Efficient Intramolecular C–H Insertion Catalyzed by Iridium Porphyrin Complexes

Cristóbal López-Sánchez, Míriam Álvarez-Corral, Manuel Muñoz-Dorado, Ignacio Rodríguez-García*

Department of Organic Chemistry, University of Almería, 04120 Almería, Spain
Fax +34(950)015481; E-mail: irodrigu@ual.es

Received: 10.05.2012; Accepted after revision: 23.08.2012

Abstract: Octaethylporphyrin and tetraphenylporphyrin Ir(I) and Ir(III) complexes are useful catalysts for intramolecular C–H insertion processes of stabilized diazo compounds. While the Ir(I) complex TPP[Ir(CO)$_3$]$_2$ is the most efficient and selective catalyst, the others afford mixtures of cyclization and dimerization products. The effect of the solvent polarity on the selectivity of the reaction is also presented.

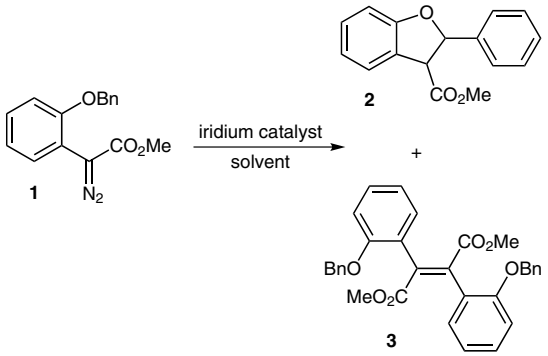
Key words: iridium complexes, porphyrins, diazo compounds, carbene complexes, intramolecular C–H insertion

Iridium complexes are excellent catalysts for a large group of reactions in organic synthesis, like hydrogenation processes,[1–3] oxidations,[4] allylic substitutions and related reactions,[5–7] cycloadditions and cycloisomerizations,[8] alkylations and carbonylations,[9] aldol condensations,[10] and cross-coupling reactions.[11] The intramolecular C–H insertion processes are among the best ways to form new C–C bonds in cyclization processes.[12] The C_{sp}^3–H insertion by carbenoid transfer reaction is a useful tool in organic synthesis[13,14] because it is an atom efficient catalytic method, which usually offers high yields and has a potential asymmetric version. Excellent applications have been described, based on the use of rhodium,[15–17] ruthenium,[18] silver,[19–21] iron,[22,23] copper[21] and gold[24] complexes. The mechanism of the C–H insertion process by treatment of diazo compounds with rhodium complexes has been studied.[25] Recently, iridium complexes have also proved to be able to convert diazo compounds into useful carbenoids. Thus, iridium(III)–salen complexes have been used by Katsuki and co-workers in intermolecular C_{sp}^3–H[26] and Si–H[27] insertions by decomposition of α-diazoacetates, and for the intramolecular benzylic amination through insertion of nitrenes into C–H bonds.[28]

The use of porphyrins as ligands in transition metal complexes has emerged as a new source of metal catalysts for C_{sp}^3–H insertion reactions through carbenoids prepared from diazo reagents.[22,23,29–31] The intramolecular version of these reactions is useful for the preparation of carbo- and heterocycles which are frequently found as the core part of important bioactive natural products. Furthermore, although the activation of C–H bonds by iridium(I) complexes have been extensively studied,[32–40] as well as the intermolecular carbene insertion to C–H by a chiral iridium(III) porphyrin complex,[41] there are no examples on the use of iridium porphyrins, or related complexes, for this type of cyclization. In addition, the use of iridium complexes can be competitive towards rhodium complexes due to its lower price, and also has a potential in green chemistry if water-soluble iridium porphyrins[42,43] could be developed as catalysts.

In this study, we report a convenient strategy to obtain oxygenated five-membered rings through intramolecular C–H insertion reaction using diazo compounds as starting materials and iridium catalysts. We present also a comparative study of Ir(I) towards Ir(III) in this cyclization process. The method can be used for the preparation of the dihydrobenzo[*b*]furan moiety present in numerous natural products.

In our initial studies, we explored the reaction of 2-(2-benzyloxyphenyl)-2-diazoacetate (**1**)[44,45] with several commercial iridium catalysts (Table 1, Scheme 1).[46]



Scheme 1 Preparation of dihydrobenzo[*b*]furan **2** and dimer **3** from diazoacetate **1**

Table 1 C–H Insertion with Several Commercial Iridium Catalysts

Entry	Catalyst	Ir	Solvent	Product	Yield (%)
1	$Ir_4(CO)_{12}$	0	toluene[a]	degradation	–
2	$Ir_4(CO)_{12}$	0	THF[a]	degradation	–
3	$[Ir(CO)_3Cl]_2$	I	toluene[a]	**3**	17
4	$[Ir(CO)_3Cl]_2$	I	THF[a]	**3**	46
5	$[Ir(cod)Cl]_2$	I	THF[a]	**2** + **3**	21 (**2**) 42 (**3**)
6	$Ir(acac)_3$	III	THF[a]	s.m.[c]	–
7	$Ir(acac)_3$	III	toluene[b]	**2**	30

[a] The reaction was performed at room temperature.
[b] The reaction was carried out at reflux.
[c] The starting material was recovered.

SYNLETT 2012, 23, 2469–2472
Advanced online publication: 21.09.2012
DOI: 10.1055/s-0032-1317296; Art ID: ST-2012-D0406-L

While the iridium(0) complex gave no results (entries 1 and 2), all the iridium(I) complexes gave the dimerization product **3** (entries 3–5).[47] In addition, $[Ir(cod)Cl]_2$ gave also the desired cyclization product, the 2,3-dihydrobenzo[*b*]furan **2**,[45] although as the minor component of a mixture with the dimer **3**. Moreover, although the iridium(III) complex $Ir(acac)_3$ did not promote any reaction at room temperature in any solvent, when the conditions were forced (refluxing toluene; Table 1, entry 7) the cyclized product was formed, although in poor yields. These results prompted us to prepare new iridium complexes to study their ability to promote this intramolecular $C_{sp}{}^3$–H insertion reaction. Complexes presented in Figure 1 were prepared[48] and spectroscopically characterized.[49] ^{14}N NMR was measured in all the porphyrin complexes. A significant shielding is observed when compared with the free porphyrin (i.e. δ = 265.90 ppm in $TPPH_2$ vs. δ = 264.08 ppm in **5**). Thus, the iridium porphyrins complexes **4**–**7** were obtained using the methodology reported by Yoshida et al.[50,51] while the iridium (III)–salen complex **8** was prepared following a Schrock[52] modified procedure.[53]

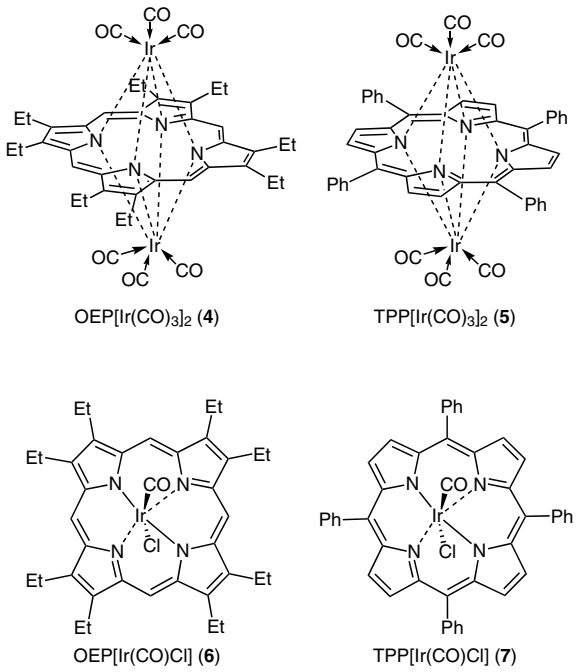


Figure 1 Iridium–porphyrin complexes

With all these complexes in hand, we could check their ability to catalyze the intramolecular C–H insertion reaction from compound **1**, under the reaction conditions shown in Table 2.

The octaethylporphyrin tricarbonyl iridium(I) complex (**4**) did not promote the reaction at room temperature, but at 40 °C (Table 2, entry 2) gave, in almost quantitative yield, both isomers of the cyclized product **2**, with the *trans* diastereomer being the major one. A small amount of the dimer **3** was also formed. To our delight, the other prepared Ir(I) complex, tetraphenylporphyrin tricarbonyl iridium(I) (**5**) gave exclusively the cyclized product in a fast and clean reaction, which can be completed in few minutes even at low temperatures (Table 2, entry 5). However, with this catalyst, no diastereoselectivity was observed, as the *cis*/*trans* ratio was 50:50, possibly due to the fact that its high catalytic activity makes the energy profiles of both pathways very similar and advantageous towards the intermolecular dimerization. The Ir(III) porphyrin complexes **6** and **7** proved to have a lower catalytic ability, needing higher temperatures and longer reaction times. In addition, mixtures of cyclized product **2** and dimer **3** were formed (Table 2, entries 6–10). Finally, the Ir(III)–salen complex also promoted the cyclization at room temperature, although with low conversion rates even with long reaction times, resulting in reduced yields by formation of decomposition side products (entry 11). High temperatures and long reaction times increased the conversion degree, but in this case, dimerization was also observed (Table 2, entries 12–14).

Table 2 C–H Insertion in Compound **1** with Iridium Porphyrins and Salen Complexes[a]

Entry	Complex	Temp (°C)	Time	Ratio **2**/**3**	Yield (%)[b]	dr of **2** (*cis*/*trans*)
1	$OEP[Ir(CO)_3]_2$	25	1 h	–	–	–
2		40	5 h	98:2	95	30:70
3	$TPP[Ir(CO)_3]_2$	25	0.5 h	100:0	98	50:50
4		0	1 h	100:0	98	50:50
5		–50	1 h	100:0	98	50:50
6	OEP[Ir(CO)Cl]	25	1 h	–	–	–
7		40	5 h	89:11	85	30:70
8	TPP[Ir(CO)Cl]	25	–	–	–	–
9		40	117 h	52:48	46	58:42
10		50	27 h	40:60	40	67:33
11	Ir[salen][toluene]	25	20 h	100:0	12	50:50
12		40	4 d	50:50	26	50:50
13		50	2 d	55:45	40	50:50
14		60	31 h	52:48	52	50:50

[a] Reaction solvent was THF.
[b] Yields are for isolated products after column chromatography.

The influence of the solvent was also studied using complex **5** (Table 3). While less polar solvents afforded only the cyclized product in excellent yield (entries 1–3), more polar solvents promoted also the formation of the dimer **3**. In DMSO, the dimerization product was formed exclusively. These results suggest that the reaction transition state leading to the cyclized product is much less polar than the transition state leading to the dimer. It is worth mentioning that, in contrast to the previously reported iridium complexes catalyzed C–H activation reactions,[26]

no intermolecular solvent reaction products were detected (like C–H insertion with THF or addition to toluene).

Table 3 C–H Insertion with TPP[Ir(CO)$_3$]$_2$ (**5**) with Different Solvents and Temperatures

Entry	Solvent	T (°C)	Time	**2**/**3**	Yield (%)	dr of **2** (*cis*/*trans*)
1	toluene	25	30 min	100:0	99	54:45
2	CH_2Cl_2	25	45 min	100:0	97	38:61
3	THF	25	60 min	100:0	98	50:50
4	$CHCl_3$	45	3 d	60:40	97	33:67
5	MeCN	70	5 d	50:50	98	50:50
6	DMSO	65	7 d	0:100	99	–

In conclusion, the use of iridium porphyrins, mainly the Ir(I) complex TPP[Ir(CO)$_3$]$_2$, has proved to be a convenient approach to synthesize dihydrobenzo[*b*]furans through intramolecular C_{sp^3}–H insertion in high yields. No intermolecular C–H insertion with the solvent was observed. No derivatives of the porphyrin nucleus due to reaction with carbenoids were formed. The oxidation state, the nature of side ligands and the stereoelectronic nature of the porphyrin have a strong influence on the catalytic activity. The reactions with the tetraphenylporphyrin complex **5** were faster than those with the other complexes used. We are currently exploring the preparation of chiral porphyrin ligands to be used in the asymmetric version of the reaction. A water-soluble porphyrin complex is also being explored.

Acknowledgment

We wish to acknowledge the Spanish Ministerio de Ciencia e Innovación for financial support (Project CTQ2010-17115), and the Universidad de Almería for a scholarship to C. López-Sánchez.

References

(1) Sakaguchi, S.; Yamaga, T.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 4710.
(2) Tani, K.; Iseki, A.; Yamagata, T. *Chem. Commun.* **1999**, 1821.
(3) Malacea, R.; Poli, R.; Manoury, E. *Coord. Chem. Rev.* **2010**, *254*, 729.
(4) Tejel, C.; Ciriano, M. A. In *Organometallic Oxidation Catalysis*, 22 ed., Meyer, F.; Limberg, C., Eds.; Springer: Berlin, **2007**, 97.
(5) Helmchen, G.; Dahnz, A.; Duebon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.
(6) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349.
(7) Teichert, J. F.; Fananas-Mastral, M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 688.
(8) Kezuka, S.; Okado, T.; Niou, E.; Takeuchi, R. *Org. Lett.* **2005**, *7*, 1711.
(9) Fujihara, T.; Iwai, T.; Terao, J.; Tsuji, Y. *Synlett* **2010**, 2537.
(10) Onodera, G.; Toeda, T.; Toda, N. N.; Shibagishi, D.; Takeuchi, R. *Tetrahedron* **2010**, *66*, 9021.
(11) Kuninobu, Y.; Asanoma, D.; Takai, K. *Synlett* **2010**, 2883.
(12) Davies, H. M. L.; Manning, J. R. *Nature (London)* **2008**, *451*, 417.
(13) Slattery, C. N.; Ford, A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 6681.
(14) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.
(15) Davies, H. M. L.; Loe, O. *Synthesis* **2004**, 2595.
(16) Davies, H. M. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6422.
(17) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
(18) Grohmann, M.; Maas, G. *Tetrahedron* **2007**, *63*, 12172.
(19) Davies, H. M. L.; Thompson, J. L. *Abstracts of Papers*, 229th ACS National Meeting, San Diego, USA, March 13-17, **2005**; Abstract ORGN-089
(20) Lovely, C. J. In *Silver in Organic Chemistry*; Harmata, M., Ed.; John Wiley & Sons: New York, **2010**, 229.
(21) Liu, X. J.; Hamilton, I. P.; Han, K. L.; Tang, Z. C. *Phys. Chem. Chem. Phys.* **2010**, *12*, 10602.
(22) Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008**, *27*, 637.
(23) Mbuvi, H. M.; Woo, L. K. *J. Porphyrins Phthalocyanines* **2009**, *13*, 136.
(24) Fructos, M. R.; Belderrain, T. R.; de Fremont, P.; Scott, N. M.; Nolan, S. P.; Diaz-Requejo, M. M.; Perez, P. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 5284.
(25) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555.
(26) Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 14218.
(27) Yasutomi, Y.; Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 4510.
(28) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 9884.
(29) Zhou, C. Y.; Huang, J. S.; Che, C. M. *Synlett* **2010**, 2681.
(30) Thu, H. Y.; Tong, G. S.-M.; Huang, J. S.; Chan, S. L.-F.; Deng, Q. H.; Che, C. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 9747.
(31) Callot, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321.
(32) Cheung, C. W.; Chan, K. S. *Organometallics* **2008**, *27*, 3043.
(33) Hoyano, J. K.; Graham, W. A. G. *J. Am. Chem. Soc.* **1982**, *104*, 3723.
(34) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1982**, *104*, 352.
(35) Hoyano, J. K.; McMaster, A. D.; Graham, W. A. G. *J. Am. Chem. Soc.* **1983**, *105*, 7190.
(36) Bianchini, C.; Masi, D.; Meli, A.; Peruzzini, M.; Sabat, M.; Zanobini, F. *Organometallics* **1986**, *5*, 2557.
(37) Viciano, M.; Poyatos, M.; Sanau, M.; Peris, E.; Rossin, A.; Ujaque, G.; Lledos, A. *Organometallics* **2006**, *25*, 1120.
(38) Feller, M.; Karton, A.; Leitus, G.; Martin, J. M. L.; Milstein, D. *J. Am. Chem. Soc.* **2006**, *128*, 12400.
(39) Conejero, S.; Paneque, M.; Poveda, M. L.; Santos, L. L.; Carmona, E. *Acc. Chem. Res.* **2010**, *43*, 572.
(40) Del Rossi, K. J.; Zhang, X. X.; Wayland, B. B. *J. Organomet. Chem.* **1995**, *504*, 47.
(41) Wang, J. C.; Xu, Z. J.; Guo, Z.; Deng, Q. H.; Zhou, C. Y.; Wan, X. L.; Che, C. M. *Chem. Commun.* **2012**, *48*, 4299.
(42) Kanemitsu, H.; Harada, R.; Ogo, S. *Chem. Commun.* **2010**, *46*, 3083.
(43) Bhagan, S.; Wayland, B. B. *Inorg. Chem.* **2011**, *50*, 11011.
(44) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(45) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.
(46) **Procedure for Intramolecular C_{sp^3}–H Insertion Reaction**: The catalyst (5% mmol) was added to a solution of diazo compound **1** (0.2 mmol) in anhyd solvent (10

mL/mmol) under a nitrogen atmosphere. The reaction was monitored by TLC until completion. Next, the solvent was removed at reduced pressure and the residue was chromatographed (SiO_2), eluting with a mixture of hexane–Et_2O (98:2). Compounds **2** and **3** were obtained in different relations and yields (see Table 1).

(47) Spectroscopic Data of Dimethyl 2,3-Bis[2-(benzyloxy)-phenyl]maleate (**3**): IR(film): 1010, 1110, 1273, 1595, 1664, 1737, 2851, 2920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.35 (s, 3 H, CO_2Me), 5.11 (s, 2 H, OCH_2Ph), 7.08 (m, 2 H, H6, H4), 7.55 (m, 5 H, H2′–H6′), 7.61 (dt, ^3J = 7.5 Hz, ^4J = 1.9 Hz, 1 H, H5), 7.93 (dd, ^3J = 7.8 Hz, ^4J = 1.9 Hz, 1 H, H3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.84 (Me, CO_2Me), 71.18 (OCH_2Ph), 112.65 (CH, C6), 121.43 (CH, C4), 122.68 (C, C2), 128.47–128.66 (CH, C2′,C3′,C4′), 130.91 (CH, C3), 133.98 (C, C=C), 135.10 (C, C1′), 136.32 (CH, C5), 159.41 (C, C1), 165.41 (CO_2Me).

(48) **Representative Procedure of the Synthesis of Iridium Porphyrin Complexes**:[50] A mixture of $(TPP)H_2$ (39 mg, 0.06 mmol) and $[Ir(CO)_3Cl]_2$ (20 mg, 0.06 mmol) in xylene (3 mL) was stirred at reflux temperature for 15 h under a N_2 atmosphere. The resulting solution was evaporated at reduced pressure and the residue was chromatographed on a silica gel column with several solvent mixtures to afford three fractions. The first one (hexane–Et_2O, 9:1), was non-reacted tetraphenylporphyrin, which could be recycled. The second fraction (toluene–acetone, 3:1) was a brown-red solid, and the third fraction a purple solid. This was recrystallized in EtOH to afford the iridium(III) complex **7**. The second fraction (brown-red solid) was recromatographed with different mixtures of toluene and acetone (100:0, 95:5, 8:2, 6:4 and 1:1) affording a red solid which was identified as the iridium(I) complex **5**.

(49) Spectroscopic data of $OEP[Ir(CO)_3]_2$ (**4**) have been described previously.[50] ^{14}N NMR (36.15 MHz, $CDCl_3$): δ = 263.92. Spectroscopic data of $TPP[Ir(CO)_3]_2$ (**5**): IR (film): 2923, 2852, 2052, 1982, 1596, 1441, 1357, 1073, 1017 cm^{-1}. HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{50}H_{28}N_4O_6Ir_2$: 1166.1267; found: 1166.3176. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (m, 3 H, H3′, H4′, H5′), 8.15 (m, 2 H, H2′, H6′), 8.90 (br s, 2 H, $H_β$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 123.18 (C, C_{meso}), 124.35 (CH, C3′, C4′, C5′), 124.72 (CH, C2′, C6′), 129.32 (CH, $C_β$), 135.59 (C, C1′), 201.53 (C, C=O). ^{14}N NMR (36.15 MHz, $CDCl_3$): δ = 264.08. Spectroscopic data of OEP[Ir(CO)Cl] (**6**) have been described previously.[50] ^{14}N NMR (36.15 MHz, $CDCl_3$): δ = 264.01. Spectroscopic data of TPP[Ir(CO)Cl] (**7**): IR (film): 2962, 2059, 1259, 1173, 1017, 870 cm^{-1}. HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{45}H_{29}N_4OClIr$: 869.1654, found: 869.1622. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (m, 3 H, H3′, H4′, H5′), 8.21 (m, 2 H, H2′, H6′), 8.82 (br s, 2 H, $H_β$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.14 (C, C_{meso}), 124.72 (CH, C3′, C4′, C5′), 125.75 (CH, C2′, C6′), 132.48 (CH, $C_β$), 140.43 (C, C1′). ^{14}N NMR (36.15 MHz, $CDCl_3$): δ = 264.2.

(50) Ogoshi, H.; Setsune, J.; Yoshida, Z. *J. Organomet. Chem.* **1978**, *159*, 317.

(51) Kadish, K. M.; Deng, Y. J.; Yao, C. L.; Anderson, J. E. *Organometallics* **1988**, *7*, 1979.

(52) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3089.

(53) Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327.

