Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 523–525.
DOI: 10.1002/jlcr.1239

Short Research Article

Investigation of isotopic exchange reactions using *N*-heterocyclic iridium (I) complexes[†]

MARK E. POWELL*, CHARLES S. ELMORE, PETER N. DORFF and J. RICHARD HEYS

CNS Chemistry, AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850, USA

Received 21 August 2006; Revised 19 December 2006; Accepted 20 December 2006

Keywords: heteroatom-directed exchange; deuteration; tritiation; iridium

Introduction

The labeling of compounds with tritium using hydrogen isotope exchange methodology is well precedented in literature using various transition metal catalysts, especially those containing iridium.[1] Catalytic exchange is attractive since the target compound is used directly and thus no synthetic steps need to be performed prior to labeling. Many catalysts have been investigated for their utility in exchange reactions and this has extended the applicability of the method to many different structural classes. However, there is much room for development of new and even more selective and effective catalysts.

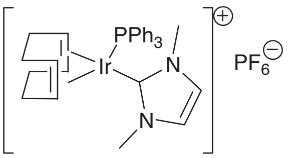
Recently, various investigators have shown *N*-heterocyclic carbene (NHC) containing iridium catalysts to have interesting catalytic activity in a variety of hydrogen transfer reactions including carbonyl reduction.[2] We thought they might be of use in exchange chemistry and show differential reactivity compared to the phosphine-based complexes heretofore explored. We synthesized four different *N,N*-dimethylimidazolium containing Ir catalysts (**1–4**) using published methodology.[2a] These catalysts were then tested in a variety of standard exchange reactions designed to probe their effectiveness as catalysts using substrates **5–10**.

Results and discussion

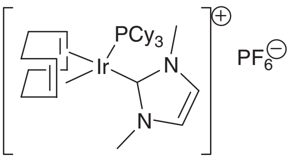
To broadly assess the ability of this class of iridium complexes to affect deuterations, a number of exchange reactions were performed in parallel, using substrates **5–8**. In some cases, the NHC catalysts were also compared to Crabtree's catalyst.[3] The conditions for all exchange reactions were 0.3 mg of substrate, 2.2 equivalents of catalyst, and 500 mbar of D_2 gas in 0.5 ml of CH_2Cl_2 with stirring overnight. The percent D incorporation was then assessed by LC/MS analysis. A summary of the results is shown in Table 1.

From this screen of catalysts, **3** ($Pn\text{Bu}_3$) appeared to be the most generally effective. It was then studied in a direct comparison with Crabtree's catalyst with substrates **5–10**, using conditions we might typically employ for tritiations. Standard reaction conditions were 0.3 mg of substrate, 2.2 equivalents of catalyst, and 100 mbar of D_2 in 0.5 ml of CH_2Cl_2 with stirring for 2.5 h. The percent deuterium incorporation was then assessed by LC/MS. Results are summarized in Table 2.

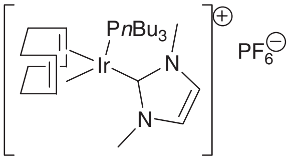
Catalyst **3** performed well in comparison to Crabtree's catalyst at low deuterium gas pressures. With the amides studied, **3** was as effective as Crabtree's catalyst or slightly better. With **7**, catalyst **3** showed better D incorporation than Crabtree's; with **8**, high D incorporation was observed, presumably from



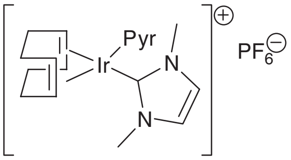
1



2



3

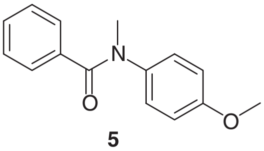


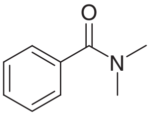
4

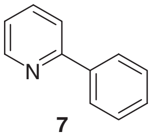
---

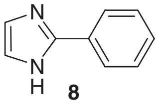
*Correspondence to: Mark E. Powell, CNS Chemistry, AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850, USA. E-mail: mark.powell2@astrazeneca.com

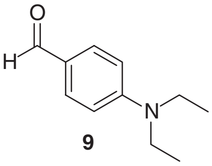
[†] Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.


5


6


7


8


9

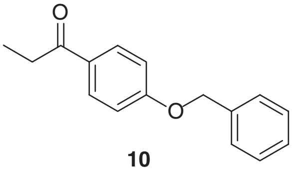

10

Table 1 Comparison of NHC catalysts in H/D exchange reactions with substrates **5–8**

Substrate	Catalyst	% D_0	% D_1	% D_2	% D_3	% D_4	% D_5	% D_6	% D_7	% D_8
5	**1**	0	6	53	27	12	2	0	0	0
	2	0	6	69	20	4	1	0	0	0
	3	0	0	3	14	36	43	2	1	0
	4	0	1	5	16	30	27	16	5	0
6	**1**	3	6	22	28	24	13	4	1	0
	2	3	7	51	30	8	2	0	0	0
	3	3	3	29	37	21	7	1	0	0
	4	1	0	2	6	16	25	28	16	5
7	**1**	1	9	88	3	0	0	0	0	0
	2	2	22	73	3	0	0	0	0	0
	3	4	6	88	3	0	0	0	0	0
	4	20	31	47	2	0	0	0	0	0
	Crabtree's	1	7	80	12	1	0	0	0	0
8	**1**	19	10	67	4	1	0	0	0	0
	2	19	14	62	5	0	0	0	0	0
	3	8	8	51	29	5	0	0	0	0
	4	45	18	32	5	1	0	0	0	0
	Crabtree's	1	7	77	15	1	0	0	0	0

Table 2 Comparison of **3** with Crabtree's catalyst using substrates **5–10**

Substrate	Catalyst	% D_0	% D_1	% D_2	% D_3	% D_4
5	**3**	5	32	59	4	0
	Crabtree's	64	33	4	0	0
6	**3**	36	44	18	2	0
	Crabtree's	31	46	21	2	0
7	**3**	1	19	81	0	0
	Crabtree's	49	40	11	0	0
8	**3**	4	12	31	34	19
	Crabtree's	28	37	31	4	0
9	**3**	4	21	59	17	0
	Crabtree's	26	40	29	6	0
10	**3**	0	25	75	0	0
	Crabtree's	15	49	35	0	0

DOI: 10.1002.jlcr

exchange at the C4 and C5 positions of the imidazole. Aldehydes and ketones also exchange well with catalyst **3** relative to Crabtree's catalyst.

REFERENCES

1. (a) Heys JR. *Chem Commun* 1992; 680; (b) Shu AYL, Saunders D, Levinson SH, Landvatter SW, Mahoney A, Senderoff SG, Mokhallalati MK, Heys JR. *J Label Compd Radiopharm* 1999; **42**: 797; (c) Shu AYL, Heys JR. *Tetrahedron Lett* 2000; **41**: 9015; (d) Hesk D, Gignan G, Lee F, Yang J, Voronin K, Magatti D, McNamara P, Koharski D, Hendershot S, Saluja S, Wang S. *J Label Compd Radiopharm* 2002; **45**: 145; (e) Ellames GJ, Gibson JS, Herbert JM, Kerr WJ, McNeill AH. *J Label Compd Radiopharm* 2004; **47**: 1; (f) Hickey MJ, Jones JR, Kingston LP, Lockley WJS, Mather AN, McAuley BM, Wilkinson DJ. *Tetrahedron Lett* 2003; **44**: 3959.
2. (a) Vazquez-Serrano LD, Owens BT, Buriak JM. *Chem Commun* 2002; 2581; (b) Lee HM, Jian T, Stevens ED, Nolan SP. *Organometallics* 2001; **20**: 1255; (c) Hillier AC, Lee HM, Stevens ED, Nolan SP. *Organometallics* 2001; **20**: 4246; (d) Vazquez-Serrano LD, Owens BT, Buriak JM. *Inorg Chim Acta* 2006; **359**: 2786.
3. (a) Crabtree RH, Felkin H, Morris GE. *J Organomet Chem* 1977; **141**: 205; (b) Crabtree RH. *Acc Chem Res* 1979; **12**: 331.

DOI: 10.1002.jlcr