Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 9333

Received 17th September 2014,
Accepted 1st October 2014

DOI: 10.1039/c4ob01979b

www.rsc.org/obc

Palladium-catalyzed coupling of *N*-tosylhydrazones and β-bromostyrene derivatives: new approach to 2*H*-chromenes†

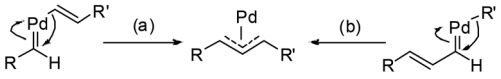
Yamu Xia,[a,b] Ying Xia,[b] Yan Zhang[b] and Jianbo Wang*[b]

2*H*-Chromene is an important structural motif that exists in natural products and non-natural compounds possessing interesting biological activities. In this investigation, a highly efficient approach toward 2*H*-chromenes has been developed based on palladium-catalyzed coupling of *N*-tosylhydrazones and β-bromostyrenes. The mechanism of this reaction is proposed that involves the formation of vinyl palladium by carbene migratory insertion and the intramolecular nucleophilic substitution.

2*H*-Chromene is a characteristic molecular structure, and the compounds based on this skeleton exhibit interesting and diverse biological activities, including anti-inflammatory, antioxidant, anti-tumour and antibacterial activity.[1] Due to their potential applications, the synthesis of 2*H*-chromenes has attracted significant attention. The typical approach toward 2*H*-chromenes is based on the condensation of salicylaldehyde derivatives with various olefins and ester derivatives in the presence of a base or an acid.[2] Recently, transition-metal-catalyzed reactions have been explored in the synthesis of 2*H*-chromenes.[3] For example, Aponick and co-workers reported a gold(I)-catalyzed synthesis of 2*H*-chromenes through *endo*-cyclization reaction of *o*-(1-hydroxyallyl)phenols, which are readily prepared from salicylaldehydes.[3b] Stratakis and co-workers reported the application of Au/TiO_2 as a heterogeneous gold-based catalyst to catalyze the selective cycloisomerisation of aryl propargyl ethers to afford 2*H*-chromenes.[3c] Recently, de Bruin and co-workers have developed an approach to 2*H*-chromenes that involves the [Co^{II}(Por)]-catalyzed metalloradical coupling-cyclization.[4] Although many efforts have been devoted to the synthesis of 2*H*-chromenes, the existing approaches still suffer from drawbacks such as complicated catalytic systems and low efficiency, therefore further development of new synthetic methods to 2*H*-chromene is highly desirable.

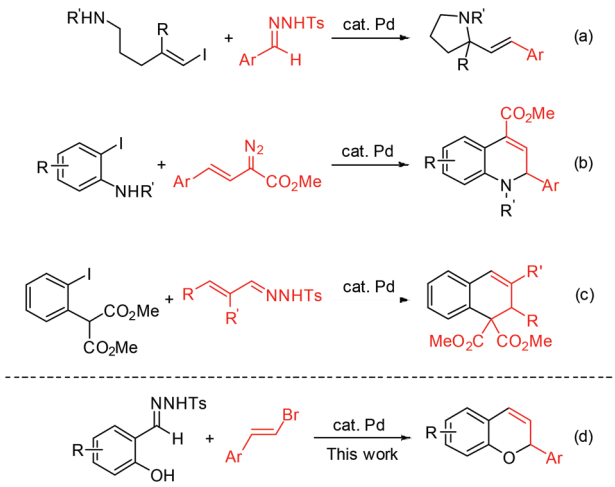
On the other hand, since the pioneering work of Van Vranken and co-workers,[5,6] the metal-catalyzed reactions with the carbene migratory insertion have emerged as a new type of cross-coupling reactions for the construction of carbon–carbon and carbon–heteroatom bonds.[7] Based on the migratory insertion process, cascade reactions have been designed to construct complex molecular structures.[7e] In particular, the π-allyllic palladium intermediate can be generated from carbene migratory insertion, which is further incorporated into a series of transformations.[8] In principle, the π-allyllic palladium intermediate is generated in two ways: (a) through the migration of a vinyl ligand from palladium to carbenic carbon; (b) through the migration of the R′ group (mostly an aromatic group) from palladium to vinyl carbenic carbon (Scheme 1). The π-allyllic palladium intermediate thus generated is trapped by a nucleophile, in either an intramolecular or an intermolecular manner. In the case of intramolecular reaction, various ring structures can be constructed efficiently.

In this context, Van Vranken and co-workers have reported a series of three-component cascade reactions, which involves π-allyl palladium species generated from palladium carbene migratory insertion and subsequent nucleophilic addition.[8d–f] The intramolecular reaction of this type has been successfully applied in the construction of pyrrollidines and piperidines (Scheme 2, a).[8g] Liang and co-workers have reported similar cascade reactions for the synthesis of 1,2-dihydroquinoline and dihydronaphthalene derivatives.[8h,i] It is noteworthy that in these transformations, only nitrogen and carbon nucleophiles have been employed to trap the η^3-allyl palladium species. Herein we report the exploration of using hydroxyl group as an



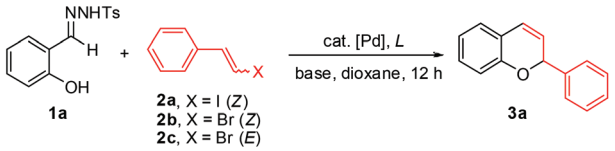
Scheme 1 π-Allyllic palladium intermediate generated from carbene migratory insertion.

[a]*College and Chemical Engineering, Qingdao University of Science & Technology, Qingdao 266042, China*
[b]*Beijing National Laboratory of Molecular Sciences (BNLMS), 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*
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob01979b



Scheme 2 The palladium-catalyzed cascade reactions involving carbene migratory insertion.

Table 1 Optimization of the reaction conditions[a]

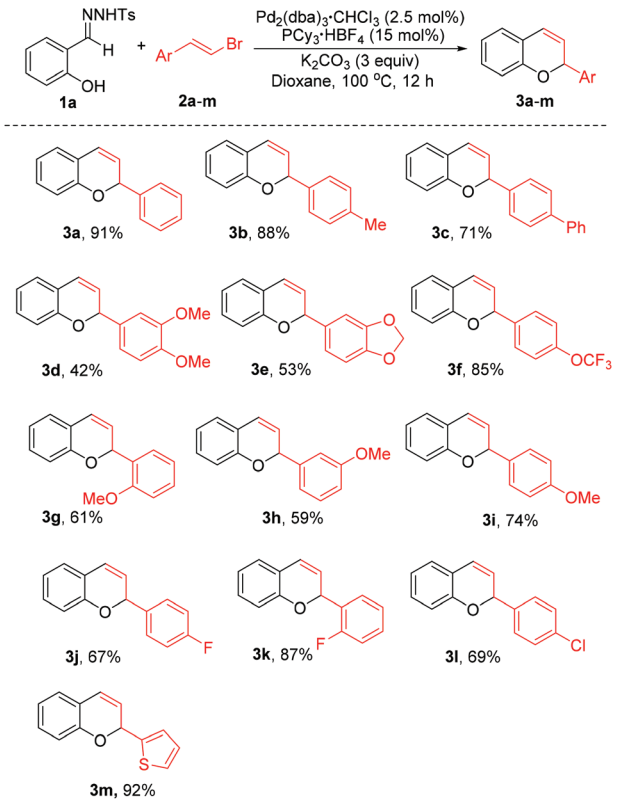


Entry	Cat. (mol%)/L (mol%)	2	Base	T (°C)	Yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$(5)	**2a**	K_2CO_3	90	Trace
2	$Pd(PPh_3)_2(OAc)_2$(5)	**2a**	K_2CO_3	90	Trace
3	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/PPh_3(15)	**2a**	K_2CO_3	90	31
4	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/PPh_3(15)	**2a**	K_3PO_4	90	15
5	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/PPh_3(15)	**2a**	Cs_2CO_3	90	Trace
6	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/DPPP(15)[c]	**2a**	K_2CO_3	90	12
7	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)[d]	**2a**	K_2CO_3	90	41
8	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)	**2b**	K_2CO_3	90	61
9	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)	**2b**	K_2CO_3	100	67
10	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)	**2b**	K_2CO_3	120	58
11[e]	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)	**2b**	K_2CO_3	100	75
12[f]	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)	**2b**	K_2CO_3	100	90
13[f]	$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)	**2c**	K_2CO_3	100	91
14[f]	**$Pd_2(dba)_3{\cdot}CHCl_3$(2.5)/L1(15)**	**2c**	**K_2CO_3**	**100**	**83**

[a] All the reactions were carried out with **1a** (0.20 mmol), **2** (0.20 mmol) and base (3.0 equiv.) in dioxane (2 mL) for 12 h. [b] Yield of the isolated product. [c] DPPP: 1,3-bis(diphenylphosphino)propane. [d] L1 = $PCy_3{\cdot}HBF_4$. [e] The ratio of **1a** : **2** is 1.5 : 1. [f] The ratio of **1a** : **2** is 2.0 : 1.

oxygen nucleophile in this type of reaction. The reaction constitutes an efficient approach toward 2*H*-chromenes starting with readily accessible salicyl *N*-tosylhydrazones.

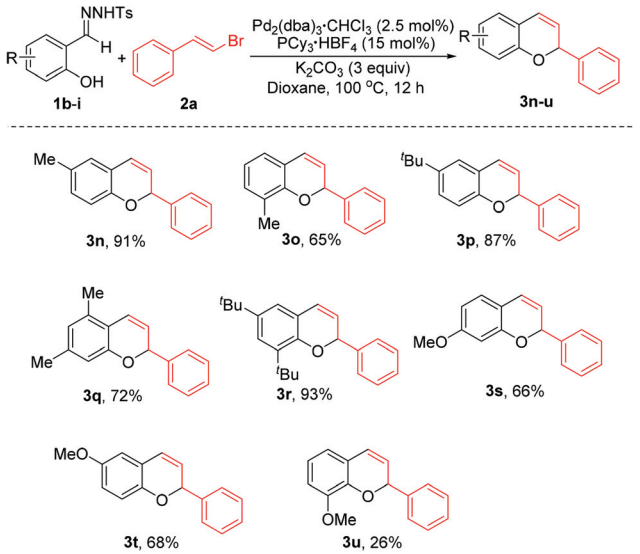
At the outset of the investigation, *N*-tosylhydrazone (**1a**) and 2-halovinyl benzene (**2a–c**) were used as the substrates to optimize the reactions (Table 1). After some initial experiments, **3a** could be obtained in 31% yield under the following conditions: with **2a** as the substrate, 90 °C, PPh_3 as the ligand, K_2CO_3 as the base and dioxane as the solvent (entry 3). Since the substrates and the ligands may significantly affect the reaction, phosphine ligands and other β-halostyrene substrates (**2b** and **2c**) were examined. The yields could be improved to 61% in the presence of the $PCy_3{\cdot}HBF_4$ ligand with **2b** as the substrate (entry 8). The reaction temperature has only a marginal effect on the reaction (entries 9 and 10). Since the *N*-tosylhydrazone (**1a**) was observed to undergo side reactions, the increase of **1a** led to the improvement of the yield (entries 11 and 12). Notably, it was observed that the more readily available *E*-(2-bromovinyl)benzene **2c** could provide the product with comparable yields (entries 13 and 14).



Scheme 3 The scope of β-bromostyrenes.

With the optimized conditions, we set out to investigate the scope of the reaction (Schemes 3 and 4). First, β-bromostyrenes **2a–m** with various substituents on the aromatic ring were employed in the reaction with **1a**. The reaction in general afforded the corresponding products in moderate to good yields. The effect of alkyl substituents was trivial (**3b**); however, both the strong electron-withdrawing and -donating groups led to slightly diminished yields (**3c–l**). It was observed that β-bromostyrene with fluoro substituents gave the corresponding products in moderate to good yields (**3j**, **3k**). It is also noteworthy that the reaction with (*Z*)-2-(2-bromovinyl)thiophene as the substrate afforded the product in 92% yield (**3m**). In addition, some β-bromostyrenes with the α- or β-substituent as substrates were examined, but the reaction yields were not satisfactory.

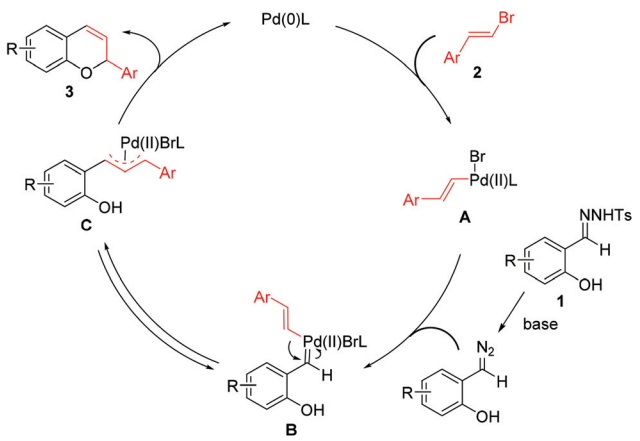
Next, the substrate scope of *N*-tosylhydrazone was studied. We found that *N*-tosylhydrazones with the electron-withdrawing substituents on the aromatic ring, such as nitro, chloro



Scheme 4 The scope of *N*-tosylhydrazones.

and bromo groups, did not afford the corresponding 2*H*-chromene product. However, the *N*-tosylhydrazones bearing electron-donating substituents could give the corresponding 2*H*-chromenes in moderate to good yields (Scheme 4). *N*-Tosylhydrazones with alkyl substitutions provided good yields (**3n–r**). In the case of strong electron-donating substituent, such as methoxy, the reaction resulted in diminished yields (**3s–u**). Furthermore, the position of the methoxy substituent on the aromatic ring could obviously affect the reaction.

Based on our understanding about the palladium-catalyzed coupling reaction and the cascade reactions, we proposed a possible mechanism as shown in Scheme 5. First, the Pd(II) intermediates **A** is formed by the oxidative addition of β-bromostyrene **2** to Pd(0) catalyst. The diazo compound, generated *in situ* from the *N*-tosylhydrazone **1**, is decomposed by Pd(II) species **A** to generate palladium carbenes **B**. Migratory insertion of a vinyl group gives the η^1-allyl palladium species, which is in equilibrium with the η^3-allyl palladium species **C**. Finally, nucleophilic addition by the intramolecular hydroxyl group



Scheme 5 Proposed reaction mechanism.

forms 2*H*-chromene **3**, with regeneration of the palladium(0) catalyst.

In summary, we have developed a new approach to synthesize 2*H*-chromenes. The reaction uses salicyl *N*-tosylhydrazones and β-bromostyrenes as the substrates. The reaction involves oxidative addition of β-bromostyrene to Pd(0), Pd(II) carbene formation and migratory insertion, and intramolecular nucleophilic substitution. The mild conditions and an effective cascade method make this reaction potentially useful for the synthesis of 2*H*-chromenes.

This project was supported by 973 Program (2012CB821600) and NSFC of China (grant 21272010 and 21332002).

Notes and references

1 For selected reports, see: (*a*) P. Williams, A. Sorribas and M.-J. R. Howes, *Nat. Prod. Rep.*, 2011, **28**, 48–77; (*b*) W.-H. Chen, R. Wang and Y.-P. Shi, *J. Nat. Prod.*, 2010, **73**, 1398–1403; (*c*) N. Iwata and S. Kitanaka, *J. Nat. Prod.*, 2010, **73**, 1203–1206; (*d*) M. Fridén-Saxin, T. Seifert, M. R. Landergren, T. Suuronen, M. Lahtela-Kakkonen, E. M. Jarho and K. Luthman, *J. Med. Chem.*, 2012, **55**, 7104–7113.

2 For examples, see: (*a*) Q. Wang and M. G. Finn, *Org. Lett.*, 2000, **2**, 4063–4065; (*b*) M. Rueping, U. Uria, M.-Y. Lin and I. Atodiresei, *J. Am. Chem. Soc.*, 2011, **133**, 3732–3735; (*c*) M. Jiang and M. Shi, *Org. Lett.*, 2010, **12**, 2606–2609.

3 (*a*) Y. Minami, Y. Shiraishi, K. Yamada and T. Hiyama, *J. Am. Chem. Soc.*, 2012, **134**, 6124–6127; (*b*) A. Aponick, B. Biannic and M. R. Jong, *Chem. Commun.*, 2010, **46**, 6849–6851; (*c*) C. Efe, I. N. Lykakis and M. Stratakis, *Chem. Commun.*, 2011, **47**, 803–805; (*d*) H. He, K.-Y. Ye, Q.-F. Wu, L.-X. Dai and S.-L. You, *Adv. Synth. Catal.*, 2012, **354**, 1084–1094; (*e*) T. J. A. Graham and A. G. Doyle, *Org. Lett.*, 2012, **14**, 1616–1619.

4 N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang and B. de Bruin, *J. Am. Chem. Soc.*, 2014, **136**, 1090–1096.

5 K. L. Greenman, D. S. Carter and D. L. Van Vranken, *Tetrahedron*, 2001, **57**, 5219–5225.

6 For the first report on the Pd-catalyzed coupling with *N*-tosylhydrazones, see: J. Barluenga, P. Moriel, C. Valdés and F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 5587–5590.

7 For reviews, see: (*a*) Y. Zhang and J. Wang, *Eur. J. Org. Chem.*, 2011, 1015–1026; (*b*) J. Barluenga and C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **50**, 7486–7500; (*c*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560–572; (*d*) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236–247; (*e*) Y. Xia, Y. Zhang and J. Wang, *ACS Catal.*, 2013, **3**, 2586–2598; (*f*) Z. Liu and J. Wang, *J. Org. Chem.*, 2013, **78**, 10024–10030.

8 (*a*) Q. Xiao, B. Wang, L. Tian, Y. Yang, J. Ma, Y. Zhang, S. Cheng and J. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 9305–9308; (*b*) X. Liu, X. Ma, Y. Huang and Z. Gu, *Org. Lett.*, 2013, **15**, 4814–4817; (*c*) Z. Liu, Y. Xia, S. Zhou, L. Wang, Y. Zhang and J. Wang, *Org. Lett.*, 2013, **15**, 5032–5035;

(*d*) S. K. L. Devine and D. L. Van Vranken, *Org. Lett.*, 2007, **9**, 2047–2049; (*e*) S. K. L. Devine and D. L. Van Vranken, *Org. Lett.*, 2008, **10**, 1909–1911; (*f*) R. Kudirka, S. K. J. Devine, C. S. Adams and D. L. Van Vranken, *Angew. Chem., Int. Ed.*, 2009, **48**, 3677–3680; (*g*) A. Khanna, C. Maung, K. R. Johnson, T. T. Luong and D. L. Van Vranken, *Org. Lett.*, 2012, **14**, 3233–3235; (*h*) P.-X. Zhou, Z.-Z. Zhou, Z.-S. Chen, Y.-Y. Ye, L.-B. Zhao, Y.-F. Yang, X.-F. Xia, J.-Y. Luo and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 561–563; (*i*) Y.-Y. Ye, P.-X. Zhou, J.-Y. Luo, M.-J. Zhong and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 10190–10192; (*j*) P.-X. Zhou, J.-Y. Luo, L.-B. Zhao, Y.-Y. Ye and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 3254–3256; (*k*) P.-X. Zhou, Y.-Y. Ye and Y.-M. Liang, *Org. Lett.*, 2013, **15**, 5080–5083.