Pd-catalyzed oxidative cross-coupling of *N*-tosylhydrazones with arylboronic acids†

Xia Zhao,[a] Jing Jing,[a] Kui Lu,[a] Yan Zhang[a] and Jianbo Wang*[ab]

Received (in College Park, MD, USA) 7th December 2009, Accepted 20th January 2010
First published as an Advance Article on the web 3rd February 2010
DOI: 10.1039/b925590g

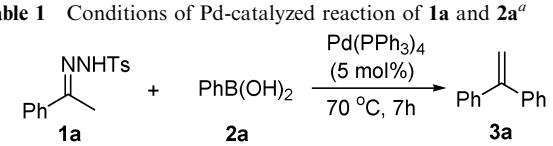
The Pd-catalyzed reaction of *N*-tosylhydrazones and arylboronic acids provides olefin derivatives. This oxidative cross-coupling is suggested to proceed through a migratory insertion process of a Pd carbene intermediate.

Pd-catalyzed cross-coupling reactions of diazo compounds have recently emerged as a new type of cross-coupling reaction.[1–4] We have reported a Pd-catalyzed cross-coupling reaction of α-diazocarbonyl compounds with boronic acids, which affords α,β-unsaturated carbonyl compounds in high yields.[1e] The reaction presumably proceeds through a migratory insertion process of the Pd carbene intermediate.[5] To further extend the scope of this cross-coupling reaction, we conceived to employ diazo compounds that do not bear electron withdrawing substituents as the substrates in this reaction. Diazo compounds without electron withdrawing groups are usually unstable and thus difficult to handle. The recently developed methods of *in situ* generation of diazo compounds have largely circumvented this problem. Treatment of *N*-tosylhydrazones with base is the most widely practised method for this purpose.[6] The reaction conditions are compatible with the Pd-catalyzed cross-coupling reaction, as demonstrated by Barluenga and co-workers' reports on a Pd-catalyzed reaction of *N*-tosylhydrazones with aryl bromides in the presence of lithium *tert*-butoxide,[1b,c] and by our own recent report on the Pd-catalyzed reaction of *N*-tosylhydrazones with benzyl halides.[2c] As a continuation, we report in this communication the Pd-catalyzed oxidative cross-coupling of *N*-tosylhydrazone with aromatic boronic acids.

Initially, the cross-coupling reaction between acetophenone *N*-tosylhydrazone **1a** and phenyl boronic acid **2a** was carried out under various conditions. From the mechanistic rational (*vide infra*), the cross-coupling reaction starts from the transmetallation of boronic acid to the Pd(II) catalyst.[7] At the end of the reaction, a Pd(0) species is released, which needs to be oxidized in order to regenerate the Pd(II) catalyst. Initially, Ag_2CO_3 was employed as the oxidant. Thus, with $Pd(PPh_3)_4$ as catalyst and LiO^tBu as base, the reaction of *N*-tosylhydrazone **1a** and boronic acid **2a** in dioxane at 70 °C affords 1,1-diphenylethylene **3a** in 16% yield (Table 1, entry 1). Further optimization of the reaction was focused on the search for a suitable oxidant. A number of oxidants such as Ag_2CO_3, $^tBuOO^tBu$, $KBrO_3$, $CuCl_2$ and $Cu(OAc)_2$ were screened and none of them was efficient for the reaction (entries 2–6). To our delight, we observed that the combination of CuCl and oxygen under balloon pressure was effective and promoted the reaction in moderate to high yield (entry 7).

Next, we observed that solvent significantly affected this coupling reaction. Toluene, MeCN and DMSO were tested, but they were all less effective as compared with dioxane (entries 8–10). To further optimize the reaction, some copper salts were examined.† We found that both Cu(II) and Cu(I) could work for the reaction (entries 13–16). For CuCl, the molar percentage could be reduced to 10%, affording the highest yield (entry 12). Since the base used in the reaction also plays an important role, several bases such as KO^tBu, NaO^tBu, Cs_2CO_3, were also examined. However, they are all less efficient compared with LiO^tBu. Finally, we studied different palladium catalysts.† Although either Pd(0) or Pd(II) catalysts could catalyze the cross-coupling reaction, none of them exceeded the simple $Pd(PPh_3)_4$. Thus, the optimized reaction conditions were as follows: **1a** (0.25 mmol), **2a** (0.75 mmol), $Pd(PPh_3)_4$ (5 mol%), CuCl (10 mol%), LiO^tBu (1.25 mmol), in dioxane at 70 °C.

Table 1 Conditions of Pd-catalyzed reaction of **1a** and **2a**[a]



Entry	Oxidant (% mol)	Base (equiv.)	Solvent	Yield (%)[b]
1	Ag_2CO_3 (200)	LiO^tBu (3)	Dioxane	16
2	$^tBuOO^tBu$ (200)	LiO^tBu (3)	Dioxane	10
3	$^tBuOO^tBu$ (300)	LiO^tBu (3)	Dioxane	13
4	$Cu(OAc)_2$ (200)	LiO^tBu (4)	Dioxane	Trace
5	$CuCl_2$ (200)	LiO^tBu (4)	Dioxane	Trace
6	$KBrO_3$ (150)	LiO^tBu (5)	Dioxane	8
7	O_2, CuCl (20)	LiO^tBu (4)	Dioxane	47
8	O_2, CuCl (20)	LiO^tBu (4)	Toluene	34
9	O_2, CuCl (20)	LiO^tBu (4)	MeCN	22
10	O_2, CuCl (10)	LiO^tBu (5)	DMSO	7
11	O_2, CuCl (20)	LiO^tBu (5)	Dioxane	68
12	O_2, CuCl (10)	LiO^tBu (5)	Dioxane	71
13	O_2, CuBr (20)	LiO^tBu (5)	Dioxane	60
14	O_2, $CuCl_2$ (20)	LiO^tBu (5)	Dioxane	64[c]
15	O_2, CuI (20)	LiO^tBu (5)	Dioxane	13
16	O_2, CuOTf (10)	LiO^tBu (5)	Dioxane	26

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), $Pd(PPh_3)_4$ (5 mol%), solvent (2 mL). [b] Isolated yield. [c] In an atmosphere of $O_2 : N_2 = 1 : 4$.

[a] *Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China. E-mail: wangjb@pku.edu.cn*
[b] *The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

† Electronic supplementary information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/b925590g

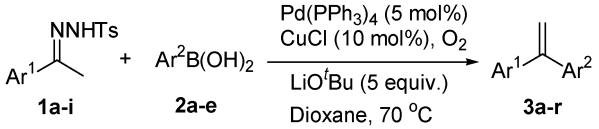
A series of substituted acetophenone *N*-tosylhydrazones **1a–i** and arylboronic acids **2a–e** were examined under the optimal reaction conditions. As shown in Table 2, the reaction gave moderate to good yields in most cases. The results do not show a significant electronic effect in this reaction. Since the homocoupling of arylboronic acids is inevitable as a side reaction,[8] in all cases 3 equiv. of arylboronic acids were needed in order to completely transform the *N*-tosylhydrazones to the products.

The reaction could be extended to hydrazone substrates bearing substituents other than a methyl group. Thus, the Pd-catalyzed reaction of **4a–g** and **2a**,**b** under identical reaction conditions afforded **5a–h** in good yields in most cases (Scheme 1).

A plausible mechanism for this Pd-catalyzed oxidative coupling is proposed in Scheme 2. The reaction is initiated by the oxidation of the CuCl to Cu(II) species by oxygen, which then oxidize Pd(0) to Pd(II) species. Transmetallation of the Pd(II) species with the arylboronic acid affords aryl-palladium species **A**, which reacts with the *in situ* generated diazo substrate to give Pd carbene complex **B**. Migratory insertion of the aryl group to the carbenic carbon of the Pd carbene species affords the intermediate **C**.[1–5] Finally, β-hydride elimination of **C** affords the product and regenerates the Pd(0) species in the presence of base.

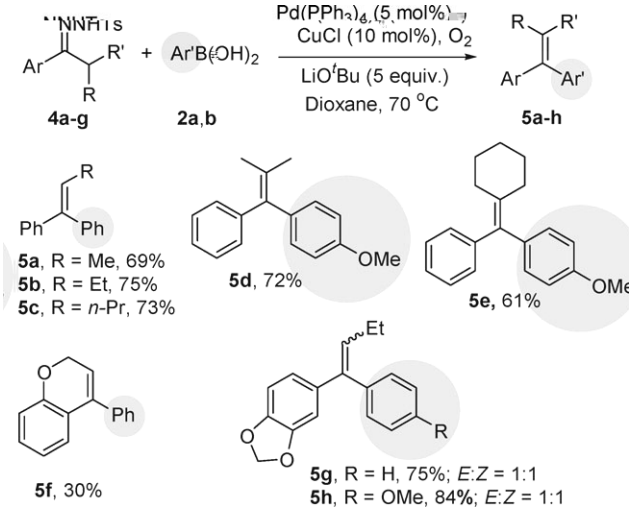
However, the possibility exists that the Pd carbene is generated directly from Pd(II) and the diazo substrate. The formation of the olefin product may be due to the 1,2-H shift

Table 2 $Pd(PPh_3)_4$-catalyzed reactions of **1a–i** and **2a–e**[a]



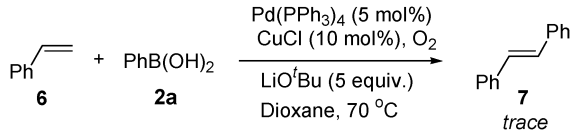
Entry	**1**, Ar^1	**2**, Ar^2	*t*/h	Yield (**3**, %)[b]
1	**1a**, C_6H_5	**2a**, C_6H_5	7	**3a**, 71[c]
2	**1a**, C_6H_5	**2b**, *p*-$MeOC_6H_4$	7	**3b**, 70
3	**1a**, C_6H_5	**2c**, *m*-ClC_6H_4	7	**3c**, 47
4	**1b**, *p*-MeC_6H_4	**2a**, C_6H_5	6.5	**3d**, 70[c]
5	**1b**, *p*-MeC_6H_4	**2b**, *p*-$MeOC_6H_4$	10	**3e**, 71
6	**1b**, *p*-MeC_6H_4	**2d**, *p*-MeC_6H_4	10	**3f**, 67[d]
7	**1c**, *p*-ClC_6H_4	**2a**, C_6H_5	9	**3g**, 52
8	**1c**, *p*-ClC_6H_4	**2b**, *p*-$MeOC_6H_4$	8	**3h**, 67
9	**1d**, *m*-$MeOC_6H_4$	**2a**, C_6H_5	8.5	**3i**, 57
10	**1d**, *m*-$MeOC_6H_4$	**2d**, *p*-MeC_6H_4	7	**3j**, 68
11	**1e**, *p*-$MeOC_6H_4$	**2a**, C_6H_5	7	**3b**, 67
12	**1e**, *p*-$MeOC_6H_4$	**2b**, *p*-$MeOC_6H_4$	7	**3k**, 76
13	**1e**, *p*-$MeOC_6H_4$	**2c**, *m*-ClC_6H_4	7	**3l**, 40
14	**1e**, *p*-$MeOC_6H_4$	**2d**, *p*-MeC_6H_4	7	**3e**, 82
15	**1e**, *p*-$MeOC_6H_4$	**2e**, *m*-MeC_6H_4	7	**3m**, 71
16	**1f**, 3,4-$Me_2C_6H_3$	**2a**, C_6H_5	9	**3n**, 57[c]
17	**1g**, 3,5-$Me_2C_6H_3$	**2a**, C_6H_5	7	**3o**, 63[c]
18	**1g**, 3,5-$Me_2C_6H_3$	**2b**, *p*-$MeOC_6H_4$	9	**3p**, 30
19	**1h**, *p*-$CF_3C_6H_4$	**2b**, *p*-$MeOC_6H_4$	6	**3q**, 64
20	**1i**, *p*-NCC_6H_4	**2a**, C_6H_5	5	**3r**, 51

[a] Reaction conditions: **1a–i** (0.25 mmol), **2a–e** (0.75 mmol), $Pd(PPh_3)_4$ (5 mol%), CuCl (10 mol%), LiO^tBu (1.25 mmol), dioxane (2 mL), 70 °C. [b] Yield of isolated product after chromatography. [c] The product and by-product biphenyl were inseparable on a column. The yield was determined by ^1H NMR. [d] The product and by-product 4,4′-dimethylbiphenyl were inseparable on a column. The yield was determined by ^1H NMR.



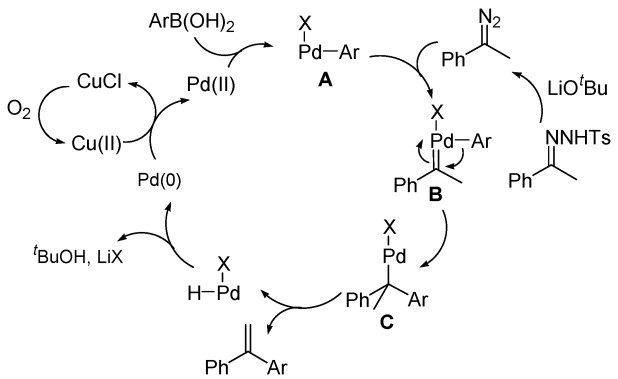
Scheme 1 Pd-catalyzed reaction of **4a–g** with **2a**,**b**.

of the Pd carbene intermediate and subsequent Heck–Mizoroki-type reaction.[9,10] To confirm this possible pathway, styrene **6** and phenyl boronic acid **2a** were reacted under the identical conditions (eqn (1)). Only a trace amount of 1,2-diphenylethylene **7** was observed and no 1,1-diphenylethylene could be detected in the ^1H NMR spectrum of the crude product. Consequently, this pathway can be excluded.



(1)

To gain further insight into the reaction mechanism, we examined the kinetic isotope effect (KIE) of the reaction (Scheme 3). At first, intermolecular competition was carried out with d_3-deuterated *N*-tosylhydrazone **8** and **1a**. The competition reaction gave **3b** and **9** in equal amount (k_H/k_D = 1.0). On the other hand, the intramolecular competition experiment with d_1-deuterated *N*-tosylhydrazone **10** gave a KIE of 2.54. The significant KIE in the β-hydride elimination step and lack of KIE for the overall reaction (intermolecular competition) clearly suggest that β-hydride elimination is not in the rate determining step. It is noted that the KIE value observed in the intramolecular competition is comparable to those



Scheme 2 Possible reaction pathways.

reported for β-hydride elimination in Pd-catalyzed reactions.[11] Thus, the KIE results are in accordance with the proposed reaction mechanism shown in Scheme 2.

In conclusion, we have reported the first oxidative cross-coupling reaction between *N*-tosylhydrazone and arylboronic acids. This study shows that the coupling of *N*-tosylhydrazone and arylboronic acids under oxidative conditions can compete with the oxidative homocoupling of arylboronic acids, which indicates that the interaction of arylpalladium species with diazo substrates and the subsequent processes are both highly efficient. This study further demonstrates the generality of the transformations based on Pd carbene processes.

The project was supported by the NSFC (Grant No. 20832002, 20772003, 20821062) and 973 Program (No. 2009CB825300).

Notes and references

1 (*a*) K. L. Greenman, D. S. Carter and D. L. Van Vranken, *Tetrahedron*, 2001, **57**, 5219; (*b*) J. Barluenga, P. Moriel, C. Valdés and F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 5587; (*c*) J. Barluenga, M. Tomás-Gamasa, P. Moriel, F. Aznar and C. Valdés, *Chem.–Eur. J.*, 2008, **14**, 4792; (*d*) R. Kudirka and D. L. Van Vranken, *J. Org. Chem.*, 2008, **73**, 3585; (*e*) C. Peng, Y. Wang and J. Wang, *J. Am. Chem. Soc.*, 2008, **130**, 1566.

2 (*a*) K. L. Greenman and D. L. Van Vranken, *Tetrahedron*, 2005, **61**, 6438; (*b*) W.-Y. Yu, Y.-T. Tsoi, Z. Zhou and A. S. C. Chan, *Org. Lett.*, 2009, **11**, 469; (*c*) Q. Xiao, J. Ma, Y. Yang, Y. Zhang and J. Wang, *Org. Lett.*, 2009, **11**, 4732.

3 (*a*) S. K. J. Devine and D. L. Van Vranken, *Org. Lett.*, 2007, **9**, 2047; (*b*) S. K. J. Devine and D. L. Van Vranken, *Org. Lett.*, 2008, **10**, 1909; (*c*) R. Kudirka, S. K. J. Devine, C. S. Adams and D. L. Van Vranken, *Angew. Chem., Int. Ed.*, 2009, **48**, 3677.

4 S. Chen and J. Wang, *Chem. Commun.*, 2008, 4198.

5 For reports on the migratory insertion process of stable Pd carbene species, see: (*a*) A. C. Albéniz, P. Espinet, R. Manrique and A. Pérez-Mao7p, *Angew. Chem., Int. Ed.*, 2002, **41**, 2363; (*b*) M. Bröring, C. D. Brandt and S. Stellwag, *Chem. Commun.*, 2003, 2344; (*c*) D. Solé, L. Vallverdú, X. Solans, M. Font-Bardia and J. Bonjoch, *Organometallics*, 2004, **23**, 1438; (*d*) A. C. Albéniz, P. Espinet, R. Manrique and A. Pérez-Mao7p,*Chem.–Eur. J.*, 2005, **11**, 1565; (*e*) A. C. Albéniz, P. Espinet, A. Pérez-Mao7p, A. Nova and G. Ujaque, *Organometallics*, 2006, **25**, 1293.

6 J. R. Fulton, V. K. Aggarwal and J. de Vicente, *Eur. J. Org. Chem.*, 2005, 1479.

7 For selected reviews on Pd-catalyzed coupling reactions with arylboronic compounds, see: (*a*) A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178; (*b*) N15.5200-AM Suzukn,