Rh(II)-nitrene intermediates. Further studies on the extension of substrate scope as well as theoretical studies are currently in progress.³⁰

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Notes and references

- (a) H. Tabata, J. Nakagomi, D. Morizono, T. Oshitari, H. Takahashi and H. Natsugari, *Angew. Chem. Int. Ed.*, 2011, **50**, 3075; (b) S. J. Dixon, K. M. Lemberg, M. R. Lamprecht, R. Skouta, E. M. Zaitsev, C. E. Gleason, D. N. Patel, A. J. Bauer, A. M. Cantley, W. S. Yang, B. Morrison III and B. R. Stockwell, *Cell*, 2012, **149**, 1060; (c) K. Samanta, N. Srivastava, S. Sahab and G. Panda, *Org. Biomol. Chem.*, 2012, **10**, 1553; (d) A. N. Matthew, J. Zephyr, C. J. Hill, M. Jahangir, A. Newton, C. J. Petropoulos, W. Huang, N. Kurt-Yilmaz, C. A. Schiffer and A. Ali, *J. Med. Chem.*, 2017, **60**, 5699. and references therein.
- 2 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.
- 3 Ortho C-H azidation and nitration of anilines are also effective for the synthesis of precursor of 1,2diaminobenzenes. (a) C. Tang and N. Jiao, J. Am. Chem. Soc., 2012, 134, 18924; (b) G. G. Pawar, A. Brahmanandan and M. Kapur, Org. Lett., 2016, 18, 448.
- 4 While the formation of metallacycles from N,Ndialkylbenzylamines is well-known, there is no report of the formation of four membered metallacycles from N,Ndialkylanilines. (a) G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, J. Am. Chem. Soc., 2007, **129**, 7666; (b) A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, Nature, 2014, **510**, 129.
- 5 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.
- 6 (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.
- 7 (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.

- 8 Very recentry, Kawabata, Ueda and co-workers reported a Rh(II)-catalyzed para C-H amination of phenyl ethers using TrocNHOTs as a nitrene precursor; K. Arai, Y. Ueda, K. Morisaki, T. Furuta, T. Sasamori, N. Tokitoh and T. Kawabata, Chem. Commun., 2018, 54, 2264.
- 9 In 2004, Che and co-workers reported that the reaction of furan with TsN=IPh provided C(sp²)-H amination product in 21% under the catalysis of Rh₂(OAc)₄. L. He, P. W. H. Chan, W.-M. Tsui, W.-Y. Yu and C.-M. Che, *Org. Lett.*, 2004, 6, 2405.
- 10 For examples of Rh(II)-catalyzed intramolecular C(sp²)–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.
- 11 For intermorecular C(sp²)–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.
- 12 M. Ito, A. Tanaka, K. Higuchi and S. Sugiyama, *Eur. J. Org. Chem.*, 2017, 1272.
- 13 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.
- 14 For examples of Rh(II)- and Ag-catalyzed N-N bond formation reactions of tertiary amines, see: (a) B. M. Trost, B. M. O'Boyle, W. Torres and M. K. Ameriks, *Chem. Eur. J.*, 2011, **17**, 7890; (b) J. Li, J. S. Cisar, C.-Y. Zhou, B. Vera, H. Williams, A. D. Rodríguez, B. F. Cravatt and D. Romo, *Nature Chem.*, 2013, **5**, 510; (c) S. A. Pujari, L. Guénée and J. Lacour, *Org. Lett.*, 2013, **15**, 3930; (d) L. Maestre, R. Dorel, Ó. Pablo, I. Escofet, W. M. C. Sameera, E. Álvarez, F. Maseras, M. Mar Díaz-Requejo, A. M. Echavarren and P. J. Pérez, *J. Am. Chem. Soc.*, 2017, **139**, 2216.
- 15 Bulky dialkylamino group plays a pivotal role in prevention of over-oxidation of *ortho* amination products **2**. See reference 19 and Scheme S1 in ESI.
- 16 We previously reported that Rh₂(HNCOCF₃)₄ displayed superior performance to Rh₂(esp)₂ in reactions with sterically congested *ortho*-substituted anilines. See reference 12.
- 17 No reaction was observed with *N*-isopropylacetanilide probably due to the low nucleophilicity of the substrate.
- 18 Ortho-substituted anilines were not examined because of difficulty in preparation of the substrates.
- 19 CCDC 1828111 contains the supplementary crystallographic data for this paper.
- 20 Competition experiments between 1d and 7 or 1d and 2v under the C-H amination conditions indicated that a bulky dialkylamino group plays a crucial role in prevention of over-oxidation of 2 as well as dealkylation of substrates 1 (see Table 1, entries 1–4). See Scheme S1 in ESI for details.
- 21 T. Kawakami, K. Murakami and K. Itami, J. Am. Chem. Soc., 2015, **137**, 2460.
- (a) W. D. Mackay and J. S. Johnson, Org. Lett. 2016, 18, 536;
 (b) G. S. Fleming and A. B. Beeler, Org. Lett. 2017, 19, 5268.
- 23 J. Ciesielski, G. Dequirez, P. Retailleau, V. Gandon and P. Dauban, *Chem. Eur. J.*, 2016, **22**, 9338.
- 24 Recently, Musaev and Berry reported that Rh-nitrene species derived from Rh(II) amidate has a Rh–Rh–N π^* orbital, which is heavily polarized toward the nitrogen atom. A. Varela-

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Álvarez, T. Yang, H. Jennings, K. P. Kornecki, S. N. Macmillan, K. M. Lancaster, J. B. C. Mack, J. Du Bois, J. F. Berry and D. G. Musaev, *J. Am. Chem. Soc.*, 2016, **138**, 2327.

- 25 J. M. Alderson, J. R. Corbin and J. M. Schomaker, Acc. Chem. Res., 2017, 50, 2147.
- 26 With respect to the formation of intermediate II from I, radical pathway can not be ruled out. While the C–H amination of 1d proceeded even in the presence of radical trapping agent galvinoxyl, the result is not conclusive evidence to negate the pathway. A pathway including aromatic aziridination followed by opening of aziridine ring is also possible. (a) K. Chen, Z.-Z. Zhu, J.-X. Liu, X.-Y. Tang, Y. Weib and M. Shi, *Chem. Commun.*, 2016, **52**, 350; (b) S. Beaumont, V. Pons, P. Retailleau, R. H. Dodd and P. Dauban, *Angew. Chem. Int. Ed.*, 2010, **49**, 1634.
- 27 For an example of regiocontrol in C(sp³)–H amination via outer-sphere mechanism, see: X. Xiao, C. Hou, Z. Zhang, Z. Ke, J. Lan, H. Jiang and W. Zeng, Angew. Chem. Int. Ed., 2016, 55, 11897.
- 28 3,5-Dimethoxyaniline **1z** provided a *para* C–H insertion product in 50% yield by the reaction with a Rh(II)-carbene derived from $Rh_2(HNCOCF_3)_4$.

Rh₂(HNCOCF₃)₄ (2 mol%) [/]Pr Ph、_CO₂Me



- 29 Zhang and co-workers reported that gold-catalyzed C–H insertion of carbenes with phenols and *N*-acylanilides displayed *para* selectivity. (a) Z. Yu, B. Ma, M. Chen, H.-H. Wu, L. Liu and J. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 6904; (b) Y. Liu, Z.Yu, J. Z. Zhang, L. Liu, F. Xia and J. Zhang, *Chem. Sci.* **2016**, *7*, 1988.
- 30 To demonstrate the utility of our ortho C-H amination, elaboration of chiral tetrahydrquinoxaline and 1,5benzodiazepine was performed. See Scheme S3 in ESI.

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