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Palladium-catalyzed annulation of internal alkynes in aqueous medium†

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To facilitate precatalyst recovery and reuse, we have developed a fluorous, oxime-based palladacycle **1** and demonstrated that it is a very efficient and versatile precatalyst for carbo- and heteroannulation of internal alkynes with functionalized aryl halides in aqueous medium. A uniform reaction condition for these annulation reactions was also developed.

Introduction

Annulation of internal alkynes with functionalized aryl halides is a versatile and useful method for the synthesis of a wide variety of carbo- and heterocycles (Fig. 1).[1–8] To date, many homogeneous transition metal-based catalytic systems have been developed for this transformation.[9] Although homogeneous catalysis have many advantages, difficulties in separation and recovery of the catalyst and product contamination with traces of the heavy metal are common problems encountered which restrict their applications in the industries.[10] To circumvent this problem, various annulation strategies involving heterogeneous catalysis have been developed.[11] Heterogeneous catalysts can be separated from the reaction mixture in a straightforward manner, such as by filtration, but on the other hand, diffusion of the reactants to the solid catalyst occurs less readily, thus affecting the reaction rate.

An alternative strategy is fluorous catalysis which combines the advantages of homogenous catalysis for reactivity and heterogeneous catalysis for catalyst recovery.[12] Since the seminal work by Horváth and Rábai,[12b] a selection of fluorous ligands and catalysts have been developed for the catalysis of a variety of reactions. However to the best of our knowledge, there are no previous reports on the fluorous catalysis of carbo- and heteroannulation of internal alkynes with functionalized aryl halides. Previously, we reported the synthesis of a chemically and thermally stable fluorous, oxime-based palladacycle **1** (Fig. 2) and demonstrated its application as a precatalyst in a wide variety of C–C coupling reactions in aqueous and organic media under microwave irradiation.[13] As palladacycle **1** is a "light fluorous" compound, it can be easily recovered using reusable fluorous silica gel[14] eluted with common organic solvents. This avoids the use of perfluorinated solvent which is persistent in the environment.[15] The lower toxicity and persistence of "light fluorous" compounds thus make it comparably more environmentally friendly than its "heavy fluorous" counterpart.

Analysis of the homogeneous and heterogeneous palladium-catalyzed carbo- and heteroannulation of internal alkynes with functionalized aryl halides (Fig. 1) revealed that they were highly dependent on the choice of solvent, base, and additives.[9,11a,b] Herein we investigate the possibility of developing a uniform reaction condition suitable for all these annulation reactions. More importantly, we explore the application of palladacycle **1** as a recyclable precatalyst for carbo- and heteroannulation reactions in aqueous medium.

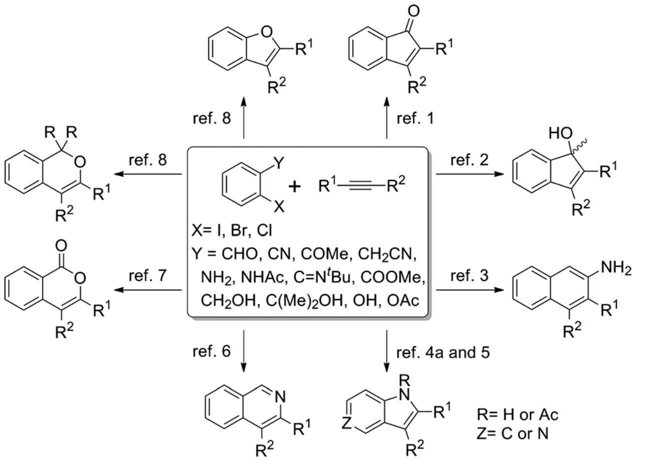

Fig. 1 Typical Pd-catalyzed annulation of functionalized aryl halides with internal alkynes.

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† Electronic supplementary information (ESI) available: Spectral data for compounds **3a–d**, **3d′**, **5a–d**, **5d′**, **7a–e**, **9a–m**, **11a–e**, **11e′**, **13a–e**, and **15a–g** are included in the ESI. See DOI: 10.1039/c3ra46010j

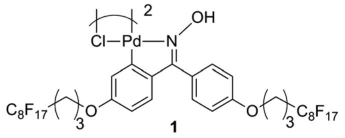


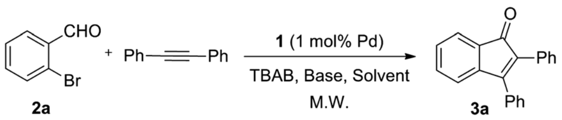
Fig. 2 Structure of palladacycle **1**.

Results and discussion

Carboannulation of aromatic carbonyl compounds with internal alkynes

Initial assessment of the annulation reaction was conducted using 2-bromobenzaldehyde **2a** and diphenylacetylene with palladacycle **1** as precatalyst (1 mol% Pd), K_2CO_3 as base, DMF as solvent and tetra-*n*-butylammonium bromide (TBAB) as an additive under conventional heating at 130 °C. The desired indenone **3a** was obtained after 1.5 h in 92% yield (Table 1, entry 1). To facilitate an expedient synthesis of **3a**, we explored the same reaction under microwave irradiation at 150 °C. The reaction was completed in 25 min and gave indenone **3a** in 98% yield (Table 1, entry 2). To develop a more environmentally friendly condition for this synthesis, we examined using water as a reaction solvent. However, when DMF was replaced with water, the yield of compound **3a** decreased to 57% (Table 1, entry 3). To optimize the reaction, we first varied the base and found that the reaction in aqueous medium proceeded most efficiently with Na_2CO_3 (Table 1, entries 4–11). Next, we investigated the effect of temperature on the reaction. The results indicated that although the reaction completed more rapidly at a higher temperature, compound **3a** was obtained in lower yields when the reaction temperature was increased to 160 °C or lowered to 140 °C (Table 1, entries 12–13). We also examined the effect of the loading of palladacycle **1** on the reaction. When the amount of palladacycle **1** was lowered (0.5 mol% Pd), the reaction required a longer time to complete and compound **3a** was obtained in a lower yield (Table 1, entry 14). Finally replacement of TBAB with LiCl did not provide any improvement in the reaction either and Pd black was observed to form during the reaction (Table 1, entry 15).

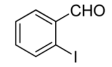
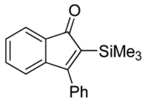
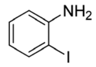
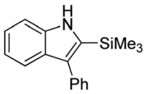
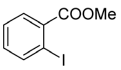
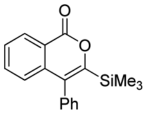
Table 1 Optimization of the palladium-catalyzed carboannulation reaction between 2-bromobenzaldehyde and diphenylacetylene^a



Entry	Base	Solvent	Temp. (°C)	Time (min)	Yield of **3a**^{b} (%)
1^c	K_2CO_3	DMF	130	90	92
2	K_2CO_3	DMF	150	25	98
3	K_2CO_3	H_2O	150	120	57
4	KO^{t}Bu	H_2O	150	40	52
5	KOAc	H_2O	150	20	68
6	KOH	H_2O	150	35	9
7	NH_4OAc	H_2O	150	120	0
8	TEA	H_2O	150	120	0
9	NaOAc	H_2O	150	35	72
10	NaOAc	H_2O	170	10	71
11	Na_2CO_3	H_2O	150	30	96
12	Na_2CO_3	H_2O	160	15	82
13	Na_2CO_3	H_2O	140	50	92
14^d	Na_2CO_3	H_2O	150	50	88
15^e	Na_2CO_3	H_2O	150	25	85

[a] 1 equivalent of **2a** (0.25 mmol) and 1.5 equivalent of diphenylacetylene. [b] Isolated yields. [c] Conventional heating. [d] 0.5 mol% Pd. [e] LiCl used instead of TBAB.

Table 2 Effect of alkyne stoichiometry on annulation^a

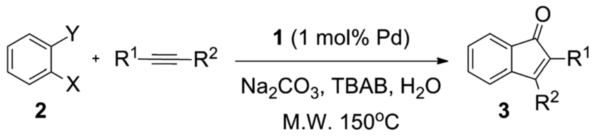
Entry	Aryl halide	Alkyne (equiv.)	Product	Yield^b (%)
1^c		Ph—≡—SiMe$_3$ (1.5)		59
2^c		(3)		65
3^c		(5)		65
4^d		(1.5)		75
5^d		(3)		80
6^d		(5)		80
7^e		(1.5)		60
8^e		(3)		62
9^e		(5)		63

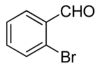
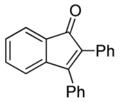
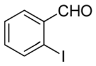
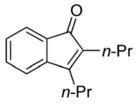
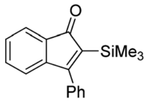
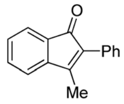
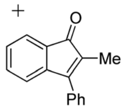
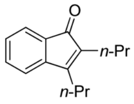
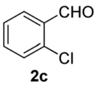
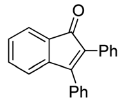
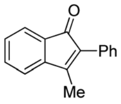
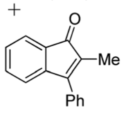
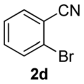
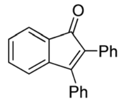
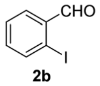
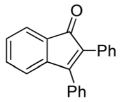
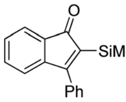
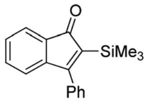
[a] *Reaction conditions*: aryl halide (1 equiv.), alkyne (see Table 2), palladacycle **1** (1 mol %), TBAB (1 equiv.), Na_2CO_3 (2 equiv.) and H_2O (0.25 M). [b] Isolated yields. [c] M.W. at 150 °C for 20 min. [d] M.W. at 150 °C for 30 min. [e] M.W. at 150 °C for 27 min.

Larock *et al.*[4] have reported earlier that the volatility of liquid alkynes could have an effect on the reaction rate and product yield. Thus, we have also investigated the effect of the stoichiometry of liquid alkyne on the reaction (Table 2). Using the optimized reaction conditions, various aryl halides were used to determine the optimal concentration of alkyne. When 1 equivalent of alkyne was employed, the reaction was incomplete (based on TLC analysis). It required 1.5 equivalents of alkyne for the reaction to proceed to completion. Increasing the amount of alkyne to 3 equivalents resulted in a higher yield of the respective desired product (Table 2, entries 2, 5 and 8). However further increasing the amount of alkyne to 5 equivalents did not provide any improvement in yields (Table 2, entries 3, 6 and 9).

To demonstrate the generality of this reaction condition for the synthesis of 2,3-disubstituted-1-indenones **3**, we applied it on various substrates (Table 3). Besides **2a**, *o*-iodo or *o*-chlorobenzaldehyde and *o*-bromobenzonitrile can also be employed successfully to the carboannulation reaction, with the iodide showing the highest reactivity. In addition, palladacycle **1** gave comparable yield of indenone **3** as compared to its non-fluorous analog and higher yields as compared to other Pd catalysts.

Table 3 Synthesis of 2,3-disubstituted-1-indenones using palladacycle **1**



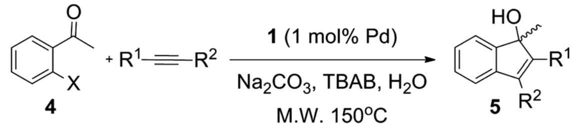
		Alkyne						Alkyne			
Entry	2	R^1	R^2	Time (min)	Product(s) (yield^a)	Entry	2	R^1	R^2	Time (min)	Product(s) (yield^a)
1	 **2a**	Ph	Ph	30 (2^b h, 36^c h, 30^d)	 **3a** (96%, 98%^{b}, 82%^{c}, 68%^{d})	7^i	 **2b**	*n*-Pr	*n*-Pr	18 (3^e h)	 **3c** (62%, 52%^{e,g})
2		SiMe$_3$	Ph	23	 **3b** (40%)	8		Ph	Me	15 (1.5^{e,h} h)	 **3d** (40%) +  **3d'** (36%)
3		*n*-Pr	*n*-Pr	25	 **3c** (56%)	9^i	 **2c**	Ph	Ph	60 (6^b h)	 **3a** (91%, 60%^{b})
4		Ph	Me	22 (1^{e,f} h)	 **3d** (36%) +  **3d'** (30%)	10	 **2d**	Ph	Ph	23	 **3a** (79%)
5	 **2b**	Ph	Ph	20 (13^c h)	 **3a** (94%, 84%^{c})	11		SiMe$_3$	Ph	15	 **3b** (50%)
6		SiMe$_3$	Ph	12 (17^e h)	 **3b** (65%, 42%^{e})						

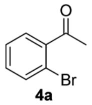
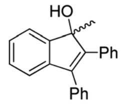
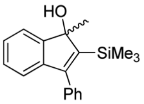
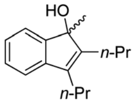
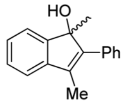
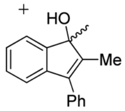
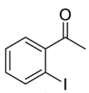
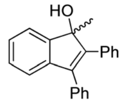
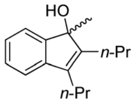
[a] Isolated yields. [b] Using 4,4′-dichlorobenzophenone oxime palladacycle: 1 mol% Pd, K_2CO_3, TBAB, DMF, 130/160 °C.[9g] [c] Using $Pd(OAc)_2$: 5 mol% Pd, NaOAc, TBAC, DMF, 100 °C.[1] [d] Using 4,4′-dimethoxybenzophenone oxime palladacycle: 1 mol% Pd, Na_2CO_3, TBAB, H_2O, M.W. 150 °C. [e] Using $Pd(OAc)_2$: 5 mol% Pd, Na_2CO_3, TBAC, DMA, 100 °C.[1] [f] Reaction provides a 1 : 1 mixture of regioisomers **3d** and **3d′** in 56% total yield. [g] In addition to compound **3c**, the isomerized product, β,γ-enone was formed in ∼1 : 1 ratio.[1] [h] Reaction provides a 1 : 1 mixture of regioisomers **3d** and **3d′** in 62% total yield. [i] 170 °C.

Earlier studies have shown that isomerization to β,γ-enones is a frequent problem during the synthesis of indenones bearing a primary alkyl group in the 3-position.[1] However it is gratifying to note that carboannulation with palladacycle **1** provided solely the α,β-enones, and the β,γ-enone isomer was not observed (Table 3, entries 3 and 7). It is also worth noting that the carboannulation process using palladacycle **1** is regiospecific for alkynes containing a hindered group such as a trimethylsilyl group, yielding only the isomer with the hindered group on the 2-position (Table 3, entries 2 and 6). This is an improvement over the carboannulation process with $Pd(OAc)_2$ where the reaction is regioselective and indenone **3b** is obtained as a major product.[1] However, when the steric hindrance between the two ends of the triple bond becomes less apparent as in the case of 1-phenyl-1-propyne, palladacycle **1**, like $Pd(OAc)_2$, produces an approximate 1 : 1 ratio of the regioisomers (Table 3, entries 4 and 8).

Encouraged by these results, we extended our studies to the carboannulation of aromatic ketones **4** which gave 2,3-disubstituted-1-indenol **5** in good to moderate yields (Table 4). Excellent regioselectivity was similarly observed when **4a** was reacted with alkynes carrying a larger steric discrepancy (Table 4, entry 2). On the other hand, the reaction of **4a** with 1-phenyl-1-propyne was less regioselective and provided a mixture of regioisomers in 2 : 1 ratio (Table 4, entry 4). 2-Iodoacetophenone **4b** also underwent the same reaction but afforded the indenols in lower yields (Table 4, entries 5 and 6), which is consistent with previously reported results.[2]

Table 4 Synthesis of 2,3-disubstituted-1-indenols using palladacycle **1**



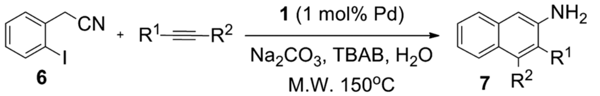
Entry	4	Alkyne R¹	 R²	Time (min)	Product(s) (yield^a)
1	 **4a**	Ph	Ph	30 (20^b h)	 **5a** (79%, 63%^{b})
2		$SiMe_3$	Ph	23	 **5b** (65%)
3		*n*-Pr	*n*-Pr	38 (20^b h)	 **5c** (90%, 82%^{b})
4		Ph	Me	25 (15^b h)	 **5d** (53%, 48%^{b}) +  **5d'** (25%, 20%^{b})
5	 **4b**	Ph	Ph	22	 **5a** (39%)
6		*n*-Pr	*n*-Pr	26	 **5c** (63%)

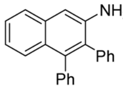
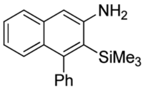
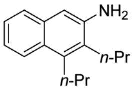
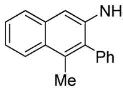
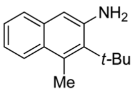
[a] Isolated yields. [b] Using $Pd(OAc)_2$: 5 mol% Pd, KOAc, DMF, 100 °C.[2]

Carboannulation of nitriles with internal alkynes

Next, we explored applying palladacycle **1** to the synthesis of 3,4-disubstituted-2-naphthylamines by using 2-(2-iodophenyl) acetonitrile **6** as the substrate (Table 5). Comparison of palladacycle **1** with the $Pd(OAc)_2$ catalyst showed that the carboannulation reaction with palladacycle **1** gave a higher yield of the product and occurred in a regiospecific manner with the more hindered substituent of the unsymmetrical alkyne placed in the 3-position (Table 5, entries 2 and 5). It is interesting to note that Larock *et al.*[3] had reported the reaction of 1-phenyl-2-(trimethylsilyl)acetylene with compound **6** in the presence of $Pd(OAc)_2$, which afforded exclusively the desilylated product, 2-

Table 5 Synthesis of 3,4-disubstituted-2-naphthylamines using palladacycle **1**



Entry	Alkyne R¹	 R²	Time (min)	Product(s) (yield^a)
1	Ph	Ph	26 (48^b h)	 **7a** (86%, 83%^{b})
2	$SiMe_3$	Ph	25 (48^b h)	 **7b** (66%, 58%^{b,c})
3	*n*-Pr	*n*-Pr	30 (48^b h)	 **7c** (42%, 30%^{b,d})
4	Ph	Me	23 (48^b h)	 **7d** (72%, 65%^{b})
5	*t*-Bu	Me	35 (48^b h)	 **7e** (83%, 75%^{b})

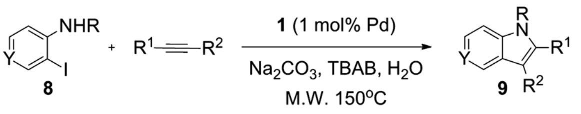
[a] Isolated yields. [b] Using $Pd(OAc)_2$: 5 mol% Pd, Et_3N, TBAC, DMF, 100 °C.[3] [c] Yield of desilylated coupling product: 2-(2-(phenylethynyl)phenyl) acetonitrile. [d] Yield of unsaturated product: (*E*)-3-(prop-1-en-1-yl)-4-propylnaphthalen-2-amine.

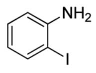
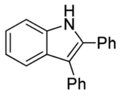
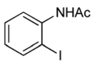
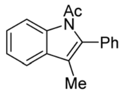
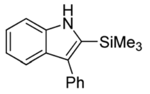
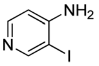
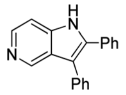
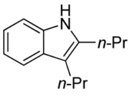
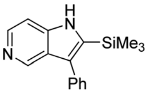
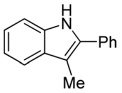
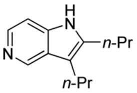
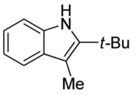
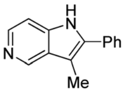
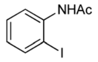
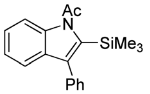
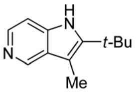
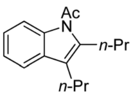
(2-(phenylethynyl)phenyl)acetonitrile, instead of the desired product **7b**. On the contrary, with our reaction conditions, naphthylamine **7b** was obtained as the sole product in 66% yield (Table 5, entry 2). In addition, the annulation reaction with 4-octyne provided compound **7c** while with $Pd(OAc)_2$ the sole product obtained was (*E*)-3-(prop-1-en-1-yl)-4-propylnaphthalen-2-amine (Table 5, entry 3). These results indicate the palladacycle **1** is generally a suitable palladium source for the synthesis of 3,4-disubstituted-2-naphthylamines *via* the annulation of internal alkynes by (2-iodophenyl) acetonitrile.

Heteroannulation of haloaniline and derivatives with internal alkynes

To investigate the general usefulness of palladacycle **1** in annulation chemistry, we extended our studies to the heteroannulation of internal alkynes for the formation of C–N bonds in the synthesis of 2,3-disubstituted indoles and azaindoles. The results were gratifying as the heteroannulation process with palladacycle **1** gave product **9** as a single regioisomer in generally higher yields than other palladium sources (Table 6). Earlier studies by Monguchi *et al.*[4c] have shown that *N*-acetyl group of substrate **8b** was labile during the heteroannulation reaction

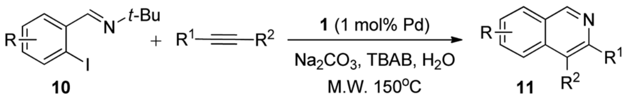
Table 6 Synthesis of 2,3-disubstituted-1-indoles and 2,3-disubstituted-5-azaindoles using palladacycle **1**

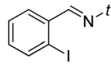
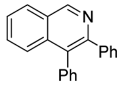
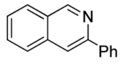
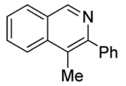
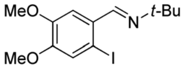
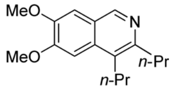
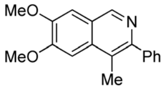
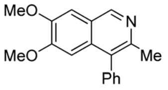


Entry	8	Alkyne R¹	R²	Time (min)	Product(s) (yield[a])	Entry	8	Alkyne R¹	R²	Time (min)	Product(s) (yield[a])
1	 8a	Ph	Ph	30 (7[b] h, 10[c] h, 24[d] h)	 9a (78%, 67%[b], 50%[c], 67%[d])	8	 8b	Ph	Me	18 (24[e] h)	 9h (80%, 75%[e])
2		$SiMe_3$	Ph	22 (16[e] h)	 9b (80%, 65%[e])	9	 8c	Ph	Ph	30 (15[g] h)	 9i (76%, 22%[g])
3		*n*-Pr	*n*-Pr	20 (9[c] h, 20[e] h, 12[f] h)	 9c (90%, 55%[c], 80%[e], 28%[f])	10		$SiMe_3$	Ph	25	 9j (62%)
4		Ph	Me	28	 9d (77%)	11		*n*-Pr	*n*-Pr	22 (15[g] h)	 9k (79%, 78%[g])
5		*t*-Bu	Me	24 (24[e] h)	 9e (94%, 82%[e])	12		Ph	Me	30	 9l (65%)
6	 8b	$SiMe_3$	Ph	15	 9f (81%)	13		*t*-Bu	Me	26	 9m (68%)
7		*n*-Pr	*n*-Pr	22 (24[e] h)	 9g (91%, 91%[e])						

[a] Isolated yields. [b] *Reaction conditions*: palladacycle **1**, Na_2CO_3, TBAB, DMF, conventional heating (130 °C). [c] Using 4,4′-dichlorobenzophenone oxime palladacycle: 1 mol% Pd, K_2CO_3, TBAB, DMF, 130 °C.[9g] [d] Heterogeneous catalysis using Pd/C: 2 mol% Pd, LiCl, Na_2CO_3, DMPU, 120 °C.[11c] [e] Using $Pd(OAc)_2$: 5 mol% Pd, TBAC, DMF, 100 °C.[4a] [f] Using $Ni(cod)_2$ (10 mol%), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (10 mol%), LiO*t*-Bu, toluene, 100 °C.[9e] [g] Using $Pd(dppf)_2Cl_2$: 5 mol% Pd, LiCl, Na_2CO_3, DMF, 100 °C.[5]

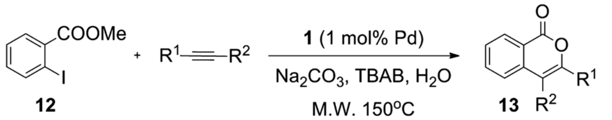
Table 7 Synthesis of 3,4-disubstituted isoquinoline using palladacycle **1**

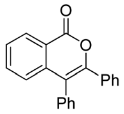
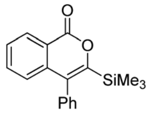
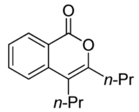
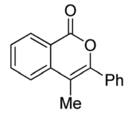
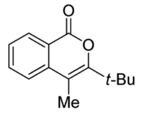


		Alkyne			
Entry	**10**	R^1	R^2	Time (min)	Product (yield^a)
1	 **10a**	Ph	Ph	25 (24^b h)	 **11a** (94%, 96%^{b})
2		$SiMe_3$	Ph	17 (21^b h)	 **11b** (88%, 85%^{b,c})
3		Ph	Me	20 (21^b h)	 **11c** (89%, 84%^{b})
4	 **10b**	*n*-Pr	*n*-Pr	28 (24^b h)	 **11d** (72%, 67%^{b})
5		Ph	Me	30 (29^b h)	 **11e** (69%, 67%^{b}) +  **11e'** (6%, 17%^{b})

[a] Isolated yields. [b] Using $Pd(OAc)_2$: 5 mol% Pd, 10 mol% PPh_3, Na_2CO_3, DMF, 100 °C.[6] [c] Desilyated product: 3-phenylisoquinoline.

Table 8 Synthesis of 3,4-disubstituted isocoumarins using palladacycle **1**



	Alkyne			
Entry	R^1	R^2	Time (min)	Product(s) (yield^a)
1	Ph	Ph	27 (216^b h)	 **13a** (79%, 74%^{b,c})
2	$SiMe_3$	Ph	23 (84^b h)	 **13b** (62%, 63%^{b,c})
3	*n*-Pr	*n*-Pr	20	 **13c** (75%)
4	Ph	Me	18	 **13d** (74%)
5	*t*-Bu	Me	20 (24^b h)	 **13e** (81%, 72%^{b})

[a] Isolated yields. [b] Using $Pd(OAc)_2$: 5 mol% Pd, Na_2CO_3, LiCl, DMF, 100 °C.[7] [c] CH_3CN as solvent.

with Pd/C in the presence of LiCl, Na_2CO_3 and DMPU. Thus the *N*-deacylated product was obtained as the major product. However with palladacycle **1**, the heteroannulation process proceeded without decomposition of the acetyl moiety and the desired *N*-acetylindole was afforded in good yields (Table 6, entries 6–8). The same trend of regioselectivity was also observed as discussed previously (Table 6, entries 2, 4–6, 8, 10, 12 and 13).

Heteroannulation of haloimines

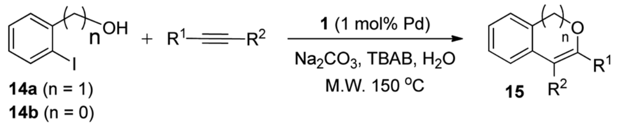
Besides aniline-based substrates, imine-based substrate, such as *tert*-butylimine **10**, was also successfully applied to the annulation of aryl- and alkyl-substituted alkynes to provide 3,4-disubstituted isoquinoline **11** (Table 7). However when imine **10a** was annulated with trimethylsilyl-substituted alkyne, the only product was the desilylated compound **11b** (Table 7, entry 2). In addition, annulation of imine **10b** with 1-phenyl-1-propyne also occurred with good regioselectivity to afford **11e** in 69% yield, whereas compound **11e′** was obtained as the minor isomer in 6% yield (Table 7, entry 5). These observations were consistent with previously reported results.[6]

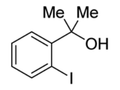
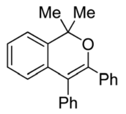
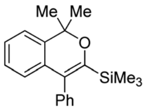
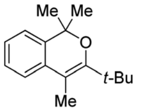
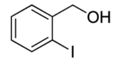
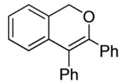
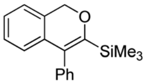
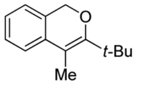
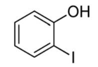
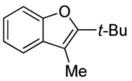
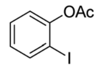
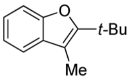
Heteroannulation of halobenzoates with internal alkynes

Next we explored the possibility of using the heteroannulation reaction for the formation of C–O bond. This reaction was first exemplified in the synthesis of 3,4-disubstituted isocoumarin **13** *via* the palladacycle **1** catalyzed heteroannulation of methyl 2-iodobenzoate **12** with internal alkynes (Table 8). Compound **13** was obtained in good yields and, as in previous annulation reactions with palladacycle **1**, the reaction proceeded in a regiospecific manner with unsymmetrical alkynes to provide the isomer with the more hindered substituent of the alkyne placed in the 3-position (Table 8, entries 2, 4 and 5).

To investigate other examples of C–O bond formation in the heteroannulation reaction, we applied the reaction to benzylic alcohol **14a**, 2-iodophenol **14b**, and their derivatives (Table 9). It

Table 9 Synthesis of 3,4-disubstituted-1*H*-isochromenes and 2,3-disubstituted benzofurans using palladacycle **1**



		Alkyne			
Entry	14	R^1	R^2	Time (min)	Product(s) (yield^a)
1	 **14a1**	Ph	Ph	35 (24^b h)	 **15a** (62%, 52%^{b})
2		$SiMe_3$	Ph	22	 **15b** (64%)
3		*t*-Bu	Me	25 (20^b h)	 **15c** (61%, 52%^{b})
4	 **14a2**	Ph	Ph	40	 **15d** (75%)
5		$SiMe_3$	Ph	30	 **15e** (70%)
6		*t*-Bu	Me	40 (48^b h)	 **15f** (63%, 65%^{b})
7	 **14b1**	*t*-Bu	Me	35 (24^b h)	 **15g** (72%, 66%^{b})
8	 **14b2**	*t*-Bu	Me	27	 **15g** (86%)

^{a} Isolated yields. ^{b} Using $Pd(OAc)_2$: 5 mol% Pd, Na_2CO_3 or K_2CO_3, DMF, 100 °C.[8]

was observed that the heteroannulation of the oxygen analogs **14a** and **14b** with internal alkynes proved slightly more difficult than analogous reactions with the nitrogen analogs **8** and **10**, and generally a longer reaction time was required. In addition, comparison of the heteroannulation reactions of **14a1** and **14a2** showed that the presence of a dimethyl substituent on the benzylic position appears to shorten the reaction time although higher yields of benzopyrans **15** were obtained with **14a2**. As in previous annulation reactions, the heteroannulation of **14a** and **14b** with internal alkynes also proceed in a regiospecific manner providing solely the isomer with the bulky substituent of the alkyne on the carbon that is adjacent to the oxygen (Table 9, entries 2, 3, 5 and 6). When the reactions were carried out under the same condition using *o*-iodophenol **14b1** and derivative **14b2**, the corresponding benzofuran **15g** was obtained in high yields (Table 9, entries 7 and 8). In both examples, excellent regioselectivity was observed.

Recycling of palladacycle 1

Finally we investigated the possibility of recycling and reusing palladacycle **1** from the annulation reactions for the formation of C–C, C–N and C–O bonds. These three different annulation reactions were performed under the optimized reaction condition and the recycling experiments were carried out over 5 cycles (Table 10). Gratifyingly, the recovered palladacycle **1** was indistinguishable from the original precatalyst and showed a slow decline in catalytic activity after multiple recovery steps. The recycling experiments were also followed by comparing the yields in each cycle after a fixed reaction time and determining the amount of unreacted aryl halide as well as the recovery of palladacycle **1**. Recovery of palladacycle **1** was good except for the fifth cycle and ICP-OES analysis of the crude product indicated that the Pd content was low.

Conclusions

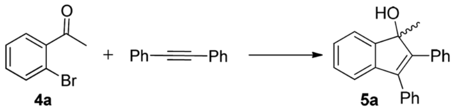
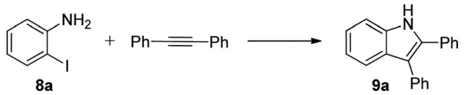
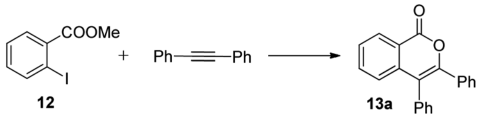
A uniform and environmentally benign procedure for the palladium-catalyzed annulation of a variety of functionalized aryl halides with internal alkynes in aqueous medium under microwave irradiation has been developed. Both symmetrical and unsymmetrical internal alkynes bearing alkyl, aryl and silyl groups are suitable for this chemistry. This methodology could be applied to the syntheses of 2,3-disubstituted 1-indenones, 1-indenols, 1-indoles, 5-azaindoles, and benzofurans, as well as 3,4-disubstituted 2-naphthylamines, isoquinolines, isocoumarins, and 1*H*-isochromenes The annulation reactions exhibit excellent regioselectivity providing only one or a major product where the bulkiest group is on the 2-position for 2,3-disubstituted compounds or 3-position for 3,4-disubstituted compounds. Recycling was also possible with palladacycle **1** which could be reused five times in an annulation reaction. Palladium leaching was also low.

Experimental

General procedures

All chemicals purchased were used without further purification. Palladacycle 1 was synthesized according to previously reported procedure.[13a] Starting materials **8b**,[4] **10**,[16] **14a**,[17] and **16b** (ref. 18) were synthesized according to literature procedures. Moisture-sensitive reactions were carried out under nitrogen with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on precoated F254 silica plates and visualized with UV light. Column

Table 10 Recycling of palladacycle **1**[a]

Cycle	Time (min)	Yield of product[b] (%)	Recovered **1**[c] (wt%)	Pd leaching[d] (mg Pd per g product)
				
1	30	79 (79[e], 0[f])	89 (89[e])	0.23
2	38	75 (70[e], 10[f])	84 (84[e])	0.23
3	48	70 (59[e], 17[f])	79 (79[e])	0.23
4	60	67 (51[e], 25[f])	76 (76[e])	0.17
5	75	61 (45[e], 31[f])	55 (62[e])	0.15
				
1	28	78 (78[g], 0[f])	94 (94[g])	0.41
2	33	74 (70[g], 5[f])	91 (92[g])	0.38
3	41	71 (64[g], 12[f])	85 (89[g])	0.41
4	52	68 (56[g], 20[f])	81 (81[g])	0.42
5	65	63 (48[g], 29[f])	60 (68[g])	0.39
				
1	27	79 (79[h], 0[f])	90 (90[h])	0.24
2	31	76 (72[h], 10[f])	85 (87[h])	0.16
3	37	73 (68[h], 13[f])	86 (86[h])	0.31
4	48	69 (60[h], 18[f])	83 (83[h])	0.18
5	60	63 (51[h], 25[f])	73 (79[h])	0.54

[a] Using palladacycle **1** (1 mol% Pd), Na_2CO_3, TBAB, H_2O, M.W. 150 °C. [b] Isolated yields. [c] Recovered *via* F-SPE. [d] Determined by ICP-OES of the crude product. [e] M.W. for 30 min. [f] Recovered aryl halide. [g] M.W. for 28 min. [h] M.W. for 27 min.

chromatography was performed with silica (Merck, 230–400 mesh). F-SPE was performed with FluoroFlash® silica gel (40 micron). ^{1}H and ^{13}C NMR spectra were recorded at 298 K. Chemical shifts are expressed in terms of δ (ppm) relative to the internal standard tetramethylsilane (TMS). Mass spectra were recorded under EI or ESI mode. Microwave reactions were performed on the Biotage Initiator™ microwave synthesizer in quartz pressure tubes. Pd leaching values were obtained on a Dual-view Optima 5300 DV (inductively coupled plasma) ICP-OES system.

General procedure for the palladium-catalyzed annulation of internal alkyne under microwave irradiation

A mixture of the functionalized aryl halide (0.25 mmol), internal alkyne (1.5 equivalents for solid alkyne or 3 equivalents for liquid alkyne), TBAB (81 mg, 0.25 mmol), Na_2CO_3 (53 mg, 0.50 mmol), palladacycle **1** (1 mol% Pd) and water (1.0 mL) was heated in a pressure tube at 150 °C under microwave irradiation. The reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into EtOAc (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and purified by column chromatography.

General procedure for the recycling experiment using F-SPE

Recycling experiments were carried out on a 1.25 mmol scale using the general procedure described above. The crude product was first diluted with THF–H_2O = 8 : 2 (1 mL) and loaded into a F-SPE fluorous silica column (column diameter: 2.20 cm; amount of fluorous silica required: 10% of crude product by weight). The crude product was then eluted using THF–H_2O = 8 : 2 (30 mL) as eluent and the palladacycle **1** (see Table 10 for amount of recovered **1**) was subsequently eluted with THF (20 mL). The fluorous silica was regenerated and reused (5 times) after washing with acetone (10 mL). For elemental analysis of Pd leaching, a small volume of a solution of the crude product was concentrated and analysed by ICP-OES. To determine the amount of product formed after each recycling experiment, the solution of crude product was concentrated, diluted with EtOAc (20 mL) and washed with water (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and then purified by column chromatography.

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Notes and references

1 R. C. Larock and M. J. Doty, *J. Org. Chem.*, 1993, **58**, 4579.
2 L. G. Quan, V. Gevorgyan and Y. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 3545.
3 Q. Tian, A. A. Pletnev and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 339.
4 (*a*) R. C. Larock, E. K. Yum and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652; (*b*) D. Zhang, E. K. Yum, Z. Liu and R. C. Larock, *Org. Lett.*, 2005, **7**, 4963; (*c*) Y. Monguchi, S. Mori, S. Aoyagi, A. Tsutsui, T. Maegawa and H. Sajiki, *Org. Biomol. Chem.*, 2010, **8**, 3338.
5 F. Ujjainwalla and D. Warner, *Tetrahedron Lett.*, 1998, **39**, 5355.
6 K. R. Roesch, H. Zhang and R. C. Larock, *J. Org. Chem.*, 2001, **66**, 8042.
7 R. C. Larock, M. J. Doty and X. Han, *J. Org. Chem.*, 1999, **64**, 8770.
8 R. C. Larock, US5596100A, 19970121, 1997.
9 (*a*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644; (*b*) Y. Wang, L. Liu and L. Zhang, *Chem. Sci.*, 2013, **4**, 739; J. J. Li, *Name Reactions in Heterocyclic Chemistry II*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2011, p. 146; (*c*) D. Yue and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 1905; (*d*) J. Tsuji, *Palladium in Organic Synthesis*, Springer-Verlag, Berlin, 2005, p. 147; (*e*) Y. Yoshida, T. Kurahashi and S. Matsubara, *Chem. Lett.*, 2011, **40**, 1067; (*f*) R. P. Korivi and C.-H. Cheng, *J. Org. Chem.*, 2006, **71**, 7079; (*g*) D. A. Alonso, C. Nájera and M. C. Pacheco, *Adv. Synth. Catal.*, 2002, **344**, 172.
10 (*a*) E. B. Mubofu, J. H. Clark and D. Macquarrie, *Green Chem.*, 2001, **3**, 23; (*b*) D. Rosario-Amorin, X. Wang, M. Gaboyard, R. Clérac, S. Nlate and K. Heuzé, *Chem. – Eur. J.*, 2009, **15**, 12636.
11 (*a*) N. Batail, V. Dufaud and L. Djakovitch, *Tetrahedron Lett.*, 2011, **52**, 1916; (*b*) H.-C. Zhang, K. K. Brumfield and B. E. Maryanoff, *Tetrahedron Lett.*, 1997, **38**, 2439; (*c*) Y. Monguchi, S. Mori, S. Aoyagi, A. Tsutsui, T. Maegawa and H. Sajiki, *Org. Biomol. Chem.*, 2010, **8**, 3338; (*d*) L. Djakovitch, N. Bartail and M. Genelot, *Molecules*, 2011, **16**, 5241.
12 (*a*) J.-M. Vincent, *Top. Curr. Chem.*, 2012, **308**, 153; (*b*) I. T. Horváth and J. Rábai, *Science*, 1994, **266**, 72.
13 (*a*) W. Susanto, C.-Y. Chu, W. J. Ang, T.-C. Chou, L.-C. Lo and Y. Lam, *Green Chem.*, 2012, **14**, 77; (*b*) W. Susanto, C.-Y. Chu, W. J. Ang, T.-C. Chou, L.-C. Lo and Y. Lam, *J. Org. Chem.*, 2012, **77**, 2729.
14 W. Zhang and D. P. Curran, *Tetrahedron*, 2006, **62**, 11837.
15 M. A. K. Khalil, R. A. Rasmussen, J. A. Culbertson, J. M. Prins, E. P. Grimsrud and M. J. Shearer, *Environ. Sci. Technol.*, 2003, **37**, 4358.
16 K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 1998, **63**, 5306.
17 Y. C. Fan and O. Kwan, *Org. Lett.*, 2012, **14**, 3264.
18 H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 1765.