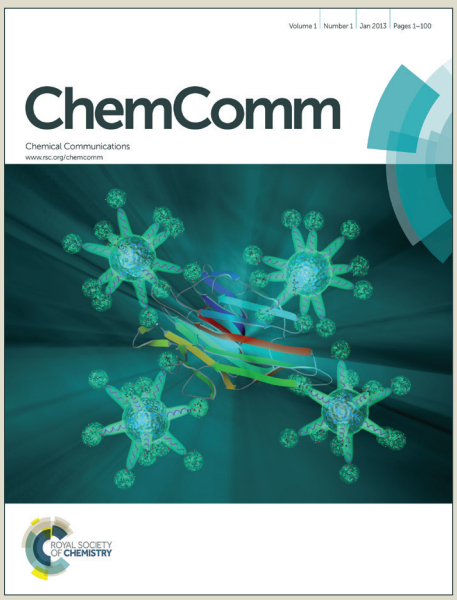
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

COMMUNICATION

Acid-free regioselective aminocarbonylation of alkenes

Cite this: DOI: 10.1039/x0xx00000x

Huizhen Liu*, Ning Yan and Paul J. Dyson

Received
Accepted

DOI: 10.1039/x0xx00000x

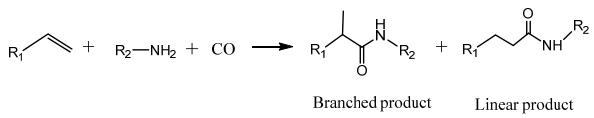
www.rsc.org/

An efficient method for the synthesis of N-aryl monosubstituted carboxamides via the Pd–catalyzed carbonylation of alkenes with CO and amines is described. Mechanistic insights for this highly selective reaction are provided.

Despite the importance of amides in chemistry and biology most of the well-established methods for their synthesis are not very efficient[1,2]. While considerable progress has been made in recent years, e.g. the direct catalytic conversion of alcohols and amines[3], new routes to amides are still needed. Two important reviews were published in 2011 highlighting developments in this area[4,5].

The synthesis of amides via the carbonylation of C−X (X = H, Br, I, etc.) bonds has received considerable attention[6]. Notable developments include palladium catalyzed carbonylation reactions of aryl bromides and alk–1–ynes[7], transition metal–free alkoxycarbonylation of aryl halides[8] and the synthesis of amides via the activation of aromatic C−H bonds[9]. Recently, we reported that $PdCl_2$ combined with various wide bite-angle bis–phosphines including xantphos, nixantphos, (±)-binapo or (R)-phanephos catalyzes the formation of amides in the absence of acid or base, by the direct activation of C(sp^3)−H bonds with subsequent CO insertion. However, the selectivity of this reaction is low, e.g. the ratio of branched to linear products in the reaction of ethylbenzene and aniline in the presence of CO, is 46:13 with $PdCl_2$/xantphos and 53:12 with $PdCl_2$/(R)-phanephos[10].

The synthesis of amides from alkenes and amines in the presence of CO represents an ideal, atom economic and environmentally benign route (Scheme 1), with the potential for asymmetric transformations. However, to the best of our knowledge, reports on this reaction are rare[11,12], and moreover, high regioselectivity is important as both linear and branched products can be obtained. Linear carboxamides have been obtaining in yields of up to 90% with a cobalt catalyst immobilized on charcoal[11]. Aminocarbonylation of olefins with aromatic amines and nitroarenes using $Pd(acac)_2$ and N-phenylpyrrole-based bis-phosphine ligands in the presence of p-TsOH leads to the formation of linear products in up to 99%[12]. Branched carboxamides, on the other hand, are useful scaffolds for biologically active molecules[13] and oxindoles, which are commonly encountered substructures in natural products and bioactive molecules, can be synthesized directly from branched carboxamides[14]. Recently, a palladium-catalyzed amidation–hydrolysis reaction was shown to afford branched carboxamides from gem-dihaloalkene and aryl amines[15].



Scheme 1. The conversion of alkenes, amines and CO to amides.

Table 1 Optimization of the reaction of styrene with aniline and CO to afford N,2-diphenylpropanamide.

Entry	Metal salt	Ligand	Yield (%)	B/L
1	$PdCl_2$	PPh_3	94	94:6
2	$PdCl_2$	$P(2\text{-}OMePh)_3$	95	>99:<1
3	$PdCl_2$	$P(4\text{-}OMePh)_3$	92	94:6
4	$PdCl_2$	$P(2,6\text{-}OMePh)_3$	8	>99:<1
5	$PdCl_2$	$P(2\text{-}MePh)_3$	86	>99:<1
6	$PdCl_2$	dmpp	8	>99:<1
7	$PdCl_2$	xantphos[a]	91	39:61
8	$PdCl_2$	dppf[a]	92	39:61
9	$PdCl_2$	dppe[a]	0	-
10	$PdCl_2$	dppb[a]	0	-
11	$PdBr_2$	$P(2\text{-}OMePh)_3$	94	92:8
12	$Pd(OAc)_2$	$P(2\text{-}OMePh)_3$	trace	-
13	$Pd(acac)_2$	$P(2\text{-}OMePh)_3$	trace	-
14	$CoCl_2$	$P(2\text{-}OMePh)_3$	1	>99:<1
15	$RhCl_3$	$P(2\text{-}OMePh)_3$	17	>99:<1
16	$RuCl_3$	$P(2\text{-}OMePh)_3$	3	>99:<1
17	$Ru_3(CO)_{12}$	$P(2\text{-}OMePh)_3$	trace	-
18	$Co_2(CO)_8$	$P(2\text{-}OMePh)_3$	trace	-
19[a]	$Re_2(CO)_{10}$	$P(2\text{-}OMePh)_3$	trace	-
20[b]	$Pd_2(dba)_3$	$P(2\text{-}OMePh)_3$	trace	-
21	$Pd(PPh_3)_4$	-	17	>99:<1
22[c]	$PdCl_2$	$P(2\text{-}OMePh)_3$	67	>99:<1
23[d]	$PdCl_2$	$P(2\text{-}OMePh)_3$	26	>99:<1
24[e]	$PdCl_2$	$P(2\text{-}OMePh)_3$	92	>99:<1
25[f]	$PdCl_2$	$P(2\text{-}OMePh)_3$	90	>99:<1
26[g]	$PdCl_2$	$P(2\text{-}OMePh)_3$	94	>99:<1

Reaction conditions: styrene (11 mmol), aniline (1 mmol), $PdCl_2$ (5 mol% based on aniline), ligand (0.12 mmol), THF 10 ml, CO (50 atm), T (125°C), t (2 h). [a] Ligand (0.06 mmol). [b] Ligand (0.24 mmol). [c] Reaction was performed in the presence of air (1 atm) and CO (50 atm). [d] Toluene (10 ml) used as the solvent. [e] CH_3CN (10 ml) used as solvent. [f] Styrene (1 mmol) and aniline (1 mmol). [g] CO (10 atm). P(2-OMePh)$_3$ = tris(2-methoxyphenyl)phosphine, P(4-OMePh)$_3$ = tris(4-methoxyphenyl)phosphine, P(2,6-OMePh)$_3$ = tris(2,6-dimethoxyphenyl)phosphine, P(2-MePh)$_3$ = tris(2-methyphenyl)phosphine, dmpp = dimethyl phenylphosphonite, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppe = 1,2-bis(diphenylphosphino)ethane, dppb = 1,2-bis(diphenylphosphino)benzene. Yields were determined by GC analysis relative to aniline using n-decane as an internal standard.

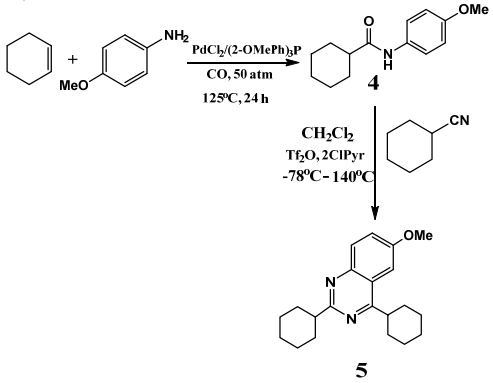
Herein, we describe a simple, homogeneous PdX_2/tris(2-methoxyphenyl)phosphine system (X = Cl or Br) that catalyzes the aminocarbonylation of alkenes with the regioselectivity for branched carboxamides often exceeding 99%.

The reaction was optimized with respect to the substrate rations, temperature and pressure and Pd:ligand ration using styrene and aniline as the substrates with various combinations of $PdCl_2$-ligand catalysts(see supporting information). The highest yield and selectivity of the desired amide product, i.e. N,2-diphenylpropanamide, was obtained in the presence of tris(2-methoxyphenyl)phosphine under 50 atm of CO at 125°C (see Supporting Information). The nature of the ligand strongly influences the reaction and monophosphine ligands such as PPh_3, tris(2-methoxyphenyl)phosphine, tris(4-methoxyphenyl)phosphine tris(2,6-dimethoxyphenyl)phosphine and tris(2-methyphenyl)phosphine lead to higher selectivities for the branched product, although the yield with tris(2,6-methoxyphenyl)phosphine and tri-(2-tolyl)phosphine is lower (Table 1, entries 1 – 6). Bis-phosphine ligands afford less selective and less active catalysts (Table 1, entries 7 – 10) – notably with 1,2-bis(diphenylphosphino)ethane and 1,2-bis(diphenylphosphino)benzene no product is obtained. Conducting the reaction in toluene results in a lower conversion (Table 1, entry 23) and acetonitrile is also a good solvent for the reaction (Table 1, entry 24). At a styrene:aniline ratio of 1:1 the yield of the desired product reaches 90% at longer reaction times, i.e. 4 hours and at a lower CO pressure, i.e. 10 atm, the yield is 94% after 4 hours (Table 1, entries 25 and 26, respectively).

$PdBr_2$ can also be used as a catalyst precursor for this reaction although the selectivity is slightly lower than that obtained with $PdCl_2$ (Table 1, cf. entries 2 and 11). The other metal salts evaluated were less efficient than $PdCl_2$ and $PdBr_2$ (Table 1, entries 14-16). Notably, other palladium(II) precursors (Table 1, entries 12-13) and palladium(0) compounds (Table 1, entries 20-21) as well as the transition metal carbonyl complexes (Table 1, entries 17-19) afford considerably less active catalysts. The low yield obtained with $Pd(acac)_2$ is consistent with other studies[12]. In the presence of CO and air diphenylurea is obtained in 24% yield and the yield of branched product is only 67% (Table 1, Entry 22).

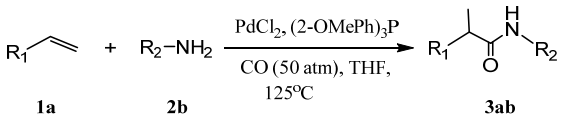
The substrate scope of the reaction was explored under optimized conditions (CO 50 atm, 125°C) using $PdCl_2$ (5 mol%) and two equivalents of the tris(2-methoxyphenyl)phosphine co-catalyst (Table 2). The system is active for anilines with both electron withdrawing or donating substituents. Under the standard conditions most aromatic anilines react with styrene to afford the desired product in yields exceeding 90% with the exception of 3- and 4-nitroaniline and N-methylaniline. The system is also active for aliphatic alkenes, e.g. the reaction of 1-hexene with aniline in the presence of CO affords the desired product in 80% yield, and for cyclohexene, the yield of the desired product can reached to 96%. With nitrile substituted aliphatic alkene the yield of the product is 63% and for allylbenzene the yield of corresponding product reaches 72% after 20 hours. However, the catalytic system is inactive for aliphatic amines.

The aminocarbonylation reaction was used to generate N-(4-methoxyphenyl)cyclohexanecarboxamide (**4**) which was subsequently converted to pyrimidine derivatives 5 (Scheme 2 see supporting information)[19]

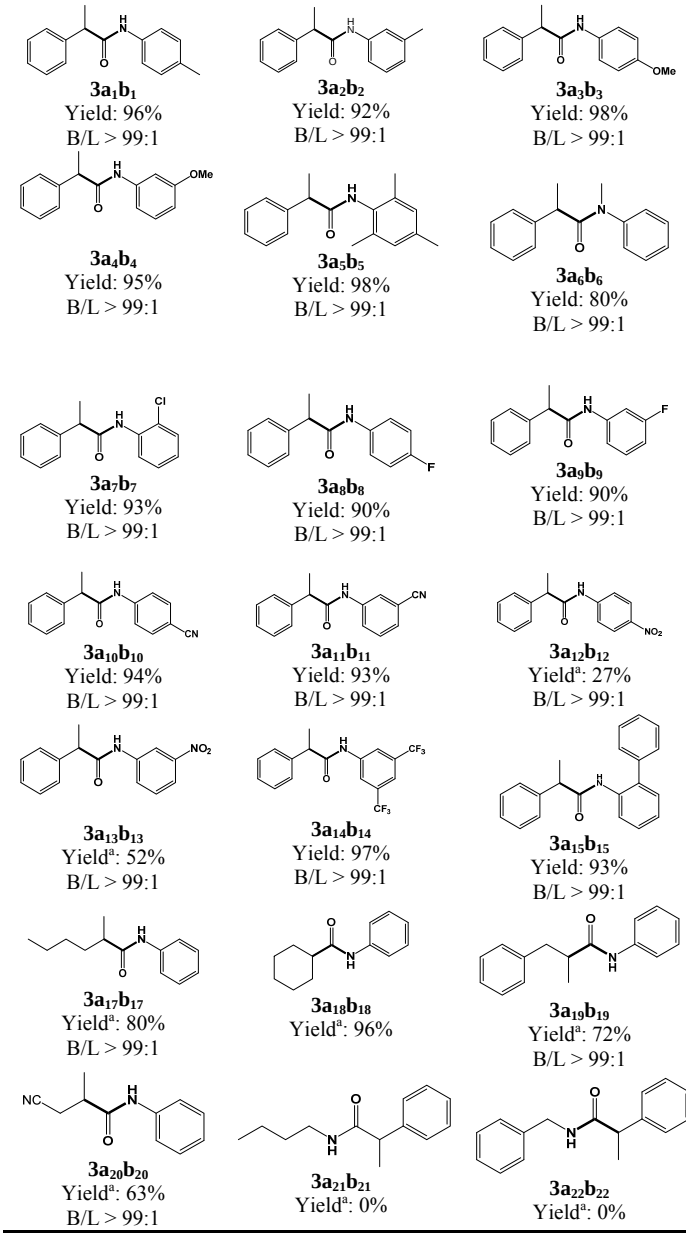


Scheme 2. Transformation of amide to useful compound

Table 2 Substrate scope of the palladium catalysed aminocarbonylation of alkenes (**1a**) with animes (**2a**).



1a **2b** **3ab**



Reaction conditions: **1** (11 mmol), **2** (1 mmol), $PdCl_2$ (5 mol% based on **2**). $P(2\text{-}OMePh)_3$ (0.12 mmol), THF (10 ml), CO (50 atm), T: 125 °C, t: 2 h, [a] t: 20 h, Yields quoted correspond to isolated yields.

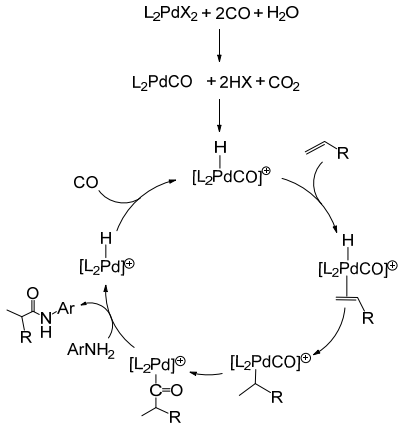
The data shown in Table S5 implies that the yield of the product is related to the N-H bond dissociation energy[16], i.e. the lower the bond dissociation energy the higher yield of the product, and is therefore implicated in the rate determining step of the catalytic cycle (see below).

The addition of aniline to activated alkenes using palladium/phosphine catalysts typically requires co-catalytic amounts of acid[17] and, similarly, aminocarbonylation of alkenes using $Pd(acac)_2$ requires p-TsOH[12]. In both cases the co-catalyst is needed to generate the active palladium hydride species. Carbonylation reactions involving metal hydride species assisted by

the presence of acid have been reported[18]. However, using the PdX_2/tris(2-methoxyphenyl)phosphine (X = Cl or Br) catalysts the acid is generated in situ (see below).

The hydroamination of alkenes also needs additional acid to produce metal hydride species and the reaction conditions are similiar to those used for the aminocarbonylation of alkenes[20]. However, PdX_2/tris(2-methoxyphenyl)phosphine (X = Cl or Br) is not active for the hydroamination of alkenes in the absence of acid, and therefore it seems likely that CO not only acts as a substrate but also helps to regenerate the active Pd(0) catalyst and generate HCl in situ, also explaining why palladium(II) halides are the most efficient catalyst precursors. Indeed, an ESI mass spectrum was recorded of the post-reaction solution and a peak at m/z 811 is observed that may be tentative assigned to $[L_2PdH]^+$ (L = tris(2-methoxyphenyl)phosphine), and based on this observation a catalytic cycle may be proposed, see Scheme 2. In this catalytic cycle water is required to generate the active catalyst, and in agreement with this hypothesis the yield of the product is 10% when the reaction is performed in dry THF, and on addition of water (40 mg) the yield of desired product increases to 92%. Importantly, insertion of the hydride usually takes place at the most sterically crowded carbon atom of a coordinated alkene, but with this catalystic system the opposite is observed, hence giving high yields of the branched product. This is presumably due to the use of bulky monophosphine ligands that result in a pseudo-linear geometry (P-Pd-P angle of ca. 180°) which favors attach at the less crowded carbon atom.

Two principal pathways appear to be involved, the one mentioned above involving initial activation of the alkene, which is presumably the dominant route, and another involving primary activation of the amine (Scheme S1). In the ESI mass spectrum a peak at m/z 845.08 may be attributed to $[L_2PdCl]^+$ and one at m/z 938.75 to $[L_2PdClNH_2Ph]^+$ indicative of this latter pathway (Figure S1). Indeed, Milstein and co-workers reported the Ir(I)-catalyzed addition of aniline to norbornylene via N-H activation in absence of a Bronsted acid[21], which supports a secondary mechanism involving amine activation.



Scheme 2. Proposed catalytic cycle commencing with activation of the alkene (X = Cl or Br).

Conclusions

A simple palladium-based catalyst is described for the general and selective aminocarbonylation of alkenes that affords N-aryl monosubstituted carboxamides. A wide range of aromatic amines may be efficiently transformed in good yield and usually with high regioselectivity. Notably, the catalyst does not require acid, base or any other promoters and employs a commercially available bulky monophosphine ligand thus facilitating reaction scale-up. It seems plausible that a pseudo-linear, cationic P-Pd-P species is involved in the process that facilitates insertion of the hydride to the least sterically crowded C-atom of the coordinated alkene.

Notes and references

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland. E-mail: huizhen.liu@epfl.ch;
Fax: +41-21-6939865

‡ Electronic supplementary information (ESI) available: Full experimental details including instrumentation, catalytic procedures, mechanistic studies and spectroscopic data. See DOI: 10.1039/c3cc47015f

1 a) T. Cupido, J. T. Puche, J. Spengler, F. Albericio, Curr. Opin. Drug Discovery Dev. 2007, 10, 768-831; b) J. W. Bode, Curr. Opin. Drug Discovery Dev. 2006, 9, 765-775; c) J. M. Humphrey, A. R. Chamberlin, Chem. Rev. 1997, 97, 2243-2266.
2 C. Singh, V. Kumar, U. Sharma, N. Kumar, B. Singh, Curr. Org. Syn. 2013, 10, 241-264. (The references cited in this publication).
3 C. Gunanathan, Y. B. David, D. Milstein, Science 2011, 317, 790-792.
4 V. R. Pattabiraman, J. W. Bode, Nature 2011, 480, 471-479.
5 C. L. Allen, J. M. Williams, J. Chem. Soc. Rev. 2011, 40, 3405-3415.
6 a) A. Brennfhrer, H. Neumann, M. Beller, Angew. Chem. Int. Ed. 2009,48, 4114; b) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, N. G. Simon, M. R. Tyler, G. C. Gag, K. I. L. Jones, B. Milburn, Angew. Chem. Int. Ed. 2009, 48, 1830-1833; c) R. Giri, J. Q. Yu, J. Am. Chem. Soc. 2008, 130, 14082-14083; d) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, J. Am. Chem. Soc. 2009, 131, 6898-6899; e) R. Lang, L. J. Shi, D. F. Li, C. G. Xia, F. W. Li, Org. Lett. 2012, 14(16), 4130-4133; f) A. Takacs, A. Czompa, G. Krajsovszky, P. Matyus, L. Kollar, Tetrahedron 2012, 68, 7855-7860. g) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, J. Org. Chem. 2008, 73, 7102-7107; h) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, Angew. Chem. Int. Ed. 2007, 46, 8460 –8463. i) Ziyauddin S. Qureshi, Santosh A. Revankar, Mayur V. Khedkar, Bhalchandra M. Bhanage Catal. Today 2012, 198 148– 153.
7 Y. Izawa, I. Shimizu, A. Yamamoto, Bull. Chem. Soc. Jpn. 2004, 77, 2033-2045.
8 H. Zhang, R. Y. Shi, A. X. Ding, L. J. Lu, B. Chen, A. W. Lei, Angew. Chem. Int. Ed. 2012, 51, 12542-12545.
9 D. D. Liang, Z. W. Hu, J. L. Peng, J. B. Huang, Q. Zhu, Chem. Commun. 2013, 49, 173.
10 H. Liu, G. Laurenczy, N. Yan, P. Dyson, Chem. Comm 2014, 50, 341-343.
11 S. I. Lee, S. U. Son, Y. K. Chung, Chem. Comm. 2002, 1310-1311.
12 X. J. Fang, R. Jackstell, M. Beller, Angew. Chem. Int. Ed. 2013, 52, 14089-14093.
13 (a) J. Sakowski, M. Bohm, I. Sattler, H. M. Dahse, M. Schlitzer, J. Med. Chem., 2001, 44, 2886-2899; (b) S. Kiren, L. J. Williams, Org. Lett., 2005, 7, 2905-2908; (c) J. M. Pedersen, W. R. Bowman, M. R. J. Elsegood, A. J. Fletcher and P. J. Lovell, J. Org. Chem., 2005, 70, 10615-10618; (d) Q. Lu, D. S. Wang, C. S. Chen, Y. D. Hu, C. S. Chen, J. Med. Chem., 2005, 48, 5530-5535; (e) M. R. Yadav, D. M. Nimekar, A. Ananthakrishnan, P. S. Brahmkshatriya, S. T. Shirude, R. Giridhar, A. Parmar and R. Balaraman, Bioorg. Med. Chem., 2006, 14, 8701-8706; (f) A. Moriconi, M. C. Cesta, M. N. Cervellera, A. Aramini, S. Coniglio, S. Colagioia, A. R. Beccari, C. Bizzarri, M. R. Cavicchia, M. Locati, E. Galliera, P. D. Benedetto, P. Vigilante, R. Bertini and M. Allegretti, J. Med. Chem., 2007, 50, 3984-4002; (g) Y. Jiang, C. A. Chen, K. Lu, I. Daniewska, J. D. Leon, R. Kong, C. Forray, B. Li, L. G. Hegde, T. D. Wolinsky, D. A. Craig, J. M. Wetzel, K. Andersen and M. R. Marzabadi, J. Med. Chem., 2007, 50, 3870-3882.
14 Y. X. Jia, E. P. Kundig, Angew. Chem. Int. Ed. 2009, 48, 1636 –1639.
15 W. C. Ye, J. Mo, T. K. Zhao, B. Xu, Chem Comm. 2009, 3246-3248.
16 Y. R. Luo, Handbook of Bond Dissociation Energies in Organic Compounds, CRC Press, Boca Raton, FL, 2002.
17 A. L. Seligson, W. C. Trogler, Organometallics 1993, 12, 744-751.
18 Q. Liu, L. P. Wu, H. J. Jiao, X. J. Fang, R. Jackstell, M. Beller, Angew. Chem. Int. Ed. 2013, 125, 8222 –8226.
19 M. Movassaghi, M. D. Hill, J. Am. Chem. Soc. 2006, 128 14254-14255.
20 J. F. Hartwig, Pure Appl. Chem., 2004, 76(3), 507–516.
21 L. C. Albert, J. C. Calabrese, D. Milstein J. Am. Chem. Soc. 1988, 110(20) 6738-6744.