[Fe(F_{20}TPP)Cl] catalyzed intramolecular C–N bond formation for alkaloid synthesis using aryl azides as nitrogen source†

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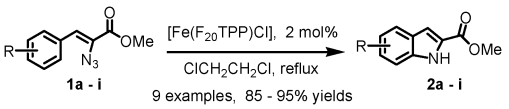
The syntheses of alkaloids including indoles, indolines, tetrahydroquinolines, dihydroquinazolinones and quinazolinones have been accomplished in moderate to excellent yields *via* [Fe(F_{20}TPP)Cl] catalyzed intramolecular C–N bond formation using aryl azides as nitrogen source.

Transition metal mediated nitrene insertion into sp^2 and sp^3 C–H bonds is an appealing methodology for C–N bond formation,[1] and a number of metal catalysts such as those of Mn, Ru, Co, Cu, Ag and Au have been reported to display potent activity toward this type of C–N bond formation reactions.[2,3] An important development in this endeavour is the introduction of dirhodium(II, II) complexes as catalysts.[4] However, due to the low natural abundance of rhodium on earth, there is a surge of interest to develop inexpensive and biocompatible metal complexes as alternatives to dirhodium(II, II) catalysts.

Alkaloids are a family of nitrogen atom containing natural products with active pharmaceutical properties.[5] Nitrene transfer and insertion reactions for the formation of C–N bonds can be used for preparing alkaloids. For example, Du Bois and co-workers reported the synthesis of (−)-tetrodotoxin through intramolecular nitrene insertion into C–H bonds catalyzed by dirhodium(II, II) complex.[4a] Driver and co-workers reported the preparation of indole and indoline compounds using rhodium and iridium complexes as catalysts.[6] Recently, there has been a growing interest in developing iron catalysts for the construction of C–N bonds.[7]

In recent work, we found that [Fe(F_{20}TPP)Cl] (H_2F_{20}TPP = *meso*-tetrakis(pentafluorophenyl)porphyrin) is an effective catalyst for aziridination of alkenes, sulfimidation of both alkyl and aryl sulfides, allylic amination of α-methyl styrenes and amination of saturated C–H bonds using sulfonyl and aryl azides as the nitrogen source.[8] Herein we report that [Fe(F_{20}TPP)Cl] is an effective catalyst for preparing alkaloids including indoles, indolines, tetrahydroquinolines, dihydroquinazolinones and quinazolinones *via* intramolecular amination of sp^2 and sp^3 C–H bonds with aryl azides as the nitrogen source.

At the outset, indole formation was selected as the model reaction (Scheme 1). With [Fe(F_{20}TPP)Cl] as catalyst, substituted methyl α-azido-cinnamates **1** including the ones with electron-withdrawing or electron-donating substituents gave indoles **2** in 85–95% yields (9 examples, see the Supporting Information) and with complete azide consumption. The results



Scheme 1 Indole formation catalyzed by [Fe(F_{20}TPP)Cl].

are comparable to those reported by Driver wherein dirhodium(II, II) catalyst was employed.[6a] On the other hand, the indole moiety can also be formed by insertion of aryl nitrene into the α-position of cinnamates (Table 1). With [Fe(F_{20}TPP)Cl] as catalyst, all of the *ortho*-azido-cinnamates **3** gave the corresponding indoles **2** in 86–91% yields (7 examples) and with complete azide consumption.

Next, the syntheses of indolines **8**, **10** and tetrahydroquinolines **9**, **11** *via* direct amination of saturated benzylic C–H bonds were studied (Table 2). With [Fe(F_{20}TPP)Cl] as catalyst, all of these four substrates **4a**, **4b** and **5a**, **5b** gave the corresponding indolines **8** and tetrahydroquinolines **9** in good yields and with complete azide consumption (Table 2, entries 1–4). However, when compounds **6a** and **6b** were used as the substrates, 2-phenyl indoles **12a** and **12b** were obtained (entries 5, 6). Even after protection of the OH group by methylation, compound **6c** still gave 2-phenyl indole (**12a**) as the major product (entry 7). Compound **6d** gave 3-methoxy indoline **10d** (*cis* : *trans* = 1 : 0.58) in 75% yield with complete azide consumption (entry 8). Interestingly, the OH group in compounds **7a–7d** could tolerate the reaction conditions and 2-phenyl-3-hydroxy tetrahydroquinolines **11a–11d** were obtained in good yields with moderate diastereoselectivities (entries 9–12).

The syntheses of dihydroquinazolinones **14** (63–83% yields) were achieved from *ortho*-azidobenzamide derivatives **13** *via* direct amination of saturated C–H bonds (Table 3). With [Fe(F_{20}TPP)Cl] as catalyst, amination of benzylic C–H bonds of dibenzyl amine **13a** and isoindoline **13b** gave the corresponding dihydroquinazolinones **14a** and **14b** in good yields (Table 3, entries 1, 2). Amination of tetrahydroisoquinoline **13c** (Table 3, entry 3) gave **14c** in moderate yield and quinazolinone **15c** was detected as a minor product. Importantly, the intramolecular amination at the 2° C–H bonds of piperidine **13d**, pyrrolidine **13e**, and diethyl amine **13f** have been accomplished to give dihydroquinazolinones **14d–f** in moderate yields with quinazolinones **15d–f** as the minor products, respectively (Table 3, entries 4–6). Even the insertion at 1° C–H bonds of dimethylamine **13g** could proceed to give **14g** in moderate yield with **15g** as a minor product (Table 3, entry 7). Amination at the 3° C–H bonds of isopropylamine **13h** proceeded smoothly to give the product **14h** in 71% yield (Table 3, entry 8).

The amination of sp^2 C–H bonds catalyzed by [Fe(F_{20}TPP)Cl] (Scheme 1 and Table 1) possibly involves

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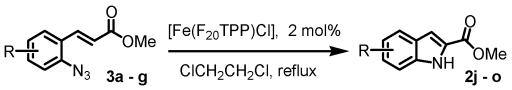
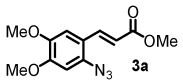
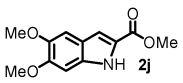
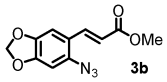
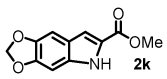
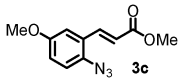
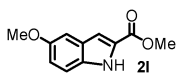
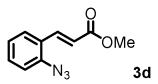
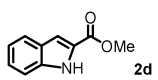
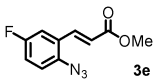
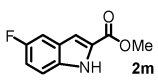
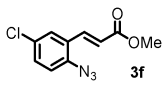
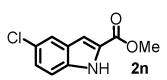
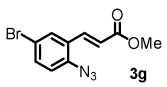
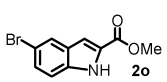
† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. See DOI: 10.1039/c0cc01825b

Table 1 Indole formation catalyzed by [Fe(F_{20}TPP)Cl][a]



Entry	Substrate	Product	Time/h	Yield (%)[b]
1	 3a	 2j	16	86
2	 3b	 2k	18	89
3	 3c	 2l	18	88
4	 3d	 2d	24	89
5	 3e	 2m	24	91
6	 3f	 2n	24	90
7	 3g	 2o	24	89

[a] All reactions were performed with 0.20 mmol azide, 0.004 mmol [Fe(F_{20}TPP)Cl], and 60 mg 4 Å molecular sieves in 1 mL of anhydrous $ClCH_2CH_2Cl$ under N_2. [b] Isolated yield.

iron-nitrene/imido intermediates and might proceed through mechanisms analogous to those proposed by Driver and co-workers for dirhodium-catalyzed analogues.[6a,b] For [Fe(F_{20}TPP)Cl] catalyzed amination of sp^3 C–H bonds (Tables 2 and 3), a hydrogen atom abstraction mechanism[3m,9] is proposed (Scheme 2, using substrate **6d** as an example). Firstly, [Fe(F_{20}TPP)Cl] catalyzes the decomposition of aryl azide to give an iron-nitrene/imido complex **A**.[10] Then, a benzyl radical intermediate **B** could be generated by an intramolecular hydrogen atom abstraction pathway. Formation of the C–N bond is accomplished after the proposed benzyl radical intermediate undergoes collapse and rotation/collapse processes to give a mixture of *cis*- and *trans*-isomer **10d** (*cis* : *trans* = 1 : 0.58). In addition, a mixture of *cis*- and *trans*-**10a** was isolated in a ratio of ~1 : 1 in the course of the reaction when **6a** was employed as the substrate (Scheme 3). But compound **10a** is unstable and is converted to **12a** under the reaction conditions.

In summary, the commercially-available and air-stable [Fe(F_{20}TPP)Cl] complex is an effective catalyst for preparing indoles, indolines, tetrahydroquinolines, dihydroquinazolinones and quinazolinones *via* intramolecular amination of sp^2 and sp^3 C–H bonds with aryl azides as the nitrogen source.

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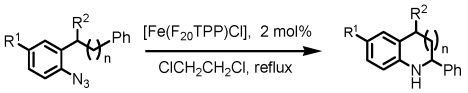
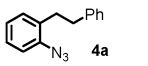
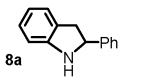
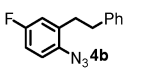
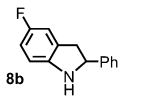
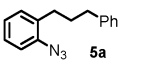
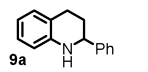
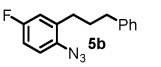
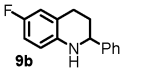
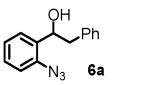
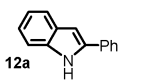
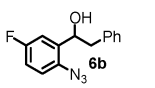
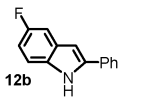
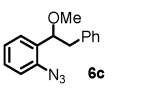
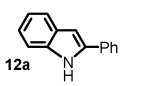
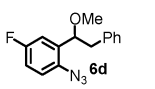
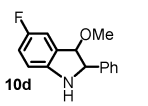
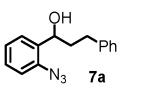
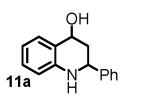
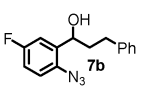
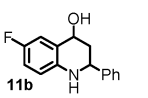
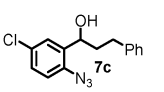
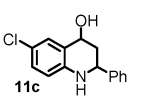
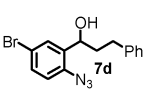
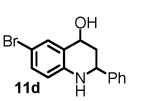
Table 2 Indoline and tetrahydroquinoline formation catalyzed by [Fe(F_{20}TPP)Cl][a]

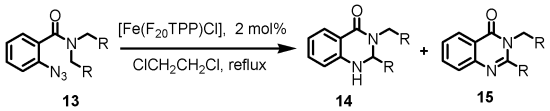


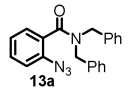
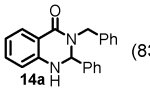
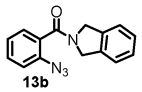
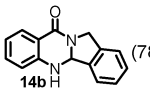
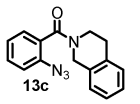
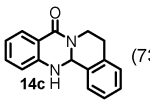
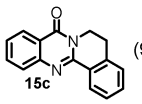
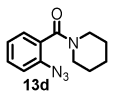
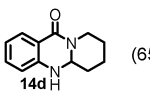
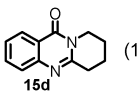
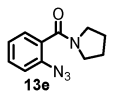
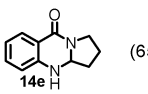
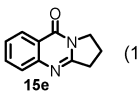
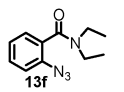
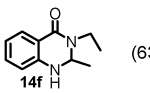
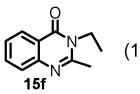
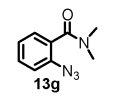
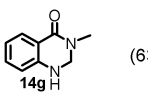
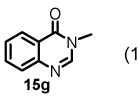
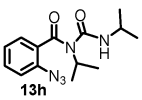
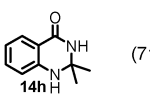
4 R^2 = H, n = 1 **6** R^2 = OH, n = 1 **8** R^2 = H, n = 0 **10** R^2 = OH, n = 0
5 R^2 = H, n = 2 **7** R^2 = OH, n = 2 **9** R^2 = H, n = 1 **11** R^2 = OH, n = 1

Entry	Substrate	Product	Time/h	Yield (%)[b]
1	 4a	 8a	14	80
2	 4b	 8b	14	82
3	 5a	 9a	14	79
4	 5b	 9b	14	81
5	 6a	 12a	15	74
6	 6b	 12b	15	78
7	 6c	 12a	18	76
8	 6d	 10d	18	75[c]
9	 7a	 11a	16	72[d]
10	 7b	 11b	16	79[e]
11	 7c	 11c	18	75[f]
12	 7d	 11d	20	73[g]

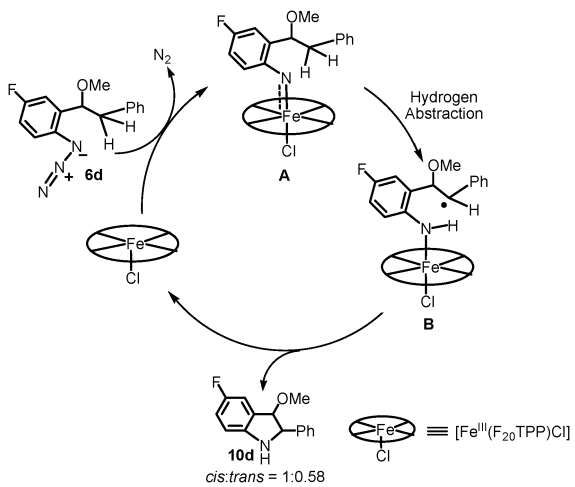
[a] All reactions were performed with 0.20 mmol azide, 0.004 mmol [Fe(F_{20}TPP)Cl], and 60 mg 4 Å molecular sieves in 1 mL of anhydrous $ClCH_2CH_2Cl$ under N_2. [b] Isolated yield. [c] *cis* : *trans* = 1 : 0.58. [d] *dr* = 1 : 0.38. [e] *dr* = 1 : 0.24. [f] *dr* = 1 : 0.29. [g] *dr* = 1 : 0.35.

Table 3 Dihydroquinazolinone and quinazolinone formation catalyzed by [Fe(F_{20}TPP)Cl][a]

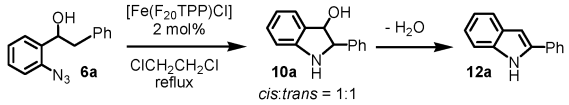


Entry	Substrate	Time/h	**14** (yield %)[b]	**15** (yield %)[b]
1		18	 (83)	—
2		18	 (78)	—
3		18	 (73)	 (9)
4		24	 (65)	 (16)
5		24	 (65)	 (14)
6		24	 (63)	 (17)
7		24	 (63)	 (13)
8		30	 (71)	—

[a] All reactions were performed with 0.20 mmol azide, 0.004 mmol [Fe(F_{20}TPP)Cl], and 60 mg 4 Å molecular sieves in 1 mL of anhydrous $ClCH_2CH_2Cl$ under N_2. [b] Isolated yield.



Scheme 2 Possible pathway of C–N bond formation.



Scheme 3 Formation of 2-phenylindolin-3-ol (**10a**).

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