Tetrahedron Letters 50 (2009) 6126–6129

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed aminocarbonylation of heteroaryl halides using di-*tert*-butylphosphinoferrocene

Bo Qu *, Nizar Haddad, Zhengxu S. Han, Sonia Rodriguez, Jon C. Lorenz, Nelu Grinberg, Heewon Lee, Carl A. Busacca, DhileepKumar Krishnamurthy, Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877-0368, USA

ARTICLE INFO

Article history:
Received 27 July 2009
Revised 19 August 2009
Accepted 20 August 2009
Available online 24 August 2009

Keywords:
Aminocarbonylation
Heteroaryls
Di-*tert*-butylphosphinoferrocene
Palladium

ABSTRACT

Pd-catalyzed aminocarbonylation of heteroaryl halides, using monodentate ligand di-*tert*-butylphosphinoferrocene tetrafluoroborate is reported. Good to high yields were obtained with chiral amines on a variety of substrates including 2-bromo heteroaryls.

1. Introduction

Since the seminal report by Heck and Schoenburg in 1974,[1] palladium-catalyzed three-component coupling reaction of an aryl halide, CO, and a nucleophile has become a highly efficient method for the synthesis of aromatic carbonyl-containing compounds. Aminocarbonylation is a valuable and atom-efficient transformation for preparing amides of primary or secondary amines, including chiral amino acids, as *N*-nucleophiles.[2,3] In spite of the many reports on aminocarbonylation, its potential utility with heteroaryl halides has not been fully explored.[4–9] While many ligands have been successfully applied in palladium-catalyzed aminocarbonylation reactions, few of them can be applied on large scale applications due to the difficulty in synthesis or due to the highly sensitive nature of the often pyrophoric phosphine ligands. To the best of our knowledge, the application of monodentate ligand di-*tert*-butylphosphinoferrocene P(Fc)(*t*-Bu)$_2$ (Fc = ferrocenyl) in palladium-catalyzed aminocarbonylation reactions has not been reported. Limited success of this ligand was observed in aromatic carbon–oxygen bond formations[10,11] and Hartwig–Buchwald amination reactions.[12]

Herein, we report our recent findings on aminocarbonylation of heteroaryl bromides using di-*tert*-butylphosphinoferrocene as a supporting ligand. P(Fc)(*t*-Bu)$_2$[11] was prepared and isolated as air stable tetrafluoroboric acid adduct on multi-gram scale.

Di-*tert*-butylphosphinoferrocene·HBF$_4$ was initially tested in the aminocarbonylation of (*R*)-phenylethylamine and (D)-glycine ethyl ester with iodobenzene (Table 1). Over 80% yields were obtained using 3 mol % Pd(OAc)$_2$ and 6 mol % of ligand at 50 psi of CO pressure at 120 °C for 4 h (entries 1 and 2). Di-isopropylethylamine was used as a base and acetonitrile or NMP was used as a solvent.

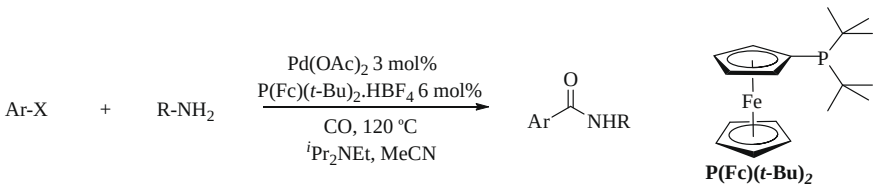
Encouraged by the preliminary results, ligand P(Fc)(*t*-Bu)$_2$·HBF$_4$ was further examined in aminocarbonylation of bromobenzene and heteroaryl bromides. We found that the typical conditions have produced the desired products in modest to good yields. The reaction of 5-bromo-1-methyl-1*H*-imidazole with either (*R*)-phenylethylamine or (D)-glycine ethyl ester produced similar yields (entries 4 and 5). 5-Bromopyrimidine was readily converted to the desired product in 80% yield (entry 8). Slightly higher CO pressure (200 psi) and longer reaction time (9 h) were needed to obtain full conversion of amine with 3-bromoquinoline and bromobenzene (entries 3 and 6). No epimerization of the chiral center occurred during the reaction, aminocarbonylation product of bromobenzene with either 1-(*R*)-ethylbenzylamine (99% ee) or 1-(*S*)-ethylbenzylamine (99% ee) was obtained in 99% ee after 9 h of reaction time at 120 °C and 200 psi of CO pressure.[13]

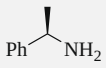
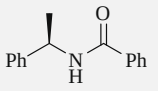
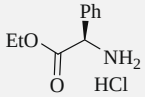
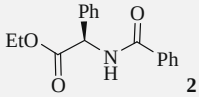
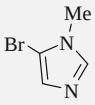
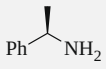
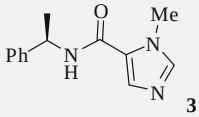
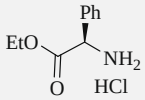
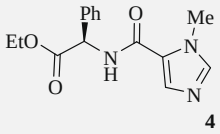
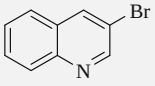
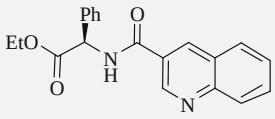
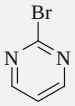
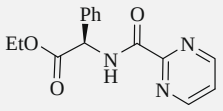
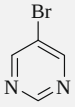
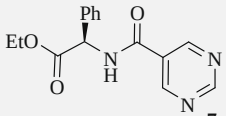
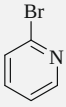
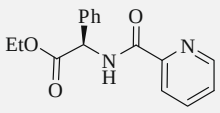
Aminocarbonylation of 2-bromo-heteroaryls was found to be challenging under the typical reaction conditions. Arylbromide self-dimerization was identified as the major side product along with a small amount of direct coupling product without CO insertion in the reactions of either 2-bromopyridine or 2-bromopyrimidine with (D)-glycine ethyl ester. This suggests that CO insertion

* Corresponding author. Tel.: +1 203 791 6177; fax: +1 203 791 6130.
E-mail address: bo.qu@boehringer-ingelheim.com (B. Qu).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.065

Table 1
Aminocarbonylation reaction of aryl halides with amines

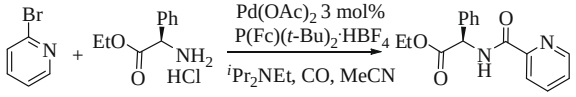


Entry	Ar–X	R–NH_2	Product	Pressure (psi)	Time (h)	Yield* (%)
1	PhI		 **1**	50	4	87
2	PhI		 **2**	50	4	82
3	PhBr			200	9	69
4			 **3**	50	4	71
5			 **4**	50	4	65
6			 **5**	200	9	68[a]
7			 **6**	100	5	74[b]
8			 **7**	50	4	80
9			 **8**	200	4	91[b]

[a] 20% of quinoline-3-carboxylic acid was also isolated.
[b] Pd/L = 3.
* Isolated yield.

might be a rate-limiting step, since it takes place after oxidative-addition step and prior to the transmetallation step. After oxidative insertion of the Pd(0) to aryl–Br bond, instead of CO insertion, the catalyst may form a dimeric Pd(II) structure by coordination to the heteroatom on the arylbromide, which leads either to the self-dimerization side product or catalyst deactivation.[14] Slight modification of the reaction temperature, CO pressure, and ligand to palladium ratio has significantly favored the desired aminocarb-

Table 2
Aminocarbonylation at different pressures and temperatures

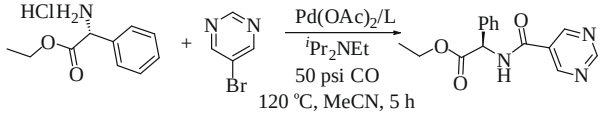


Entry	Pd/L	Pressure (psi)	Temperature (°C)	Yield*
1	1:2	50	120	30
2	1:2	100	120	71
3	1:2	400	120	94
4	1:2	400	90	94
5	1:3	50	90	97
6	1:3	200	90	98
7	1:3	400	90	85
8	1:3	50	120	59
9	1:3	100	120	82
10	1:3	300	120	95

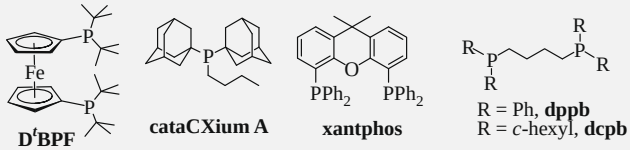
* HPLC yields of average of two runs.

onylation reaction (Table 2). When Pd/ligand ratio stays at 1:2, over 90% yield was obtained by increasing the pressure to 400 psi at a temperature range of 90–120 °C (entries 3 and 4); both amination side reaction and bromide self-dimerization were suppressed by employing slight increase in the CO pressure. It should be noted that no double carbonylation product was observed at increased pressure. When Pd/ligand ratio was increased to 1:3 respectively, quantitative yield was obtained with lower temperature 90 °C and 50 psi CO pressure (entry 5). Further decrease of the temperature to 70 °C led mostly to aryl bromide self-dimerization with a pressure range of 50–400 psi. Increasing the ligand to Pd ratio stabilizes Pd(0) by favorably coordinating to the phosphine ligand other than CO molecule and therefore preventing catalyst deactivation. Most aminocarbonylations of heteroaryls were reported on 3-bromoaryls, only a few were investigated on 2-bromopyridine using $Mo(CO)_6$ as the CO source under microwave or conventional heating, and lower yield was obtained.[4,5] The ligand P(Fc)(*t*-Bu)$_2$·HBF$_4$ furnished the desired product in 91% yield under optimized conditions.

Table 3
Aminocarbonylation reactions with different ligands



Entry	$Pd(OAc)_2$ mol %	Ligand	Pd/L	Yield* (%)
1	1	P(Fc)(*t*-Bu)$_2$·HBF$_4$	1:3	91
2	1	Xantphos	1:2	90
3	1	P(*t*-Bu)$_3$·HBF$_4$	1:3	92
4	1	D^{t}BPF	1:2	54[a]
5	3	CataCXium A	1:3	36[a]
6	3	Q-PHOS	1:3	23[a]
7	3	dppb	1:2	43[a]
8	3	dcpb	1:2	2



[a] Incomplete reaction.
* HPLC yields of average of two runs.

The reactivity of ligand P(Fc)(*t*-Bu)$_2$·HBF$_4$ was evaluated in comparison to that of other ligands[7,15] that have been successfully demonstrated in palladium-catalyzed carbonylation reactions (Table 3). The reactions of 5-bromopyrimidine and D-glycine ethyl ester were examined using 1 mol % $Pd(OAc)_2$ with 3 mol % monodentate ligand or 2 mol % bidentate ligands at 120 °C, 50 psi of CO. Xantphos, a bidentate ligand possessing a large bite angle, P(*t*-Bu)$_3$·HBF$_4$, and bis-di(*tert*-butylphosphino)ferrocene (D^{t}BPF) have demonstrated similar reactivity to P(Fc)(*t*-Bu)$_2$·HBF$_4$ (entries 1–4). Catacxium A, a superior ligand for aminocarbonylation of other substrates in our hands, was found to be inferior in this case even with 3 mol % of catalyst. Poor yield was also observed in the reaction of 5-bromo-1-methyl-1*H*-imidazole with D-glycine ethyl ester using cataCXium A. Low yields were also obtained with Q-PHOS, 1,4-diphenylphosphinobutane (dppb), and dicyclohexylphosphinobutane (dcpb) as ligands. In situ IR monitoring of the aminocarbonylation of 5-bromopyrimidine indicated complete conversion in 2 h at 90 °C and 50 psi of CO using 1 mol % $Pd(OAc)_2$ and 3 mol % P(Fc)(*t*-Bu)$_2$·HBF$_4$, providing the desired product **7** in over 90% yield.

In summary, we have demonstrated the application of air stable ligand P(Fc)(*t*-Bu)$_2$·HBF$_4$ in palladium-catalyzed aminocarbonylation of heteroaryl bromides with amines. The ligand was conveniently prepared and isolated on multi-gram scale and successfully applied in the preparation of a series of heteroaromatic amide derivatives in good yields.

2. Synthesis of P(Fc)(*t*-Bu)$_2$·HBF$_4$

To a dried 2 L flask under argon were charged ferrocene (5 g, 26.9 mmol), anhydrous THF (150 mL), and *t*-BuOK (0.12 equiv). The mixture was cooled to −78 °C before *t*-BuLi (2.0 equiv) was added slowly while keeping the temperature below −70 °C. After stirring for an additional 1 h, the mixture was warmed to ambient temperature, stirred for 2 h, and then *t*-Bu$_2$PCl (1.1 equiv) was added in one portion. After stirring at room temperature for 2 h, degassed water (100 mL) was added and the mixture was concentrated to remove 2/3 of THF and backfilled with argon. Ethyl acetate (100 mL) was added followed by saturated $NaHCO_3$ solution (1.5 equiv). The aqueous phase was removed, then HBF_4 (48% in water) (2 equiv) was added to the organic fraction. The mixture was stirred for 4 h, then washed with brine (50 mL). The solvent was removed under reduced pressure, the residue stirred with ethyl acetate (200–300 mL) to form a slurry that was filtered and dried to give 8.5 g orange solid in 75% yield. ^{1}H NMR (400 Hz in $CDCl_3$): 1.50 (s, 9H), 1.54 (s, 9H), 4.44 (s, 5H), 4.66 (s, 2H), 4.79 (s, 2H), 6.87 (d, 1H, J = 394 Hz). ^{13}C NMR (400 Hz in $CDCl_3$): 28.61, 34.45, 34.75, 71.95, 73.60, 73.68, 74.11, 74.18. ^{31}P NMR: 54.26.

3. General procedure for the aminocarbonylation reactions

All experiments were operated on a Biotage Endeavor system equipped with mechanical stirrers. Reagents were used as received. Anhydrous MeCN and NMP were nitrogen purged before use. At the end of the reaction, monitored by HPLC based on the disappearance of amines, the reaction mixture was concentrated and then the residue was purified on silica.

4. Representative procedure of preparing (*R*)-1-methyl-N-(1-phenylethyl)-1*H*-imidazole-5-carboxamide (3)

(*R*)-1-Phenylethylamine (218 mg, 1.8 mmol), 5-bromo-1-methyl-1*H*-imidazole (434 mg, 2.7 mmol), $Pd(OAc)_2$ (12.1 mg, 0.054 mmol), di-*tert*-butylphosphinoferrocene·HBF$_4$ (45 mg, 0.108 mmol), and ^{i}Pr$_2$NEt (1.25 mL, 7.2 mmol) were added to the

10-mL reaction vessel followed by 4 mL of MeCN. The reaction mixture was then purged two times with N_2, then one time with CO, heated to 120 °C, and pressurized to 50 psi for 4 h. The reaction mixture was then cooled down to 23 °C and purged with N_2 for two times. The mixture was purified on silica using CH_2Cl_2/MeOH 95:5 to give 293 mg (71%) of the desired aminocarbonylation product as a colorless liquid. ^{1}H NMR (400 Hz in $CDCl_3$): 7.63 (br s, 1H), 7.48 (s, 1H), 7.32–7.18 (m, 6H), 5.22 (quint, 1H, J = 7.12 Hz), 3.79 (s, 3H), 1.48 (d, 3 H, J = 7.0 Hz). ^{13}C NMR (100 Hz in $CDCl_3$): 159.47, 143.22, 141.08, 131.44, 128.26, 126.90, 126.05, 125.97, 48.18, 33.75, 21.39. HRMS (ESI) calcd for $C_{13}H_{16}N_3O$ $[M+H]^+$: 230.1287; found 230.1297, error = 3.9598 ppm.

4.1. (*R*)-Ethyl-2-(1-methyl-1*H*-imidazole-5-carboxamido)-2-phenylacetate (4)

336 mg (65%) colorless liquid was obtained by a column using CH_2Cl_2/MeOH 95:5. ^{1}H NMR (400 Hz in $CDCl_3$): 7.84 (br s, 1H), 7.48 (s, 1H), 7.35–7.23 (m, 6H), 5.62 (d, 1H, J = 7.2 Hz), 4.19–4.08 (m, 2H), 3.75 (s, 3H), 1.15 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 Hz in $CDCl_3$): 170.48, 159.54, 141.44, 136.06, 132.26, 128.51, 128.09, 127.23, 125.13, 61.52, 56.16, 33.66, 13.65. HRMS (ESI) calcd for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1342; found 288.1333, error = 3.3598 ppm.

4.2. (*R*)-Ethyl-2-phenyl-2-(pyrimidine-2-carboxamido)-acetate (6)

380 mg (74%) white solid was obtained by a column using 100% EtOAc. ^{1}HNMR (400 Hz in $CDCl_3$): 8.83 (br d, 1H), 8.77 (d, 2H, J = 4.88 Hz), 7.34–7.40 (m, 3H), 7.21–7.30 (m, 3H), 5.78 (d, 1H, J = 7.6 Hz), 4.08–4.21 (m, 2H), 1.15 (t, 3H, J = 6.8 Hz). ^{13}CNMR (100 Hz in $CDCl_3$): 170.29, 161.30, 157.32, 157.06, 136.21, 128.75, 128.35, 127.11, 122.57, 61.79, 56.47, 13.81. HRMS (ESI) calcd for $C_{15}H_{16}N_3O_3$ $[M+H]^+$: 286.1186; found 286.1179, error = 2.5094 ppm.

4.3. (*R*)-Ethyl-2-phenyl-2-(pyrimidine-5-carboxamido)-acetate (7)

410 mg (80%) white solid was obtained by a column using hexane/EtOAc 50:50. ^{1}H NMR (400 Hz in $CDCl_3$): 9.28 (s, 1H), 9.12 (s, 2H), 7.44 (br d, NH, J = 6.4 Hz), 7.41–7.32 (m, 5H), 5.74 (d, 1H, J = 6.8 Hz), 4.29–4.16 (m, 2H), 1.23 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 Hz in $CDCl_3$): 170.54, 162.70, 160.70, 155.74, 135.89, 129.05, 128.79, 127.23, 62.36, 56.92, 13.92. HRMS (ESI) calcd for $C_{15}H_{16}N_3O_3$ $[M+H]^+$: 286.1186; found 286.1195, error = 3.0826 ppm.

4.4. (*R*)-Ethyl 2-phenyl-2-(picolinamido)acetate (8)

465 mg (91%) colorless liquid was obtained by a column using hexane/EtOAc 70:30. ^{1}H NMR (400 Hz in $CDCl_3$): 8.95 (br d, 1H), 8.58 (d, 1H, J = 4.76 Hz), 8.15 (d, 1H, J = 7.84 Hz), 7.81 (dt, 1H, J = 7.76 Hz and 1.64 Hz), 7.48 (d, 2H, J = 7.88 Hz), 7.36–7.30 (m, 4H), 5.76 (d, 1H, J = 7.6 Hz), 4.20 (m, 2H), 1.23 (t, 3H, J = 7.0 Hz) ^{13}C NMR (100 Hz in $CDCl_3$): 170.57, 163.72, 149.34, 148.25, 137.19, 136.66, 128.88, 128.40, 127.29, 126.34, 122.26, 61.81, 56.61, 13.97. HRMS (ESI) calcd for $C_{15}H_{17}N_2O_3$ $[M+H]^+$: 285.1233; found 285.1237, error = 1.1707 ppm.

Supplementary data

Supplementary data (analytical data of compounds **1**, **2** and **5** and NMR spectra of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.065.

References and notes

1. Schoenburg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
2. Kuik, Á.; Skoda-Földes, R.; Jánosi, L.; Kollár, L. *Synthesis* **2007**, 1456.
3. Horváth, L.; Berente, Z.; Kollár, L. *Lett. Org. Chem.* **2007**, *4*, 236.
4. Begouin, A.; Queiroz, M. R. P. *Eur. J. Org. Chem.* **2009**, 2820.
5. Letavic, M. A.; Ly, K. S. *Tetrahedron Lett.* **2007**, *48*, 2339.
6. Fairlamb, I. J. S.; Grant, S.; McCormack, P.; Whittall, J. *Dalton Trans.* **2007**, 859.
7. Neumann, H.; Brennführer, A.; Groβ, P.; Riermeier, T.; Almena, J.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 1255. and references cited therein.
8. Takács, A.; Jakab, B.; Petz, A.; Kollár, L. *Tetrahedron* **2007**, *63*, 10372.
9. Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460.
10. Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
11. Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224.
12. Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861.
13. Chiralcel OD-H column used for ee determination with 90/10 of heptane/*n*-propanol.
14. Beller, M.; Mägerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, 1098.
15. Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. *J. Org. Chem.* **2008**, *73*, 7102. and references cited therein.