Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 661–663

Palladium–imidazole derivatives as highly active catalysts for Heck reactions

K. Rajender Reddy* and G. Gopi Krishna

Inorganic Chemicals Division, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India

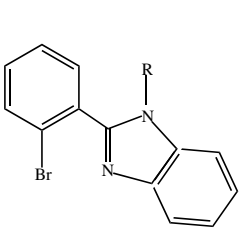
Received 26 September 2004; revised 16 November 2004; accepted 25 November 2004
Available online 10 December 2004

Abstract—*N*-Substituted 2-(2-bromophenyl)benzimidazole derivatives have been synthesized and used in palladium catalyzed Heck reactions to give coupled products in good yields.

The imidazole ring system is a key structural fragment found in many natural products.[1] It also serves as a good ligand for various metal ions.[2] Metal binding properties of imidazole-based ligands have been explored in detail due to their presence at the active site of metallo-proteins or enzymes involved in several important metabolic processes.[3] Numerous synthetic approaches have been described for imidazole derivatives because of their medicinal applications.[4]

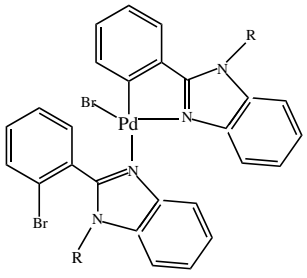
More recently such ligands have attracted attention from a catalytic point of view because of the tunable basicities associated with the ligating nitrogen.[5,6] A change in ligand basicity has a marked effect on metal–ligand bond strengths, which in turn effect the catalytic properties. Recently Busacca et al., have shown the influence of *N*-substitution versus catalytic activities with phosphinoimidazolines in palladium catalyzed asymmetric Heck reactions.[7] To our knowledge no such studies have been reported with imidazoles. We here report different *N*-substituted *ortho*-brominated benzimidazoles and their activity in palladium catalyzed Heck reactions.

Ligands **1**–**4**, Figure (a) were readily synthesized by simple Phillips condensation of 2-bromobenzoic acid with 1,2-phenylenediamine[8] and *N*-alkylation following the general procedure reported for *N*-substituted imidazole derivatives.[9,10]



1. R=*n*-butyl
2. R=benzyl
3. R=benzoyl
4. R=tosyl

fig(a)



R= *n*-butyl
[M^+-Br]=685 (100%)

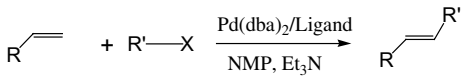
fig(b)

To examine the catalytic activity of ligands **1**–**4** in palladium catalyzed Heck reactions, we tested the reaction between iodobenzene and methyl acrylate (MA), which resulted in a quantitative yield of product with $Pd(dba)_2$ as pre-catalyst (Table 1, entry 1).[11] The reactivity was maintained even at low temperature and no difference in reactivity was observed on changing the ligands (entries 2–5). In order to probe the influence of the ligand on the reactivity, reactions with bromobenzene were attempted. No reaction was observed during the blank (entry 6). However under similar conditions ~9% of product formation was observed in the presence of ligand **2** (entry 7), which clearly indicated association of the ligand with the pre-catalyst. Furthermore, the complex from the pre-catalyst and ligand **1** was isolated and characterized by mass spectral studies, which clearly indicated the formation of a palladacycle, Figure (b). Formation of such palladacycles is well known in the literature and they are known to be highly active catalysts

Keywords: Heck reactions; Imidazole; Palladacycle.
* Corresponding author. Tel.: +91 40 271 93510; fax: +91 40 271 60921; e-mail: rajender@iict.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.124

Table 1. Heck reactions between alkenes and aryl halides catalyzed by Pd-benzimidazole derived ligands **1**–**4**[a]



Entry	Ligand (mol %)	R′–X		Time (h)	Temp (°C)	Isolated yield (%)
1	**2** (0.2)	Ph–I	MA	16	116	100
2	**2** (0.2)	Ph–I	MA	20	50	84
3	**2** (0.2)	Ph–I	BA[b]	20	50	89
4	**1** (0.2)	Ph–I	MA	20	50	86
5	**4** (0.2)	Ph–I	MA	20	50	81
6	—	Ph–Br	MA	23	100	—
7	**2** (1.0)	Ph–Br	MA	23	100	9
8	**2** (1.0)	Ph–Br	MA	21	116	41
9	**1** (1.0)	Ph–Br	MA	21	116	45
10	**3** (1.0)	Ph–Br	MA	21	116	14
11	**4** (1.0)	Ph–Br	MA	21	116	23
12	**1** (0.5)	PBAP	MA	21	116	88
13	**1** (0.5)	PBA	MA	21	116	12

[a] Reaction conditions: ligand and $Pd(dba)_2$ in a 3:1 ratio (1 mol %), aryl halide (1 mmol), alkene (1.5 mmol), Et_3N (2 mmol), NMP (3 mL).
[b] BA: *n*-butyl acrylate.

for various coupling reactions.[12] Increasing the temperature from 100 to 116 °C improved the conversion (entries 7 and 8), however, a further increase to 140 °C resulted in inconsistent results, possibly due to slow decomposition of the metal complexes. Recently Alper has reported thermal instabilities associated with bis-imidazole–Pd(II) complexes during recycling studies on Heck reactions in ionic liquids.[13] Optimization studies with different solvents and bases proved the *N*-methyl-2-pyrrolidone (NMP) and triethylamine (NEt_3) combination as the best. Further investigations were carried out using this combination.

Ligands **1** and **2** having electron-donating groups on the imidazole nitrogen showed higher activities (entries 8 and 9) compared to those possessing electron-accepting groups **3** and **4** (entries 10 and 11). One possible explanation for the higher activity associated with the electron donating groups could be the higher basicity of the coordinating nitrogen. X-ray structural analysis of Pd(II) complexes containing the pyridine–imidazoline ligand showed that the Pd–N bond is much stronger when the imidazoline nitrogen is substituted with an electron donating benzyl group compared with the electron withdrawing triflate group.[14]

As is observed in Heck reactions, activated aryl bromides, such as 4-bromoacetophenone (PBAP) resulted in higher conversions (entry 12) in comparison to those possessing deactivating groups, for example, 4-bromoanisole (PBA) (entry 13). These conversions were higher than with the recently reported thiourea derived Pd-catalysts.[15] Such an observation implicates the higher stability of the preformed palladacycle complexes as well as the electronic influences associated with the metal complexes upon *N*-substitution.

In conclusion, we have synthesized *N*-substituted 2-(2-bromophenyl)-benzimidazole derivatives. The newly synthesized ligands were successfully used in palladium catalyzed Heck reactions to give the coupled products in good yields. It is clear that the catalytic activities are associated with the *N*-substitution on the imidazole ligands. Further investigations on the improvement of these imidazole ligands as well as the use of chiral analogues are in progress.

Acknowledgements

We wish to thank the CSIR for financial support under the Task Force Project COR-0003.

References and notes

1. (a) Grimmet, M. R. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 4, pp 345–498; (b) Grimmet, M. R. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Pergamon: Oxford, 1996; Vol. 3, pp 77–220.
2. Navarro, J. A. R.; Lippert, B. *Coord. Chem. Rev.* **2001**, *222*, 219–250.
3. Fausto da Silva, J. J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements: The Inorganic Chemistry of Life*; Clarendon Press: Oxford, 1991.
4. (a) Zhong, Y. L.; Lee, J.; Reamer, R. A.; Askin, D. *Org. Lett.* **2004**, *6*, 929–931; (b) Bleicher, K. H.; Gerber, F.; Wuthrich, Y.; Alanine, A.; Capretta, A. *Tetrahedron Lett.* **2002**, *43*, 7687–7690; (c) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893–1895; (d) Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. *Tetrahedron Lett.* **1998**, *39*, 8939–8942.
5. Jalil, M. A.; Fujinami, S.; Nishikawa, H. *J. Chem. Soc., Dalton Trans.* **2001**, 1091–1098.
6. Ozdemir, I.; Centinkaya, B.; Demir, S. *J. Mol. Catal. A* **2004**, *208*, 109–114.
7. Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595–598.
8. Phillips, M. A. *J. Chem. Soc.* **1928**, 172.
9. Crane, J. D.; Sinn, E.; Tann, B. *Polyhedron* **1999**, *18*, 1527–1532.

10. Typical procedure for ligand synthesis: (i) Preparation of benzimidazoles: 2-bromobenzoic acid (40 mmol) and 1,2-phenylenediamine (40 mmol) were taken in polyphosphoric acid (56 g) and heated to 150 °C for 6 h. The reaction mixture was poured over crushed ice and kept in a refrigerator overnight. The resulting violet solid precipitate was filtered and added to 0.5 M Na_2CO_3 solution (500 mL), stirred for 30 min and filtered. The precipitate was dissolved in methanol (300 mL), carbon black was added and the suspension stirred for 1 h. The methanol solution was heated on a water bath for 5 min and filtered through celite whilst hot to give a white solid (6.5 g, 60%). (ii) *N*-Alkylation of benzimidazoles: To the benzimidazole (3.66 mmol) in acetone (20 mL), KOH (7.32 mmol) was added and the solution stirred at rt for 30 min. To this was added RX (R = butyl, benzyl, benzoyl, *p*-toluenesulfonyl; X = Br for **1** and **2**, Cl for **3** and **4**) and the mixture refluxed for 2 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and subjected to column chromatography on silica gel. Spectroscopic data: **1**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 (3H, t, J 7.5 Hz), 1.10–1.30 (2H, m), 1.60–1.75 (2H, m), 4.05 (2H, t, J 7.5 Hz), 7.20–7.30 (2H, m), 7.35–7.55 (4H, m), 7.70 (1H, m), 7.80 (1H, m). MS(EI) m/z 329 (M^++2, 79.4%). Compound **2**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.25 (2H, s), 7.00–7.15 (2H, m), 7.24–7.40 (9H, m), 7.75 (1H, m), 7.85 (1H, m). MS(EI): m/z 363 (M^++2, 13%). Compound **3**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.00–8.00 (11H, m), 7.75 (1H, m), 7.86 (1H, m). MS(FAB): m/z 379 (M^++2, 44 %). Compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.40 (3H, s), 7.10–7.20 (2H, m), 7.35–7.60 (7H, m), 7.61–7.88 (2H, m), 8.10–8.20 (1H, m). MS(FAB): m/z 429 (M^++2, 12%).
11. Typical procedure for the Heck reaction: The ligand and $Pd(dba)_2$ (3:1) were taken in NMP and stirred at room temperature for 1 h. To this reaction mixture methyl acrylate, NEt_3 and aryl halide were added sequentially and heated at 116 °C for the specified time (see Table 1) under an argon atmosphere. After completion, the reaction mixture was diluted with chloroform and washed twice with 5 N HCl and the organic layer was concentrated and the residue was purified by silica gel column chromatography.
12. Bedford, R. B. *Chem. Commun.* **2003**, 1787–1796.
13. Park, S. B.; Alper, H. *Org. Lett.* **2003**, *5*, 3205–3212.
14. Bastero, A.; Ruiz, A.; Claver, C.; Milani, B.; Zangrando, E. *Organometallics* **2002**, *21*, 5820–5829.
15. Yang, D.; Chen, Y. C.; Zhu, N. Y. *Org. Lett.* **2004**, *6*, 1577–1580.