HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 893 - 900. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 4th August, 2014, Accepted, 14th October, 2014, Published online, 20th October, 2014
DOI: 10.3987/COM-14-S(K)102

SYNTHESIS OF 2,7-DISUBSTITUTED 5,10-DIARYL-5,10-DIHYDROPHENAZINES VIA IRON-CATALYZED INTRAMOLECULAR RING-CLOSING C–H AMINATION

Yuma Aoki,[a,b] Ryuji Imayoshi,[a,b†] Takuji Hatakeyama,[a,b,c‡] Hikaru Takaya,[a,b] and Masaharu Nakamura[a,b*]

[a] International Research Center for Elements Science (IRCELS), Institute for Chemical Research (ICR), Kyoto University, Uji, Kyoto 611-0011, Japan. [b] Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan. [c] Elements Strategy Initiative for Catalysts and Batteries (ESICB), Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan. [†] Present address: Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-8656, Japan. [‡] Present address: Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan. [*] E-mail: masaharu@scl.kyoto-u.ac.jp

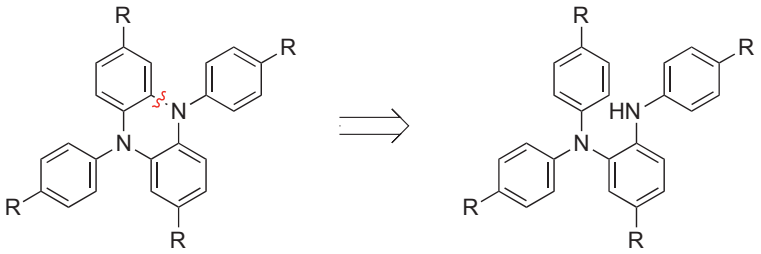
Abstract – A novel iron-catalyzed intramolecular ring-closing C–H amination reaction of *o*-phenylenediamines was developed, affording the corresponding 2,7-disubstituted 5,10-diaryl-5,10-dihydrophenazines in acceptable yields. The reaction proceeded via the *in-situ* generation of the magnesium amides of the starting secondary amines in the presence of a catalytic amount of an iron salt and a stoichiometric amount of 1,2-dibromoethane as the terminal oxidant. The substituted dihydrophenazine derivatives can potentially be used as hole-injection materials in organic electroluminescence (OEL) devices and also offer scaffolds for further synthetic elaborations of OEL materials.

This paper is dedicated to Professor Dr. Isao Kuwajima on the occasion of his 77th birthday.

Nitrogen-containing polycyclic aromatic compounds are of significant interest because of their versatile redox properties and applications in organic electronic materials,[1] and pharmaceuticals as biologically active ingredients.[2] 5,10-Diaryl-5,10-dihydrophenazines have promising physical properties[3,4] and attract considerable attention because of their potential use as hole-injection materials in organic electroluminescence (OEL) devices.[3] The synthesis of 5,10-diaryl-5,10-dihydrophenazines has been mainly carried out by the arylation reaction of the parent phenazine or 5,10-dihydrophenazine. In 1957, Gilman and Dietrich reported the synthesis of 5,10-diphenyl-5,10-dihydrophenazine via the copper-catalyzed cross-coupling reaction of iodobenzene with 5-phenyldihydrophenazinyllithium, which was prepared by the addition of phenyllithium to phenazine.[4] In 2003, Okamoto et al. developed an efficient synthetic method for 5,10-diaryl-5,10-dihydrophenazines: the palladium-catalyzed double-arylation reactions (Buchwald–Hartwig reaction[5]) of 5,10-dihydrophenazine afforded symmetrical compounds and the sequential *N*-arylation with aryllithium addition and the Buchwald–Hartwig reaction of the resulting 5-aryl-5,10-dihydrophenazine provided unsymmetrical compounds possessing different aryl groups on the nitrogen atoms.[6]

Although diverse aryl groups can be introduced on the nitrogen atoms using these *N*-arylation methods, the regioselective functionalization of the core aromatic units of 5,10-diaryl-5,10-dihydrophenazines has been an arduous task: The classical Wohl–Aue reaction needs harsh conditions (high temperature and strong base) and usually results in a low yield of the desired substituted phenazines.[7] The thermal decomposition of tetraarylhydrazine provides the core-substituted 5,10-diaryl-5,10-dihydrophenazines as a mixture of the target compounds, the corresponding diarylamines, and the oligomers of the diarylamines.[8] Phenazine and dihydrophenazine substrates bearing core substituents can be synthesized via the transition-metal-catalyzed cross-coupling reactions of aniline derivatives.[9] However, these syntheses also require the multistep and regioselective preparation of polysubstituted aniline precursors.

Because of the lack of a suitable direct core-functionalization method, an alternative approach to core-substituted dihydrophenazine derivatives can involve the intramolecular C–H amination of *o*-phenylenediamines bearing aryl groups at appropriate positions (Scheme 1). Despite the recent remarkable advances in intramolecular C–H amination reactions,[10,11] no such catalytic C–H amination reaction for 5,10-diaryl-5,10-dihydrophenazines has been reported to the best of our knowledge, probably because of the instability of the densely arylated diamine precursors and overoxidation of the dihydrophenazine products under conventional oxidative conditions.[12] In this communication, we report our preliminary findings on the first catalytic intramolecular C–H amination of *o*-phenylenediamines that affords 2,7-disubstituted 5,10-diaryl-5,10-dihydrophenazines. The key to the success of the reaction is the conversion of *o*-phenylenediamines to the corresponding magnesium amides and the use of an iron catalyst in the presence of 1,2-dibromoethane as an oxidant.



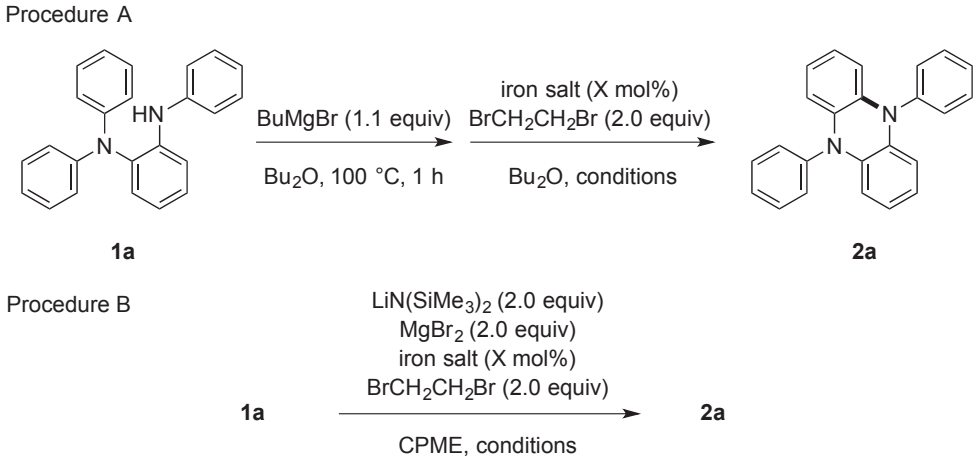
Scheme 1. Synthesis of 2,7-Disubstituted 5,10-Diaryl-5,10-dihydrophenazines via Intramolecular C–H Amination

The study commenced with a screening of reaction conditions for the conversion of N^1,N^1,N^2-triphenyl-*o*-phenylenediamine (**1a**) to 5,10-diphenyl-5,10-dihydrophenazine (**2a**). Both the compounds were obtained as by-products during our previous study on iron-catalyzed amination reaction,[13] and we envisaged that iron would catalyze the ring-closing C–H amination reaction of **1a**. The reaction was thus investigated, and the screening of reaction conditions and reagents identified two different procedures as shown in Table 1. In procedure A, a solution of BuMgBr in Bu_2O was added to a solution of **1a** in Bu_2O at 0 °C to generate the magnesium amide of the secondary amine (NH). After stirring the mixture at 100 °C for 1 h to complete the deprotonation, a catalytic amount of an iron salt and 2.0 equiv of 1,2-dibromoethane were added to the resulting magnesium amide. The C–H amination reactions were found to proceed at 80 °C with a reasonable rate of conversion although the reactions ceased when 33–50% of **1a** was consumed. In procedure B, a mixture of **1a**, lithium bis(trimethylsilyl)amide $LiN(SiMe_3)_2$, $MgBr_2$, an iron salt, and 1,2-dibromoethane in cyclopentyl methyl ether, hereafter abbreviated as CPME, was heated at 100 °C for 15 to 21 h to obtain **2a** up to 39% yield. The reactions were monitored by GC and quenched when the reaction stopped.

Table 1 summarizes the results of the ring-closing C–H amination reactions of **1a**. Although the reactions using ferrous halides, $FeCl_2$ or $FeBr_2$, as the catalyst did not give the desired dihydrophenazine at all (data not shown), the ferric halide catalysts, $FeCl_3$ and $FeBr_3$, promoted the reaction to afford **2a** in 15% and 19% yields, respectively (entries 1 and 2). The yields are almost the same for $FeCl_3$ and $FeBr_3$, while a slightly improved material balance was achieved with the latter catalyst. An increase in catalyst loading from 5 mol% to 20 mol% did not improve the yield of **2a** significantly (entry 3). Because the conversion of **1a** to **2a** requires the elimination of hydrogen atoms, probably as protons, protonation of the starting magnesium amide may compete during the reaction to decrease the yield of **2a**. Therefore, an additional base was employed in procedure B, in which an excess amount of the magnesium amide base was generated using 2.0 equiv of $LiN(SiMe_3)_2$ and $MgBr_2$. In this procedure, 5 mol% of $FeBr_3$ afforded the desired product in 12% yield (entry 4). Notably, $FeCl_2$ was found to work well in procedure B, affording **2a** in 11% yield with an improved material balance (entry 5). Finally, the yield of **2a** was improved to 39% with an increased

amount of $FeCl_2$ (20 mol%) (entry 6). Some unidentified by-products were observed, particularly in the low material balance cases, and these may be oligomers of **1a**, as inferred by the GPC analyses of the crude products (data not shown).

Table 1. Iron-Catalyzed Intramolecular Ring-Closing C–H Amination of **1a**[a]



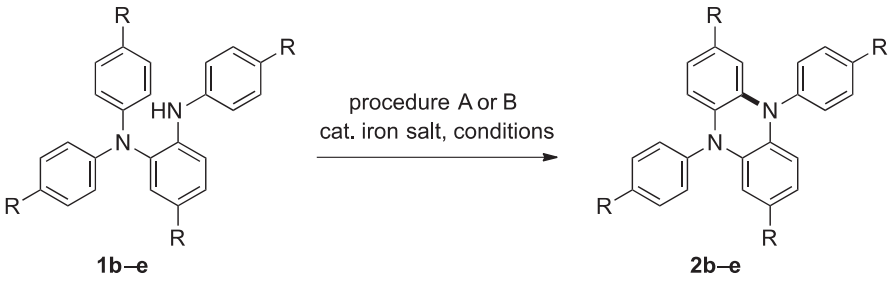
entry	procedure	iron salt (X mol%)	conditions	yield (%)[b]	recovery of **1a** (%)
1	A	$FeCl_3$ (5)	80 °C, 1 h	15	50
2	A	$FeBr_3$ (5)	80 °C, 1 h	19	67
3[c]	A	$FeBr_3$ (20)	80 °C, 1 h	21	54
4	B	$FeBr_3$ (5)	100 °C, 15 h	12	34
5	B	$FeCl_2$ (5)	100 °C, 15 h	11	70
6	B	$FeCl_2$ (20)	100 °C, 21 h	39	12

[a]Reactions were carried out on a 0.10 mmol scale except entry 3. [b]The yields were determined by GC analysis using undecane as an internal standard unless otherwise noted. [c]Reaction was carried out on a 2.00 mmol scale, and the isolated yield of **2a** is shown.

Diverse *o*-phenylenediamine substrates **1b**–**1e** were subjected to the ring-closing amination conditions (procedure A or B), and the results are summarized in Table 2. Under conditions of procedure B, the reaction of methyl substrate **1b** afforded 2,7-dimethyl-5,10-di-*p*-tolyl-5,10-dihydrophenazine (**2b**) in 39% yield (entry 1). Fluoro substrate **1c** showed high reactivity: the ring-closing reaction proceeded at 70 °C to afford a new compound, 2,7-difluoro-5,10-bis(4-fluorophenyl)-5,10-dihydrophenazine (**2c**), albeit in a low yield (20%) because the oligomerization of **1c** competed with the desired reaction (entry 2). The reaction of chloro substrate **1d** afforded 2,7-dichloro-5,10-bis(4-chlorophenyl)-5,10-dihydrophenazine (**2d**), in 27% yield under conditions of procedure B (entry 3). Under the reaction conditions, the dechlorination reaction was observed to compete with the C–H amination to some extent, making the isolation of the pure product difficult. Therefore, procedure A was applied to this reaction, and **2d** was obtained in 35% yield in an analytically pure form (entry 4).[14] Although procedure B did not work well with bromo substrate **1e**

because of the undesired debromination reaction, 2,7-dibromo-5,10-bis(4-bromophenyl)-5,10-dihydrophenazine (**2e**) was obtained in 22% yield using procedure A (entry 5).

Table 2. Synthesis of 2,7-Disubstituted 5,10-Diaryl-5,10-dihydrophenazines[a]

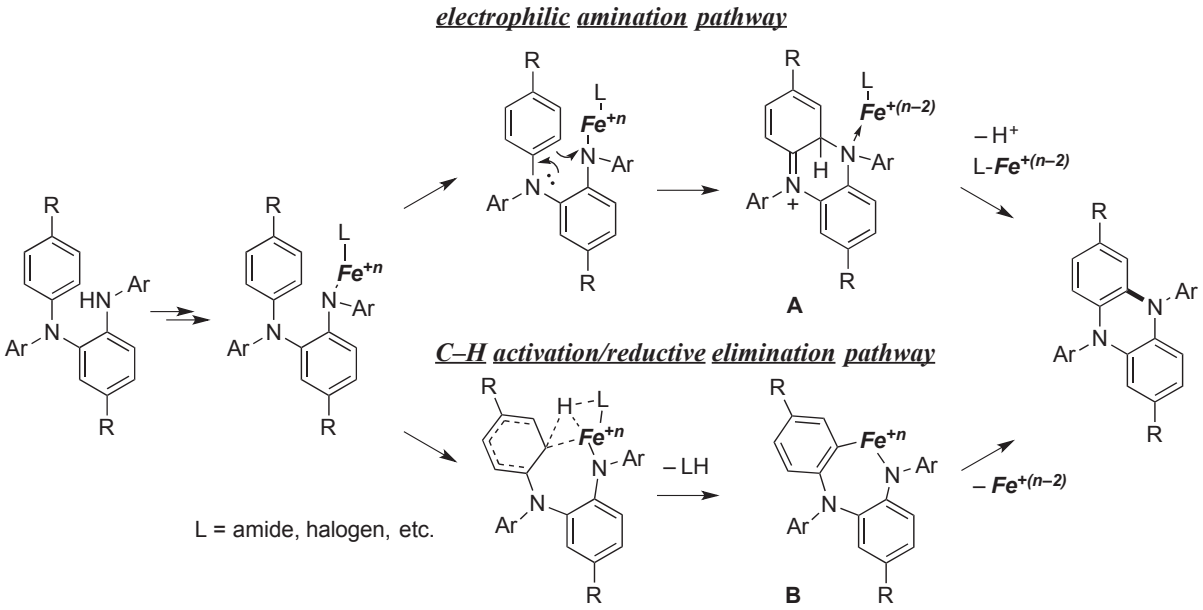


1b–e **2b–e**

entry	procedure	iron salt (X mol%)	conditions	product	yield (%)[b,c]
1	B	$FeCl_2$ (20 mol%)	100 °C, 15 h	**2b**: R = Me	39 (54)
2	B	$FeCl_2$ (20 mol%)	70 °C, 15 h	**2c**: R = F	20 (22)
3	B	$FeCl_2$ (20 mol%)	90 °C, 15 h	**2d**: R = Cl	27 (27)
4	A	$FeBr_3$ (5 mol%)	90 °C, 3 h	**2d**: R = Cl	35 (65)
5	A	$FeBr_3$ (5 mol%)	80 °C, 3 h	**2e**: R = Br	22[d] (38)

[a]Reactions were carried out on a 0.20 mmol scale except entry 2 (0.25 mmol scale). [b]Isolated yield. [c]Yields in parentheses are based on the consumption of the starting material. [d]93% GC purity. An unidentified compound (*ca.* 3%) and starting material (*ca.* 4%) are included.

Although the mechanism of the C–H amination reaction is unclear at present, presumably this reaction proceeds via the formation of an iron-amide species,[15] followed by C–H bond cleavage and C–N bond formation reactions. Scheme 2 shows two possible reaction pathways: (i) *electrophilic amination pathway* and (ii) *C–H activation/reductive elimination pathway*. In the former pathway, the electrophilic addition of the nitrogen of the iron-amide species to the neighboring arene ring (electrophilic amination)[16] generates a cationic intermediate **A**, which provides the dihydrophenazine product upon the release of the iron species and a proton. In the latter pathway, a C–H bond of the arene ring is activated by the iron catalyst to generate a ferracycle[17] by oxidative addition, or more probably by a concerted metalation–deprotonation mechanism,[18] followed by reductive elimination to afford the dihydrophenazine. The reduced iron species may undergo two-electron oxidation by 1,2-dibromoethane to regenerate the catalytically active high-valent iron species.



Scheme 2. Possible Pathways for C–H Amination

In summary, we developed a novel iron-catalyzed intramolecular ring-closing C–H amination of *o*-phenylenediamines. This reaction provides a facile access to diverse 5,10-diaryl-5,10-dihydrophenazines with the regioselective installation of methyl, fluoro, chloro, and bromo substituents at the 2,7-positions of phenazine core. Some of these products are amenable to further synthetic elaborations such as the extension of π-conjugation and introduction of additional amino groups or heteroatoms by standard cross-coupling reactions. Further study is underway to elucidate the mechanism of the reaction and to improve the reaction efficiency.

ACKNOWLEDGEMENTS

This research was supported by the Japan Society for the Promotion of Science (JSPS) through the "Funding Program for Next-Generation World-Leading Researchers (NEXT Program)," initiated by the Council for Science and Technology Policy (CSTP) and also supported in part by the Japan Science and Technology Agency (JST), the Core Research for Evolutional Science and Technology (CREST 1102545) Program, and MEXT program "Elements Strategy Initiative to Form Core Research Center." We are grateful to Tosoh Organic Chemical Co., Ltd., Nissan Chemical Industry Ltd., and JX Nippon Oil & Energy Corporation for financial support. The generous gift of CPME from Zeon Corporation is acknowledged. We also thank RIKEN for the provision of beam time in SPring-8 (BL14B2: 2013A1798; 2013B1855, BL27Su: 2013A1685; 2013B1115, and BL40XU: 2013B1736; 2014A1717). ^{1}H and ^{13}C NMR measurements (800 and 201 MHz, respectively) were supported by JURC at ICR, Kyoto University.

REFERENCES AND NOTES

1. (a) Y. Shirota, *J. Mater. Chem.*, 2000, **10**, 1; (b) Y. Shirota, *J. Mater. Chem.*, 2005, **15**, 75; (c) Z. Ning and H. Tian, *Chem. Commun.*, 2009, 5483; (d) L. Duan, L. Hou, T.-W. Lee, J. Qiao, D. Zhang, G. Dong, L. Wang, and Y. Qiu, *J. Mater. Chem.*, 2010, **20**, 6392.
2. (a) A. W. Schmidt, K. R. Reddy, and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193; (b) C. Sánchez, C. Méndez, and J. A. Salas, *Nat. Prod. Rep.*, 2006, **23**, 1007.
3. E. Terada, T. Okamoto, K. Sato, T. Takui, and K. Okada, *J. Org. Chem.*, 2005, **70**, 10073.
4. H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.*, 1957, **79**, 6178.
5. (a) J. Paradies, in *Metal-Catalyzed Cross-Coupling Reactions and More*, ed. by A. de Meijere, S. Bräse, and M. Oestreich, Wiley-VCH, Weinheim, 2014, pp. 995–1066; (b) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27; (c) J. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534.
6. T. Okamoto, E. Terada, M. Kozaki, M. Uchida, S. Kikukawa, and K. Okada, *Org. Lett.*, 2003, **5**, 373.
7. (a) A. Wohl and A. Aue, *Chem. Ber.*, 1901, **34**, 2442; (b) U. Bahnmüller, W. Keller-Schierlein, M. Brandl, H. Zähner, and H. Diddens, *J. Antibiot.,* 1988, **41***,* 1552; (c) Z. Wong, in *Comprehensive Organic Name Reactions and Reagents*, John Willey & Sons, Inc. 2009, pp. 3060–3063.
8. F. A. Neugebauer and H. Fischer, *Chem. Ber.*, 1971, **104**, 886 and references cited therein.
9. For synthesis of phenazines, see: (a) T. Emoto, N. Kubozaki, Y. Yamagiwa, and T. Kamikawa, *Tetrahedron Lett.*, 2000, **41**, 355; (b) M. Tietze, A. Iglesias, E. Merisor, J. Conrad, I. Klaiber, and U. Beifuss, *Org. Lett.*, 2005, **7**, 1549; (c) L. Yu, Z. Zhou, D. Wu, and H. Xiang, *J. Organomet. Chem.*, 2012, **705**, 75; For synthesis of 5,10-dihydrophenazine, see: (d) Z. Hu, W. Ye, H. Zou, and Y. Yu, *Synth. Commun.*, 2010, **40**, 222.
10. For reviews, see: (a) M.-L. Louillat and F. W. Patureau, *Chem. Soc. Rev.*, 2014, **43**, 901; (b) B. J. Stokes and T. G. Driver, *Eur. J. Org. Chem.*, 2011, 4071.
11. For carbazoles, see: (a) W. C. P. Tsang, N. Zheng, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560; (b) G. Brasche and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 1932; (c) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7603; (d) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck, and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 16184; (e) S. H. Cho, J. Yoon, and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 5996; (f) K. Takamatsu, K. Hirano, T. Satoh, and M. Miura, *Org. Lett.*, 2014, **16**, 2892; For quinolinones, see: (g) K. Inamoto, T. Saito, K. Hiroya, and T. Doi, *J. Org. Chem.*, 2010, **75**, 3900; For imidazoles, see: (h) H. Wang, Y. Wang, C. Peng, J. Zhang, and Q. Zhu, *J. Am. Chem. Soc.*, 2010, **132**, 13217; (i) X. Wang, Y. Jin, Y. Zhao, L. Zhu, and H. Fu, *Org. Lett.*, 2012, **14**, 452; For indoles, see: (j) S. Jana, M. D. Clements, B. K. Sharp, and N. Zheng, *Org. Lett.*, 2010, **12**, 3736; (k) Y. Tan and J. F. Hartwig, *J. Am.*

Chem. Soc., 2010, **132**, 3676.

12. The oxidation of electron-rich N^1,N^1,N^2-triaryl-*o*-phenylenediamines by a stoichiometric amount of $FeCl_3$ was reported to afford the corresponding 5,10-diaryl-5,10-dihydrophenazines via the formation of the overoxidized radical cation of the product. See ref 8.
13. T. Hatakeyama, R. Imayoshi, Y. Yoshimoto, S. K. Ghorai, M. Jin, H. Takaya, K. Norisuye, Y. Sohrin, and M. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 20262.
14. A representative procedure (Method A): A solution of BuMgBr in Bu_2O (275 μL, 0.799 M, 0.220 mmol) was added to a solution of **1d** (95.3 mg, 0.202 mmol) in Bu_2O (1.0 mL) at 0 °C. After stirring the mixture at 100 °C for 1 h, $FeBr_3$ (3.0 mg, 10 μmol) and 1,2-dibromoethane (75.8 mg, 0.403 mmol) were added to the resulting solution of magnesium amide at room temperature. The mixture was stirred at 90 °C for 3 h and quenched with 1 N aqueous HCl (0.4 mL) at room temperature. The aqueous layer was extracted with toluene four times. The combined organic extracts were filtered with a pad of Florisil, and then the solvent was removed *in vacuo* to obtain the crude product (104 mg). A part of the crude product (96.2 mg) was purified by recycling GPC affording **2d** as a yellow powder (31.3 mg, 35% yield based on the amount of the purified crude product, 65% yield based on the consumption of **1d**, >98% purity on GC analysis). IR (neat): ν cm^{-1} 1481, 1416, 1356, 1323, 1285, 1270, 1258, 1089, 965, 940, 842, 828, 795, 786, 724; mp 303.4–304.5 °C; ^{1}H NMR (C_6D_6, 392 MHz) δ ppm 5.34 (d, J = 8.5, 2H), 5.79 (d, J = 2.2 Hz, 2H), 6.28 (dd, J = 2.2 Hz, 8.5 Hz, 2H), 6.60 (m, 4H), 6.97 (m, 4H); ^{13}C NMR (C_6D_6, 98.5 MHz) δ ppm 113.04 (2C), 114.01 (2C), 121.08 (2C), 127.38 (2C), 132.13 (4C), 132.21 (4C), 134.72 (2C), 134.73 (2C), 137.45 (2C), 137.49 (2C); HRMS (FAB) Calcd for $C_{24}H_{14}Cl_4N_2$ $[M]^+$: 469.9911. Found: 469.9911; Anal. Calcd for $C_{24}H_{14}Cl_4N_2$: C, 61.05; H, 2.99; N, 5.93. Found: C, 61.15; H, 3.04; N, 5.85.
15. M. M. Olmstead, P. P. Power, and S. C. Shoner, *Inorg. Chem.*, 1991, **30**, 2547. See also ref. 13.
16. L. A. Paquette, *J. Am. Chem. Soc.*, 1963, **85**, 3288.
17. T. Matsubara, S. Asako, L. Ilies, and E. Nakamura, *J. Am. Chem. Soc.*, 2014, **136**, 646.
18. D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118.