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Development and application of highly active and selective palladium catalysts

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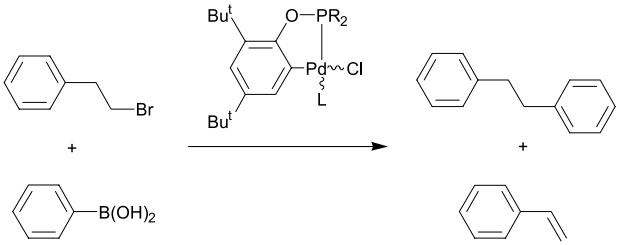
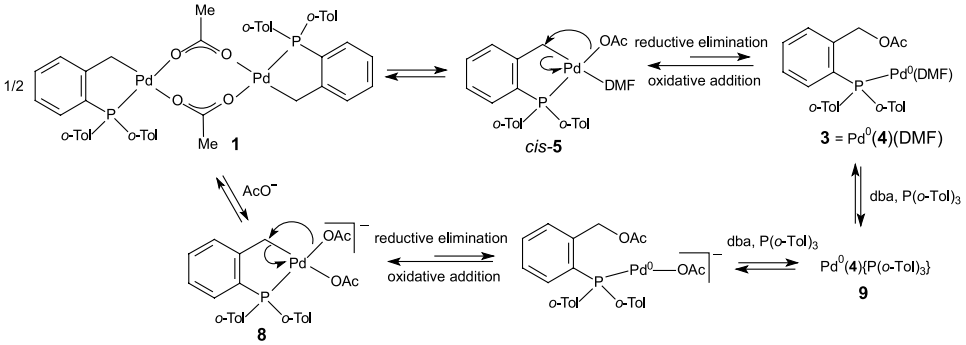
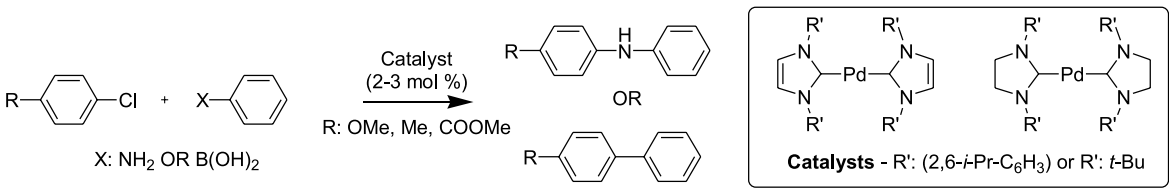
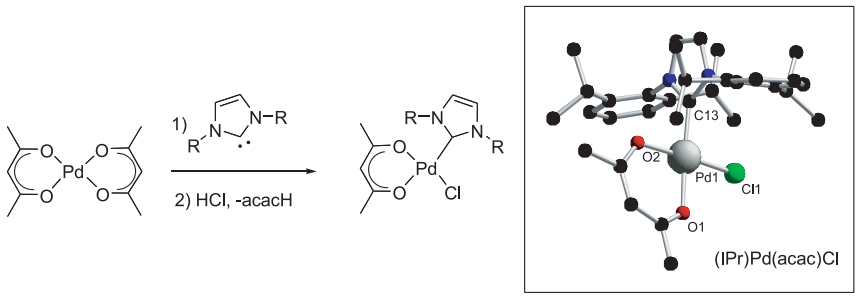
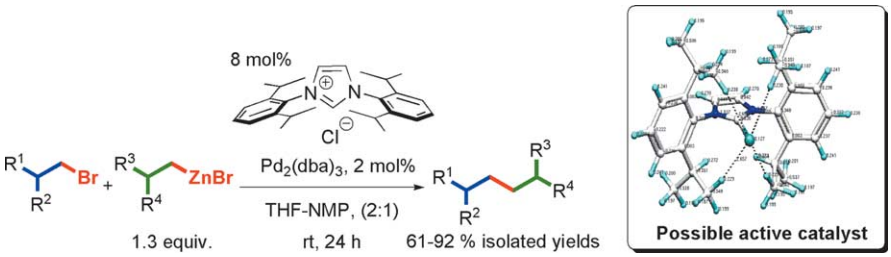
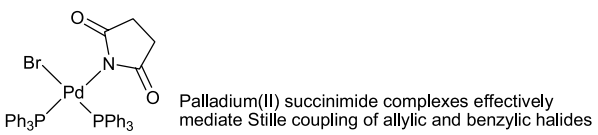


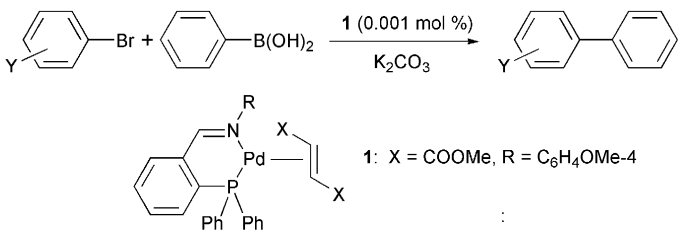


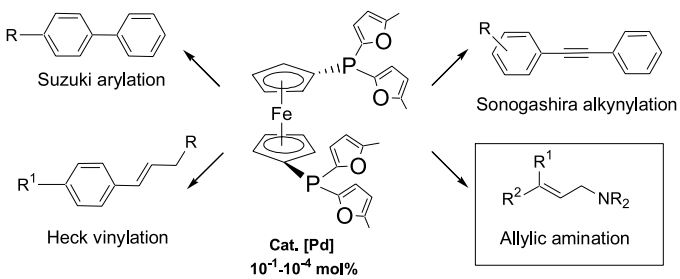


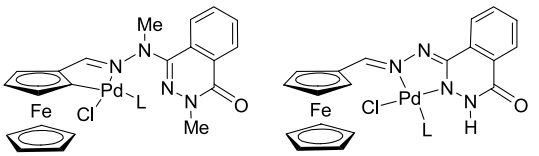


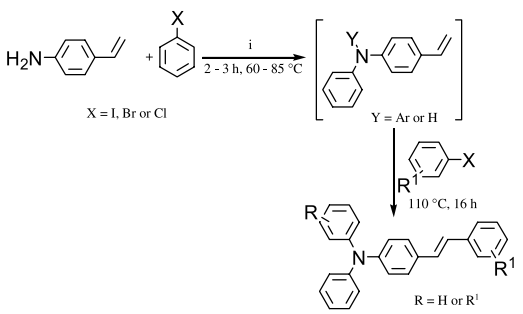


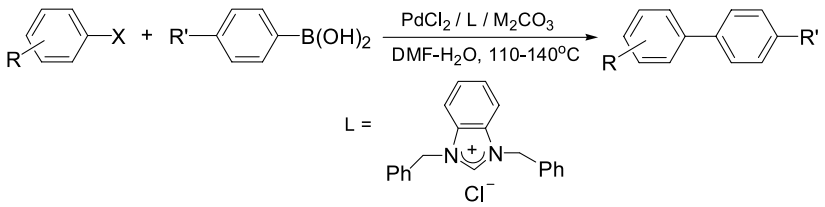


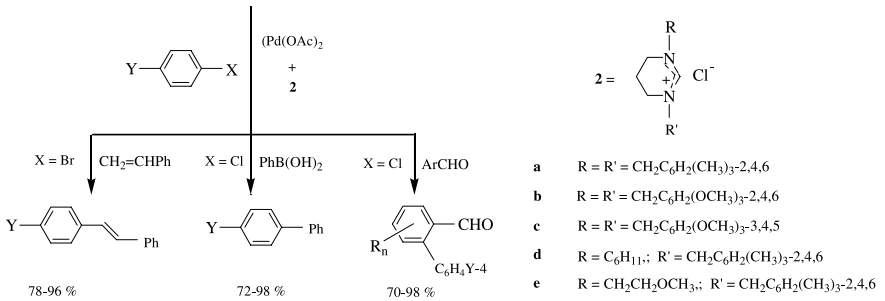


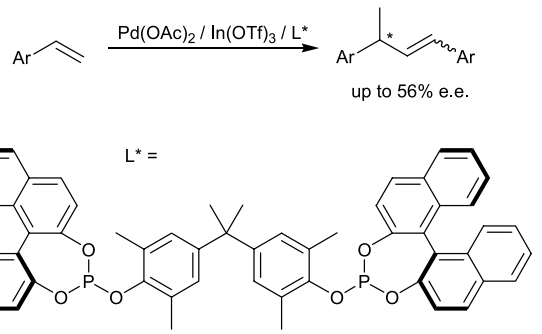




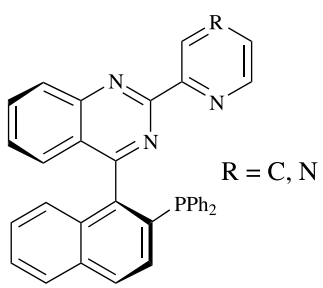


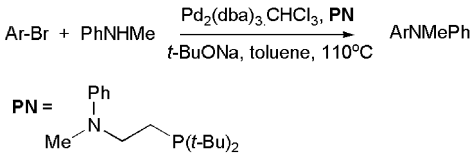


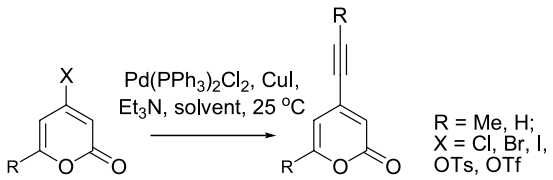




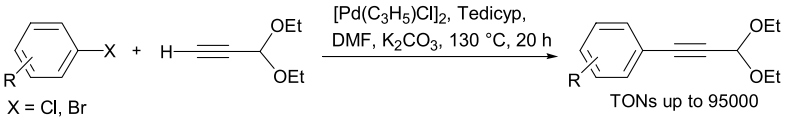
The preparation and resolution of the axially chiral ligands, 2-(2-pyridyl)-and 2-(2-pyrazinyl)-Quinazolinap, is described. They were prepared as racemates in good yield in eight steps and were resolved by the separation of diastereomeric palladacycles. X-ray crystal structures of the (*S*,*R*)-palladacycles were determined and are discussed. Application in palladium-catalysed allylic alkylation of dimethyl malonate and 1,3-diphenylpropenyl acetate afforded ees up to 81%.





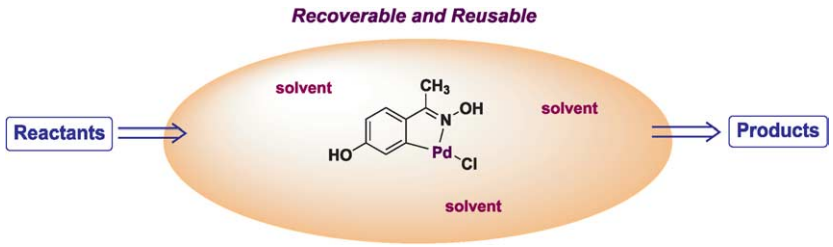


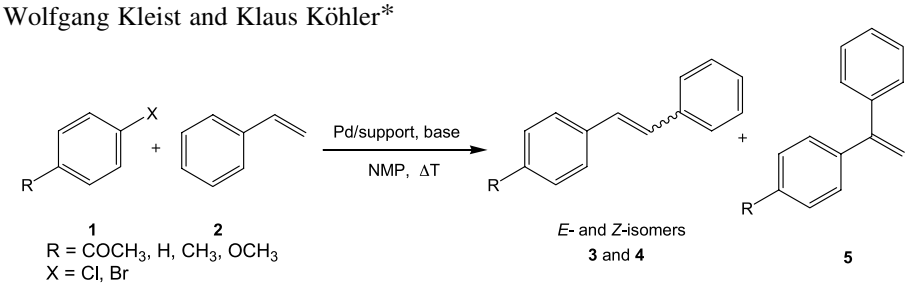
Turnover frequency and turnover number increases with lower Pd concentration (down to 0.025 mol% Pd)



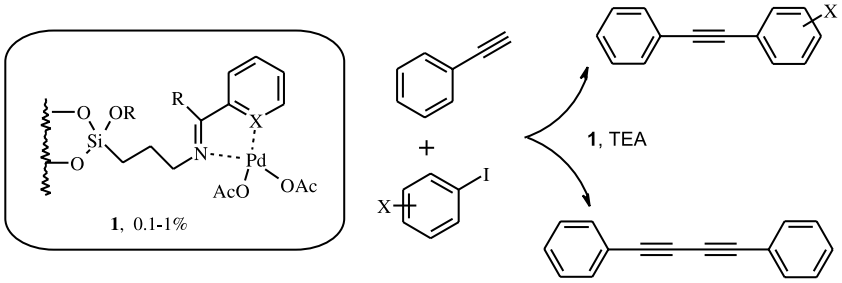
X = Cl, Br
R = H, Me, *t*-Bu, OMe, F, CF_3, NO_2, CN, COMe, CO_2Me, CHO, COPh, NMe_2

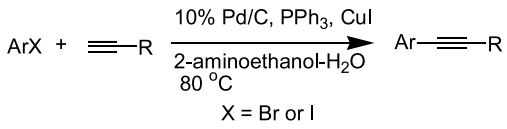
The thermal stability of a palladium complex has been assessed in different green solvents. The catalytic activity of the complex for the Suzuki and Sonogashira couplings increases with the degree of stability, being polyethyleneglycol (PEG) the solvent of choice. A reusable, homogeneous PEG–Pd system has been developed.

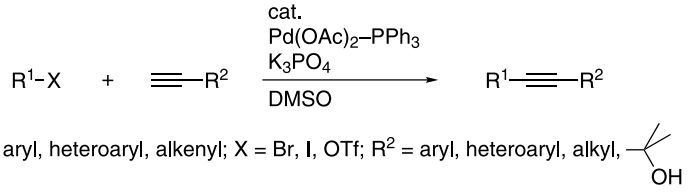


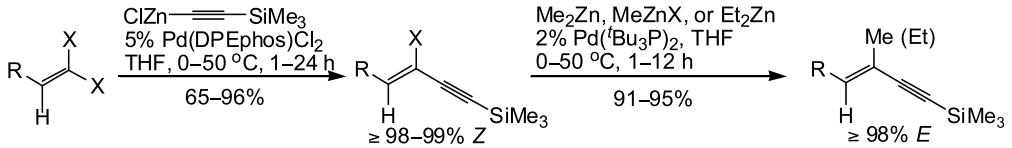


Simple, stable, ligand free heterogeneous Pd catalysts convert aryl bromides and chlorides with high yields (100% selectivity) in Heck reactions within few hours. The high activity is achieved by Pd species temporarily dissolved from the solid support.

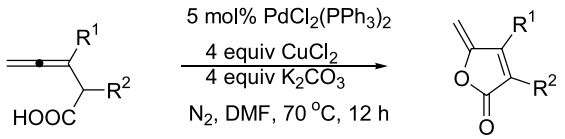


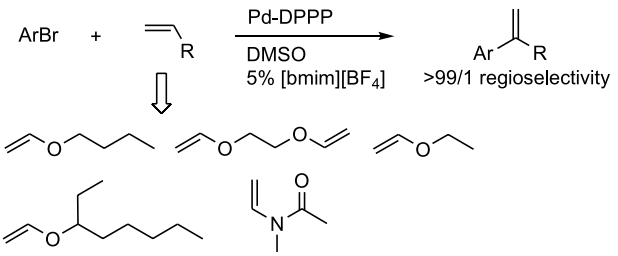




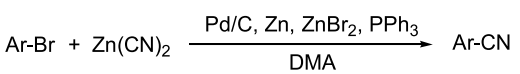


The reaction of 1,1-dibromo- and 1,1-dichloro-1-alkenes with $ClZnC{\equiv}CSiMe_3$ and 5% $Pd(DPEphos)Cl_2$ followed by that with methylzincs and ethylzincs produces (*E*)-3-alkyl-1-trialkylsilyl-3-alken-1-ynes ($\geq$98% *E*) in >90% yields.





Highly regioselective Heck arylation of electron-rich olefins by aryl bromides without using any halide scavengers is demonstrated in a solvent cocktail containing as little as 5% of an ionic liquid.



Ar: substituted phenyl, heteroaryl with a substituent involving sterically congested electron-rich groups.

OTHER CONTENTS

*Corresponding author

COVER

The cover picture shows the black-box that is often associated with palladium chemistry. Various products and catalysts come out of the box, which are representative examples of structures that are part of the symposium-in-print. The black-box still contains a highly contentious Pd(IV) species, proposed for several Pd-mediated reactions, but never detected in a catalytic process (so far...). The guest editor is grateful to Dr. Adrian C. Whitwood (York) for constructing/designing the cover picture.

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Preface

Palladium catalysis in synthesis: where next?

Over the past 30 or so years organometallic chemistry has revolutionised synthesis. The increasing number of synthetic transformations facilitated by transition metal catalysts shows no sign of abating. Of all the organometallic compounds known, those derived from palladium have become the most important catalysts for an eclectic array of synthetic manipulations in basic feedstocks, to fine chemicals through to more elaborate, often complicated, natural products or π-conjugated materials. Since around 1995, the general synthetic applications of palladium have expanded significantly. It has matured into an area which is a mainstay in the synthetic chemists' armoury, providing a myriad of versatile transformations, in ways that facilitate exquisite control in the conversion of simple starting materials into targets of varying complexity. Selectivity is a key facet in palladium-mediated synthesis, for example, in the chemo-, regio- and stereo-selective processes that often result, allowing one to access some of the most intricate synthetic targets, not available by traditional methods.

When was the last time that you read a synthetic journal that did not report the application of a palladium-mediated process; the de novo design of a highly active palladium catalyst, or the beneficial effect of another super-additive or co-catalyst? This area of chemistry is a special one, and still presents many opportunities in terms of application and development. The reactions discovered by Kumada and Corriu; Heck; Hiyama; Negishi; Suzuki and Miyaura; Kosugi, Migita and Stille; Sonogashira and others, have inspired us to apply this state-of-the-art technology to real synthetic problems, but moreover to understand the mechanism(s) of these processes—to exploit the outcome in new challenges and to drive the identification and development of highly active and selective catalysts. The recent, well known, contributions of Buchwald et al. (see, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348) and Hartwig's group (see, *Tetrahedron Lett.* **1995**, *36*, 3609) brought about a new dawn in the development of C–N and C–O bond formation to provide derivatised anilines and aryl ethers. Although other approaches are known, these two publications triggered an avalanche of activity in both academic and industrial research groups. Importantly, medicinal chemistry has benefited tremendously from these step-changing technologies. For a more historical perspective on the development of palladium-catalysed processes the reader is directed to other expert commentaries (see, *Adv. Synth. Catal.* **2004**, *346*, 1519 and 1522).

Importantly, it is often the unusual observations that drive the expansion of this field, in terms of both development and mechanistic understanding. The latter aspect, although sometimes complicated, is necessary for an appreciation of the subtleties involved in what is often referred to as the black-box of palladium chemistry. In this respect, we sometimes believe our traditional textbooks too much, without questioning the overall complexity of palladium catalysis—why should only one catalytic cycle be operative? For example, Amatore and Jutand have taught us that an anionic Pd(0)/Pd(II) cycle is operative in cross-coupling chemistry, as well as the classic neutral Pd(0)/Pd(II) cycle (see, *Acc. Chem. Res.* **2000**, *33*, 314). This allows us to understand the partial role played by halide/pseudohalide additives in such reactions. The same scientists also demonstrated the non-innocent behaviour of dibenzylidene acetone (dba) ligands in reactions mediated by Pd_2dba_3/phosphine combinations (see, *Coord. Chem. Rev.* **1998**, *178–180*, 511). On the other hand, several influential scientists have shown us the importance of palladium colloids/clusters in catalysis (see, *Chem. Commun.* **2004**, 1559 and *J. Am. Chem. Soc.* **2005**, *127*, 3298). However, this area is still in its infancy and one that remains to be exploited in terms of the development of highly active and selective catalysts from polynuclear palladium species, and also in applied chemical synthesis.

Generally, palladium has achieved a prominent role in catalysis and synthesis due to its electronegativity (2.2), which facilitates the formation of relatively strong Pd–H and Pd–C bonds, but also gives rise to polarised Pd–X bonds. It also allows easy access to 0 and +II oxidative states, where palladium-centred reactions such as oxidative addition, transmetallation and reductive elimination processes, occur with dynamic changes in geometry on palladium. However, one must not forget that +I, +III and +IV oxidation states are possible, yet these are rarely mentioned, and that Pd(VI) (formally) has been proposed (see, *Science* **2002**, *295*, 308), albeit disputed by theoretical studies (see, *Angew. Chem., Int. Ed.* **2002**, *41*, 1953 and 1956). Pd(II)/(IV) catalytic cycles have been proposed by scientists over the years, but have generally proved contentious. Although disproved in the majority of cases, particularly in reactions employing palladacycles (see, *J. Organomet. Chem.* **2004**, *689*, 4055 and *Chem. Rev.* **2005**, 105, 2527), such catalytic cycles are not ill-conceived, particularly given the fact that many Pd(IV) complexes are known (see, *Acc. Chem. Res.* **1992**, *25*, 83), and following the recent discovery by Sanford that such species are important in C–H activation/oxidation and C–C bond

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forming processes (see, *J. Am. Chem. Soc.* **2004**, *126*, 2300 and *J. Am. Chem. Soc.* **2005**, *127*, 7330). It is certainly worth studying these more unusual oxidation states to probe new levels of reactivity. One suspects that the Pd(II)/(IV) cycle will continue to be debated in special cases.

So, where next for palladium catalysis in synthesis? The answer certainly lies in tandem strategies to complex targets and C–H activation processes. The creation of a technology that allows us to selectively activate C–H bonds in alkanes, alkenes, alkynes, aryls and heteroatom-substituted derivatives certainly seems feasible. Reliability, good catalytic activity, diverse substrate scope, and more importantly, the ability to perform reactions under standard laboratory conditions (non-glove box), will certainly bring about the broad application of this technology, which ultimately will reduce waste products such as salts, produced in a large number of palladium-mediated reactions, and provide near atom-efficient organic transformations. One important practical consideration is that ligands and palladium catalysts should be commercially available (and cheap), or at the very least be readily prepared in one to two steps. Specifically tailored catalysts for heteroaromatic substrates should also be considered, particularly given that side reactions (hydrodehalogenation, hydrodemetallation, homocoupling, etc.) are often seen when new substrates are evaluated (see, *Chem. Commun.* **2003**, 632).

Contributions to this Symposium-in-Print on development and application of highly active and selective palladium catalysts are made by many of the leading researchers in this field. The subject coverage is broad and applied. The specific topics included are: alkyl bromide coupling to aryl boronic acids (Suzuki–Miyaura coupling); several reports on reactions employing aryl chlorides; the cyclisation of 3,4-alkadienoic acids; an asymmetric styrene dimerisation process; a trans-selective alkynylation–alkylation tandem process; a protocol for the cyanation of aryl bromides using Pd/C; practical catalysts for the Buchwald–Hartwig reaction (using aryl chlorides); selective catalysts for Stille coupling of allylic and benzylic substrates; classical Sonogashira coupling, including studies on aryl alkynylation versus alkyne homocoupling, reactions mediated by Pd/C in water and consequences for sample analysis by gas chromatography. Ionic liquids have been applied in cross-coupling processes, including a molecular solvent-ionic liquid cocktail for the Heck arylation of electron-rich olefins. Various homogeneous and heterogeneous Heck alkenylation processes are described. Elegant mechanistic studies showing the formation of Pd(0) from a P,C-palladacycle are presented. The role of the olefin in Pd catalyst stabilization in Suzuki–Miyaura coupling has been evaluated, which once again shows the importance of such olefins as ligands for palladium, and builds on the known non-innocent role for dba in catalysis. An enlightening article detailing a combined experimental and computational approach to the rational design of palladium-*N*-heterocyclic carbene catalysts for cross-coupling processes is also detailed. Overall, the Symposium-in-Print clearly illustrates the vibrant research taking place at the cutting edge in palladium catalyst development and application.

Acknowledgements

I would like to thank Professors Richard Taylor and Harry Wasserman for the invitation to edit this special issue on the development and application of highly active and selective palladium catalysts. I am also indebted to the Tetrahedron office in York for their guidance and help in collating all the papers. Without the excellent contributions made by the authors and the expert opinion of the referees, this issue would not have been possible. In this respect, I am sincerely grateful for the significant efforts they have made in making this Symposium-in-Print become a reality.

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An evaluation of phosphine and carbene adducts of phosphite- and phosphinite-based palladacycles in the coupling of alkyl bromides with aryl boronic acids

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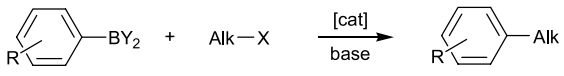
Abstract—A range of palladacyclic catalysts and their phosphine and carbene adducts were tested in the Suzuki coupling of an alkyl bromide with phenylboronic acid and showed modest activity in some cases. Unlike with aryl halide substrates it appears that there is no particular benefit in the use of palladacycles as the palladium source. Initial data indicate that the rate determining step is not the oxidative addition of the alkyl halide substrate, but rather lies later in the catalytic cycle.

1. Introduction

Coupling reactions leading to the formation of new C–C bonds, typically catalysed by ubiquitous palladium complexes, form the bedrock of many contemporary syntheses.[1] Despite the undoubted usefulness of such processes, there are still holes in the general methodologies currently available that limit their applicability. Much research is focused on addressing these shortcomings and the last few years have seen substantial advances. One area that has proved particularly problematic is the extension of Suzuki coupling of aryl boron nucleophiles to alkyl halides bearing β-hydrogens (Scheme 1).[2]



Scheme 1. Suzuki coupling of aryl boron nucleophiles with alkyl halides.

The problems associated with this process are two-fold. Firstly, the oxidative addition of the C–X bond is believed to be more difficult for alkyl halides as a result of the higher bond strength compared with aryl halides.[3] Secondly, β-elimination of the Pd–alkyl complex formed after oxidative addition can lead to competitive alkene formation rather than subsequent coupling, depending on the relative rates of the two processes (Scheme 2).

As long ago as 1992 Suzuki and co-workers showed that alkyl iodides could be coupled with alkyl- and aryl-(9-BBN) reagents (9-BBN = 9-borabicyclo[3.3.1]nonane) using $[Pd(PPh_3)_4]$ as catalyst and K_3PO_4 as base at 60 °C, giving the coupled products in reasonable yield.[4] By contrast, no activity was seen with alkyl bromides. Fu and co-workers have focused on the problem of using substrates other than alkyl iodides and found that primary alkyl bromides can be coupled with both alkyl- and vinyl-(9-BBN) reagents at rt in THF using palladium acetate/tricyclohexylphosphine as the catalyst and potassium phosphate as a mild base.[5] When the base is replaced with cesium hydroxide and the reactions performed in dioxane at 90 °C, then primary alkyl chlorides can be used as coupling partners with alkyl-(9-BBN) reagents.[6] Both alkyl- and aryl-(9-BBN) reagents can be coupled with alkyl tosylates at 50 °C in dioxane using sodium hydroxide as base employing a catalyst formed in situ from palladium acetate and $PMe(^tBu)_2$.[7] Caddick, Cloke and co-workers have shown that *N*-heterocyclic carbene adducts of palladium, formed in situ from palladium bis(dibenzylideneacetone) and the salt **1**, can

Keywords: Alkyl halide; Suzuki reaction; Palladacycles; Coupling; Catalysis.
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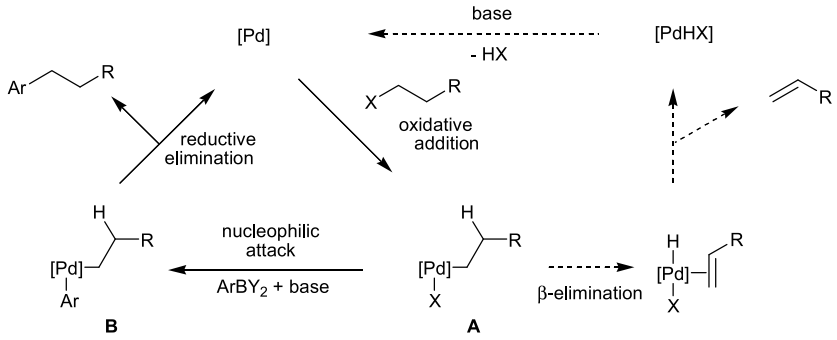
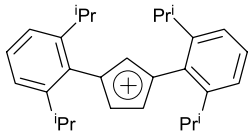
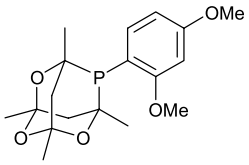


Scheme 2. Simplified catalytic cycles for competing coupling and β-elimination pathways.

also be used to couple primary alkyl bromides with alkyl- and vinyl-(9-BBN) reagents, using potassium *tert*-butoxide as base at 40 °C in THF.[8]



1



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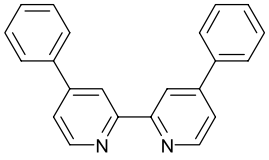


3

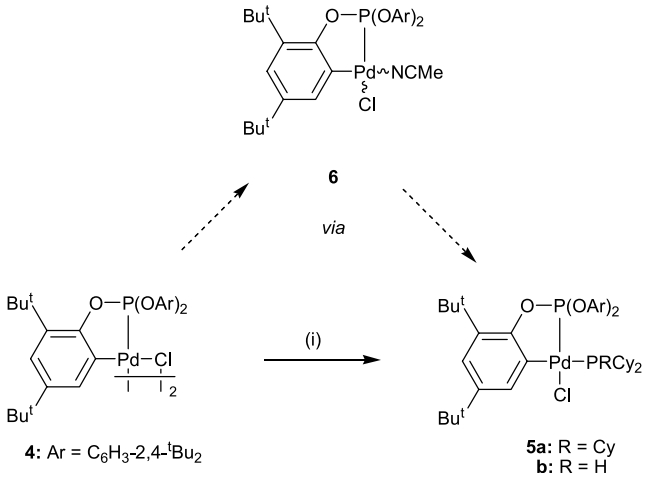
While such reactions are useful, the low commercial availability of alkyl- and aryl-(9-BBN) reagents and their air-sensitivity limits their appeal. In contrast aryl boronic acids reagents are widely available and easily handled. Therefore, Fu and co-workers investigated the possibility of using them as coupling partners with alkyl halides.[9] They found that the catalyst formed in situ from $Pd(OAc)_2$/$PMe(^tBu)_2$ couples primary alkyl bromides with aryl- and vinyl-boronic acids at rt when KO^tBu is used as the base in *tert*-amyl alcohol. Capretta and co-workers recently demonstrated that palladium catalysts containing the phosphaadamantyl ligand **2** can be used to good effect in the rt coupling of primary alkyl bromides and chlorides with aryl boronic acids, using potassium *tert*-butoxide in dioxane.[10] Interestingly, they even found that a moderate yield of coupled product results when the secondary alkyl bromide bromocyclohexane is used as a substrate. Zhou and Fu have also investigated the coupling of secondary alkyl halides with aryl- and vinyl-boronic acids and find that optimum activity is obtained with a nickel-based catalyst formed in situ from $[Ni(COD)_2]$ and bathophenanthroline, **3**, in *sec*-butanol using potassium *tert*-butoxide as base.[11]

We have been interested in the use phosphite- and phosphinite-based palladacyclic catalysts and their phosphine and carbene adducts in a range of Suzuki couplings of aryl halides with aryl and alkyl boronic acids.[12,13] Often the phosphines tested show far better activity when used in conjunction with palladacyclic precursors than classical palladium sources such as palladium acetate or palladium dibenzylideneacetone complexes.[14] We were interested to see whether this would hold true in the Suzuki coupling of alkyl halides with aryl boronic acids (Scheme 1, Y=OH), the results of an evaluative study are presented below.

2. Results and discussion

2.1. Synthesis and characterisation of catalysts

We have previously found that the reaction of the palladacyclic phosphite complex **4** with tricyclohexylphosphine at rt in dichloromethane leads to the formation of the phosphine adduct **5a**. However, under these conditions, the reaction does not go to completion, but rather gives a mixture of **4**, **5a** and PCy_3.[12b] Pure complex **5a** can be synthesized by the reaction of **4** with PCy_3CS_2, however, we wished to design a synthesis that exploits the free phosphine. This proves to be straightforward; the use of acetonitrile as solvent gives clean **5a** from **4** and PCy_3, presumably via the intermediate formation of a mono-nuclear acetonitrile complex **6** (Scheme 3).



Scheme 3. Synthesis of phosphine adducts of a phosphite palladacycle. Conditions: (i) $PRCy_2$, MeCN, rt, 18 h.

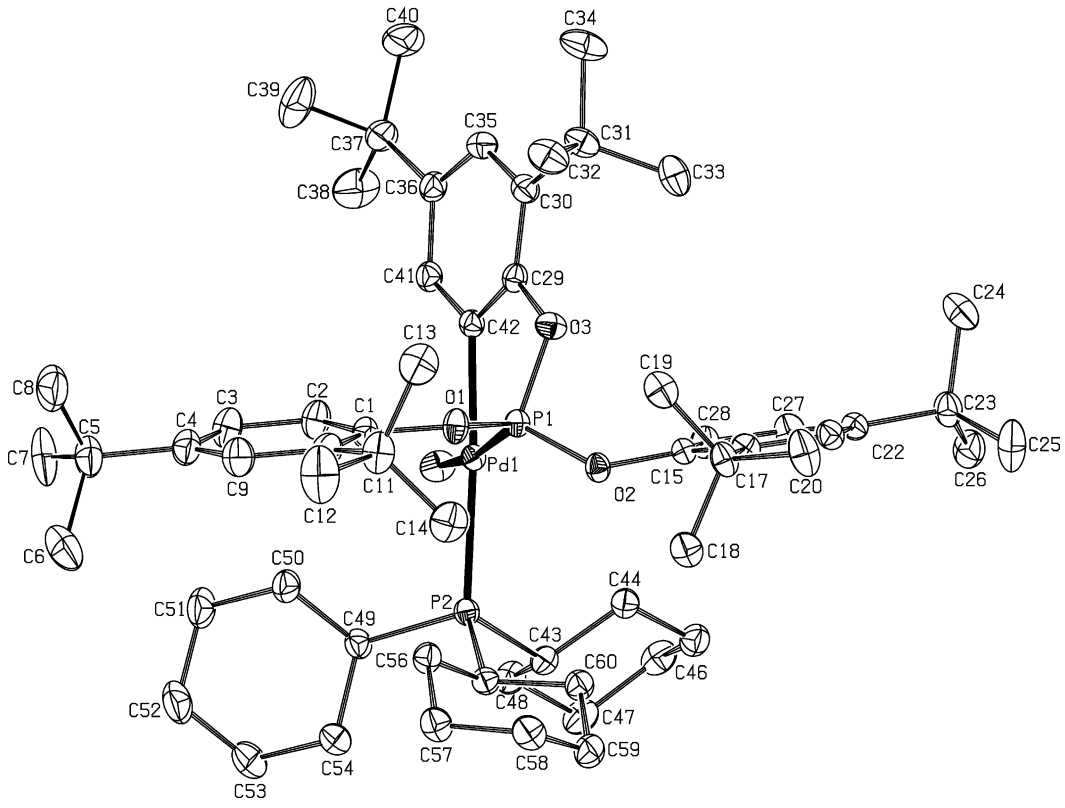
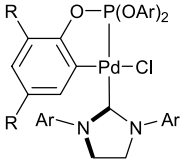


Figure 1. The molecular structure of **5a** with an ethanol solvate and disorder in two *tert*-butyl groups removed for clarity.

The ^{31}P spectrum of **5a** shows doublets at δ 136.0 and 26.2 ppm corresponding to the phosphite and phosphine donors, respectively, with a mutual coupling of 40.7 Hz. This relatively small coupling is indicative of a cis-disposition of the two phosphorus donors. Both this ^{31}P and the ^{1}H NMR spectral data are consistent with those obtained previously.[12b] The structure of complex **5a** was confirmed by single crystal X-ray analysis and the molecule is shown in Figure 1, whilst selected data are presented in Table 1. The structural analysis confirms the cis-disposition of the two P-donor groups. This is in marked contrast to the related carbene adducts **7**, which show the carbene ligand trans to the phosphite donor.[13]



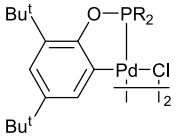
7a: R = ^{t}Bu; OAr = C_6H_3-2,4-$^{t}Bu_2$; Ar = mesityl
b: R = ^{t}Bu; OAr = C_6H_3-2,4-$^{t}Bu_2$; C_6H_3-2,6-$^{i}Pr_2$
c: R = H; OAr = OPh; Ar = mesityl

The synthetic methodology outlined above can also be applied to the synthesis of the novel secondary alkylphosphine adduct **5b**. The $^{31}P\{^{1}H\}$ NMR spectrum of **5b** shows doublets at δ 131.4 (phosphite) and 4.4 (phosphine) ppm with a mutual cis coupling of 46.2 Hz. These data are consistent with complex **5b** adopting a similar structure to **5a**. The proton-coupled ^{31}P spectrum shows a doublet of doublets at 134.2 ppm corresponding to the phosphite donor with a 47 Hz coupling to the phosphine phosphorus and a $^{3}J_{PH}$ of 14 Hz to the phosphine P–H and a doublet of doublets at 4.5 ppm with a large $^{1}J_{PH}$ of 312 Hz and a $^{2}J_{PP}$ of 41 Hz. The resonance for the P–H hydrogen is seen as a doublet of doublets of triplets in the ^{1}H NMR spectrum at 3.57 ppm with a large $^{1}J_{PH}$ of 310.5 Hz, a small $^{3}J_{PP}$ coupling of 15 Hz to the phosphite and a small $^{3}J_{HH}$ of 7 Hz to the two equivalent cyclohexyl PC*H*s. The $^{1}J_{PH}$ coupling is considerably larger than that of the free phosphine (170 Hz).

Table 1. Selected bond lengths and angles for complex **5a**

Bond lengths (Å)			
Pd1–P1	2.1770(5)	Pd1–P2	2.4052(5)
Pd1–C42	2.0842(18)	Pd1–Cl1	2.3488(5)
Bond angles (°)			
P1–Pd1–C42	77.83(5)	P1–Pd1–P2	106.044(17)
P2–Pd1–Cl1	84.946(17)	C42–Pd1–Cl1	91.37(5)
P1–Pd1–Cl1	168.029(18)	P2–Pd1–C42	175.64(5)

Attempts to produce phosphine adducts of **4** with the larger phosphines $P^{t}Bu_3$, PR_2(*o*-biphenyl) (R = Cy, ^{t}Bu), $PPh^{t}Bu_2$ using this method either failed or gave mixtures. The reaction of the two orthometallated phosphinite complexes **8a** and **8b** with PCy_3 again gave a mixture of products.

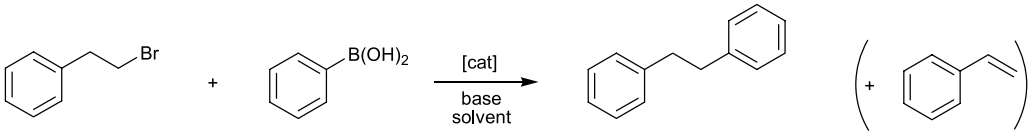


8a: R = Ph
b: R = ^{i}Pr

2.2. Catalysis

In the first instance we performed an optimisation study using the complex **5a** as catalyst in the coupling of

Table 2. Optimisation of solvents and bases[a]

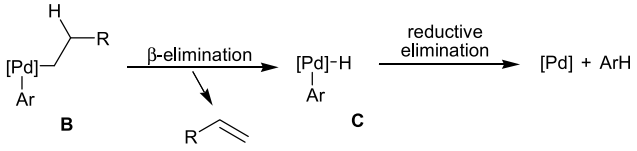


Entry	Solvent	Base	Conversion to 1,2-diphenyl ethane (%)[b]	Conversion to styrene (%)[b]
1	NMP	Cs_2CO_3	0	30
2	NMP	K_3PO_4	1	18
3	NMP	K_2CO_3	0	29
4	Toluene	Cs_2CO_3	2	6
5	Toluene	K_3PO_4	30	5
6	Toluene	K_2CO_3	5	4
7	Dioxane	Cs_2CO_3	6	13
8	Dioxane	K_3PO_4	31	4
9	Dioxane	K_2CO_3	36	1
10	Dioxane	KO^{t}Bu	0	64
11	Dioxane	KF	24	7
12	Dioxane	KF/K_3PO_4 1:1	11	6
13	DME	K_3PO_4	20	12
14	DME	K_2CO_3	4	2
15	DME	Cs_2CO_3	13	26
16	DME	KF	8	10
17	*sec*-Butanol	K_3PO_4	47	10
18	*sec*-Butanol	K_2CO_3	23	8
19	*sec*-Butanol	Cs_2CO_3	11	31
20	*sec*-Butanol	KO^{t}Bu	0	49
21	*tert*-Amyl alcohol	K_3PO_4	30	8
22	*tert*-Amyl alcohol	K_2CO_3	48	15
23	*tert*-Amyl alcohol	Cs_2CO_3	22	41
24	*tert*-Amyl alcohol	KO^{t}Bu	0	77

[a] Conditions: $BrCH_2CH_2Ph$ (5.0 mmol), $PhB(OH)_2$ (7.5 mmol), base (15.0 mmol), solvent (10 ml), 110 °C (external temperature).
[b] Conversion determined by GC (hexadecane internal standard).

(2-bromoethyl)benzene with phenylboronic acid with a range of solvents and bases; the results from this are summarized in Table 2. As can be seen, with respect to conversion to the desired 1,2-diphenylethane, the use of potassium phosphate in *sec*-butanol or potassium carbonate on *tert*-amyl alcohol gives the best activities (entries 17 and 22, respectively). However, in both cases substantial amounts of styrene are formed. While the use of potassium carbonate in 1,4-dioxane gives lower conversion to the desired product, the selectivity is much higher with very little styrene observed (entry 9). In stark contrast with the findings outlined in the introduction, potassium *tert*-butoxide proves to be a very poor choice of base with this catalyst (entries 10, 20, 24) giving little or no conversion to the desired product and substantial amounts of styrene via β-elimination, particularly when *tert*-amyl alcohol is used as the solvent.[8–11]

It is apparent from the relative conversions to the desired coupled product 1,2-diphenylethane and styrene that when the former is relatively low then the latter is relatively high. This is consistent with a manifold in which the rate determining step is not the oxidative addition of the alkyl bromide, but occurs after the formation of a palladium alkyl intermediate (Scheme 2, **A**). It is to be expected that the base plays an intimate role in the formation of the Pd-aryl intermediate (**B**) and if the rate-determining step is associated with this process a slow rate of formation of **B** from **A** would lead to greater amounts of β-eliminated product, in line with observation. Alternatively it is possible that the rate-determining step is reductive elimination, in which case β-elimination may also occur from the intermediate **B**. If this is true then an intermediate of the form **C** would be produced (Scheme 4), which would undergo reductive elimination to reform the active catalysts and an arene, in this case benzene. This certainly appears to be occurring; GC analysis of the product mixture formed in the reaction with cesium carbonate as base in *tert*-amyl alcohol (Table 2, entry 23) shows the presence of a substantial quantity of benzene, although at this stage we have not been able to determine the precise amount.



Scheme 4.

We next examined the effect of varying catalyst loading in the reaction in dioxane with K_2CO_3 acting as base and the results of this are shown in Figure 2. As can be seen the optimum conversion is achieved at 1.5 mol% catalyst loading but lowering the loading to 0.1 mol% leads to a maximum TON (turn-over number, mol product/mol catalyst) of 70. This is as expected since lowering the catalyst concentration would lead to a lower rate of catalyst decomposition by aggregation.

Then we examined the use of a range of catalysts, both

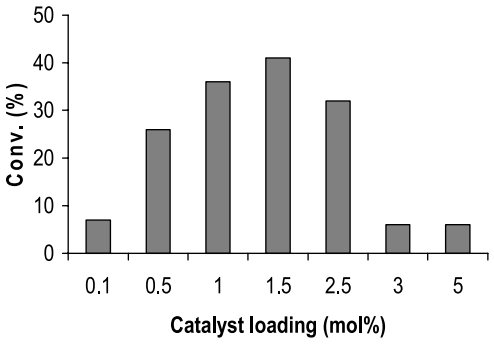


Figure 2. Variation in catalyst loading.

pre-formed or formed in situ, in the standard reaction. Dioxane was chosen as solvent and potassium carbonate as base for this study despite the fact that these conditions do not give the highest conversion, but rather because they show good selectivity for the desired product. The results from this study are presented in Table 3.

Table 3. Variation in catalyst[a]

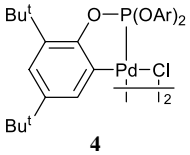
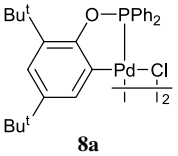
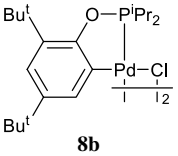
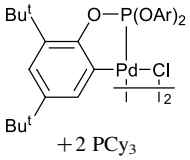
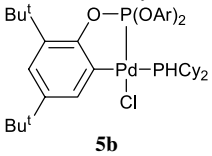
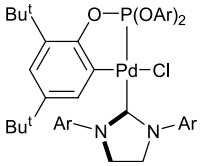
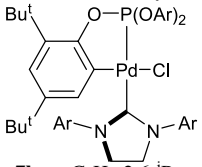
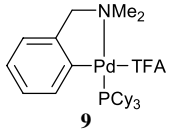
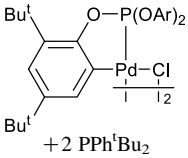
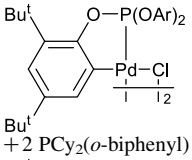
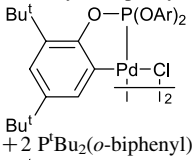
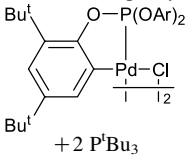
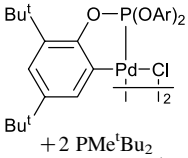
Entry	Catalyst	Conversion to 1,2-diphenylethane (%)[b]	Conversion to styrene (%)[b]
1	 **4**	2	8
2	 **8a**	0	6
3	 **8b**	0	10
4	 +2 PCy_3	17	6
5	**8a** +2 PCy_3	0	7
6	**8b** +2 PCy_3	6	7
7	 **5b**	6	4
8	 **7a**: Ar = mesityl	6	8
9	 **7b**: $=C_6H_3$-2,6-$^{i}Pr_2$	8	7

Table 3 (*continued*)

Entry	Catalyst	Conversion to 1,2-diphenylethane (%)[b]	Conversion to styrene (%)[b]
10	 **9**	11	4
11	 +2 $PPh^{t}Bu_2$	25	4
12	 +2 PCy_2(*o*-biphenyl)	26	11
13	 +2 $P^{t}Bu_2$(*o*-biphenyl)	3	6
14	 +2 $P^{t}Bu_3$	0	18
15	 +2 $PMe^{t}Bu_2$	16	7
16	$Pd(OAc)_2$ +2 $PMe^{t}Bu_2$	1	39
17	$Pd(OAc)_2$ +2 PCy_3	32	10
18	$Pd_2(dba)_3$ +4 PCy_3	15	7

[a] Conditions: $BrCH_2CH_2Ph$ (5.0 mmol), $PhB(OH)_2$ (7.5 mmol), K_2CO_3 (15.0 mmol), 1,4-dioxane (10 ml), 110 °C (external temperature).
[b] Conversion determined by GC (hexadecane internal standard).

The dimeric phosphite- and phosphinite-based palladacycles **4**, **8a** and **8b** all show little or no activity (entries 1–3). Comparing the activity of the catalysts formed in situ from dimer **4** and tricyclohexylphosphine (entry 4) with the preformed catalyst **5a** (Table 2, entry 9) indicates that it is important to pre-synthesise the catalysts, if possible. It is, therefore, perhaps not surprising that the catalysts formed in situ from the dimers **8** and PCy_3 show very poor activity (Table 3, entries 5 and 6). Indolese, Studer and co-workers have shown that palladacyclic catalysts with secondary alkylphosphine co-ligands are effective in the Suzuki biaryl coupling reaction of aryl chlorides.[15] Therefore, we were interested to see how the preformed catalyst **5b** would fare, unfortunately it proved to be disappointing (entry 7). It is perhaps not surprising that the carbene-containing complexes **7** did not prove to be any use (entries 8 and 9) since we have found them to be unimpressive in the Suzuki coupling of aryl chlorides.[13] In contrast, we have shown that

the preformed *N*-palladacyclic catalyst **9** shows good activity in the Suzuki biaryl coupling of aryl chlorides and were interested to see if it would work well in this instance.[16] Unfortunately it too proved essentially ineffective (entry 10).

Since we were unable to pre-form phosphine adducts of **5a** with bulkier phosphines, we tested the performance of catalysts produced in situ (entries 11–15). Both PPh^tBu_2 and PCy_2(*o*-biphenyl) (entries 11 and 12) show better conversions to product than the catalyst formed in situ with PCy_3 (entry 4), the latter at the expense of selectivity with respect to competitive styrene formation. Neither P(*o*-biphenyl)$^tBu_2$ or P^tBu_3 (entries 13 and 14) are promising. The phosphine ligand PMe^tBu_2 has been shown by Fu and co-workers to give optimum activity under their conditions in the Suzuki coupling of alkyl halides.[9] When it is used in conjunction with the palladacyclic complex **4** it shows poor activity (entry 15). However, the catalysts formed in situ from the phosphine and palladium acetate performed even worse with no conversion to coupled product and substantial styrene formation observed (entry 16). By contrast the catalyst formed in situ from tricyclohexylphosphine and palladium acetate shows similar activity (entry 17) to catalyst **5a** (Table 2, entry 9). Lower activity is seen when [Pd(dba)$_2$] is used as the palladium source (Table 3, entry 18).

We were surprised that PMe^tBu_2 performed so badly, given its good activity in the coupling of alkyl halides and tosylates with alkyl- and aryl-(9-BBN) or boronic acid reagents.[7,9] It is possible that the temperature of the reaction is too high and consequently the high relative rate of β-elimination precludes substantial coupling. In order to test this we performed the reaction again at 80 °C, at which temperature no product was observed despite the fact that the formation of styrene had been dramatically curtailed (4%). Similarly, when the reaction catalysed by **5a** was repeated at this temperature, very low (3%) conversion to product was observed. No conversion to product with either catalyst system is observed at rt or 50 °C.

3. Conclusions

In summary, unlike in the Suzuki biaryl coupling where the use of palladacyclic pre-catalysts can have a substantial benefit on activity compared with classical palladium precursors, when alkyl halides are used as substrates there is no discernible advantage in their use over palladium acetate. Preliminary data indicate that the rate-determining step in the coupling of alkyl bromides with aryl boronic acids is not oxidative addition, but rather lies later in the catalytic cycle. Mechanistic work is ongoing in our group to try to help optimize future catalyst structures.

We thank the EPSRC (Advanced Research Fellowship for RBB, DTA for RMF) and Kingston Chemicals for funding and Johnson Matthey for the loan of palladium salts.

4. Experimental

4.1. General

All reactions and manipulations of air-sensitive materials were performed under nitrogen, either in a glove-box or using standard Schlenk techniques. Solvents were distilled from appropriate drying reagents prior to use. Complexes **4**, **7–9** were prepared according to literature procedures.[12b,13,16b,17] All other material were obtained commercially and used as received. GC analysis was performed on a Varian 3800 GC fitted with a 25 m CP Sil 5CB column and data were recorded on a Star workstation. All catalytic reactions were performed on a Radleys Carousel Reactor™. This consists of 12 ca. 45 ml tubes, which are fitted with screw-on Teflon caps that are equipped with valves for the introduction of inert gas and septa for the introduction of reagents. The 12 reaction tubes sit in two stacked aluminium blocks, the lower one fits on a hotplate-stirrer and can be maintained at a constant temperature with a thermostat, while the upper block has water circulating, which cools the top of the tubes, allowing reactions to be performed at reflux temperature.

4.1.1. Synthesis of [PdCl{κ^2-*P*,*C*-(OC_6H_2–2,4-$^tBu_2$)(OC_6H_3–2,4-$^tBu_2$)$_2$}PCy_3], 5a. A mixture of complex **4** (0.79 g, 0.50 mmol) and tricyclohexylphosphine (0.31 g, 1.10 mmol) in acetonitrile was stirred at rt overnight. The solvent was then removed in vacuo, the resulting solid was dissolved in dichloromethane (10 ml), ethanol (10 ml) was added and the solution was concentrated in vacuo to induce precipitation. The resultant precipitate was recrystallised (dichloromethane/ethanol) to give complex **5a** as a colourless solid (0.65 g, 61%). Anal. Calcd for $C_{60}H_{95}O_3P_2PdCl$: C, 67.5; H, 9.0. Found: C, 66.9; H, 8.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (br s, 30H, CH_2 of Cy); 1.30 (br s, 18H, ^{t}Bu of orthometallated ring); 1.48 (br s, 36H, ^{t}Bu of non-orthometallated rings); 2.32 (m, 3H, C*H* of Cy); 6.92 (d, 2H, $^3J_{HH}$=2.6 Hz, non-orthometallated ring H6); 6.94 (dd, 2H, $^3J_{HH}$=2.6 Hz, $^4J_{HH}$=2.45 Hz, non-orthometallated ring H5); 7.27 (br m, 2H, non-orthometallated ring H3); 7.59 (d, 1H, $^4J_{HH}$=3.0 Hz, orthometallated ring), 7.62 (d, 1H, $^4J_{HH}$=3.0 Hz, orthometallated ring). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 27.0 (d, J_{PP}=41.6 Hz, PCy_3); 136.6 (d, J_{PP}=41.6 Hz, P(OAr)$_3$).

4.2. Crystal structure determination for complex 5a

Data were collected at 120 K on an Nonius Kappa CCD area detector diffractometer located at the window of a Nonius FR591 rotating anode X-ray generator, equipped with a molybdenum target (λ Mo k$_\alpha$=0.71073 Å). Structures were solved and refined using the SHELX-97 suite of programs.[18] Data were corrected for absorption effects by means of comparison of equivalent reflections using the program SORTAV[19]. Non-hydrogen atoms were refined anisotropically, whilst hydrogen atoms were generally fixed in idealised positions with their thermal parameters riding on the values of their parent atoms. Positional disorder was found to be present in two tertiary butyl groups and the ethanol solvent molecule, which was modelled as 50% partial occupancy for each orientation. $C_{61}H_{98}ClO_{3.5}P_2Pd$, triclinic, *P*-1, a=12.4913(1), b=13.0629(1), c=20.7063(3) Å, α=99.150(1), β=99.642(1) γ=110.827(1)°, volume=3024.47(6) Å^3, Z=2, D_c=1.198 Mg/m^3, μ=0.445 mm^{-1}, 57,222 measured, 13,800 unique (R_{int}=0.0476) and 12,220 ($I>2\sigma(I)$) reflections, $R1$ (obs)=0.0345 and $wR2$ (all data)=0.08795

$\rho_{max}/\rho_{min}=0.847/-0.613$ eÅ^{-3}. Supplementary data have been deposited with the Cambridge Crystallographic Data Cente (Deposition number=CCDC270788).

4.2.1. Synthesis of [PdCl{κ^2-*P*,*C*-(OC_6H_3–2,4-^{t}Bu$_2$)(OC_6H_3–2,4-^{t}Bu$_2$)$_2$}$PHCy_2$], 5b. This as prepared using the same method for the synthesis of **5a**, with $PHCy_2$ in place of PCy_3. Complex **5b** was obtained as a colourless solid (0.304 g, 62%). Anal. Calcd for $C_{54}H_{85}O_3P_2PdCl\cdot(0.5\ CH_2Cl_2)$: C, 63.64; H, 8.43. Found: C, 63.61; H, 9.11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (br m, 2H Cy); 0.96 (br m, 4H, Cy); 1.07 (br s, 9H, ^{t}Bu of orthometallated ring); 1.16 (br m, 4H, Cy); 1.24 (br s, 18H, ^{t}Bu of non-orthometallated rings); 1.32 (br m, 4H, Cy); 1.39 (br s, 9H, ^{t}Bu of orthometallated ring); 1.46 (br m, 4H, Cy); 1.52 (br s, 18H, ^{t}Bu of non-orthometallated rings); 1.65 (br m, 2H, Cy); 1.80 (br m, 2H, Cy); 3.57 (ddt, 1H, $^1J_{PH}=310.5$ Hz, $^3J_{PH}=15.0$ Hz, $^3J_{HH}=7$ Hz P*H*Cy_2); 7.00 (dd, 2H, $^3J_{HH}=8.5$ Hz, $^4J_{HH}=2.4$ Hz, non-orthometallated ring H5); 7.12 (t, 2H, $^3J_{HH}=2.4$ Hz, non-orthometallated ring H6); 7.37 (br m, 2H, non-orthometallated ring H3); 7.39 (d, 1H, $^4J_{HH}=2.2$ Hz, orthometallated ring), 7.42 (d, 1H, $^4J_{HH}=2.2$ Hz, orthometallated ring). ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 4.40 (d, $J_{PP}=46.2$ Hz, PCy_3); 134.1 (d, $J_{PP}=46.2$ Hz, $P(OAr)_3$).

4.3. Procedure for cross-coupling of (2-bromoethyl) benzene with phenylboronic acid

A Radleys Carousel tube was loaded with the appropriate amount of desired catalyst, then (2-bromoethyl)benzene (0.68 ml, 5.0 mmol) was added followed by the solvent (10 ml), base (15.0 mmol) and finally phenylboronic acid (7.5 mmol). The mixture was then heated to 110 °C (external temperature) for 18 h, allowed to cool to rt and then aqueous HCl (2 M, 10 ml) was added. The mixture was extracted with dichloromethane and the combined extracts dried ($MgSO_4$). Hexadecane (0.17 M in dichloromethane, 1.00 ml) was added and the product mixture analysed by GC. GC, GC–MS and ^{1}H spectroscopy of product mixtures were consistent with data obtained using commercial samples of styrene and 1,2-diphenylethane (Aldrich).

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In situ formation of palladium(0) from a *P*,*C*-palladacycle

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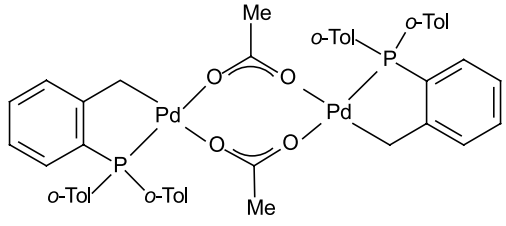
Abstract—In DMF at 80 °C, a Pd^0 complex is generated in situ from the dimeric *P*,*C*-palladacycle (**1**) in the absence of any reducing agents, presumably via a reductive elimination. The Pd^0 complex formed in an endergonic equilibrium has been trapped and stabilized by an additional $P(o\text{-Tol})_3$ and has been detected in cyclic voltammetry by its oxidation peak. Its formation is favored by acetate anions (often used as base in Heck reactions) via the formation of a monomeric anionic *P*,*C*-palladacycle ligated by acetate ions. As postulated, *P*,*C*-palladacycles are a reservoir of monophosphine–Pd^0 complexes active in oxidative additions with aryl halides.

1. Introduction

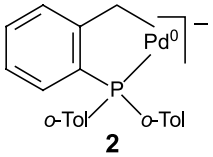
The *P*,*C*-palladacycle *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium (**1**) has proved to be efficient in palladium-catalyzed Heck, as pioneered by Beller, Herrmann et al.[1a,c] It has then been used in Suzuki, Stille and cross-coupling reactions.[1b,2] Such reactions usually involve Pd^0 complexes as true catalysts.[2]



1

Louie and Hartwig have established that Pd^0 complexes are indeed formed in Stille reactions or cross-coupling reactions of secondary amines with aryl halides.[3] The nucleophiles (organostannanes or amines) are at the origin of the formation of Pd^0 complexes in the very beginning of the catalytic reactions, (i) by transmetallation of the acetate ligand of (**1**) by the organostannane followed by reductive elimination or (ii) by cleavage of the acetate bridges in (**1**) by complexation of the secondary amine, deprotonation of the latter by a base, β-H-elimination on the resulting amide ligand followed by reductive elimination. The Pd–C bond of (**1**) is cleaved in both cases.

In Heck reactions, where a reducing agent cannot be clearly identified, a catalytic cycle involving Pd^{II}/Pd^{IV} complexes was first proposed rather than the traditional one involving Pd^0/Pd^{II} complexes, because of the stability of the palladacycle (**1**) at high temperatures.[1a,4] However, an induction period was sometimes observed before the production of the arylated alkene, which was interpreted as the time required for the in situ generation of a Pd^0 complex from the palladacycle. The first step of the catalytic cycle would then be the classical oxidative addition of the aryl halide with a Pd^0 complex, as in a classical Pd^0/Pd^{II} catalytic cycle.[2] Even in the absence of any identified reducing agent, Böhm and Herrmann have nevertheless proposed the reduction of the palladacycle (**1**) to an anionic Pd^0 complex (**2**) still ligated to the benzyl moiety of the ligand.[5,2d]



2

There is now a general agreement on the fact that, in Heck reactions, a Pd^0 complex must be the real catalyst, which induces a catalytic cycle involving Pd^0/Pd^{II} complexes.[2a,b,d,f]

We report here evidence of the in situ formation of Pd^0 complexes from the palladacycle (**1**) by reductive elimination.

Keywords: Palladacycle; Reductive elimination; Mechanism, cyclic voltammetry.
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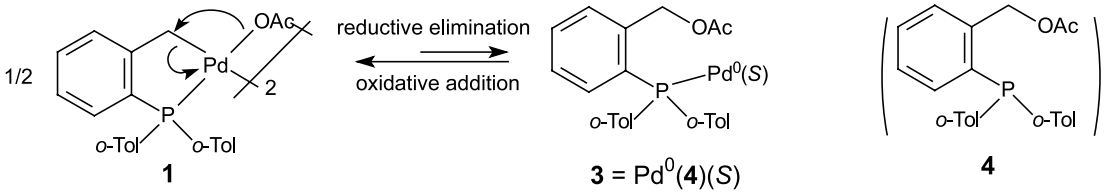


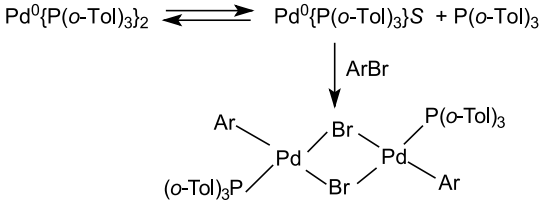
Scheme 1. Formation of a Pd^0 complex by reductive elimination (S=solvent).

2. Results and discussion

Our working hypothesis was that a Pd^0 complex would be generated in situ from the palladacycle (**1**) in an endergonic reductive elimination between one acetate ligand and the *cis*-*o*-benzyl moiety (Scheme 1). This reductive elimination would generate the monophosphine–Pd^0 complex (**3**) ligated by the new phosphine ligand (**4**) containing the *o*-benzylic acetate moiety formed in the reductive elimination.

Reductive elimination between an acetate and a benzyl ligand leading to the formation of a C–O bond is not common. It was proposed once to explain the formation of $PhCH_2$–OAc by reacting $PhCH_2$–$PdCl(PPh_3)_2$ with NaOAc or AgOAc, via the hypothetical dimeric complex $[PhCH_2$–$Pd(\mu\text{-}OAc)(PPh_3)]_2$.[6]

The complex (**3**) proposed in Scheme 1 would be a monophosphine ligated $Pd^0L(S)$ complex, very similar to the monoligated $Pd^0\{P(o\text{-}Tol)_3\}(S)$ generated from the stable $Pd^0\{P(o\text{-}Tol)_3\}_2$ and, which is involved in oxidative addition with aryl halides, as established by Hartwig et al. (Scheme 2).[7]



Scheme 2. (S=solvent).

In the case of the palladacycle (**1**), the reverse reaction (backward reaction in Scheme 1) would be an intramolecular oxidative addition of the monophosphine–Pd^0 complex (**3**) with the C–O bond of the *o*-benzylic acetate.[8] Such reaction should be very fast due to its intramolecular character. This would explain why the equilibrium in Scheme 1 lies in favor of the palladacycle (**1**). Consequently, to be able to detect the Pd^0 complex generated in the endergonic reductive elimination, we need to shift the equilibrium in Scheme 1 toward its right-hand side and to slow down the backward oxidative addition. The Pd^0 complex (**3**) might be trapped by additional ligands (dba/*trans,trans*-dibenzylideneacetone, $P(o\text{-}Tol)_3$/tri-*ortho*-tolylphosphine, AcO^-…) and stabilized as Pd^0(**4**)(dba), Pd^0(**4**)$\{P(o\text{-}Tol)_3)\}$, anionic Pd^0 complexes $Pd^0(\mathbf{4})(OAc)_n^{n-}$ and so on. $P(o\text{-}Tol)_3$ was selected since we know from Beller and Hermann's work that this phosphine cannot reduce Pd^{II} complexes ligated by acetate ligands to a Pd^0 complex.[1] This is indeed why the palladacycle (**1**) is formed by mixing $Pd(OAc)_2$ and $P(o\text{-}Tol)_3$.[1a,c]

Our strategy was to observe the in situ formation of Pd^0 from the palladacycle (**1**) in the presence of additives (dba, $P(o\text{-}Tol)_3$, AcO^-), which are not reducing agents, using cyclic voltammetry to detect any oxidation peak that might characterize a Pd^0 complex formed in situ. Electrochemistry is indeed one of the most convenient techniques to detect Pd^0 complexes that are generated in situ from Pd^{II} complexes.[9] The electrochemistry of the palladacycle (**1**) has been first investigated.

2.1. Electrochemical properties of the palladacycle (1) in DMF

The palladacycle (**1**) (2 mM) in DMF (containing $n\text{-}Bu_4NBF_4$, 0.3 M as supporting electrolyte) exhibited at room temperature two successive irreversible reduction peaks: a major one R_1 at −1.89 V versus SCE (scan rate of 0.5 V s^{-1}) and a minor one R_2 at −2.16 V versus SCE (Fig. 1a, full line). An oxidation peak O_1 was detected on the reverse scan at +0.21 V (Fig. 1a), which characterizes a Pd^0 complex generated by the electrochemical reduction of (**1**). The oxidation peak O_1 was also observed when the scan was reversed after the first reduction peak R_1 (Fig. 1a, dashed line).

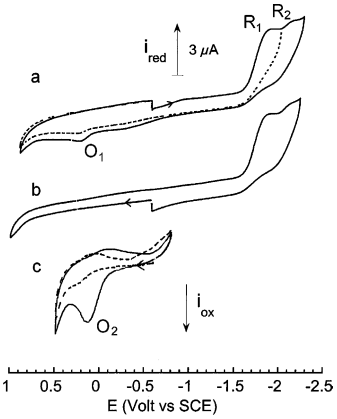


Figure 1. Cyclic voltammetry performed in DMF containing $n\text{Bu}_4\text{NBF}_4$ (0.3 M) at a steady gold disk electrode (d 0.5 mm) at a scan rate of 0.5 V s^{-1}. (a) (—) Reduction of the palladacycle (**1**) (2 mM) at 25 °C; (– – – –) idem except that the potential scan has been reversed after R_1. (b) Same as in Fig 1a but oxidation first, at 25 °C. (c) (—) Oxidation of the Pd^0 complex generated from the palladacycle (**1**) (2 mM) in the presence of $P(o\text{-}Tol)_3$ (4 mM), dba (18.9 mM) and $n\text{Bu}_4\text{NOAc}$ (18.4 mM) at 80 °C. (– – – –) in the presence of PhI (74 mM) at 80 °C, just after mixing.

When the scan rate was varied from 0.1 to 1 V s^{-1}, the reduction peak current i_{R_1} of R_1 increased but did not vary linearly with the square root of the scan rate whereas the ratio $i_{R_1}/(i_{R_1}+i_{R_2})$ decreased upon increasing the scan rate. This suggests that the reduction processes at R_1 and R_2 characterize two different species in equilibrium (CE

mechanism).[10] The plateau shaped form of the reduction peak R_1 (Fig. 1a) is also indicative of an equilibrium preceding the electron transfer (CE mechanism).[10] The ^{31}P NMR spectrum of (**1**) (2 mM) in DMF (containing 20% CD_2Cl_2 for the lock) exhibited a broad resonance at 34.23 ppm ($\Delta\nu_{1/2}=90$ Hz) indicative of an equilibrium between different species. According to literature, this would be an equilibrium between the palladacycle (**1**), the cationic complex [*o*-(di-*o*-tolylphosphino)benzyl]Pd^+ and AcO^-.[1a,11] However, when the palladacycle (**1**) (1 mM) was added to DMF (a good dissociating solvent exhibiting a residual conductivity of 0.5 μS cm^{-1}), the conductivity did not increase, ruling out the existence of ionic species at high concentration.[12] Moreover, when the cyclic voltammetry was performed directly toward oxidation potentials, no oxidation peak characterizing AcO^- was detected (Fig. 1b).[13] The oxidation potential of AcO^- in nBu$_4$NOAc performed under the same conditions in DMF is +0.87 V versus SCE. Consequently, R_1 and R_2 characterize neutral species, dimer (**1**) and neutral monomers (**5**) in equilibrium in DMF, which is a good coordinating solvent (Scheme 3).[14]

When the concentration of (**1**) was increased from 2 mM to 3 mM, the ratio i_{R_1}/i_{R_2} increased. The second reduction peak was hardly detected at the scan rate of 0.2 V s^{-1}. This indicates that the first reduction R_1 characterizes the dimeric palladacycle (**1**) whereas R_2 characterizes the monomeric palladacycles (**5**). The electrochemical reduction of both species (**1**) and (**5**) led to the same Pd^0 complex, which is the complex (**2**) proposed by Hermann et al. (Scheme 4).[2d,5]

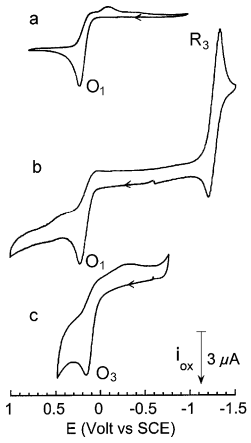
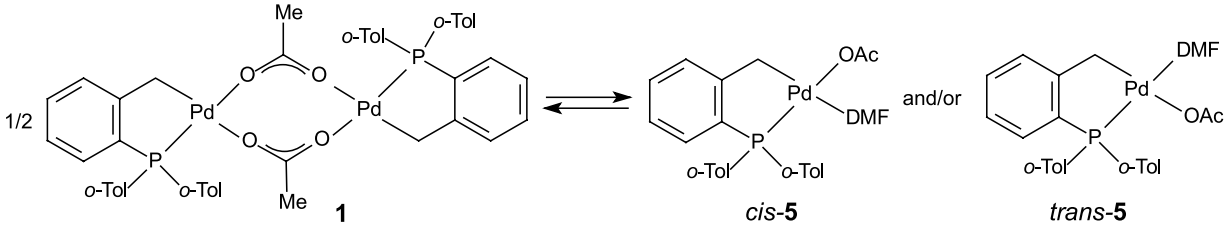


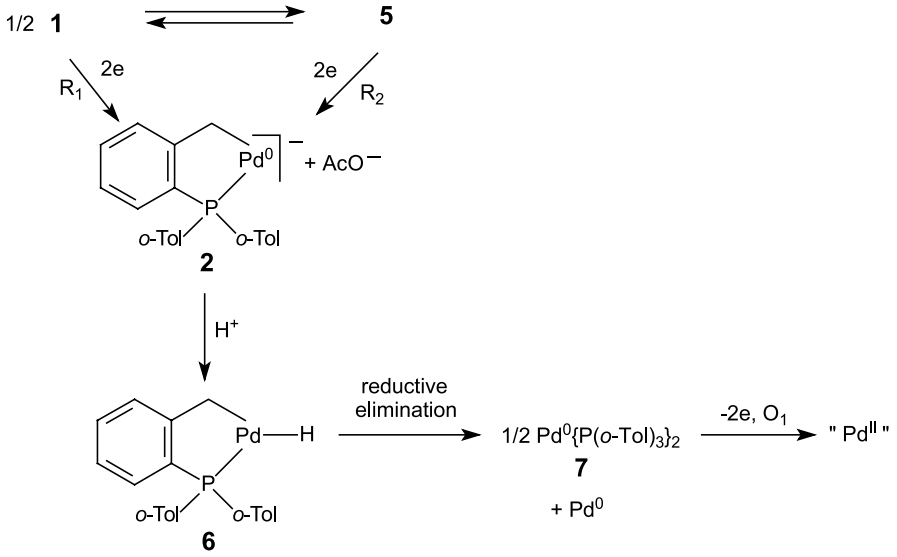
Figure 2. Cyclic voltammetry performed in DMF containing nBu$_4$NBF$_4$ (0.3 M) at a steady gold disk electrode (d 0.5 mm) with a scan rate of 0.5 V s^{-1}. (a) Oxidation of $Pd^0\{P(o\text{-Tol})_3\}_2$ (2 mM) at 25 °C. (b) Oxidation of $Pd^0\{P(o\text{-Tol})_3\}_2$ generated from $Pd^0(dba)_2$ (2 mM) and P(*o*-Tol)$_3$ (4 mM) at 25 °C. (c) Oxidation of $Pd^0\{P(o\text{-Tol})_3\}_2$ generated from $Pd^0(dba)_2$ (4 mM) and P(*o*-Tol)$_3$ (8 mM) in the presence of added dba (10.9 mM, total concentration of dba=18.9 mM) and nBu$_4$NOAc (22.4 mM) at 80 °C.

However, the oxidation peak potential of O_1, assigned to complex **2** in a first approach, was the same as the oxidation peak potential of $Pd^0\{P(o\text{-Tol})_3\}_2$ (**7**), as determined independently on an authentic sample of (**7**) (Fig. 2a, compare entries 1 and 2 in Table 1).

The anionic Pd^0 complex (**2**) generated in the



Scheme 3.



Scheme 4. Electrochemical reduction of the palladacycle (**1**) in DMF.

Table 1. Oxidation peak potentials of Pd^0 complexes in DMF containing nBu_4NBF_4 (0.3 M) at a steady gold disk electrode (*d* 0.5 mm), at a scan rate of 0.5 V s^{-1}

N	Precursor	Electroactive Pd^0	E^p_{ox} of Pd^0 (Volt vs SCE)	
			25 °C	80 °C
1	**1**[a] + 2e + (H^+)	$Pd^0\{P(o\text{-Tol})_3\}_2$ (**7**)	+0.215	nd[b]
2	$Pd^0\{P(o\text{-Tol})_3\}_2$ (**7**)	(**7**)	+0.212	+0.213
3	**1**[a] + $P(o\text{-Tol})_3$ (excess)[c] + dba[d]	(**7**)	no[e]	+0.190
4	**1**[a] + AcO^-[f] + 2$P(o\text{-Tol})_3$ + dba[g]	(**9**)	no[d]	+0.145
5	$Pd^0(dba)_2$[h] + 2$P(o\text{-Tol})_3$	(**7**)	+0.214	nd[b]
6	$Pd^0(dba)_2$[h] + 2$P(o\text{-Tol})_3$ + AcO^-[i]	(**7**)	+0.175	+0.154
7	$Pd^0(dba)_2$[j] + AcO^-[k] + 2$P(o\text{-Tol})_3$ + dba[l]	(**7**)	+0.178	+0.154

[a] Two millimolar.
[b] nd: not determined
[c] Seventy five millimolar.
[d] Seventy four millimolar.
[e] no: not observed.
[f] 18.4 mM.
[g] 18.9 mM.
[h] Two millimolar.
[i] 22.4 mM.
[j] Four millimolar.
[k] 22.4 mM.
[l] Added dba: 10.9 mM (total concentration including the dba released from $Pd^0(dba)_2$: 18.9 mM).

electrochemical reduction of (**1**) is a strong base, which was protonated in the DMF medium by residual water, within the time scale of the cyclic voltammetry. $Pd^0\{P(o\text{-Tol})_3\}_2$ (**7**) was formed after a reductive elimination (Scheme 4) and was oxidized at O_1. Due to the lack of ligand (P/Pd = 1), metallic Pd^0 must also be formed. It has been checked that the oxidation peak current of the electrogenerated complex (**7**) at O_1 indeed increased (consequently its concentration had increased) when the electrochemical reduction of (**1**) was performed in the presence of 1 equiv of $P(o\text{-Tol})_3$ (P/Pd = 2).

Therefore, in DMF, the palladacycle (**1**) is reduced to a Pd^0 complex at rather high negative potentials (comparable to the reduction power of zinc powder).

When the cyclic voltammetry of (**1**) was performed directly towards oxidative potentials (from −0.6 to +1 V), that is, without reducing (**1**), no oxidation peak was detected (Fig. 1b). This indicates that at room temperature, no Pd^0 complex was formed in situ in significant amount from the palladacycle (**1**), as it is reported for $Pd(OAc)_2(PPh_3)_2$.[9] No Pd^0 complex was detected at 80 °C. This is why additives must be introduced to have a chance to trap the Pd^0 complex hypothetically formed in the very endergonic equilibrium of Scheme 1.

2.2. Formation in situ of palladium(0) from the *P,C*-palladacycle (1)

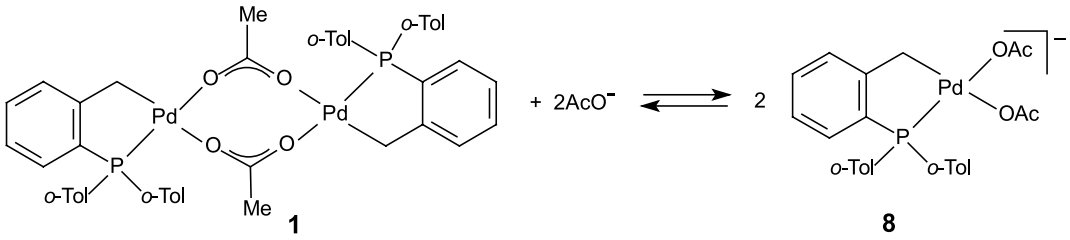
Cyclic voltammetry was used to detect the formation of a Pd^0 complex from the palladacycle (**1**) in DMF in the presence of additives (dba, $P(o\text{-Tol})_3$, AcO^-). The voltammetry was performed only towards oxidative potentials, starting from a resting potential of −0.6 V where (**1**) was not electroactive, in a potential range of −0.6 to +0.5 V in which neither AcO^- nor $P(o\text{-Tol})_3$ were oxidized (+0.87 and +1.22 V, respectively) nor dba was reduced (−1.30 V).

The effect of dba was first tested. No reaction of (**1**) (2 mM) with dba (up to 20 mM) was observed in DMF, as monitored by ^{31}P NMR and cyclic voltammetry. No Pd^0 complex was detected at 25 °C nor at 80 °C on the CV of (**1**) performed directly to oxidation potentials from −0.6 to +0.5 V, in the presence of dba.

The effect of acetate anions was tested in DMF. When 0.01 mmol of (**1**) were introduced in an NMR tube containing 0.5 mL of DMF (with 20% CD_2Cl_2), it was not quite soluble and was characterized by a broad singlet at 34.23 ppm. After addition of 0.09 mmol of AcO^- (introduced as nBu_4NOAc) into the NMR tube containing (**1**), all became soluble and the initial yellow color of (**1**) turned to pale yellow, suggesting that a new species was generated. A sharp singlet was then observed at 35.08 ppm. The same effect was observed in pure CD_2Cl_2. Upon addition of nBu_4NOAc (0.017 mmol) to a solution of (**1**) (0.0085 mmol) in 0.5 mL of CD_2Cl_2, the broad signal of (**1**) at 34.32 ppm was still observed together with a sharp singlet at 36.04 ppm in the ratio 1.6:1 in favor of (**1**). After further addition of nBu_4NOAc (total 0.155 mmol), the magnitude of the sharp singlet now located at 35.81 ppm increased at the expense of (**1**). The former ratio became equal to 0.26/1. The corresponding ^1H NMR spectrum was strongly modified compared to the ^1H NMR spectrum of pure (**1**).[15a] This means that acetate ions reacted with the palladacycle (**1**) to form the new species (**8**) (Scheme 5) in equilibrium with (**1**) since the concentration of (**8**) increased upon increasing the AcO^- concentration.

The fact that one sharp and one broad ^{31}P NMR singlet were observed together indicates that the equilibrium between (**1**) and (**8**) is the result of two successive equilibria operating at different time scales via the complexes (**5**) (Scheme 3). The anionic complex (**8**) must be formed at the very beginning of palladacycle-catalyzed Heck reactions if acetate ions are used as base.[1a,c,2a,d] Similar anionic palladacycle complexes with two bromide instead of two acetate are reported by Hermann et al.[1a]

No Pd^0 complex was detected at 25 °C nor at 80 °C on the



Scheme 5.

CV of (**1**) performed directly to oxidative potentials from −0.6 to +0.5 V in the presence of acetate ions.

The effect of the ligand P(*o*-Tol)$_3$ was also tested. When 2 equiv of P(*o*-Tol)$_3$ (P(*o*-Tol)$_3$/Pd=1) was added to a solution of the palladacycle (**1**), 2 mM in DMF, the integration of the ^{31}P NMR sharp singlet of P(*o*-Tol)$_3$ (−30.77 ppm) remained close to the integration of the broad singlet of (**1**) (35.09 ppm) even at long times (24 h), suggesting that no fast reaction occurred between (**1**) and P(*o*-Tol)$_3$.[15b] No Pd^0 complex was observed at 80 °C on the cyclic voltammogram of (**1**) performed directly to oxidative potentials from −1 to +1.4 V, in the presence of 1 equiv of P(*o*-Tol)$_3$ per Pd in DMF. The oxidation peak of the free P(*o*-Tol)$_3$ was only observed at +1.22 V versus SCE.

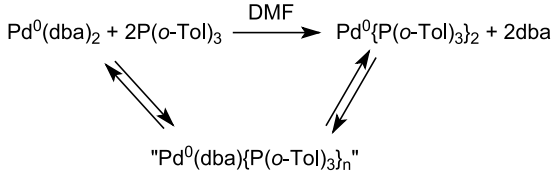
No Pd^0 complex was detected at 25 °C when dba and/or P(*o*-Tol)$_3$ and/or OAc$^-$ were added, even in large amounts, either alone or together to a solution of (**1**) in DMF. However, at 80 °C where the palladacycle **1** (2 mM) was still stable in DMF (yellow solution), an oxidation peak was detected at +0.19 V (entry 3 in Table 1) after addition of P(*o*-Tol)$_3$ (75 mM) followed by dba (74 mM). This indicates that a Pd^0 complex had been formed in situ form (**1**). The oxidation peak disappeared after addition of PhI (74 mM), confirming a posteriori the formation of a Pd^0 in situ. However, this experiment was difficult to reproduce unless AcO$^-$ was first added to (**1**), suggesting that the anionic species (**8**) could play a role in the reduction process. Indeed, a pale yellow solution of (**1**) containing *n*Bu$_4$NOAc in DMF started to darken with black Pd^0 particles deposition after 4 days at room temperature, whereas a yellow solution of (**1**) alone was stable for at least 8 days. Consequently, a series of cyclic voltammetry experiments were performed in which AcO$^-$ ions were first introduced in excess (18.4 mM) to a solution of (**1**) (2 mM) in DMF to ensure that the anionic species (**8**) was the major component (Scheme 5). It was followed by the introduction of P(*o*-Tol)$_3$ in stoichiometric amount (4 mM, P(*o*-Tol)$_3$/Pd=1). A ^{31}P NMR spectrum confirmed the presence of (**8**) at 35.09 ppm, (**1**) at 32.6 ppm and free P(*o*-Tol)$_3$ at −30.77 ppm, in the ratio: 0.65:0.35:1. Dba was then added (18.9 mM) and the temperature was increased to 80 °C. After 1 h, an oxidation peak O$_2$ was detected (Fig. 1c, full line) at a potential of +0.14 V, slightly less positive than in the experiment performed in the absence of acetate and in the presence of in excess P(*o*-Tol)$_3$ (Table 1, entries 4 and 3, respectively). The oxidation peak O$_2$ disappeared when the solution was cooled to 20 °C and appeared again upon increasing the temperature to 60–80 °C. The oxidation peak O$_2$ disappeared after addition of PhI (74 mM) (Fig. 1c, dashed line), confirming that a Pd^0 complex had been generated in situ from the palladacycle (**1**) in the absence of any reducing agent. This suggests that it has been generated by a reductive elimination in a reversible reaction, which has been shifted towards the formation of a Pd^0 complex by stabilization of the latter by additives (acetate, P(*o*-Tol)$_3$, dba), according to our working hypothesis. The minimum amount of dba and acetate, which is required to observe the in situ formation of the Pd^0 complex from (**1**) has not been determined.

2.3. Identification of the palladium(0) complex generated in situ from the *P,C*-palladacycle (1)

The fact that the Pd^0 complex appeared at 80 °C and then disappeared at 20 °C when two equiv of P(*o*-Tol)$_3$ was added to (**1**), suggests that it was in equilibrium with the starting complex. Consequently, the Pd^0 complex primary generated from (**1**) should be still ligated by (**4**) (Scheme 1), a ligand whose structure is close to that of P(*o*-Tol)$_3$. To better characterize the Pd^0 complex generated in situ from (**1**), the Pd^0 complex generated from Pd^0(dba)$_2$ and P(*o*-Tol)$_3$ in the presence of acetate ions was characterized by cyclic voltammetry.

When 2 equiv of P(*o*-Tol)$_3$ were added to a solution of Pd^0(dba)$_2$ (2 mM) in DMF containing *n*Bu$_4$NBF$_4$ (0.3 M) at 25 °C, a slow reaction occurred and the purple colored solution turned progressively to brown yellow. An oxidation peak O$_1$ was observed at +0.21 V (Fig. 2b, entry 5 in Table 1). It was fully developed after 30 min, whilst as two equiv of dba were released in solution, as determined by comparison of its reduction peak current (R$_3$ in Fig. 2b) with the reduction peak current measured independently in a solution of dba (4 mM) in DMF at the same scan rate. The oxidation peak potential at O$_1$ was the same as the oxidation peak potential of an authentic sample of Pd^0{P(*o*-Tol)$_3$}$_2$ (**7**) determined under the same conditions (Fig. 2a, entry 2 in Table 1).

When dba was added in excess (10 equiv), the oxidation peak of Pd^0{P(*o*-Tol)$_3$}$_2$ became slightly broader but no new oxidation peak, which would have characterized complexes Pd^0(dba){P(*o*-Tol)$_3$}$_n$ (n=1 or 2) was observed in DMF.[16] This suggests that Pd^0{P(*o*-Tol)$_3$}$_2$ was



Scheme 6.

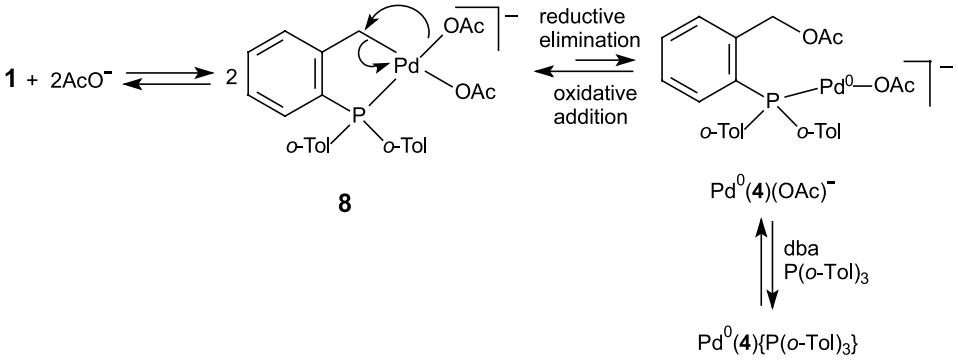
generated as the major complex from $Pd^0(dba)_2$ and 2 equiv of dba in DMF (Scheme 6) whereas $Pd^0(dba)\{P(o\text{-Tol})_3\}_n$, whenever formed,[16] was present at a non-detectable concentration or that the equilibrium between $Pd^0(dba)\{P(o\text{-Tol})_3\}_n$ and $Pd^0\{P(o\text{-Tol})_3\}_2$ was very labile and therefore easily shifted towards the formation of $Pd^0\{P(o\text{-Tol})_3\}_2$ during the time scale of the cyclic voltammetry (scan rate of $0.5\ V\ s^{-1}$), as in a CE mechanism.[10]

In an other experiment, nBu$_4$NOAc (22.4 mM) was added to $Pd^0\{P(o\text{-Tol})_3\}_2$ generated from $Pd^0(dba)_2$ (2 mM) and 2 equiv of $Pd^0\{P(o\text{-Tol})_3\}_2$ in DMF at 25 °C. A shift of the oxidation peak of $Pd^0\{P(o\text{-Tol})_3\}_2$ to more positive potential was observed (compare entries 5 and 6 in Table 1 at 25 °C). This could be due to either the formation of anionic species $Pd^0\{P(o\text{-Tol})_3\}(OAc)^-$ as proposed by Hermann et al.,[2a] which would be more easily oxidized than a neutral Pd^0 complex, or to the easier oxidation of (**7**) when performed in the presence of acetate ions (EC mechanism).[17a] Since a small potential difference of $\Delta E_{ox}=$ 40 mV was observed in the presence of excess AcO^- (11.2 equiv) at 25 °C, we are inclined to favor the second hypothesis.[17b]

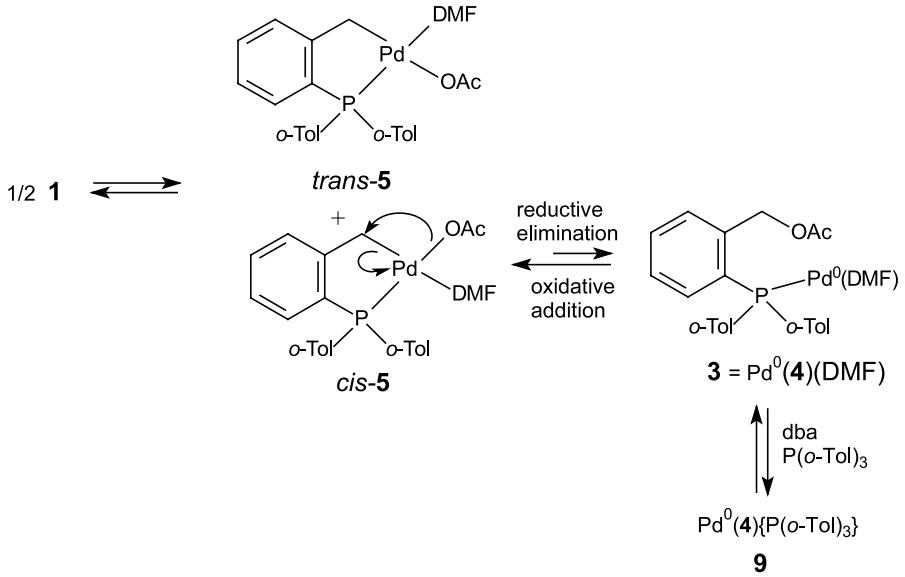
The oxidation potential of $Pd^0\{P(o\text{-Tol})_3\}_2$ generated from $Pd^0(dba)_2$ (4 mM) and $P(o\text{-Tol})_3$ (8 mM) was determined in the presence of dba (total 18.9 mM) and AcO^- (22.4 mM), that is, using the same additives concentrations as when the Pd^0 complex was formed in situ from the palladacycle (**1**). The peak potential of the resulting oxidation peak O_3 at 80 °C (Fig. 2c) was not very different from the peak potential O_2 of the Pd^0 generated in situ from the palladacycle (**1**) at 80 °C (compare Fig. 2c and Fig. 1c, entries 4 and 7 in Table 1). Since the structure of the ligand (**4**) is very close to $P(o\text{-Tol})_3$, we can assume that the Pd^0 complex generated in situ from the palladacycle (**1**) and observed in the presence of 1 equiv of $P(o\text{-Tol})_3$ per Pd, the additives dba and AcO^-, is Pd^0(**4**)$\{P(o\text{-Tol})_3\}$ (**9**) (Scheme 7).

In the absence of acetate, complex (**9**) was formed in situ from (**1**) (Scheme 8), but since it was generated in the presence of a large excess of $P(o\text{-Tol})_3$, the complex $Pd^0\{(P(o\text{-Tol})_3\}_2$ (**7**) must also be formed. The slight difference in potential (+0.19 vs +0.21 V, entries 2 and 3 in Table 1) thus results from the equilibrium between complexes **9**, **7** and $P(o\text{-Tol})_3$.

The Pd^0 complex was more easily generated in situ in the presence of acetate ions, that is, from the anionic species (**8**), due to a stabilization of the resulting Pd^0 complex by the



Scheme 7.



Scheme 8.

acetate ligand after the reductive elimination (Scheme 7). On the other hand, the palladacycle (**1**) was found to be in equilibrium with the monomeric neutral complexes *cis*-**5** and/or *trans*-**5** (Scheme 3). The reductive elimination process requires a cis position for the benzyl and the acetate ligand on the Pd^{II} center, which is not fulfilled in *trans*-**5**.

The role of dba is not quite clear since no Pd^0 complexes of the type $Pd^0(dba)L_n$ could be characterized but the transient generation of Pd^0(**4**)(dba) before the formation of Pd^0(**4**){P(*o*-Tol)$_3$} is not excluded. On the other hand, olefins are known to favor reductive elimination.[18] The olefin in a Heck reaction might play this role, which would confirm the observation by Herrmann, Beller et al. that no reaction occurred 'until the olefin is added to the mixture'.[1c]

As reported by Herrmann et al., the initial palladacycle (**1**) might not be regenerated in catalytic Heck reactions performed on aryl bromides, due to the release of bromide ions.[1a] Instead, the anionic monomeric complex (**10**) was characterized, which is similar to complex (**8**). In that case, the formation of the active Pd^0 in the Heck reaction might involve a reductive elimination reaction (C–Br bond formation), leading to the Pd^0 complex (**11**) (Scheme 9). At the end of a catalytic Heck reaction, when no more ArBr is available, the intramolecular oxidative addition in complex (**11**) would regenerate (**10**), which is effectively recovered at the end of the reaction.

Just to reinforce the idea that the formation of the primary Pd^0 complex (**3**) in Scheme 8 is reversible, the oxidative addition of the related *o*-substituted-benzyl acetate (**12**) with $Pd^0(dba)_2$ has been tested (Scheme 10).

Preliminary results indicate that complex (**13**) is formed[19] but not the expected dimeric palladacycle because the ligand (**12**), with two Ph groups, is less bulky than would be a ligand with two *o*-Tol groups as in (**1**). Cheney and Shaw[21] have reported that related dimeric *P*,*C*-palladacycles of type (**1**), with two bulky substituents (*t*Bu or/and *o*-Tol) on the phosphorous atom, are cleaved by a less bulky ligand as PPh_3 to generate a monomeric *P*,*C*-palladacycle of type (**13**) ligated by PPh_3. However, formation of complex (**13**) from (**12**) (Scheme 10) attests that cleavage of the benzyl–OAc bond of the ligand has occurred by the postulated intramolecular oxidative addition to generate a mononuclear *P*,*C*-palladacycle.

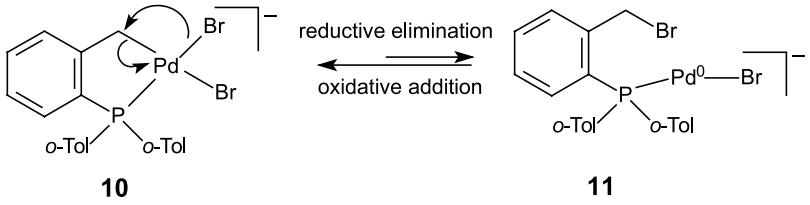
3. Conclusions

In summary, the *P*,*C*-palladacycle (**1**) is a reservoir of a monophosphine–Pd^0 complex Pd^0{P(*o*-Tol)$_2$(*o*-benzyl-OAc)}(DMF) (**3**), which is generated in situ in the absence of any reducing agents. We propose that it is generated by a reductive elimination between the OAc ligand and the *o*-benzyl moiety of the ligand. The complex (**3**) has been trapped and stabilized in the presence of additional P(*o*-Tol)$_3$. A Pd^0 complex is formed in situ from the palladacycle (**1**) is an endergonic reversible reaction because of the fast backward reaction, which is an intramolecular oxidative addition of the monophosphine–Pd^0 complex (**3**) into the benzyl–OAc bond of its ligand. This type of reaction ensures the stability of the *P*,*C*-palladacycles structure when the aryl halides are consumed in the Heck reaction. The in situ formation of a Pd^0 complex from the palladacycle (**1**) is favored by acetate anions via the formation of a monomeric anionic *P*,*C*-palladacycle complex ligated by acetate. Such reaction will occur in Heck reactions employing large amounts of metal acetate anions as base.

4. Experimental

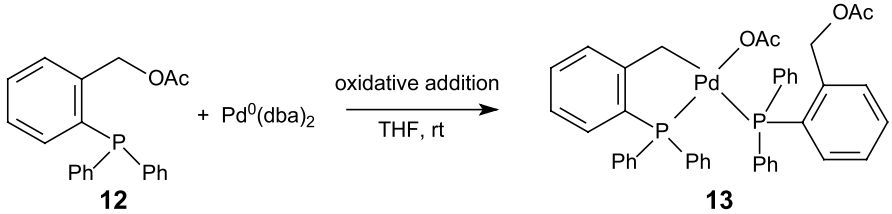
4.1. General

NMR spectra were recorded on a Bruker spectrometer (101 MHz) in DMF containing 20% of CD_2Cl_2. ^{1}H NMR were recorded on a Bruker spectrometer (250 MHz). Cyclic voltammetry was performed with a home made potentiostat and a wave form generator Tacussel GSTP4. The cyclic voltammograms were recorded on a Nicolet 301 oscilloscope.



10 **11**

Scheme 9.



12 **13**

Scheme 10.

4.2. Chemicals

DMF was distilled from calcium hydride under vacuum and kept under argon. $Pd(dba)_2$[22] and $Pd\{P(o\text{-}Tol)_3\}_2$[7b] were synthesized according to literature. nBu$_4$NOAc, dba, P(o-Tol)$_3$, PhI and (**1**) were commercial.

4.3. Electrochemical set-up and procedure for cyclic voltammetry

Typical experiments were carried out under argon in a three-electrode thermostated cell connected to a Schlenk line. The counter electrode was a platinum wire of ca. 1 cm^2 apparent surface area. The working electrode was a steady gold disk electrode (d 0.5 mm). The reference was a saturated calomel electrode (SCE) separated from the solution by a bridge filled with 1.5 mL DMF containing nBu$_4$NBF$_4$ (0.3 M).

4.3.1. Procedure for the electrochemical reduction of (1). Degassed DMF (12 mL) containing nBu$_4$NBF$_4$ (0.3 M) were introduced into the cell, followed by 22 mg (0.024 mmol) of (**1**). Cyclic voltammetry was performed first toward reductive potentials at a scan rate of 0.5 V s^{-1} (Fig 1a). The cyclic voltammetry was also performed first toward oxidative potentials at a scan rate of 0.5 V s^{-1} (Fig. 1b). The scan rate was then varied from 0.1 to 1 V s^{-1} at 25 °C to see the effect of the scan rate on the variation of the reduction peak current i_{R_1} and on the ratio $i_{R_1}/(i_{R_1}+i_{R_2})$ (see text). In another experiment, cyclic voltammetry was performed as previously described on a solution containing (**1**) (2 mM) and P(o-Tol)$_3$ (14.6 mg, 0.048 mmol, 4 mM) to see the effect of P(o-Tol)$_3$ on the oxidation peak current i_{O1} (scan rate of 0.5 V s^{-1}).

4.3.2. Procedure for the detection of the Pd^0 complex generated in situ from (1) by cyclic voltammetry. To the electrochemical cell containing 12 mL of DMF (nBu$_4$NBF$_4$ 0.3 M) and (**1**) (22.5 mg, 0.024 mmol, 2 mM) was added P(o-Tol)$_3$ (273 mg, 0.9 mmol, 75 mM). The cyclic voltammetry was performed toward oxidative potentials from −0.6 to +0.5 V at 25 and 80 °C. No oxidation peak was observed. Dba (210 mg, 0.89 mmol, 74 mM) was then added and an oxidation peak was detected at +0.19 V when the cyclic voltammetry was performed to oxidative potentials from −0.6 to +0.5 V at 80 °C. The oxidation peak disappeared after addition of 100 μL (0.89 mmol) of PhI at 80 °C, just after mixing.

To the electrochemical cell containing 12 mM of DMF (nBu$_4$NBF$_4$ 0.3 M) and (**1**) (22.5 mg, 0.024 mmol, 2 mM) was successively added nBu$_4$NOAc (66.8 mg, 0.22 mmol, 18.4 mM), P(o-Tol)$_3$ (14.6 mg, 0.048 mmol, 4 mM), dba (53 mg, 0.226 mmol, 18.9 mM). The cyclic voltammetry was performed toward oxidative potentials from −0.6 to +0.5 V at 80 °C at a scan rate of 0.5 V s^{-1}. After 1 h, an oxidation peak was detected (O_2 in Fig. 1c, full line). The temperature was decreased to 25 °C and then increased again to 80 °C to see successively the disappearance and re-appearance of the oxidation peak of the Pd^0 complex. Following addition of 100 μL (0.89 mmol) of PhI, the oxidation peak of Pd^0 was no longer observed (Fig. 1c, dashed line).

4.3.3. Procedure for the characterization of Pd^0 complexes ligated by P(o-Tol)$_3$ by cyclic voltammetry. All experiments were performed at a scan rate of 0.5 V s^{-1}. To the electrochemical cell containing 12 mL of DMF and nBu$_4$NBF$_4$ (0.3 M) was added 17 mg (0.024 mmol, 2 mM) of $Pd^0\{P(o\text{-}Tol)_3\}_2$ (**7**). The cyclic voltammetry was performed to oxidative potentials at 25 °C to determine the oxidation potential of (**7**) (Fig. 2a).

The same procedure was used to characterize the oxidation potential of the Pd^0 complex (**7**) formed in the reaction of $Pd(dba)_2$ (13.8 mg, 0.024 mmol, 2 mM) and 2 equiv P(o-Tol)$_3$ (14.6 mg, 0.048 mmol) (Fig. 2b). nBu$_4$NOAc (81 mg, 0.269 mmol) was then added to observe the effect of acetate on the oxidation peak potential of (**7**).

Finally, cyclic voltammetry was performed on a solution containing $Pd^0(dba)_2$ (27.5 mg, 0.048 mmol, 4 mM), P(o-Tol)$_3$ (29 mg, 0.096 mmol, 8 mM), nBu$_4$NOAc (81 mg, 0.269 mmol, 22.4 mM) and dba (9.2 mg, 0.13 mmol, 10.9 mM; the total dba concentration including dba released from $Pd^0(dba)_2$ is then 18.9 mM) at 80 °C (Fig. 2c). This mimics the experimental conditions in which a Pd^0 complex was formed in situ from (**1**) (2 mM) in the presence of P(o-Tol)$_3$ (4 mM), nBu$_4$NOAc (total concentration of 22.4 mM) and dba (18.9 mM) (vide supra and Fig. 1c).

Acknowledgements

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10. (a) The reduction (or oxidation) peak current of an electroactive species is proportional to its concentration and to the square root of the scan rate v: $i = AC_0v^{1/2}$ However, when two electroactive species are involved in an equilibrium, the reduction (or oxidation) of the more easily reduced (or oxidized) species induces a shift of the equilibrium towards this species due to its consumption in the diffusion layer during the electrochemical process (CE mechanism).[10b] This effect is amplified at low scan rates (long times). Consequently, the concentration of the first electroactive species as measured by its reduction (or oxidation) peak current is not the thermodynamic concentration but a higher dynamic concentration. (b) Bard, A. J.; Faulkner, L. R. *Electrochemical methods*, 2nd ed.; Wiley: New York, 2001.
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13. If the cationic species was formed, it would be more easily reduced than (**1**). Its reduction peak would then be R_1, which presently is the major one (Fig. 1a). Consequently, the acetate ions should be generated at the same concentration as the cationic complex and their oxidation peak current should be detected, which was not observed (Fig. 1b).
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15. (a) The ^{1}H NMR spectrum of (**1**) in CD_2Cl_2 at room temperature exhibited broad signals due to fluxional problems. ^{1}H NMR (250 MHz, CD_2Cl_2): δ 1.95 (s, 6H, $OCOCH_3$), 2.23 (br s, 6H, o-CH_3), 2.63 (br s, 2H, CH_{benzyl}), 2.94 (br s, 2H, CH_{benzyl}), 3.11 (br s, 6H, o-CH_3), 6.78 (m, 2H), 7.02 (m, 2H), 7.23 (m, 6H), 7.02 (m, 14H). In the presence of nBu$_4$NOAc (9.5 equiv), the spectrum was modified. The broad signal at 2.23 ppm characteristic of one o-Me in the ligand is shifted upfield overlapping the signal of $OCOCH_3$ at 1.85 ppm. The broad signal at 3.11 ppm characteristic of one o-Me has disappeared, being shifted downfield to 2.56 ppm. The benzylic protons could not be characterized due to overlapping with the signals of NCH_2 protons. The aromatic protons were better resolved due to less fluxional problems. (b) If 0.02 mmol of P(o-Tol)$_3$ are added to a solution of (**1**) (0.01 mmol) in DMF containing 0.09 mmol of AcO^-,that is, the anionic species (**8**) observed above, the sharp singlet of (**8**) was still observed at 35.10 ppm besides the signal of the free P(o-Tol)$_3$ at −30.75 ppm in the ratio 1:1, showing that no reaction occurred at short times. However, after 19 h, a broad singlet appeared at 29.12 ppm whose integration was equal to that of the free P(o-Tol)$_3$ and to that of (**1**). This broad resonance did not belong to a Pd^0 complex since no reaction occurred after addition of PhI in excess (0.25 mmol) after 4 days.
16. (a) Undefined complexes $Pd^0(dba)_m\{P(o\text{-Tol})_3\}_n$ (where m and n are unknown) are formed in benzene.[7b] For the formation of $Pd^0(dba)(PAr_3)_2$ complexes see: (b) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168–3178 and Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, 178–180 pp 511–528.
17. (a) The peak potential is controlled by the chemical reaction of acetate ions with the Pd^I complex, which is formed after the first electron uptake (EC mechanism).[10b] (b) A larger difference, $\Delta E_{ox} = 170$ mV was indeed observed when comparing the oxidation potentials of $Pd^0(PPh_3)_3$ and $Pd^0(PPh_3)_2(OAc)^-$ in DMF.[9c]
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Palladacycles bearing pendant benzamidinate ligands as catalysts for the Suzuki and Heck coupling reactions

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Abstract—Three pendant benzamidines [Ph–C(=NC_6H_5)–{$NH(CH_2)_2NMe_2$}] (**1**), [Ph–C(=NC_6H_5)–{$NH(CH_2Py)$}] (**2**) and [Ph–C(=NC_6H_5)-{$NH(o\text{-}C_6H_4)$(oxazoline)}] (**3**) are described. Reactions of **1**, **2** or **3** with one molar equivalent of $Pd(OAc)_2$ in THF give the palladacyclic complexes [Ph–C{–$NH(\eta^1\text{-}C_6H_4)$}{=$N(CH_2)_2NMe_2$}]Pd(OAc) (**4**), [Ph–C{–$NH(\eta^1\text{-}C_6H_4)$}{=N (CH_2Py)}]Pd(OAc) (**5**) and [Ph–C{–$NH(\eta^1\text{-}C_6H_4)$}{=$N(o\text{-}C_6H_4)$(oxazoline)}]Pd(OAc) (**6**), respectively. Treatment of **4**, **5** or **6** with excess of LiCl in chloroform affords [Ph–C{–$NH(\eta^1\text{-}C_6H_4)$}{=$N(CH_2)_2NMe_2$}]PdCl (**7**), [Ph–C{–$NH(\eta^1\text{-}C_6H_4)$}{=$N(CH_2Py)$}]PdCl (**8**) and [Ph–C{–$NH(\eta^1\text{-}C_6H_4)$}{=$N(o\text{-}C_6H_4)$(oxazoline)}]PdCl (**9**). The crystal and molecular structures are reported for compounds **1**, **3**, **5**, **6** and **7**. The application of these palladacyclic complexes to the Suzuki and Heck coupling reactions was examined.

1. Introduction

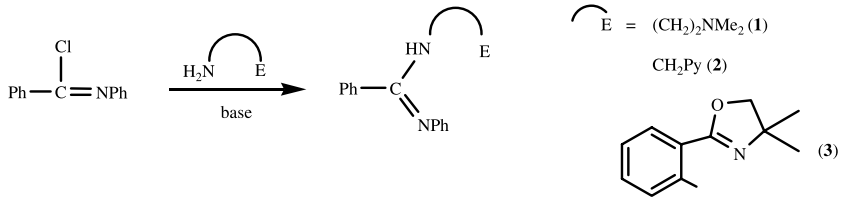
Amidinates of the general formula $[R^1C(NR^2)(NR^3)]^{-1}$, have been the focus of attention because they can often be employed extensively in main group and transition-metal coordination chemistry, organometallic chemistry and catalysis.[1–4] Over the past decades, a large diversity of metal–amidinato compounds has been synthesised and these have been reviewed by Barker and Kilner (on amidine) and Edelmann (on benzamidine).[1,2] Due to the steric and electronic properties of amidinato ligands, they can be easily substituted by variation of the substituents on either or both N and C atoms. Recently several types of amidinato ligands with pendant functionality were explored to act as three-coordinate, six-electron-donor ligands.[5–11] In some cases, the existence of pendant arm could play an important role in determining the constitution of the resulting complexes[6–10] or affecting the reactivity of metal complexes in catalytic reactions.[5] Palladium amidinato compounds have been studied for several decades.[12–18] However, palladium complexes supported by pendant benzamidinato ligands, on our knowledge, have not been reported.

In this paper, we report the preparation and structural properties of pendant benzamidines and their orthometallated palladium complexes. The catalytic activities of these palladacyclic complexes toward the Suzuki and Heck coupling reactions are investigated.

2. Results and discussion

2.1. Preparations of ligand precursors and palladacycles

Preparation of the desired amidines follows a classical route for the synthesis of *N*,*N*′-disubstituted amidines.[19]



Scheme 1.

Keywords: Pendant benzamidine; Palladacyclic complexes; Oxazoline; Suzuki reaction; Heck reaction.
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Treatment of the *N*-(phenyl)benzimidoyl chloride with 1 mol equiv of amines or substituted aniline in the presence of triethylamine affords amidines **1**, **2** and **3** in moderate yield, as shown in Scheme 1. Compounds are characterised by NMR spectroscopy as well as elemental analyses. Crystals suitable for X-ray refinement were grown from concentrated hexane (for **1**) or toluene/hexane (for **3**) solution. The crystal structures of amidines **1** and **3** have been determined and the molecular structures are shown in Figures 1 and 2. Selected bond lengths and angles are listed in Tables 1 and 2. The two C–N bonds in each amidine (1.293(3) and 1.348(3) Å for **1**; 1.269(2), 1.282(3) and 1.381(2), 1.384(3) Å for **3**) are similar in length to those reported for other benzamidines[19–21] and pendant amidine,[6,22,23] indicating the localized property of the imine C=N and amine C–N bonds. The bond angles around imino C and N atoms in each amidine are around 120°, indicating the nature of sp^2 centres.

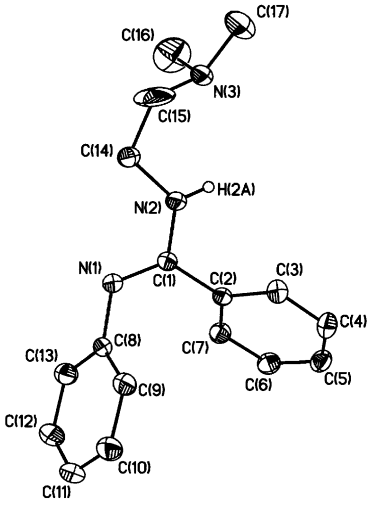


Figure 1. Molecular structure of compound **1**. Hydrogen atoms on carbon atoms omitted for clarity.

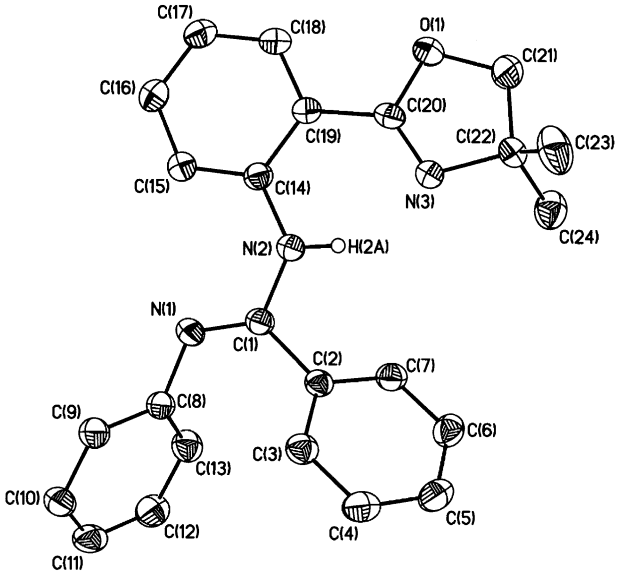


Figure 2. Molecular structure of one of the crystallographically independent molecules of complex **3**. Hydrogen atoms on carbon atoms omitted for clarity.

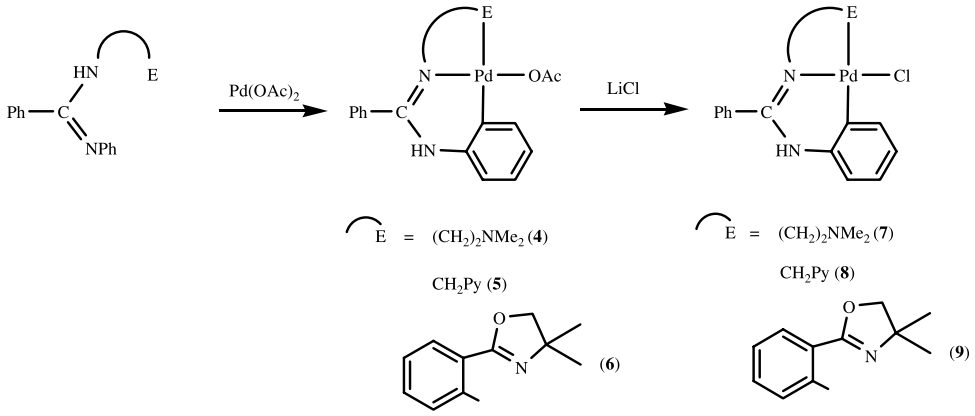
Table 1. Selected bond lengths (Å) and angles (°) for **1**

N(1)–C(1)	1.293(3)	N(2)–C(1)	1.348(3)
N(1)–C(8)	1.415(3)	N(2)–C(14)	1.433(4)
C(1)–C(2)	1.492(4)		
C(1)–N(1)–C(8)	121.0(2)	C(1)–N(2)–C(14)	124.4(3)
N(1)–C(1)–N(2)	119.0(2)	N(1)–C(1)–C(2)	125.8(2)
N(2)–C(1)–C(2)	115.2(2)		

Table 2. Selected bond lengths (Å) and angles (°) for **3**

N(1)–C(1)	1.269(2)	N(2)–C(1)	1.381(2)
N(1)–C(8)	1.409(3)	N(2)–C(14)	1.388(2)
C(1)–C(2)	1.497(3)	C(25)–C(26)	1.486(3)
N(4)–C(25)	1.282(3)	N(5)–C(25)	1.384(3)
N(4)–C(32)	1.408(3)	N(5)–C(38)	1.390(3)
C(1)–N(1)–C(8)	122.33(19)	C(1)–N(2)–C(14)	130.40(18)
N(1)–C(1)–N(2)	121.33(19)	N(1)–C(1)–C(2)	127.49(19)
N(2)–C(1)–C(2)	111.07(18)	N(5)–C(25)–C(26)	112.7(2)
C(25)–N(4)–C(32)	123.59(19)	C(25)–N(5)–C(38)	131.2(2)
N(4)–C(25)–N(5)	120.3(2)	N(4)–C(25)–C(26)	127.0(2)

Three pendant amidines react readily with 1 mol equiv of $Pd(OAc)_2$ in dichloromethane to afford complexes **4**, **5** and **6**, which are expected to form a mononuclear species[22] rather than the dimeric or oligomeric structures.[15–17] A summary of the syntheses and proposed structures of palladacycles is shown in Scheme 2. In each palladium acetate compound, one N*H* singlet around δ 9–10 ppm (9.71 ppm for **4**; 9.64 ppm for **5**; 10.10 ppm for **6**) was found on the ^{1}H NMR spectrum and one more tertiary carbon appeared in the region of phenyl ring on the $^{13}C\{^1H\}$ NMR spectrum, which indicate the preference of carbon metallation rather than the N*H* deprotonation.[16] Suitable crystals of **5** for structural determination were obtained from concentrated CH_2Cl_2 solution. The molecular structure is shown in Figure 3 and selected bond lengths and angles are listed in Table 3. The structural analysis showed the target complex as a mononuclear species. The bond angles (from 81.37(11) to 93.82(12)°) around Pd metal centre indicate a complex having a slightly distorted square planar geometry, in which the palladium metal centre is coordinated with one pyridine nitrogen atom, one imine nitrogen atom, one metallated carbon atom, and one acetate oxygen atom to form one five-membered metallacycle and one six-membered metallacycle. The bond lengths of Pd–N_{py} (2.119(3) Å) and Pd–$C_{metallated}$ (1.975(4) Å) are within those (1.964(3)–2.150(3) Å for Pd–N_{py}; 1.961(4)–2.019(2) Å for Pd–$C_{metallated}$) found in metallated palladacycles.[16,24–29] The bond length of Pd–O_{OAc} (2.064(3) Å) is among those (2.032(2)–2.126(3) Å) found in palladacycles.[28–31] The bond length of Pd–$N_{C=N}$ (1.981(3) Å) is close to those (1.969(6)–2.071(3) Å) found in palladacycles.[16,29,32–34] The C–N bond lengths of NCN moiety are not equal with 1.343(4) and 1.309(4) Å, respectively, indicating the localized nature of the imine C=N and amine C–N bonds. Suitable crystals of **6** for structural determination are obtained from CH_2Cl_2/hexane solution. The molecular structure is shown in Figure 4, and selected bond lengths and angles are listed in Table 4. Basically, compound **6** is quite similar to compound **5** with different pendant group C_6H_4Oxazoline instead of CH_2Py for **5**. The palladium metal centre is coordinated with similar coordination types as in **5** except one nitrogen atom from oxazoline instead of one pyridine nitrogen atom to form two six-membered



Scheme 2.

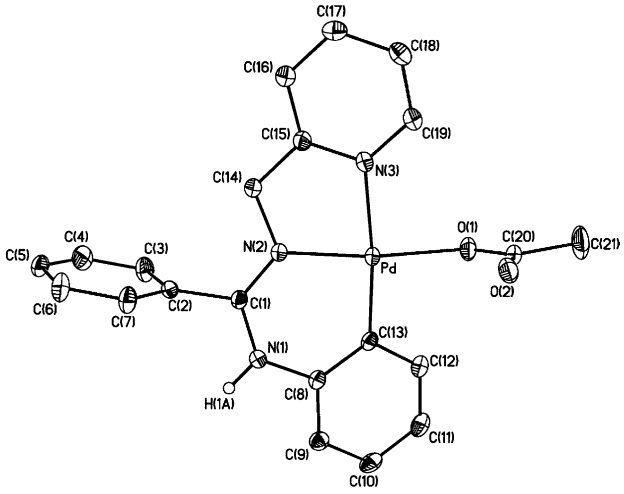


Figure 3. Molecular structure of complex **5**. Hydrogen atoms on carbon atoms omitted for clarity.

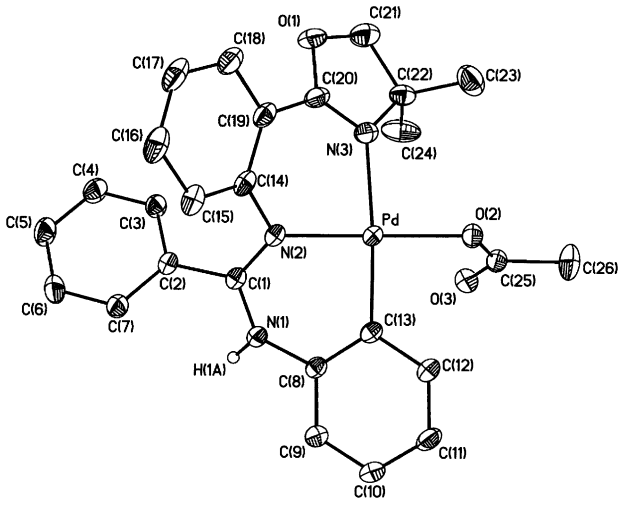


Figure 4. Molecular structure of complex **6**. Hydrogen atoms on carbon atoms omitted for clarity.

Table 3. Selected bond lengths (Å) and angles (°) for **5**

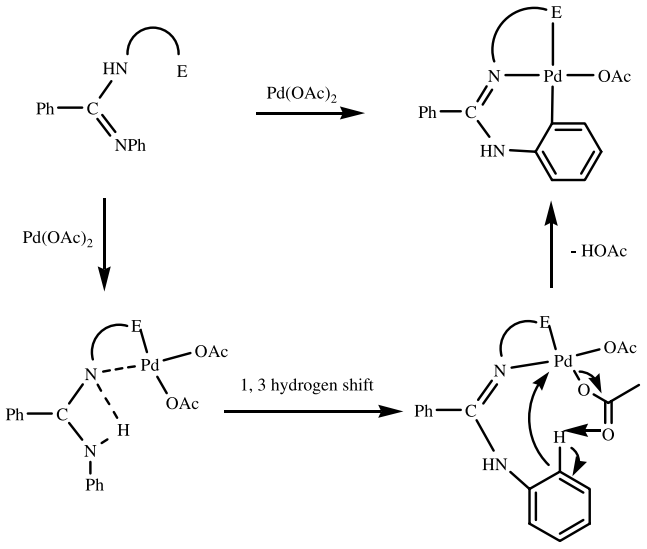
Pd–C(13)	1.975(4)	Pd–N(2)	1.981(3)
Pd–N(3)	2.119(3)	Pd–O(1)	2.064(3)
N(1)–C(1)	1.343(4)	N(1)–C(8)	1.416(4)
N(2)–C(1)	1.309(4)	N(2)–C(14)	1.462(4)
N(2)–Pd–C(13)	92.31(13)	N(2)–Pd–N(3)	81.37(11)
C(13)–Pd–O(1)	92.68(13)	N(3)–Pd–O(1)	93.82(12)
C(13)–Pd–N(3)	173.32(12)	N(2)–Pd–O(1)	172.33(11)

Table 4. Selected bond lengths (Å) and angles (°) for **6**

Pd–C(13)	1.979(3)	Pd–N(2)	2.007(3)
Pd–N(3)	2.144(3)	Pd–O(2)	2.045(2)
N(1)–C(1)	1.334(4)	N(1)–C(8)	1.428(4)
N(2)–C(1)	1.308(4)	N(2)–C(14)	1.427(4)
N(2)–Pd–C(13)	88.35(13)	N(2)–Pd–N(3)	87.77(13)
C(13)–Pd–O(2)	91.30(13)	N(3)–Pd–O(2)	92.85(12)
C(13)–Pd–N(3)	174.55(13)	N(2)–Pd,O(2)	175.73(11)

metallacycles. Bond lengths and bond angles are similar to those discussed above. Due to the rigidity of the pendant arm, the bond length of Pd–$N_{oxazoline}$ (2.144(3) Å) is a bit longer than those (1.97(2)–2.060(10) Å) found in metallated palladacycles.[35–38] Similar to compound **5**, the C–N bond lengths of NCN moiety in **6** are not equal (1.334(4) Å for C(1)–N(1) and 1.308(4) Å for C(1)–N(2)). Compare with the bond lengths (1.269(2) Å for C(1)–N(1) and 1.282(3) Å for C(25)–N(4); 1.381(2) Å for C(1)–N(2) and 1.384(3) Å for C(25)–N(5)) in **3**, a 1,3 hydrogen shift process might happen in the formation of compounds **4**–**6**. Plausible mechanism for the formation of palladium acetate complexes is proposed in Scheme 3. Possible reaction is the coordination of benzamidine to the palladium metal centre, followed by the shift of proton from the nitrogen atom on the amine group to the nitrogen atom on the imine group,[29] which is induced by the metal centre. The orthometallation is then achieved by removal of 1 equiv of HOAc to form the target compound.[28] This phenomenon could not be observed in the synthesis of palladacycles bearing amidinato ligands with symmetrical substituents on both nitrogen atoms.[16]

Complexes **7**–**9** were synthesised by the reaction of palladium acetate compounds **4**–**6** with excess lithium chloride in chloroform at room temperature. The NMR spectroscopic data and elemental analysis of each compound are indicative of cyclometallated complex with a Cl atom instead of an acetate group in those palladium acetate compounds. Suitable crystals of **7** for structural determination were obtained from CH_2Cl_2/hexane solution. The molecular structure is shown in Figure 5, and selected bond



Scheme 3.

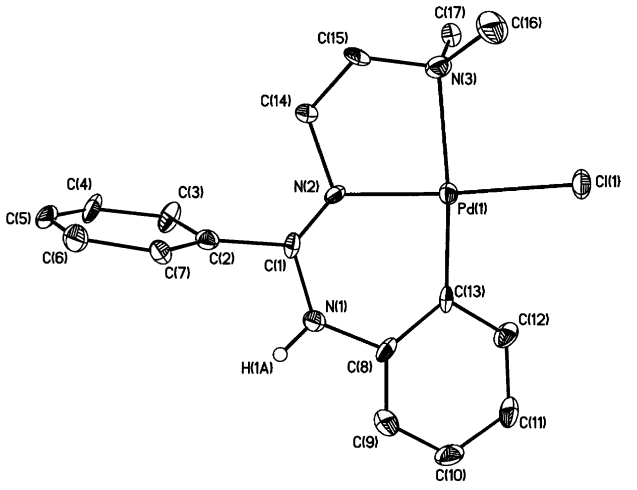


Figure 5. Molecular structure of one of the crystallographically independent molecules of complex **7**. Hydrogen atoms on carbon atoms omitted for clarity.

lengths and angles are listed in Table 5. Basically, compound **7** is similar to compound **5** with different pendant group $CH_2CH_2NMe_2$ instead of CH_2Py for **5**. The palladium metal centre is coordinated with one amine nitrogen atom, one imine nitrogen atom, one metallated carbon atom and one chloride atom to form one five-membered metallacycle and one six-membered metallacycle. Bond lengths and bond angles are similar to those discussed above. The bond lengths of Pd–N_{amine} (2.207(10) and 2.171(11) Å) is close to those (2.069(6)–2.203(3) Å) found in metallated palladacycles.[29–33,39–43] The bond lengths of Pd–Cl (2.328(4) and 2.331(4) Å) is close to those (2.304(2)–2.377(1) Å) found in metallated palladacycles.[25,27,29,32–34]

Table 5. Selected bond lengths (Å) and angles (°) for **7**

Pd(1)–C(13)	1.922(13)	Pd(1)–N(2)	2.002(10)
Pd(1)–N(3)	2.207(10)	Pd(1)–Cl(1)	2.328(4)
N(1)–C(1)	1.398(15)	N(1)–C(8)	1.426(18)
N(2)–C(1)	1.171(15)	N(2)–C(14)	1.490(15)
Pd(2)–C(30)	2.033(12)	Pd(2)–N(5)	1.984(9)
Pd(2)–N(6)	2.171(11)	Pd(2)–Cl(2)	2.331(4)
N(4)–C(18)	1.302(14)	N(4)–C(25)	1.395(17)
N(5)–C(18)	1.439(14)	N(5)–C(31)	1.439(15)
N(2)–Pd(1)–C(13)	89.3(4)	N(2)–Pd(1)–N(3)	85.0(4)
C(13)–Pd(1)–Cl(1)	94.5(3)	N(3)–Pd(1)–Cl(1)	91.1(3)
C(13)–Pd(1)–N(3)	174.2(5)	N(2)–Pd(1)–Cl(1)	176.0(3)
N(5)–Pd(2)–C(30)	92.9(5)	N(5)–Pd(2)–N(6)	81.9(4)
C(30)–Pd(2)–Cl(2)	95.1(4)	N(6)–Pd(2)–Cl(2)	90.1(3)
C(30)–Pd(2)–N(6)	174.7(5)	N(5)–Pd(2)–Cl(2)	172.0(3)

2.2. Suzuki-type reaction using CNN-type palladacycles

Since several palladacycles containing CNN-type ligands can be used as catalysts for the carbon–carbon coupling reactions,[29,45,46] the palladacyclic derivatives **4–9** were expected to work as catalysts toward the Suzuki-type coupling reaction. In order to examine the catalytic activity, optimised conditions using the coupling of 4-bromoacetophenone with 1.5 equiv phenylboronic acid catalysed by 1 mol% **4–9** in the presence of 3 equiv base at 80 °C were conducted. The rate of the Suzuki-type reaction is solvent-dependent with trials on *N*,*N*-dimethylacetamide (DMA), THF, and toluene. For the best choice of a base, we surveyed K_3PO_4, Cs_2CO_3, and KF. Selected results are listed in Table 6. Finally, we found that use of KF for **4** and **7** and K_3PO_4 for **5**, **6**, **8** and **9** in toluene leads to the best conversion within 1 h (entries 1–6). Excellent conversion is observed with 1 mol% **6** using 4-bromobenzaldehyde under the same condition (entry 7). Similar conditions were applied to examine the catalytic activities of **4–9** using 4-bromoanisole as substrate. Comparable conversions were observed within 3 h (entries 8–13). Similar conversions were observed with 1 mol% **6** using various substrates with electron-donating substituents under the optimised condition (entries 14–15). Due to the better activity and solubility of **6**, lower catalyst concentrations were investigated with **6** using catalyst/substrate ratios from 10^{-3} to 5×10^{-5}. The reactions gave degrees of conversion to 99% within 2 h for 10^{-3} ratio, 93% within 5 h for 10^{-4} ratio, and 80% within 8 h for 5×10^{-5} ratio (entries 16–18). The coupling reactions were also carried out with 1 mol% **6** using less reactive substrates under the optimised conditions. As expected, the degrees of conversion became lower with longer period of time (entries 19–21).

2.3. Heck reaction using CNN-type palladacycles

We also examined the catalytic activities of **6** in Heck reaction using the coupling of 4-bromoacetophenone with styrene. Selected results are listed in Table 7. Optimised conditions, Cs_2CO_3/toluene and Cs_2CO_3/DMA under refluxing temperatures, seem to be the best choices after several trials on the combinations of solvents and bases (entries 1–3). Similar conversions were observed using various substrates with electronically activated substituents under the optimised condition (entries 4–5). Coupling reactions were also carried out with 1 mol% **6** and Cs_2CO_3/toluene under refluxing temperature using substrates with electronically deactivated substituents. As expected, over 90% conversions were observed within longer period of time (entries 6–8). The optimised condition, Cs_2CO_3/DMA under refluxing temperature, seems not suitable for substrate with electronically deactivated substituent. Poor conversion was observed

Table 6. Suzuki-type coupling reaction catalysed by new palladium complexes[a]

Entry	Catalyst	Aryl halide	Base	Solvent	[Pd] (mol%)	*t* (h)	Conversion (%)[b]	Yield (%)[c]
1	**4**	4-Bromoacetophenone	KF	Toluene	1	1	78	70
2	**5**	4-Bromoacetophenone	K_3PO_4	Toluene	1	1	86	79
3	**6**	4-Bromoacetophenone	K_3PO_4	Toluene	1	1	99	91
4	**7**	4-Bromoacetophenone	KF	Toluene	1	1	81	74
5	**8**	4-Bromoacetophenone	K_3PO_4	Toluene	1	1	86	78
6	**9**	4-Bromoacetophenone	K_3PO_4	Toluene	1	1	98	91
7	**6**	4-Bromobenzaldehyde	K_3PO_4	Toluene	1	1	99	93
8	**4**	4-Bromoanisole	KF	Toluene	1	3	72	65
9	**5**	4-Bromoanisole	K_3PO_4	Toluene	1	3	84	75
10	**6**	4-Bromoanisole	K_3PO_4	Toluene	1	3	91	84
11	**7**	4-Bromoanisole	KF	Toluene	1	3	71	63
12	**8**	4-Bromoanisole	K_3PO_4	Toluene	1	3	79	73
13	**9**	4-Bromoanisole	K_3PO_4	Toluene	1	3	90	84
14	**6**	4-Bromotoluene	K_3PO_4	Toluene	1	3	98	92
15	**6**	1-Bromo-4-*tert*-butyl-benzene	K_3PO_4	Toluene	1	3	93	88
16	**6**	4-Bromoacetophenone	K_3PO_4	Toluene	0.1	2	99	92
17	**6**	4-Bromoacetophenone	K_3PO_4	Toluene	0.01	5	93	86
18	**6**	4-Bromoacetophenone	K_3PO_4	Toluene	0.005	8	80	74
19	**6**	4-Chloroacetophenone	K_3PO_4	Toluene	1	18	73	65
20	**6**	4-Chloro-benzoic acid methylester	K_3PO_4	Toluene	1	18	66	60
21	**6**	4-Chloroanisole	K_3PO_4	Toluene	1	24	20	–

[a] Reaction conditions: 1 mmol aryl halide, 1.5 mmol phenylboronic acid, 3.0 mmol base, 3 ml solvent, 80 °C.
[b] Determined by ^{1}H NMR.
[c] Isolated yield. (average of two experiments).

within the same period of time (entry 9). Lower catalyst concentrations were investigated with both optimised conditions using catalyst/substrate ratios from 10^{-3} to 10^{-4}. Better conversions were observed using high temperature conditions (entries 10–13). Compound **6** also showed catalytic activities in catalysing the less reactive substrates, such as 4-chloroacetophenone. Higher conversion was observed using Cs_2CO_3/DMA under refluxing temperature as reaction condition (entries 14–15). Better conversion was observed using 2 mol% catalyst loadings within 24 h (entry 16).

3. Summary

We have demonstrated the preparations and catalytic studies towards the Suzuki and Heck coupling reactions of mononuclear palladacycles supported by pendant benzamidinate ligands. Based on the structural analysis, a 1,3 hydrogen shift process might happen upon the formation of six-membered metallacycle, which could not be observed in the synthesis of palladacycles bearing amidinato ligands with symmetrical substituents on both nitrogen atoms. Plausible mechanism for the formation of the palladacycles has been proposed. The catalytic data show that palladacyclic complexes bearing pendant oxazoline group exhibit better activities than those with pendant pyridine or amine groups. Under optimised conditions, **6** exhibits catalytic efficiency with lower catalyst loadings, and with less reactive substrates in both Suzuki and Heck coupling reactions. Preliminary studies on the modification of benzamidines with different substituents and their application in the synthesis of metal complexes are currently being undertaken.

Table 7. Heck coupling reaction catalysed by new palladium complexes[a]

Entry	Catalyst	Aryl halide	Base	Solvent	[Pd] (mol%)	*T* (°C)	*t* (h)	Conversion (%)[b]	Yield (%)[c]
1	**6**	4-Bromoacetophenone	Cs_2CO_3	Toluene	1	110	2	95	90
2	**6**	4-Bromoacetophenone	Cs_2CO_3	DMA	1	135	2	99	93
3	**6**	4-Bromoacetophenone	KF	DMA	1	135	2	90	85
4	**6**	Methyl 4-bromobenzoate	Cs_2CO_3	Toluene	1	110	2	90	85
5	**6**	4-Bromobenzaldehyde	Cs_2CO_3	Toluene	1	110	2	92	83
6	**6**	4-Bromoanisole	Cs_2CO_3	Toluene	1	110	8	94	88
7	**6**	4-*tert*-Butyl-bromobenzene	Cs_2CO_3	Toluene	1	110	8	95	86
8	**6**	4-Bromotoluene	Cs_2CO_3	Toluene	1	110	8	92	84
9	**6**	4-Bromoanisole	Cs_2CO_3	DMA	1	135	8	68	–
10	**6**	4-Bromoacetophenone	Cs_2CO_3	Toluene	0.1	110	24	91	85
11	**6**	4-Bromoacetophenone	Cs_2CO_3	Toluene	0.01	110	48	40	–
12	**6**	4-Bromoacetophenone	Cs_2CO_3	DMA	0.1	135	24	98	92
13	**6**	4-Bromoacetophenone	Cs_2CO_3	DMA	0.01	135	48	57	–
14	**6**	4-Chloroacetophenone	Cs_2CO_3	Toluene	1	110	48	5	–
15	**6**	4-Chloroacetophenone	Cs_2CO_3	DMA	1	135	48	56	–
16	**6**	4-Chloroacetophenone	Cs_2CO_3	DMA	2	135	24	80	–

[a] Reaction conditions: 1 mmol aryl halide, 1.3 mmol styrene, 1.5 mmol base, 2 ml solvent.
[b] Determined by ^{1}H NMR.
[c] Isolated yield. (average of two experiments).

4. Experimental

4.1. General

All manipulations were carried out under an atmosphere of dinitrogen using standard Schlenk-line or drybox techniques. Solvents were refluxed over the appropriate drying agent and distilled prior to use. Deuterated solvents were dried over molecular sieves.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded either on Varian Mercury-400 (400 MHz) or Varian Inova-600 (600 MHz) spectrometers in chloroform-*d* at ambient temperature unless stated otherwise and referenced internally to the residual solvent peak and reported as parts per million relative to tetramethylsilane. Elemental analyses were performed by an Elementar Vario ELIV instrument.

Benzanilide (Lancaster), PCl_5 (RDH), 2-aminomethylpyridine (Acros), DMA (TEDIA), $Pd(OAc)_2$ (Acros), KF (Acros), K_3PO_4 (Lancaster), Cs_2CO_3 (Aldrich) and LiCl (Lancaster) were used as supplied. NEt_3 and *N*,*N*-dimethylethyleneamine were dried over CaH_2 and distilled before use. *N*-(phenyl)benzimidoyl chloride[19] and 2-(*o*-aminophenyl)oxazoline[44] were prepared by the modified literature's methods.

4.2. Preparations

4.2.1. [C_6H_5–C{NH(CH_2)$_2$NMe_2}=NC_6H_5] (1). A yellow solution of *N*-(phenyl)benzimidoyl chloride (0.81 g, 3.8 mmol) and NEt_3 (0.70 ml, 4.6 mmol) in CH_2Cl_2 (20 ml) was treated with *N*,*N*-dimethylethyleneamine (0.41 ml, 3.8 mmol) at room temperature. After 18 h of stirring, the volatiles were removed under reduced pressure and the residue was extracted with 50 ml hexane. The extract was concentrated and put into the fridge to afford white solid. Yield, 0.64 g, 63%. ^{1}H NMR (600 MHz): δ 2.25 (s, N(CH_3)$_2$, 6H), 2.57 (br, CH_2–CH_2, 2H), 3.56 (br, CH_2–CH_2, 2H), 5.29 (br, N*H*), 6.63 (d, C_6H_5, 2H, J=7.2 Hz), 6.78 (t, C_6H_5, 1H, J=7.2 Hz), 7.03 (t, C_6H_5, 2H, J=7.2 Hz), 7.22 (overlap, C_6H_5, 5H). $^{13}C\{^{1}H\}$ NMR (150 MHz): δ 39.0 (s, CH_2), 45.1 (s, N(CH_3)$_2$), 57.6 (s, CH_2), 121.0, 123.1, 128.1, 128.2, 128.6, 128.9(*C*H–C_6H_5), 135.2, 151.0, 157.7 (two C_{ipso}–C_6H_5 and one *C*NN). Anal. Calcd for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.17; H, 8.26; N, 15.22.

4.2.2. [C_6H_5–C{NHCH_2Py}=NC_6H_5] (2). A yellow solution of *N*-(phenyl)benzimidoyl chloride (1.08 g, 5.0 mmol) and NEt_3 (0.90 ml, 6 mmol) in CH_2Cl_2 (20 ml) was treated with 2-aminomethylpyridine (0.52 ml, 5.0 mmol) at room temperature. After 18 h of stirring, the volatiles were removed under reduced pressure and the residue was extracted with 15 ml toluene to afford white solid. The resulting solid was purified by ethyl acetate/hexane solution to afford white solid. Yield, 0.83 g, 58%. ^{1}H NMR (600 MHz): δ 4.87 (s, CH_2, 2H), 6.15 (br, N*H*, 1H), 6.68 (d, C_6H_5, 2H, J=6.6 Hz), 6.83 (br, C_6H_5, 1H), 7.07 (t, C_6H_5, 2H, J=7.2 Hz), 7.21 (t, C_6H_5, 1H, J=6.0 Hz), 7.25–7.31 (m, C_6H_5, 5H), 7.39 (d, C_6H_5, 1H, J=7.2 Hz), 7.70 (t, C_6H_5, 1H, J=7.2 Hz), 8.54 (d, C_6H_5, 1H, J=4.2 Hz). $^{13}C\{^{1}H\}$ NMR (150 MHz): δ 46.7 (s, CH_2), 121.3, 122.2, 122.3, 123.1, 128.2, 128.3, 128.7, 129.1, 136.6, 148.8(*C*H–C_6H_5 and *C*H–Py), 135.0, 150.7, 156.8, 157.2 (three C_{ipso}–C_6H_5 and one *C*NN). Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.53; H, 5.90; N, 14.56.

4.2.3. [C_6H_5–C{NHC_6H_4Oxazoline}=NC_6H_5] (3). To a yellow solution of *N*-(phenyl)benzimidoyl chloride (0.43 g, 2.0 mmol) and 2-(*o*-aminophenyl)oxazoline (0.38 g, 2 mmol) in CH_2Cl_2 (20 ml), NEt_3 (0.33 ml, 2.4 mmol) was added at room temperature. After 18 h of stirring, the resulting suspension was filtered at 0 °C and the volatiles were removed under reduced pressure. The residue was extracted with 50 ml hexane to afford pale-yellow solid. Yield, 0.54 g, 73%. ^{1}H NMR (600 MHz): δ 1.25 (s, CH_3, 6H), 4.02 (s, CH_2, 2H), 6.74 (d, 2H, J=7.2 Hz), 6.86 (t, 1H, J=7.2 Hz), 7.00 (t, 1H, J=7.2 Hz), 7.11 (t, 2H, J=7.2 Hz), 7.24–7.30 (m, 3H), 7.40 (d, 2H, J=7.2 Hz), 7.47 (t, 1H, J=7.2 Hz), 7.85 (d, 1H, J=7.8 Hz), 9.24 (d, 1H, J=8.4 Hz), 11.93 (s, N*H*, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz): δ 28.4 (s, CH_3), 67.7 (s, *C*-(CH_3)$_2$), 77.5 (s, CH_2), 119.3, 120.5, 121.5, 122.5, 127.8, 128.4, 128.9, 129.1, 129.2, 132.4(*C*H–Ph), 112.8, 135.2, 142.0, 150.3, 154.5, 162.0 (one *tert*-*C*-oxazoline, one *tert*-*C*-Ph, three C_{ipso}–C_6H_5 and one *C*NN). Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.08; H, 6.08; N, 11.41.

4.2.4. [C_6H_5–C{=N(CH_2)$_2$NMe_2}–NH–(η^1-C_6H_5)]Pd(OAc) (4). To a flask containing **1** (0.27 g, 1.0 mmol) and $Pd(OAc)_2$ (0.22 g, 1.0 mmol), 15 ml of CH_2Cl_2 was added at room temperature. After 18 h of stirring, the resulting mixture was layered 15 ml hexane and put into the fridge. The crystalline solid was isolated after several days. Yield, 0.21 g, 49%. ^{1}H NMR (600 MHz): δ 1.66 (s, O–C(=O)CH_3, 3H), 2.40 (t, CH_2, 2H, J=6.0 Hz), 2.61 (s, N(CH_3)$_2$, 6H), 3.18 (t, CH_2, 2H, J=6.0 Hz), 6.90 (t, C_6H_5, 1H, J=7.2 Hz), 6.99 (d, C_6H_5, 2H, J=7.2 Hz), 7.07 (t, C_6H_5, 1H, J=7.2 Hz), 7.31 (d, C_6H_5, 1H, J=7.8 Hz), 7.37–7.44 (m, C_6H_5, 4H), 9.71 (s, N*H*, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz): δ 24.1 (s, O–C(=O)CH_3), 47.9 (s, N(CH_3)$_2$), 52.5 (s, CH_2), 61.8 (s, CH_2), 117.0, 121.5, 123.6, 128.1, 128.7, 129.8, 135.4(*C*H–Ph), 126.3, 131.8, 135.9, 152.1 (two C_{ipso}–C_6H_5, one metallated *C*–Ph, and one *C*NN), 178.1 (s, O–*C*(=O)CH_3). Anal. Calcd for $C_{19}H_{23}N_3O_2Pd$: C, 52.85; H, 5.37; N, 9.73. Found: C, 52.85; H, 4.88; N, 9.48.

4.2.5. [C_6H_5–C{=NCH_2Py}–NH–(η^1-C_6H_5)]Pd(OAc) (5). To a flask containing **2** (0.29 g, 1.0 mmol) and $Pd(OAc)_2$ (0.22 g, 1.0 mmol), 15 ml of CH_2Cl_2 was added at room temperature. After 18 h of stirring, the resulting suspension was filtered and the precipitate was extracted with 30 ml cold THF. The combined organic solution was allowed to stand at room temperature to afford white solid after several days. Yield, 0.25 g, 55%. ^{1}H NMR (600 MHz): δ 1.90 (s, O–C(=O)CH_3, 3H), 4.58 (s, CH_2Py, 2H), 6.62 (m, C_6H_5 or Py, 1H), 6.84–6.88 (m, C_6H_5 or Py, 2H), 7.09 (m, C_6H_5 or Py, 2H), 7.13 (d, C_6H_5 or Py, 1H, J=7.8 Hz), 7.29 (m, C_6H_5 or Py, 1H), 7.46 (m, C_6H_5 or Py, 2H), 7.51 (m, C_6H_5 or Py, 1H), 7.56 (m, C_6H_5 or Py, 1H), 7.74 (m, C_6H_5 or Py, 1H), 8.39 (m, C_6H_5 or Py, 1H), 9.64 (s, N*H*, 1H). $^{13}C\{^{1}H\}$ NMR (150 MHz): δ 24.4 (s, O–C(=O)CH_3), 62.1 (s, CH_2), 116.4, 119.7, 121.2, 122.8, 123.9, 128.3,

128.7, 130.1, 135.4, 137.6, 148.4(*C*H of Ph or Py), 127.1, 131.9, 135.2, 152.3, 159.0 (three C_{ipso}–C_6H_5, one metallated *C*–Ph, and one *C*NN), 178.2 (s, O–*C*(=O)CH_3). Anal. Calcd for $C_{21}H_{19}N_3O_2Pd$: C, 55.82; H, 4.24; N, 9.30. Found: C, 55.79; H, 4.19; N, 9.52.

4.2.6. [C_6H_5–C{=NC_6H_4Oxazoline}–NH–(η^1-C_6H_5)] Pd(OAc) (6). To a flask containing **3** (0.65 g, 1.75 mmol) and $Pd(OAc)_2$ (0.39 g, 1.75 mmol), 15 ml of CH_2Cl_2 was added at room temperature. After 18 h of stirring, the resulting mixture was layered 15 ml hexane and put into the fridge. The crystalline solid was isolated after several days. Yield, 0.61 g, 65%. ^{1}H NMR (600 MHz): δ 1.59 (s, C(CH_3)$_2$, 3H), 1.89 (s, C(CH_3)$_2$, 3H), 1.92 (s, O–C(=O)CH_3, 3H), 4.34 (m, CH_2, 2H), 6.13 (m, C_6H_5, 1H), 6.21 (br, C_6H_5, 1H), 6.76–6.87 (overlap, C_6H_5, 4H), 7.16 (t, C_6H_5, 2H, J=7.8 Hz), 7.24 (m, C_6H_5, 1H), 7.29 (d, C_6H_5, 2H, J=7.2 Hz), 7.64 (m, C_6H_5, 1H), 8.58 (br, C_6H_5, 1H), 10.10 (s, N*H*, 1H). ^{13}C{^{1}H} NMR (150 MHz): δ 25.2 (s, O–C(=O)*C*H_3), 27.8 (s, C(*C*H_3)$_2$), 28.9 (s, C(*C*H_3)$_2$), 69.3 (s, *C*(CH$_3$)$_2$), 80.7 (s, *C*H$_2$), 122.9, 123.8, 124.0, 127.5, 128.6, 128.9, 130.2, 131.4, 131.6, 133.6, 135.0(C_6H_5), 117.8, 119.7, 126.2, 132.5, 147.9, 156.2, 161.2 (one *tert-C*-oxazoline, one *tert-C*-Ph, three C_{ipso}–C_6H_5, one metallated *C*-Ph, and one *C*NN), 178.0 (s, O–*C*(=O)CH_3). Anal. Calcd for d$C_{26}H_{25}N_3O_3Pd$: C, 58.49; H, 4.72; N, 7.87. Found: C, 58.28; H, 4.81; N, 7.58.

4.2.7. [C_6H_5–C{=N$(CH_2)_2NMe_2$}–NH–(η^1-C_6H_5)]PdCl (7). To a flask containing **4** (0.22 g, 0.5 mmol) and LiCl (0.085 g, 2.0 mmol), 15 ml of $CHCl_3$ was added at room temperature. After 18 h of stirring, the resulting mixture was filtered and layered 15 ml hexane. The white solid was isolated after several days. Yield, 0.16 g, 82%. ^{1}H NMR (600 MHz): δ 2.50 (t, CH_2, 2H, J=6.0 Hz), 2.72 (s, N(CH_3)$_2$, 6H), 3.47 (t, CH_2, 2H, J=6.0 Hz), 6.61 (m, C_6H_5, 1H), 6.88 (m, C_6H_5, 1H), 7.00 (m, C_6H_5, 1H), 7.02 (s, N*H*, 1H), 7.40 (m, C_6H_5, 2H), 7.55–7.59 (overlap, C_6H_5, 3H), 8.44 (m, C_6H_5, 1H). ^{13}C{^{1}H} NMR (150 MHz): δ 48.2 (s, N(*C*H_3)$_2$), 53.4 (s, *C*H$_2$), 62.5 (s, *C*H$_2$), 115.1, 122.6, 125.0, 127.2, 129.6, 130.9, 141.1(*C*H–Ph), 123.6, 132.6, 134.1, 151.6 (two C_{ipso}–C_6H_5, one metallated *C*-Ph, and one *C*NN). Anal. Calcd for $C_{17}H_{20}ClN_3Pd$: C, 50.02; H, 4.94; N, 10.29. Found: C, 50.11; H, 4.84; N, 9.92.

4.2.8. [C_6H_5–C{=NCH_2Py}–NH–(η^1-C_6H_5)]PdCl (8). To a flask containing **5** (0.23 g, 0.5 mmol) and LiCl (0.085 g, 2.0 mmol), 15 ml of $CHCl_3$ was added at room temperature. After 18 h of stirring, the resulting mixture was filtered and layered 15 ml hexane. The white solid was isolated after several days. Yield, 0.16 g, 71%. ^{1}H NMR (600 MHz): δ 4.88 (s, CH_2Py, 2H), 6.68 (m, C_6H_5 or Py, 1H), 6.95 (m, C_6H_5 or Py, 1H), 7.06 (m, C_6H_5 or Py, 1H), 7.17 (d, C_6H_5 or Py, 1H, J=7.8 Hz), 7.18 (s, N*H*, 1H), 7.34 (t, C_6H_5 or Py, 1H, J=6.6 Hz), 7.46 (m, C_6H_5 or Py, 2H), 7.60–7.65 (m, C_6H_5 or Py, 3H), 7.74 (m, C_6H_5 or Py, 1H), 8.52 (d, C_6H_5 or Py, 1H, J=7.8 Hz), 9.37 (d, C_6H_5 or Py, 1H, J=4.8 Hz). ^{13}C{^{1}H} NMR (150 MHz): δ 62.8 (s, *C*H$_2$), 115.3, 119.6, 122.8, 123.1, 125.1, 127.1, 129.8, 131.1, 137.8, 141.2, 149.6(*C*H of Ph or Py), 125.6, 132.4, 133.6, 152.4, 158.7 (three C_{ipso}–C_6H_5, one metallated *C*–Ph, and one *C*NN), Anal. Calcd for $C_{19}H_{16}ClN_3Pd$: C, 53.29; H, 3.77; N, 9.81. Found: C, 52.91; H, 4.33; N, 9.43.

4.2.9. [C_6H_5–C{=NC_6H_4Oxazoline}–NH–(η^1-C_6H_5)] PdCl (9). To a flask containing **6** (0.53 g, 0.5 mmol) and LiCl (0.17 g, 4.0 mmol), 15 ml of $CHCl_3$ was added at room temperature. After 18 h of stirring, the resulting mixture was filtered and the volatiles were removed under reduced pressure. The crude product was recrystallized from $CHCl_3$/hexane to afford yellow solid after several days. Yield, 0.38 g, 75%. ^{1}H NMR (600 MHz): δ 1.81 (s, C(CH_3)$_2$, 3H), 1.87 (s, C(CH_3)$_2$, 3H), 4.18 (d, CH_2, 1H, J=7.8 Hz), 4.38 (d, CH_2, 1H, J=8.4 Hz), 6.27 (d, C_6H_5, 1H, J=7.8 Hz), 6.91 (t, C_6H_5, 2H, J=7.8 Hz), 6.98 (t, C_6H_5, 1H, J=7.8 Hz), 7.03 (t, C_6H_5, 1H, J=7.8 Hz), 7.10 (d, C_6H_5, 1H, J=7.8 Hz), 7.29 (overlap, C_6H_5, 2H), 7.33 (t, C_6H_5, 2H, J=7.8 Hz), 7.41 (t, C_6H_5, 1H, J=7.8 Hz), 7.74 (m, C_6H_5, 2H), 8.18 (s, N*H*, 1H). ^{13}C{^{1}H} NMR (150 MHz): δ 27.5 (s, C(*C*H_3)$_2$), 28.6 (s, C(*C*H_3)$_2$), 70.7 (s, *C*(CH$_3$)$_2$), 81.2 (s, *C*H$_2$), 115.0, 124.2, 124.3, 125.2, 127.6, 129.1, 129.2, 130.2, 131.7, 132.2, 139.9(C_6H_5), 120.9, 126.0, 133.5, 146.4, 156.5, 161.1 (one *tert-C*-oxazoline, one *tert-C*-Ph, three C_{ipso}–C_6H_5, one metallated *C*–Ph, and one *C*NN; one *tert-C* is missed). Anal. Calcd for $C_{24}H_{22}ClN_3OPd$: C, 56.49; H, 4.35; N, 8.23. Found: C, 55.32; H, 4.07; N, 7.95.

4.3. General procedure for the Suzuki-type coupling reaction

Prescribed amounts of catalyst, aryl halide (1.0 equiv), phenylboronic acid (1.5 equiv), base (3.0 equiv), and a magnetic stir bar were placed in a Schlenk tube under nitrogen. Toluene (3 ml) was added by syringe, and the reaction mixture was heated in an oil bath at 80 °C for the prescribed time. After removal of the volatiles, the residue was diluted with ethyl acetate, filtered through a pad of silica gel. A sample in chloroform-*d* was taken for determination of conversion. The crude material was further purified by flash chromatography on silica gel.

4.4. General procedure for the Heck reaction

Prescribed amount of catalyst, base (1.5 equiv) and aryl halide (1 equiv) were placed in a Schlenk tube under nitrogen. Solvent (2 ml) and styrene (1.3 equiv) were added by syringe, and the reaction mixture was heated to the prescribed temperature for the prescribed time. After removal of the volatiles, the residue was diluted with ethyl acetate, filtered through a pad of silica gel. A sample in chloroform-*d* was taken for determination of conversion. The crude material was further purified by flash chromatography on silica gel.

4.5. Crystal structure data

Crystals were grown from concentrated hexane solution (**1**), toluene/hexane solution (**3**), concentrated dichloromethane solution (**5**), or CH_2Cl_2/hexane solution (**6** and **7**), and isolated by filtration. Suitable crystals of **1**, **3**, **5**, **6** or **7** were sealed in thin-walled glass capillaries under a nitrogen atmosphere and mounted on a Bruker AXS SMART 1000 diffractometer. The absorption correction was based on the symmetry equivalent reflections using the SADABS program. The space group determination was based on a check of the Laue symmetry and systematic absences and was confirmed using the structure solution. The structure

Table 8. Summary of crystal data for compounds **1**, **3**, **5**, **6** and **7**

	1	**3**	**5**	**6**	**7**
Formula	$C_{17}H_{21}N_3$	$C_{48}H_{46}N_6O_2$	$C_{21}H_{19}N_3O_2Pd$	$C_{27.50}H_{27}Cl_3N_3O_3Pd$	$C_{34}H_{40}Cl_2N_6Pd_2$
Fw	267.37	738.91	451.79	660.27	816.42
T (K)	293(2)	293(2)	293(2)	293(2)	293(2)
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic	Orthorhombic
Space group	$P2_1/n$	P-1	P-1	C2/c	$P2_12_12_1$
a (Å)	9.720(2)	10.4288(10)	9.6436(11)	24.6826(13)	12.2320(11)
b (Å)	11.651(3)	10.5934(11)	10.6773(12)	16.8272(9)	16.2444(14)
c (Å)	14.041(3)	18.6013(17)	10.8489(12)	14.1632(7)	17.1797(15)
α (°)	90	81.271(2)	109.326(2)	90	90
β (°)	92.599(5)	89.850(2)	96.282(2)	95.7540(10)	90
γ (°)	90	83.956(2)	113.133(2)	90	90
V (Å^3)	1588.5(6)	2019.7(3)	931.75(18)	5852.9(5)	3413.6(5)
Z	4	2	2	8	4
ρ_{calc} (Mg/m^3)	1.118	1.215	1.610	1.499	1.589
μ(Mo Kα) (mm^{-1})	0.067	0.076	1.017	0.941	1.243
Reflections collected	8826	11,567	5321	16,382	19,226
No. of parameters	207	505	244	339	397
$R1$[a]	0.0661	0.0486	0.0352	0.0400	0.0359
w$R2$[a]	0.1818	0.1062	0.0969	0.1191	0.0965
GoF[b]	0.928	1.020	0.798	0.934	0.765

[a] $R1=[(|F_0|-|F_c|)/|F_0|]$; w$R2=[\ w(F_0^2-F_c^2)^2/\ w(F_0^2)^2]^{1/2}$, $w=0.10$.
[b] Go$F=[w(F_0^2-F_c^2)^2/(N_{rflns}-N_{params})]^{1/2}$.

was solved by direct methods using a SHELXTL package. All non-H atoms were located from successive Fourier maps, and hydrogen atoms were refined using a riding model. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H atoms. Some details of the data collection and refinement are given in Table 8.

5. Supplementary information

Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers, CCDC no. 248112–248116 for compounds **1**, **3**, **5**, **6** and **7**, respectively. Copies of this information can be obtained, free of charge, from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or email:deposit@ccdc.cam.ac.uk].

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Chemoselective Heck arylation of acrolein diethyl acetal catalyzed by an oxime-derived palladacycle

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Dedicated to Professor Jean Pierre Genêt on the occasion of his 60th anniversary

Abstract—A dimeric 4-hydroxyacetophenone oxime-derived palladacycle has been used as a very efficient precatalyst for the chemoselective arylation of acrolein diethyl acetal to give either cinnamaldehyde derivatives or 3-arylpropanoate esters by proper choice of the reaction conditions. The synthesis of cinnamaldehyde derivatives can be performed by Heck reaction of acrolein diethyl acetal with iodo-, bromo- or chloroarenes in *N*,*N*-dimethylacetamide (DMA) using K_2CO_3 as base at 120 °C and tetra-*n*-butylammonium acetate (TBAA) and KCl as additives, followed by acid workup. In the case of 3-arylpropanoate esters the corresponding arylation of acrolein diethyl acetal with iodoarenes can be performed at 90 °C in aqueous DMA using (dicylohexyl)methylamine as base, whereas for bromoarenes the reaction has to be performed at 120 °C using tetra-*n*-butylammonium bromide (TBAB) as additive. Alternatively, this process can be performed under microwave irradiation. These couplings take place in good yields and with lower catalyst loading than with palladium(II) acetate as well as in shorter reaction times and with lower excess of acrolein diethyl acetal.

1. Introduction

Cinnamaldehyde derivatives are important compounds present in nature and widely used not only in food and cosmetic industries[1] but also exhibit antifungal,[2] antibacterial,[3] antitermitic,[4] insecticidal,[5] and antitumor[6] activities. For instance, 2′-hydroxycinnamaldehyde, isolated from the stem bark of *Cinnamonum cassia* Blume (Lauraceae), has shown in vitro activities on farnesyl transferase, angiogenesis, immunomodulation, cell–cell adhesion and cytotoxicity against tumor cell lines.[6,7] Other cinnamaldehyde derivatives have been used for the preparation of new materials in nonlinear optics.[8] A straightforward strategy for the diastereoselective preparation of cinnamaldehyde derivatives is the Heck–Mizoroki reaction[9] of acrolein with aryl halides. However, acrolein polymerizes in basic media at elevated temperatures under the typical Heck reaction conditions.[10] Jeffery has reported this coupling at room temperature for some aryl iodides by using phase-transfer catalysis conditions,[11] but long reaction times are required and low yields were obtained with deactivated iodoarenes, whereas the reaction failed with aryl bromides.[12,13] In order to avoid polymerization, Zebovitz and Heck studied the arylation of acrolein acetals with aryl iodides and bromides using $Pd(OAc)_2$/(*o*-tol)$_3$P as catalysts, Et_3N as base in DMF at 100 °C, but mixtures of cinnamaldehyde acetals and 3-arylpropanoate esters were obtained.[10] This result is due to the two possible palladium hydride eliminations from the carbopalladated intermediate (Scheme 1). Using these Heck conditions double coupling has been successfully performed with 1,4-dibromo-2,5-dimethoxybenzene and acrolein dimethyl acetal.[14] However, under these reactions conditions 3-amino-4-iodopyridine gave mixtures of competitive vinylic substitution product and ester derivative, but when using Jeffery's protocol [$Pd(OAc)_2$ (5 mol%), $NaHCO_3$, tetra-*n*-butylammonium chloride (TBAC), DMF, 70 °C] and a fast aqueous workup a clean arylation of acrolein dimethyl acetal occurred.[15] Unfortunately, the coupling with 3-halo-3-aminopyridines failed under the last reaction conditions. Very recently, Cacchi et al. have found after a careful screening of the reaction conditions that aryl iodides and bromides can be coupled chemoselectively with acrolein diethyl acetal to yield cinnamaldehyde derivatives [$Pd(OAc)_2$ (3 mol%), tetra-*n*-butylammonium acetate (TBAA), K_2CO_3, KCl, DMF, 90 °C][13] or ethyl 3-arylpropanoates [$Pd(OAc)_2$ (3 mol%), TBAC, Bu_3N, DMF, 90 °C].[16]

Keywords: Heck reaction; Cinnamaldehydes; 3-Arylpropanoates/acrolein; Palladacycles.
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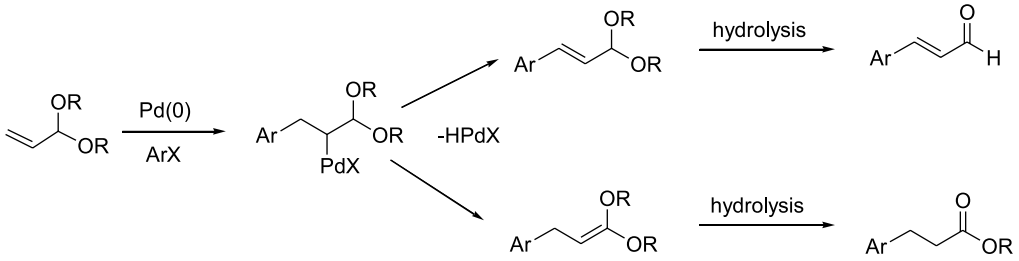
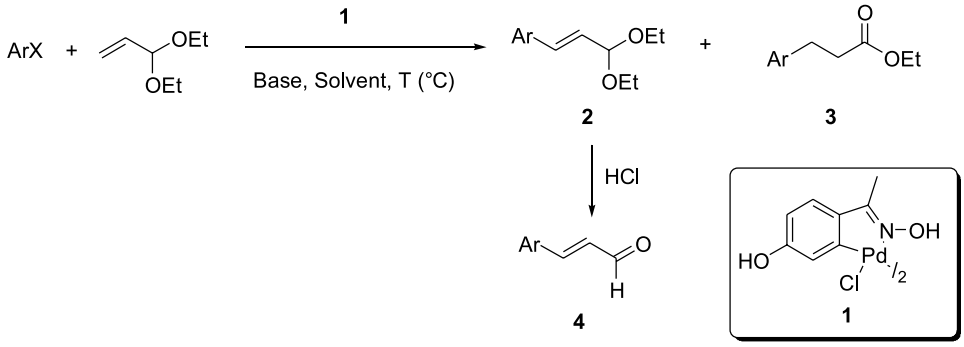


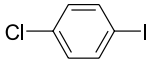
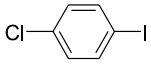
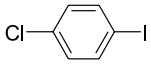
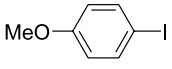
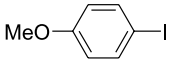
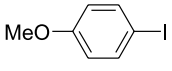
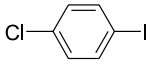
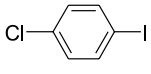
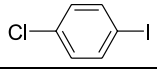
Scheme 1.

In connection with our work about the use of oxime-derived palladacycles[17] as very active precatalyst in cross-coupling reactions, such as Heck,[18] Suzuki,[19] Sonogashira,[20] and acylation of alkynes[21] in organic and aqueous solvents, we report here the scope of this type of catalysts in the chemoselective synthesis of cinnamaldehyde derivatives and ethyl 3-arylpropanoates[22] by arylation of acrolein diethyl acetal.



Scheme 2.

Table 1. Synthesis of cinnamaldehyde derivatives[a]

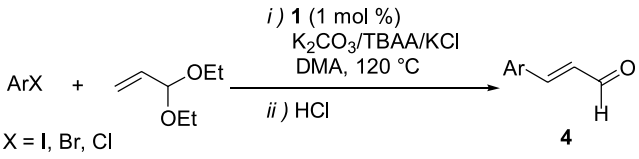
Entry	ArX	Mol% Pd	*t* (h)	Base	Solvent	*T* (°C)	Conv. (%)[b]	Ratio (**2**/**3**)[c]
1		1	8	K_2CO_3/TBAA	DMA	90	82	1:0
2		1	6	K_2CO_3/TBAA	DMA/H_2O[d]	90	99	4.9:1
3		1	14	K_2CO_3/TBAH	DMA/H_2O[d]	90	86	16.2:1
4		2	14	K_2CO_3/TBAA	DMA/H_2O[d]	120	0	—
5		1	3	K_2CO_3/TBAA/KCl	DMA/H_2O[d]	120	99	2.8:1
6		1	3	K_2CO_3/TBAA/KCl	DMA	120	99	10:1 (79)
7		1	2	K_2CO_3/TBAA/KCl	DMA	120	99	1:0 (82)
8		0.1	22	K_2CO_3/TBAA/KCl	DMA	120	99	1:0
9		1	2	K_2CO_3/TBAA/KCl[e]	DMA	120	99	10:1

Reaction conditions study.
[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), K_2CO_3 (1.5 mmol), ammonium salt (2 mmol), KCl (when added, 1 mmol), palladacycle **1** and solvent (5 mL).
[b] Determined by GLC using decane as internal standard.
[c] Determined by GLC. In brackets isolated yield of **4** after hydrolysis and flash chromatography.
[d] Volume ratio 4:1.
[e] Only 1 mmol of TBAA.

2. Results and discussion

2.1. Synthesis of cinnamaldehyde derivatives

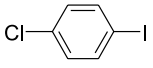
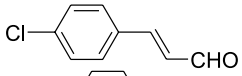
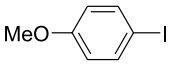
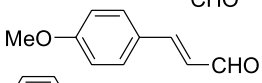
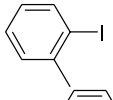
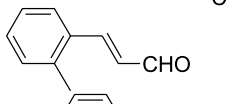
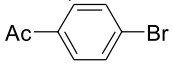
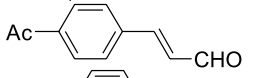
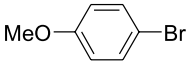
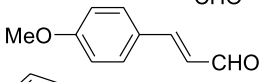
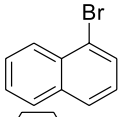
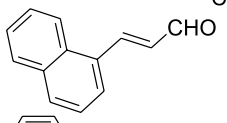
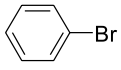
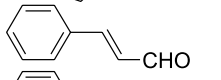
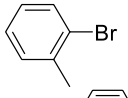
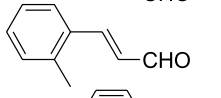
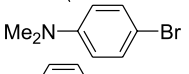
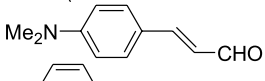
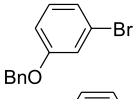
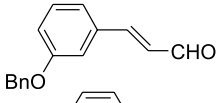
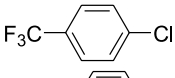
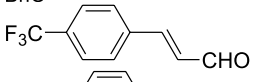
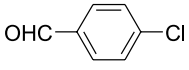
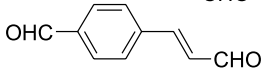
Initial studies concerning the reaction conditions for the arylation of acrolein diethyl acetal (1.5 equiv) catalyzed by 4-hydroxyacetophenone oxime-derived palladacycle **1** were performed with 1 equiv of the activated 4-chloroiodobenzene and the deactivated 4-methoxyiodobenzene (Scheme 2 and Table 1). The reactions carried out with 4-chloroiodobenzene using K_2CO_3 (1.5 equiv) and tetra-*n*-butylammonium acetate (TBAA) (2 equiv) as bases at 90 °C in *N*,*N*-dimethylacetamide (DMA) or in aqueous DMA, gave complete selectivity in neat DMA although, the reaction was faster in aqueous DMA (Table 1, entries 1 and 2). The use of tetra-*n*-butylammonium hydroxide (TBAH) instead of acetate gave a 16:1 ratio of compounds **2** and **3** in longer reaction times (Table 1, entry 3). In the case of 4-methoxyiodobenzene the reaction failed and KCl has to be added and the temperature increased at 120 °C in the absence of water in order to get a 10:1 ratio of compounds **2**/**3** (Table 1, compare entries 4–6). These reaction conditions were applied to the coupling with 4-chloroiodobenzene, which could be performed with total chemoselectivity in a shorter time (Table 1, entry 7). When lower palladium loading (0.1 mol%) was used higher reaction rate was observed for completion (Table 1, entry 8). When the amount of TBAA was decreased from 2 to 1 equiv the reaction also proceeded but with lower selectivity (Table 1, entry 9). On the other hand, attempts to perform the arylation of acrolein with *p*-cloroiodobenzene under this reaction conditions either at room temperature or at 80 °C failed.



Scheme 3.

For the synthesis of different cinnamaldehyde derivatives **4** the hydrolysis of compounds **2** was conducted in situ by addition of hydrochloric acid to the reaction mixture after arylation of acrolein diethyl acetal with aryl iodides, bromides and chlorides (Scheme 3 and Table 2). Under the best reaction conditions [**1** (0.5 mol%), TBAA, K_2CO_3, KCl, DMA at 120 °C] the arylation took place in short reaction times with good yields, only failing with

Table 2. Synthesis of cinnamaldehyde derivatives[a]

Entry	ArX	*t* (h)	No.	Product	Yield (%)[b]
1		2	**4a**		82
2		3	**4b**		79
3		3	**4c**		82
4		3	**4d**		59
5		3	**4b**		75
6		2	**4e**		80
7		2	**4f**		81
8		5	**4c**		71
9		3	**4g**		73
10		3	**4h**		67
11		14	**4i**		71[c]
12		14	**4j**		31[c]

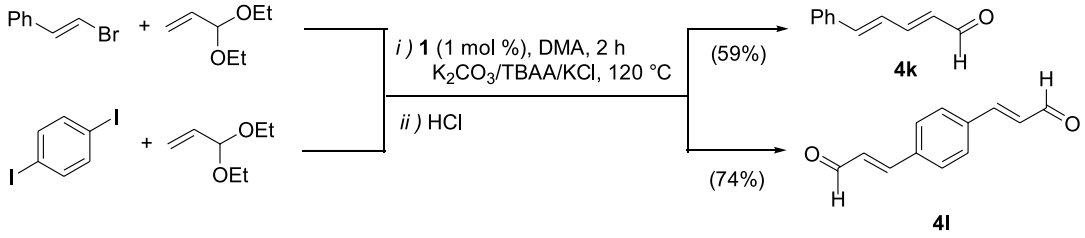
[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), K_2CO_3 (1.5 mmol), TBAA (2 mmol), palladacycle **1** (1 mol% Pd), DMAc (4 mL) and 120 °C.
[b] Isolated yields after hydrolysis and flash chromatography.
[c] Reaction performed in a 15 mL Ace pressure tube.

deactivated aryl chlorides. Ethyl 3-arylpropanoates were obtained in low yields ranging from 5 to 15%. Cinnamaldehydes **4** bearing electron-donating and -withdrawing groups were obtained in good yields. Some selected examples are *p*-(dimethylamino)cinnamaldehyde (**4g**), which is an important unit for nonlinear optics,[13] and 3-benzyloxycinnamaldehyde (**4h**), which has shown the most potent inhibitory activity against cyclin dependent kinases, specially cyclin D1-CDK4.[6b] The starting 3-(benzyloxy)phenyl bromide, used for the synthesis of the last compound **4h**, was prepared in 71% yield by benzylation of 3-bromophenol with benzyl bromide and K_2CO_3 under acetone reflux for 1 day. The reaction conditions with complex **1** are rather similar than the described conditions with $Pd(OAc)_2$ by Cacchi et al.[13] In the case of $Pd(OAc)_2$ the arylation took place with 3 mol% of catalyst in 1.5–15 h in 70–88% yields at 90 °C in DMF with 3 equiv of acrolein diethyl acetal, whereas with complex **1** this process needed lower catalyst loading, 1 mol% of Pd, at 120 °C in DMA and occurred in general in lower rates (2–5 h).

The coupling with (*E*)-2-phenylvinyl bromide gave stereoselectively the (2*E*,4*E*)-dienic aldehyde **4k** in 59% yield (Scheme 4). However, for the synthesis of the unsaturated dialdehydes the *p*-diiodobenzene gave compound **4l** after 2 h in 74% yield and the *ortho*-derivative afforded an intractable mixture of compounds. The reaction of 4-metoxyiodobenzene with acrolein diethyl acetal under microwave irradiation at 120 W and 120 °C during 10 min gave a mixture of products, mainly the ethyl 3-(4-methoxyphenyl)propanoate. In the case of 4-methoxybromobenzene no reaction was observed.

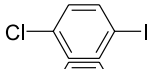
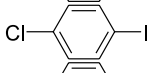
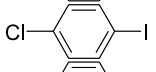
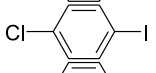
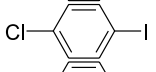
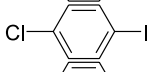
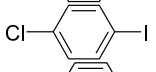
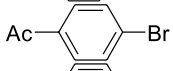
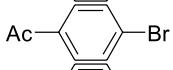
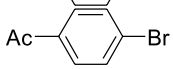
2.2. Synthesis of ethyl 3-arylpropanoates

Initial attempts to perform the preparation of ethyl 3-arylpropanoates were carried out by using 4-chloroiodobenzene and acrolein diethyl acetal (1.5 equiv) with complex **1** (0.1 mol% of Pd) as catalyst and (dicyclohexyl)-methylamine[23] as base (Table 3). When this coupling was performed in DMA as solvent, the reaction has to be heated at 120 °C (Table 3, entries 1 and 2). The reaction can also be carried out at 90 °C in a mixture of DMA/H_2O (4:1), but in neat water the arylation failed (Table 3, entries 3 and 4). When tri-*n*-butylamine was used instead of (dicyclohexyl)methylamine the reaction time increased from 4 to 7 h with a lower yield (Table 3, compare entries 3 and 5). The use of K_2CO_3 and TBAB as



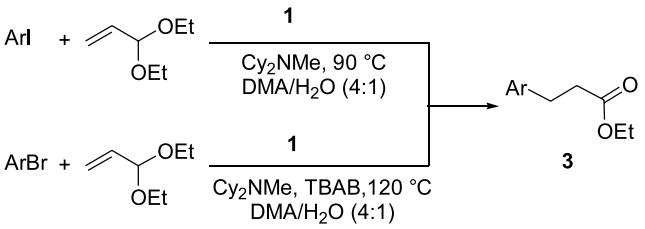
Scheme 4.

Table 3. Synthesis of ethyl 3-arylpropanoates[a]

Entry	ArX	Mol% Pd	*t* (h)	Base	Additive	Solvent	*T* (°C)	Conv.(%)[b]
1		0.1	8	Cy_2NMe	—	DMA	120	99
2		0.1	21	Cy_2NMe	—	DMA	90	0
3		0.1	4	Cy_2NMe	—	DMA/H_2O[c]	90	99 (79)
4		0.1	8	Cy_2NMe	—	H_2O	90	0
5		0.1	7	Bu_3N	—	DMA/H_2O[c]	90	87
6		1	4	K_2CO_3	TBAB	DMA/H_2O[c]	90	92
7		0.1	6	K_2CO_3	TBAB	DMA/H_2O[c]	90	0
8		0.1	3	Cy_2NMe	TBAB	DMA/H_2O[c]	90	0
9		0.1	3	Cy_2NMe	TBAB	DMA/H_2O[c]	120	99 (76)
10		0.1	3	Cy_2NMe	—	DMA/H_2O[c]	120	86

Reaction conditions study.
[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), base (1.5 mmol), additive (1 mmol), palladacycle **1** (see Table) and solvent (5 mL).
[b] Determined by GLC using decane as internal standard. In brackets isolated yield after flash chromatography.
[c] Volume ratio 4:1.

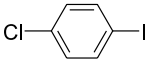
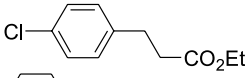
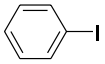
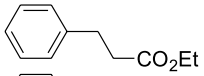
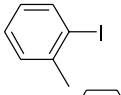
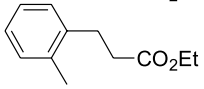
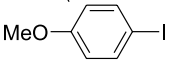
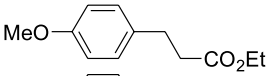
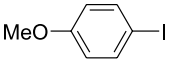
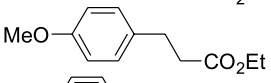
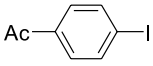
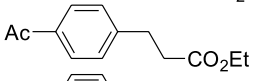
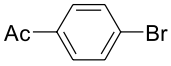
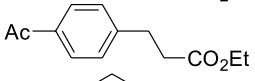
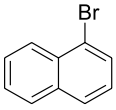
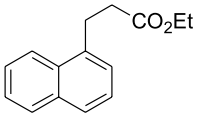
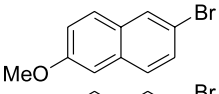
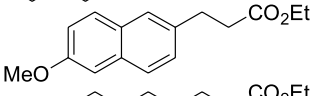
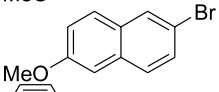
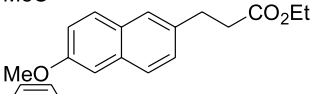
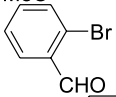
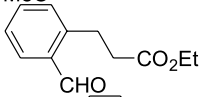
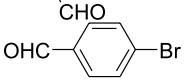
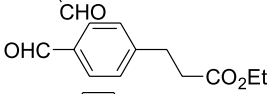
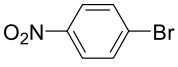
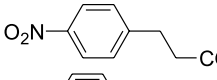
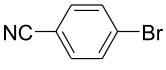
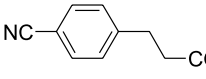
additive in aqueous DMA needed a higher catalyst loading (1 mol% of Pd) (Table 3, entries 6 and 7). Just a simple change in the additive (TBAB instead of TBAA) reversed completely the selectivity of the reaction (compare Table 1, entry 2 and Table 3, entry 6). The best conditions for the aryl iodide [Cy_2NMe, DMA/H_2O (4:1)] were applied to the reaction of acrolein diethyl acetal and 4-bromoacetophenone, revealing that in this case TBAB as additive and 120 °C have to be used in order to get good conversion in short times (Table 3, entries 8–10).



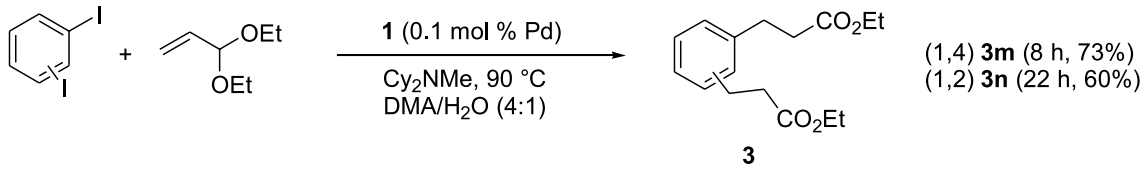
Scheme 5.

The synthesis of a variety of ethyl 3-arylpropanoates **3** can be performed with activated and deactivated aryl iodides and bromides bearing different functional groups, even at the *ortho*-position, by using Cy_2NMe as base in aqueous DMA (Scheme 5 and Table 4). For aryl iodides the arylation was performed at 90 °C and for bromides at 120 °C in the presence of TBAB. Deactivated aryl bromides, such as 4-methoxybromobenzene showed very low reactivity. In general, the reactions can be performed with lower loading of palladium than in the case of $Pd(OAc)_2$.[16] Thus, by using complex **1** between 0.1 and 1 mol% of Pd was used and the couplings took place in 2–8 h in 69–87% yield. For

Table 4. Synthesis of ethyl 3-arylpropanoates[a]

Entry	ArX	Mol% Pd	*t* (h)	No.	Product	Yield (%)[b]
1		0.1	4	**3a**		79
2		0.1	4	**3b**		79
3		0.1	6	**3c**		87
4		0.1	8	**3e**		69
5		0.1	10 min[c]	**3e**		71[d]
6		1.2×10^{-2}	23	**3f**		49
7		0.1	3	**3f**		76
8		1	5	**3g**		71
9		1	5	**3h**		53
10		1	10 min[e]	**3h**		76[d]
11		1	3	**3i**		83
12		0.1	3	**3j**		81
13		0.1	2	**3k**		86
14		0.1	3	**3l**		86

[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), Cy_2NMe (1.5 mmol), TBAB (1 mmol, only for aryl bromides), palladacycle **1** (see Table), DMA (4 mL) and H_2O (1 mL) at 90 °C for aryl iodides and 120 °C for aryl bromides.
[b] Isolated yields after flash chromatography.
[c] The reaction was performed under microwave irradiation conditions (120 W, 90 °C) at 0.5 mmol scale.
[d] Conversion determined by GC based on the aryl halide using decane at internal standard.
[e] The reaction was performed under microwave irradiation conditions (120 W, 120 °C) at 0.5 mmol scale.



Scheme 6.

comparison, in the case of $Pd(OAc)_2$ 3 mol% of Pd was used to afford similar couplings in 1–29 h and in 42–92% yield. This type of arylation can be also performed in 10 min under microwave irradiation at 120 W and 90 or 120 °C for compounds **3e** or **3h**, respectively (Table 4, entries 5 and 10). However, so far this type of arylation could not be performed with aryl chlorides under the essayed reaction conditions.

This Heck reaction with acrolein diethyl acetal were essayed with 1,4- and 1,2-diiodobenzene and the corresponding diesters **3m** and **3n** were obtained in good yields after 8 and 22 h, respectively (Scheme 6). Rather low loading of Pd (0.1 mol%) was used in comparison with the same couplings using $Pd(OAc)_2$,[6] which needed a higher catalysts loading (6 mol%) to afford compounds **3m** and **3l** in similar yields (77 and 61%) and reaction rates (3 and 24 h).

3. Conclusion

In conclusion, we have found that the arylation of acrolein diethyl acetal can be performed with lower loading of acrolein and catalyst using the 4-hydroxyacetophenone oxime-derived palladacycle **1** instead of $Pd(OAc)_2$ by choosing the appropriate base, solvent, temperature and additive. Cinnamaldehyde derivatives can be prepared by using aryl iodides, bromides and activated chlorides, whereas ethyl 3-arylpropanoates have been prepared using iodides and bromides under thermal or microwave irradiation conditions.

4. Experimental

4.1. General

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin-layer chromatography was perfomed on Polygram® SIL G/UV_{254} plates. Melting point were determined on a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on a HP-6890 instrument equipped with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophotometer in cm^{-1}. ^1H NMR spectra were recorded on Bruker AC-300 (300 MHz). Chemical shifts are reported in ppm using tetramethylsilane (TMS, 0.00 ppm) as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as the internal reference. EI-MS were measured on a mass selective detector G2579A from Agilent Technologies 5973N in *m/z* (rel int. in % of base peak). HRMS were performed on a Finningan MAT95S apparatus. Elemental analysis were carried out in a Carlo Erba EA 1108 (CHNS–O) by the corresponding services at the University of Alicante. The catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with precision of 1 μg. Microwave reactions were performed with a CEM discover synthesis unit in glass vessels (10 mL) sealed with a septum under magnetic stirring.

4.2. General procedure for the synthesis of cinnamaldehyde derivatives (4)

A suspension of aryl halide (1 mmol), acrolein diethyl acetal (229 μL, 1.5 mmol), potassium carbonate (207 mg, 1.5 mmol), tetra-*n*-butylammonium acetate (602 mg, 2 mmol), potassium chloride (75 mg, 1 mmol), **1** (2.918 mg, 0.005 mmol, 1 mol% Pd) and *N*,*N*-dimethylacetamide (4 mL) was stirred at 120 °C (bath temperature) in air, and the reaction progress was analyzed by GLC. After the reaction was completed, it was cooled and an aqueous solution of 2 M HCl (10 mL) was added slowly and the mixture was stirred at room temperature for 10 min. Then the reaction crude was poured into ethyl acetate (20 mL) and washed successively with 2 M HCl (20 mL) and H_2O (2×20 mL). The organic layer was dried over Na_2SO_4, evaporated (15 mmHg) and the resulting residue purified by flash chromatography to provide compounds **4**.

The compounds cinnamaldehyde, *p*-(dimethylamino)-cinnamaldehyde, *p*-chlorocinnamaldehyde, *p*-methoxycinnamaldehyde and *o*-methyl-cinnamaldehyde are commercially available and *p*-acetylcinnamaldehyde,[13] *m*-benzyloxycinnamaldehyde,[6b] *p*-(trifluoromethyl)cinnamaldehyde,[25] *p*-formylcinnamaldehyde,[13] 5-phenyl-2,4-pentadienal[26] and 1,4-phenylenediacrylaldehyde[27] have been previously reported and were characterized by comparison with their reported data. The characterization data of compounds previously not reported is given below.

4.2.1. 3-(1-Naphthyl)acrolein. R_f 0.20 (hexane–EtOAc: 9/1); mp 49–51 °C; IR (KBr): ν=2826, 1679 cm^{-1}; ^1H NMR: δ=6.76 (dd, 1H, *J*=15.8, 7.8 Hz, C*H*CHO), 7.42–7.60 (m, 3H, ArH), 7.72 (d, 1H, *J*=7.2 Hz, ArH), 7.84–7.90 (m, 2H, ArH), 8.11 (d, 1H, *J*=8.3 Hz, ArH), 8.22 (d, 1H, *J*=15.8 Hz, C*H*CHCHO), 9.78 (d, 1H, *J*=7.8 Hz, CHO); ^{13}C NMR: δ=122.7, 125.4, 125.6, 126.3, 127.2, 128.9, 130.7, 130.8, 131.1, 131.6, 133.7, 149.2, 193.4, 197.3; MS: *m/z* (rel int.) 182 (M^+, 53), 181 (M^+-1, 100), 165 (14), 154 (24), 153 (95), 152 (77), 151 (30), 150 (17), 128 (15), 127 (10), 126 (14), 77 (20), 76 (39), 75 (16), 63 (22), 62 (11), 51 (22), 50 (17). Anal. Calcd for $C_{13}H_{10}O$: C 85.69, H 5.53; found: C 84.99, H 5.51.

4.3. General procedure for the synthesis of ethyl 3-arylpropanoates (3)

A solution of aryl halide (1 mmol), acrolein diethyl acetal (229 μL, 1.5 mmol), dicyclohexylmethylamine (321 μL, 1.5 mmol), tetra-*n*-butylammonium bromide (322 mg, 1 mmol, only for aryl bromides), **1** (0.1–1 mol% Pd) in *N*,*N*-dimethylacetamide (4 mL) and water (1 mL) was stirred at 90 °C or at 120 °C (bath temperature) for aryl iodides or aryl bromides respectively, in air, and the reaction progress was analyzed by GLC. After the reaction was completed, the resulting solution was cooled, poured into ethyl acetate (20 mL) and washed successively with 2 M HCl (2×20 mL) and H_2O (20 mL). The organic layer was dried over Na_2SO_4, evaporated (15 mmHg) and the residue was purified by flash chromatography to afford products **3**.

The compounds ethyl 3-(*p*-chlorophenyl)propanoate,[28] ethyl 3-phenylpropanoate,[29] ethyl 3-(*o*-tolyl)propanoate,[30] ethyl 3-(*p*-methoxyphenyl)propanoate,[29] ethyl 3-(*p*-acetylphenyl)propanoate,[29] ethyl 3-(1-naphtyl)propanoate,[31] ethyl 3-(6-methoxy-2-naphtyl)propanoate,[28] ethyl 3-(*p*-cyanophenyl)propanoate,[32] ethyl 3-[4-(2-ethoxycarbonylethyl)-phenyl]propanoate,[16] and ethyl 3-[2-(2-ethoxycarbonylethyl)phenyl]-propanoate[16] have been previously reported and were characterized by comparison with their reported data. Data of not described compounds are given below.

4.3.1. Ethyl 3-(2-formylphenyl)propanoate. R_f 0.27 (hexane–EtOAc: 9/1); oil; IR (film): ν=2740, 1731, 1694 cm^{-1}; ^1H NMR: δ=1.22 (t, 3H, J=7.2 Hz, CH_3), 2.64 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 3.36 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 4.11 (c, 2H, J=7.1 Hz, CH_2CH_3), 7.33 (d, 1H, J=7.5 Hz, ArH), 7.34–7.54 (m, 2H, ArH), 7.82 (dd, 1H, J=7.5, 1.4 Hz, ArH), 10.22 (s, 1H, CHO); ^{13}C NMR: δ=4.2, 28.0, 35.5, 60.4, 127.0, 131.2, 133.4, 133.8, 142.9, 172.6, 192.7; MS: *m*/*z* (rel int.) 206 (M^+, 5), 188 (19), 162 (22), 161 (27), 160 (38), 134 (10), 133 (58), 132 (91), 131 (43), 118 (21), 115 (28), 105 (72), 104 (100), 103 (36), 91 (60), 79 (40), 78 (33), 77 (68), 66 (18), 65 (33), 63 (17), 51 (50); HRMS: calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0944.

4.3.2. Ethyl 3-(4-formylphenyl)propanoate. R_f 0.20 (hexane–EtOAc: 9/1); oil; IR (KBr): ν=2736, 1732, 1702 cm^{-1}; ^1H NMR: δ=1.23 (t, 3H, J=7.1 Hz, CH_3), 2.66 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 3.04 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 4.13 (c, 2H, J=7.1 Hz, CH_2CH_3), 7.38 (d, 2H, J=8.0 Hz, ArH), 7.81 (d, 2H, J=8.0 Hz, ArH); ^{13}C NMR: δ=14.2, 31.0, 35.2, 60.6, 129.0, 130.0, 134.8, 147.9, 172.4, 191.9; MS: *m*/*z* (rel int.) 206 (M^+, 33), 177 (15), 161 (13), 135 (36), 133 (31), 132 (63), 131 (28), 119 (19), 107 (13), 105 (28), 104 (20), 103 (21), 91 (31), 79 (24), 78 (18), 77 (34), 76 (12), 66 (12), 65 (15), 63 (12), 60 (29), 51 (32); HRMS: calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0942.

4.3.3. Ethyl 3-(4-nitrophenyl)propanoate. R_f 0.17 (hexane–EtOAc: 9/1); oil; IR (film): ν=1732, 1519, 1346 cm^{-1}; ^1H NMR: δ=1.24 (t, 3H, J=7.1 Hz, CH_3), 2.70 (t, 2H, J=7.5 Hz, $ArCH_2CH_2$), 3.08 (t, 2H, J=7.5 Hz, $ArCH_2CH_2$), 4.14 (c, 2H, J=7.1 Hz, CH_2CH_3), 7.40 (d, 2H, J=8.5 Hz, ArH) 8.15 (d, 2H, J=8.5 Hz, ArH); ^{13}C NMR: δ=14.1, 30.5, 34.9, 60.5, 123.6, 129.2, 146.5, 148.3, 172.0; MS: *m*/*z* (rel int.) 223 (M^+, 29), 195 (M^+-28, 9), 178 (M^+-45, 23), 153 (15), 152 (31), 150 (37), 149 (100), 136 (18), 133 (10), 119 (16), 103 (30), 91 (23), 78 (35), 77 (35), 63 (17); HRMS: calcd for $C_{11}H_{13}NO_4$: 223.0845; found: 223.0842.

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8-Methylquinoline palladacycles: stable and efficient catalysts for carbon–carbon bond formation

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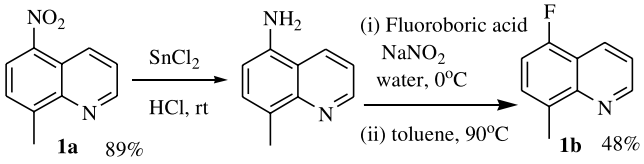
Abstract—Cyclopalladated, phosphine free, 8-methyl quinoline based complexes (**2a–j**) are excellent catalysts for the Heck vinylation of aryl iodides and bromides with turnover numbers of greater than 25 million observed in some cases. The catalysts are air and moisture stable.

Palladium mediated reactions are firmly positioned as one of the 'power tools' of modern organic synthesis. A variety of diverse catalytic manipulations may be accomplished using its salts and complexes. For example, the Heck reaction,[1] is a versatile and widely used method for C–C bond formation where much recent attention has focused on finding novel catalysts with high turnover numbers (TON). New developments in the area of high turnover palladium catalysts principally consist of palladacycles[2,3] and coordinatively unsaturated palladium catalysts featuring bulky phosphanes of high σ-donor abilities.[3] A variety of palladacycles incorporating cyclometallated phosphines,[4] phosphites,[5] carbenes,[6] imines,[7] heterocycles,[8] thioethers[9] and oximes[10] have been reported with high turnover numbers for this process. These precatalysts invariably contain sp^2 carbon–palladium bonds but the utility of palladacycles in other non-catalytic roles is also expanding.[11]

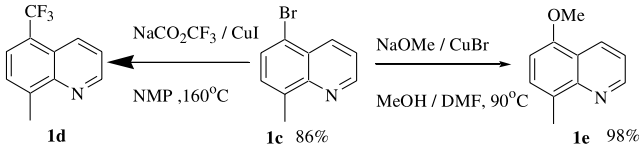
1. Introduction

We now report that palladacycles (**2a–j**) are good catalysts for both the Heck reaction and three component cascade reactions. Notably these systems differ from other phosphine free, nitrogen based palladacycles used in the Heck reaction in that they posses an sp^3 carbon–palladium bond rather than an sp^2 carbon–palladium bond. A series of 5-substituted 8-methylquinolines (**1a–d**) were synthesised from 8-methylquinoline. A standard nitration was carried out to give 5-nitro-8-methylquinoline (**1a**), which was converted to 5-fluoro-8-methylquinoline (**1b**) via the corresponding diazonium salt (Scheme 1).[12]



Scheme 1.

Bromination of 8-methylquinoline at C-(5) to afford (**1c**) was achieved by bromine in the presence of silver sulfate[13] whilst 5-trifluoromethyl 8-methylquinoline (**1d**) was prepared from (**1c**) using sodium trifluoroacetate in the presence of copper (I) iodide (Scheme 2).[13] 5-Methoxy-8-methylquninoline (**1e**) was also derived from (**1c**) using



Scheme 2.

Keywords: Precatalyst; Allene; Cascade.
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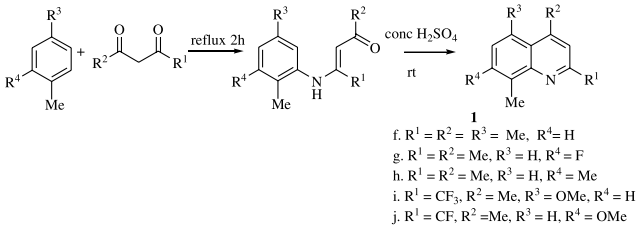
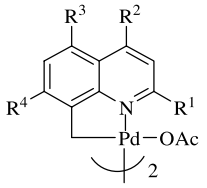
sodium methoxide together with copper (I) bromide (Scheme 2).[14]

The substituted 8-methylquinolines (**1f–j**) were synthesised by a two step procedure adapted from the literature[15] from the appropriate aniline and 1,3-diketone in 82–96% yield (Scheme 3).



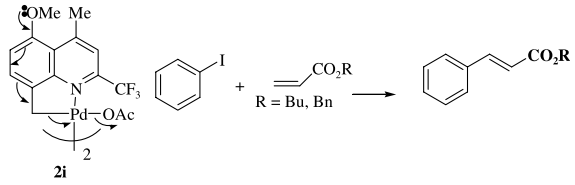
Scheme 3.



2 a. $R^1 = R^2 = R^3 = R^4 = H$
b. $R^1 = R^2 = H$, $R^3 = NO_2$, $R^4 = H$
c. $R^1 = R^2 = H$, $R^3 = F$, $R^4 = H$
d. $R^1 = R^2 = H$, $R^3 = CF_3$, $R^4 = H$
e. $R^1 = R^2 = H$, $R^3 = OMe$, $R^4 = H$
f. $R^1 = R^2 = R^3 = Me$, $R^4 = H$
g. $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = F$
h. $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Me$
i. $R^1 = CF_3$, $R^2 = Me$, $R^3 = OMe$, $R^4 = H$
j. $R^1 = CF_3$, $R^2 = Me$, $R^3 = H$, $R^4 = OMe$

Following a procedure adapted from literature the 8-methyl quinoline derivatives and palladium acetate (1 equiv) were heated in glacial acetic acid at 100 °C[16] to afford the desired palladacyclic dimers (**2a–j**) in 55–65% yield. The mixture of isomeric species (cis and trans dimers) is clearly evident in the proton NMR spectra of (**2a–j**) from the set of broad AB signals, due to the diastereotopic C(8)–CH_2 protons (see Section 2) and the corresponding additional complexity of the aromatic proton signals.

We explored the Heck reaction between iodobenzene and *n*-butyl acrylate or benzyl acrylate in the presence of (**2a–j**) in DMF/DMA at 140 °C (Table 1) (Scheme 4). Introducing a C(5)-electron donating group, increases the rate of reaction and TON (Table 1, entry 6).



Scheme 4.

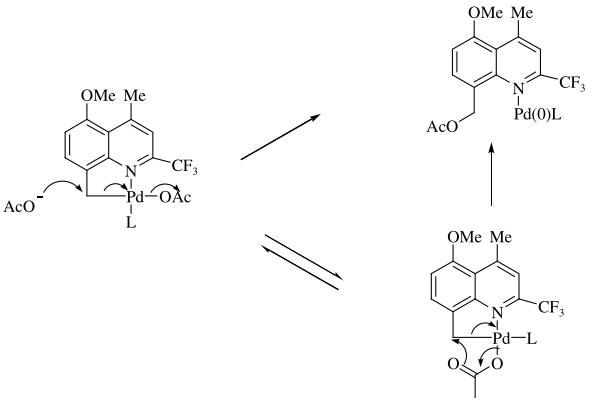
Introducing a C(2)-electron withdrawing group further increases the rate and TON (Table 1, entry 9). A C(7)-electron donating group combined with a C(2)-electron withdrawing group also produces a highly active catalyst (Table 1, entry 11). Introducing fluorine (-I and π-donor) substituents at C(5) and C(7) did not produce a higher TON (Table 1, entries 3 and 8). However, a C(5)–CF_3 group gave a good TON (Table 1, entry 5). We also carried out an experiment on (**2i**) to determine the recyclability of the catalyst. Thus, a fresh charge of iodobenzene, *n*-butyl acrylate and base were added to the reaction mixture after 100% conversion of the previous run. In this way it was found that catalyst was still active after 30 days and a TON of 25 million (Table 1, entry 10). In this latter case PVP polyvinyl pyrrolidone (Pd/PVP = 13:1) was added at the start of the reaction (Table 1, entry 10). This additive is known to prolong catalyst life by the polymer chains 'wrapping up' the individual palladium nanoparticles thus preventing them colliding with each other and aggregating, that is, stablises the nanoparticles.[17] The palladacycles (**2a–j**) could operate via Pd(II)/Pd(IV)[18] or Pd(0)/Pd(II) catalytic cycles.[19] It appears probable, on our current

Table 1. Catalytic Heck reaction of iodobenzene with *n*-butyl acrylate (2 equiv) or benzyl acrylate (2 equiv) with palladacycles (**2a–j**) precatalysts

Entry	Catalyst (mol%)	Temperature (°C)	Solvent	Time (h)	Base (2 equiv)	Conversion (%)[a]	TON[b]
1[c]	**2a** (0.01)	100	DMF	60	K_2CO_3	85	8,500
2[c]	**2b** (0.00017)	100	DMF	16	K_2CO_3	99	581,600
3	**2c** (0.001)	140	DMF	96	K_2CO_3	89	89,000
4	**2c** (0.0001)	140	DMA	96	CsOAc	34	340,000
5	**2d** (0.00001)	140	DMA	96	CsOAc	87	8,700,000
6	**2e** (0.00001)	140	DMF	96	CsOAc	98	9,800,000
7	**2f** (0.0001)	140	DMF	44	KOAc	70[d]	700,000
8	**2g** (0.001)	140	DMF	16	KOAc	100	100,000
9	**2i** (0.00001)	140	DMF	47	CsOAc	100	10,000,000
10	**2i** (0.0001)	140	DMF	720	KOAc	—[e]	25,500,000
11	**2j** (0.00001)	140	DMF	94	CsOAc	78	7,800,000

[a] Conversion by NMR.
[b] TON based on consumption of iodobenzene.
[c] Benzyl acrylate and Et_4NCl (1 equiv) were used.
[d] GC conversion.
[e] PVP (M_w 3000) (pd/PVP = 13:1) were used.

evidence, that the active species are Pd(0) nanoparticles.[20] We have also shown that treatment of palladacycles or palladium salts with carbon monoxide (1 atm) in DMF or toluene at room temperature results in a solution of palladium nanoparticles whose morphology depends on the palladacycle or palladium salt precursors.[21] Blackmond et al. have developed a detailed kinetic model of a Heck reaction catalysed by dimeric palladacycles.[22] This model explains the experimental observations and is consistent with an active species being slowly metered into the reaction. Comparison between phosphine and non-phosphine based palladacycles suggests that they follow the same reaction mechanism. They have also highlighted the role of water in accelerating the formation of the active catalyst species. Thus, the rate-determining 'metering' step is outside the true catalytic cycle, in the case of aryl iodides and activated aryl bromides and this has important consequences for the use of these catalysts. This, of course, does not apply to cases of 'unreactive' aryl chlorides and bromides where oxidative addition is rate determining. Seminal contributions to these multifactorial processes have also been made by van Leeuwen's and Hartwig's groups[19a,23] and by Amatore and Jutand.[24] TONs with these palladacycles would appear even more impressive if based on the actual amount of Pd present in the catalytic cycle itself. The function of the substitutents in (**2a–j**) can be interpreted as perturbing the sp^3 C–Pd covalent bond and the N–Pd dative bond and in so doing controlling the rate of release of Pd nanoparticles into solution. In the most active catalyst (**2i**) the substitutent effects conspire to weaken both bonds by a combination of mesomeric [C(5)–OMe] and inductive effects [C(2)–CF_3] (Scheme 4, **2i**, arrows). The reductive elimination implied by (**2i**, arrows) could also proceed via bridge splitting and intramolecular acetate transfer or an SN2 process (Scheme 5). This is considered infinitely more probable than an alternative olefin insertion in the C–Pd bond as the initiation step followed by β-hydride elimination, resulting in palladium nanoparticles, which has also been proposed.[25]



Scheme 5.

Next, we briefly studied the effects of base in the Heck reactions employing palladacycle (**2d**) and (**2f**) precatalysts. These results are summarised in Table 2. Sodium acetate was the least effective of the bases evaluated (Table 2, entries 1 and 6), closely followed by potassium carbonate. Potassium acetate and cesium acetate were the best of those studied (Table 2, entries 3, 4 and 7). The nature of the inorganic base has a clear effect on TON/conversion (Tables 1 and 2). This is ascribed to involvement of the base in formation of the catalytically active Pd(0) species as well documented by the work of Amatore and Jutand[24] and as noted in Scheme 5. Caution is necessary in applying these conclusions more widely since it is likely the base order is palladacycle dependent. The effect of inorganic bases in Heck reaction is an area that is still imperfectly understood. It is clear both anion and cation play a role and this suggests that anionic palladium complexes,[24] incorporating the base anion, associated with the base cation, play a significant role in the catalysis. Recently Beletskaya et al. briefly reported the catalytic activity of **2a**[26] in the Heck reaction. We briefly explored the Heck reaction of bromo and chlorobenzene with (**2a**) and (**2e**) and *n*-butyl acrylate in DMA at 140 °C (Table 3).

Table 2. Effect of base on the Heck reaction of iodobenzene with *n*-butyl acrylate (2 equiv) using catalysts **2d** and **2f**

Entry	Catalyst[a]	Time (h)	Base (2 equiv)	Conversion (%)[b]
1	**2d**	48	NaOAc	24
2	**2d**	48	K_2CO_3	35
3	**2d**	48	KOAc	99
4	**2d**	48	CsOAc	97
5	**2f**	24	K_2CO_3	10[c]
6	**2f**	61	NaOAc	8[c]
7	**2f**	20	KOAc	100[c]

[a] 0.001 mol% catalyst.
[b] Conversion by NMR.
[c] GC conversion.

Thus, 4-bromoacetophenone with catalyst **2e** afforded TON's of up to a million (Table 3, entry 5).In the absence of any additives, rates of the reaction, when bromobenzene was the substrate were poor (Table 3, entry 10). However, the addition of 2 mol equiv of tetrabutylammonium bromide increased the TON's to reasonable values (Table 3, entry 13). The role of halide ions in stablising Pd(0) species has been extensively studied and documented by Amatore and Jutand,[25] Reetz et al.[27] and others.[19] In the case of dimeric palladacycles the role of the soluble Bu_4NBr in bridge splitting to furnish monomeric species and in participating in processes analogus to those in Scheme 5 also needs to be considered. Again the effect is on catalyst metering and or structure with the results (Table 3) indicating the Pd(0) species is now able to process bromobenzene (oxidative—addition not rate determining) whilst oxidative addition of ArCl (Table 3, entry 14) remains rate determining.

Finally we explored a three component cascade involving aryl halides, allenes and secondary amines in the presence of K_2CO_3 as a base in DMF (Scheme 6) using precatalysts (**2d**), (**2e**) and (**2i**). All three precatalysts functioned efficiently at 80 °C at the 1 mol% level (Table 4, entries 1–7) affording the 2-arylallylamines (**4a–c**) in 76–90% yield over 24 h. When the precatalyst loading was reduced to 0.25 mol% of (**2i**) the process was less efficient at 80 °C (Table 4, entry 9) but on raising the temperature to 120 °C

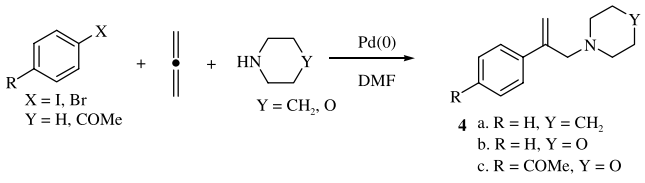
Table 3. Palladacycles in Heck reactions with aryl bromides[a]

Entry	Catalyst (mol%)	Aryl halide	Additive	Conversion (%)[b]	TON
1	**2a** (0.01)	4-Bromoacetophenone	—	100	1,000
2	**2a** (0.001)	4-Bromoacetophenone	—	88	88,000
3	**2e** (0.01)	4-Bromoacetophenone	—	100	10,000
4	**2e** (0.001)	4-Bromoacetophenone	—	100	10,0000
5	**2e** (0.0001)	4-Bromoacetophenone	—	100	1,000,000
6	**2e** (0.00001)	4-Bromoacetophenone	—	44	4,400,000
7	**2a** (0.1)	Bromobenzene	—	10	100
8	**2a** (0.1)	Bromobenzene	Bu_4NBr	100	1,000
9	**2a** (0.01)	Bromobenzene	Bu_4NBr	40	4,000
10	**2e** (0.1)	Bromobenzene	—	47	470
11	**2e** (0.1)	Bromobenzene	Bu_4NBr	100	1,000
12	**2e** (0.01)	Bromobenzene	Bu_4NBr	100	10,000
13	**2e** (0.0001)	Bromobenzene	Bu_4NBr	96	960,000
14	**2e** (1)	4-Chloroacetophenone	Bu_4NBr	0	0

[a] Reactions carried out in DMA for 48 h at 140 °C employing aryl halide (1 mmol), *n*-butyl acrylate (2 mmol), Bu_4NBr (2 mmol) and CsOAc (2 mmol).
[b] Conversion measured by GLC.

the precatalyst performed as well as the 1 mol% loading at 80 °C (Table 4, entries 8, 10 and 11). This trend accords with the temperature controlled breakdown of (**2i**) metering the release of the catalytically active Pd nanoparticles.

In summary we have developed a range of non-phosphine 8-methyl quinoline based dimeric palladacycles, possessing an sp^3 C–Pd bond, which are efficient precatalysts for both Heck reactions and a 3-component cascade process. The palladacycles function via a temperature controlled breakdown of the precatalysts (**2a**–**j**) to Pd nanoparticles, which are metered into the reaction mixture. The precatalyst → active catalyst breakdown/metering mechanism is sensitive to substitution on the quinoline ring. Substituents that facilitate sp^3 C–Pd σ-bond and N–Pd dative bond cleavage deliver Pd nanoparticles more rapidly and this process is strongly influenced by metal acetate and Bu_4NBr additives. The hitherto neglected area of sp^3 C–Pd palladacycles[28] will, we believe, find many more applications in the future.



Scheme 6.

2. Experimental

2.1. General

Melting points were determined using a Reichert apparatus and are uncorrected. Mass spectral data was obtained from a VG Autospec mass spectrometer operating at 70 cV at the National MS Service, Swansea. Nuclear magnetic resonance spectra were recorded on Bruker 250, 300, 400 and 500 MHz machines. Unless otherwise specified deutereochloroform was used as solvent with tetramethylsilane as internal standard. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. Thin-layer chromatography was carried out on Whatmann PGSILG/UV polyster plate coated with a 0.2 mm layer of silica gel 60 (Merck 9385). Petroleum ether refers to the fraction with bp 40–60 °C. anhydrous DMF and DMA were commercially available (Aldrich). PVP (M_w 30,000) was purchased from Aldrich and used as received. Conversions measured by GLC. (GC-FID was performed on a GC equipped with 12QC31 BP5 column 0.5 μm diameter, using the following program. Flow rates, He = 20 mL/min, starting temperature 70 °C rising by 20 °C/min to 170 °C then 1 °C/min. Retention time = 13 min).

2.1.1. 8-Methyl-5-nitroquinoline (1a).[12] Concentrated sulfuric acid (4.7 mL) was added dropwise over 10 min to 8-methylquinoline (3 mL, 21.60 mmol) at 0 °C. A mixture

Table 4. Three component cascade involving aryl iodide or bromide, allene and a secondary amine in the presence of (**2d**, **2e**, **2i**)[a]

Entry	Catalyst (mol%)	Temperature (°C)	Aryl halide	Product	Yield (%)[b]
1	**2d** (1.0)	80	Iodobenzene	**3a**	89
2	**2d** (1.0)	80	Iodobenzene	**3b**	94
3	**2d** (1.0)	80	4-Bromoacetophenone	**3c**	85
4	**2e** (1.0)	80	Iodobenzene	**3a**	79
5	**2e** (1.0)	80	Iodobenzene	**3b**	82
6	**2e** (1.0)	80	4-Bromoacetophenone	**3c**	76
7	**2i** (1.0)	80	Iodobenzene	**3a**	90
8	**2i** (0.25)	120	Iodobenzene	**3a**	90
9	**2i** (0.25)	80	Iodobenzene	**3b**	55
10	**2i** (0.25)	120	Iodobenzene	**3b**	80
11	**2i** (0.25)	120	4-Bromoacetophenone	**3c**	73

[a] Reactions carried out in DMF for 24 h at 80 or 120 °C employing aryl halide (1 mmol), amine (1.2 mol equiv), allene (1 atm) and K_2CO_3 (2 mol equiv).
[b] Isolated yield.

of concentrated nitric acid (2.7 mL) and concentrated sulfuric acid (2.3 mL) was then added dropwise over 20 min. The reaction mixture was stirred for 2 days at 0 °C then poured onto ice and neutralised using sodium hydroxide solution. The product was extracted into ether (×3), the combined organic extracts washed with brine, dried ($MgSO_4$), filtered and the filtrate concentrated to give the product (3.62 g, 89%) as pale yellow prisms, mp 94–95 °C (lit. 93–93.5 °C). δ_H (300 MHz): 2.91 (3H, s, Me), 7.65 (2H, m, ArH), 8.33 (1H, d, J=7.9 Hz, ArH), 9.06 (2H, m, ArH), m/z (%) (EI): 188 (M^+, 100), 158 (39), 142 (62), 115 (18).

2.1.2. 5-Amino-8-methylquinoline.[12] Concentrated hydrochloric acid (35 mL) was added dropwise over 20 min to 8-methyl-5-nitroquinoline (3.0 g, 15.94 mmol) at 0 °C. Tin (II) chloride (6.04 g, 31.88 mmol) was then added and the reaction mixture was allowed to reach room temperature and stirred for 48 h then neutralised by careful addition of sodium hydroxide solution. The product was extracted into ether (×3) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the filtrate concentrated to give the product (1.99 g, 79%) as yellow prisms, mp 144–145 °C (lit. 143–143.5 °C). δ_H (300 MHz): 2.91 (3H, s, Me), 7.66 (2H, m, ArH), 8.32 (1H, d, J=7.9 Hz, ArH), 9.06 (2H, m, ArH), m/z (%) (EI): 158 (M^+, 65), 142 (100), 115 (33), 89 (15), 63 (22).

2.1.3. 5-Fluoro-8-methylquinoline (1b).[12] 5-Amino-8-methylquinoline (2.60 g, 16.43 mmol) was dissolved in fluoroboric acid (50 mL) and cooled to 0 °C. Sodium nitrite (1.19 g, 17.26 mmol) in water (10 mL) was added and the mixture stirred at 0 °C for 30 min. The resulting colourless precipitate was filtered off and thoroughly dried in a desiccator for 16 h. The dried tetrafluoroborate salt was suspended in toluene (20 mL), heated to reflux for 32 h, and quenched with 10% hydrochloric acid solution. The layers were separated, the aqueous layer basified to pH 9–10 with 2 M sodium hydroxide solution and the mixture extracted with ether (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the filtrate concentrated. The residual brown oil was purified by flash column chromatography, eluting with 2:3v/v ether–petroleum ether to give the product (1.27 g, 48% yield) as a colourless oil. δ_H (300 MHz): 2.76 (3H, s, Me), 7.12 (1H, t, J=8.0 Hz, ArH), 7.47 (2H, m, ArH), 8.42 (1H, d, J=8.4 Hz, ArH), 8.99 (1H, m, ArH), m/z (%) (EI): 161 (M^+, 100), 143 (16), 133 (13), 71 (17).

2.1.4. 5-Bromo-8-methylquinoline (1c).[13] Bromine (0.76 mL, 14.69 mmol) was added dropwise over 15 min to a solution of 8-methylquinoline (2.0 mL, 14.69 mmol) and silver sulphate (2.29 g, 7.35 mmol) in concentrated sulphuric acid (15 mL). The reaction mixture was stirred for 30 min at room temperature then poured into water and basified using sodium hydroxide solution. The mixture was extracted with ether (×3) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated to give the product (2.80 g, 86% yield) as pale fawn prisms, mp 38–39 °C (lit. 37–38 °C). δ_H (300 MHz): 2.76 (3H, s, Me), 7.41 (1H, d, J=7.6 Hz, ArH), 7.50 (1H, m, ArH), 7.70 (1H, d, J=7.6 Hz, ArH), 8.52 (1H, d, J=8.5 Hz, ArH), 8.95 (1H, d, J=4.2 Hz, ArH), m/z (%) (EI): 222 (M^+, 97), 142 (100), 115 (25), 70 (30), 63 (20).

2.1.5. 8-Methyl-5-(trifluoromethyl)quinoline (1d).[13] 5-Bromo-8-methylquinoline (2.50 g, 11.26 mmol), sodium trifluoroacetate (6.74 g, 49.53 mmol) and cuprous iodide (4.76 g, 24.99 mmol) were combined in *N*-methylpyrrolidone (80 mL) and heated to 160 °C for 5 days. After cooling the reaction mixture was poured into water and extracted with ether (×3). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the filtrate concentrated. The residual brown oil was purified by flash column chromatography, eluting with 10% ether in petroleum ether to give the product (1.40 g, 59% yield) as a pale yellow oil. Found: C, 62.55; H, 4.10; N, 6.70; $C_{11}H_8F_3N$ requires C, 62.55; H, 3.85; N, 6.65%, δ_H (300 MHz): 2.86 (3H, s, Me), 7.55 (1H, m, ArH), 7.60 (1H, d, J=7.5 Hz, ArH), 7.81 (1H, d, J=7.5 Hz, ArH), 8.49 (1H, d, J=8.7 Hz, ArH), 9.02 (1H, m, ArH), m/z (%) (EI): 211 (M^+, 100), 142 (26), ν_{max}/cm^{-1} (film): 1118.8 (s, C–F), 1321.4 (s, C–F), 1506.6 (m, aromatic ring).

2.1.6. 5-Methoxy-8-methylquinoline (1e).[14] A mixture of 5-bromo-8-methylquinoline (1.00 g, 4.50 mmol), sodium methoxide (2.43 g, 45.03 mmol), DMF (6 mL) and methanol (15 mL) was stirred and heated at 90 °C under nitrogen. Cuprous bromide (0.32 g, 2.25 mmol) was added and the reaction mixture was maintained at 90 °C for 16 h, poured into water and extracted with ether (×3). The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and the filtrate concentrated. The residual brown oil was purified by flash column chromatography, eluting with 10% ether in petroleum ether to give the product (762 mg, 98% yield) as a pale yellow oil. Found: C, 75.40; H, 6.50; N, 8.05; $C_{11}H_{11}NO$ requires C, 76.30; H, 6.40; N, 8.10%, δ_H (300 MHz): 2.71 (3H, s, Me), 3.91 (3H, s, OMe), 6.68 (1H, d, J=7.8 Hz, ArH), 7.33 (1H, m, ArH), 7.39 (1H, d, J=7.8 Hz, ArH), 8.53 (1H, d, J=8.4 Hz, ArH), 8.92 (1H, m, ArH), m/z (%) (EI): 173 (M^+, 51), 158 (100), 130 (19), 77 (17), ν_{max}/cm^{-1} (film): 1091.8 (s, C–O), 1402.4 and 1475.7 (m, C–H deformations), 1593.4 (s, aromatic ring), 2848 (m, OMe).

2.2. General procedure for anilide synthesis[15]

Anilides were synthesised by the literature procedure. A mixture of the appropriately substituted aniline (1.0 equiv) and the dicarbonyl compound (1.1 equiv) was heated in an oil bath under reflux for 4 h. After cooling to room temperature, water (100 mL) was added and the mixture extracted with DCM (3×100 mL). The DCM layer was dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residual solid was crystallised from petroleum ether.

2.3. General procedure for quinoline synthesis from anilides[15]

Anilide (10.0 mmol) was added to 98% sulfuric acid (20 mL) and the mixture stirred for 4 h at room temperature. The reaction mixture was then carefully poured into ice-water (200 mL) with swirling. NaOH pellets were then added carefully until the mixture was strongly basic

(pH 10–12). The mixture was extracted with DCM (3× 100 mL), the combined organic layer dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The solid residue was purified by crystallisation from an appropriate solvent.

2.3.1. 2,4,5,8-Tetramethyquinoline (1f). Synthesised by the general procedure from 2,5-dimethyl aniline (12.1 g, 100 mmol, 1.0 equiv) and 2,4-pentanedione (11.3 mL, 110 mmol, 1.1 equiv) over 5 h at 130 °C. The crude anilide was reacted according to the general procedure to give the product (11.0 g, 59.5%), which crystallised from petroleum ether as colourless plates, mp 36–38 °C. Found: C, 84.50; H, 8.20; N, 7.50; $C_{13}H_{15}N$ requires C, 84.30; H, 8.10; N, 7.60%. δ_H (250 MHz, $CDCl_3$) 2.65, 2.70, 2.80. 2.81 (4×3H, 4×s, 4×Me), 7.0 (1H, s, ArH), 7.1 (1H, d, J=7.2 Hz, ArH), 7.3 (1H, d, J=7.2 Hz, ArH), *m/z* (FAB): 186 (100%, M^++H), 172 (53), 158 (20), 141 (10), 128 (25) and 115 (16). ν_{max}/cm^{-1} (solid) 2962, 2918, 2840, 1864, 1721, 1602, 1572, 1460, 1438, 1383, 1366, 1328, 1144, 1041, 862, 818, 696 and 618.

2.3.2. 7-Fluoro-2,4,8-trimethyquinoline (1g). The anilide was synthesised by the general procedure from 3-fluoro-2-methyl aniline (3.13 g, 25.0 mmol, 1.0 equiv) and 2,4-pentanedione (2.83 mL, 27.4 mmol, 1.1 equiv) over 5 h at 130 °C. The crude anilide was reacted according to the general procedure to give the product (2.0 g, 98%), which crystallised from petroleum ether as colourless needles, mp 26–28 °C. Found: C, 76.10; H, 6.45; N, 7.30; $C_{12}H_{12}FN$ requires C, 76.20; H, 6.35; N, 7.40%. δ_H (250 MHz, $CDCl_3$) 2.6, 2.65, 2.70 (3×3H, 3×s, 3×Me), 7.1 (1H, s, ArH), 7.2 (1H, t, J=9.0 Hz, ArH) (J H–H≈J H–^{19}F), 7.8 (1H, dd, J= 9.0, 6.1 Hz, ArH), *m/z* (FAB): 190 (100%, M^++H), 174 (14), 146 (10), 97 (8) and 83 (16). ν_{max}/cm^{-1} (solid) 2956, 2923, 1605, 1510, 1439, 1378, 1338, 1317, 1229, 1210, 1155, 1080, 1036, 963, 936, 874, 816 and 781.

2.3.3. 2,4,7,8-Tetramethyquinoline (1h). The anilide was synthesised by the general procedure from 2,3-dimethyl aniline (30 mL, 247.0 mmol, 1.0 equiv) and 2,4-pentanedione (28 mL, 274.0 mmol, 1.1 equiv) over 4 h at 155 °C. Crystallisation from petroleum ether afforded the product (20.0 g, 79%) as colourless plates, mp 90–92 °C (lit.[15] 83–84 °C).

Anilide (2.0 g, 9.85 mmol) was converted to the quinoline **1h** by the general procedure to give the product (1.8 g, 98%) as colourless needles, mp 26–28 °C (lit.[15] 30–31 °C).

2.3.4. 5-Methoxy-4,8-dimethyl-2-(trifluoromethyl)quinoline (1i). The anilide was synthesised by the general procedure from 5-methoxy-2-methyl aniline (0.62 g, 5.0 mmol, 1.0 equiv) and 1,1,1-trifluoro-2,4-pentanedione (0.73 mL, 6.0 mmol, 1.1 equiv) over 5 h at 130 °C. Crystallisation from petroleum ether gave the product (0.92 g, 70%) as colourless plates, mp 53–55 °C. Found: C, 57.10; H, 5.20; N, 5.00; $C_{13}H_{14}F_3NO_2$ requires C, 57.10; H, 5.10; N, 5.10%. δ_H (250 MHz, $CDCl_3$) 2.0, 2.2 (2×3H, 2×s, 2×Me), 3.8 (3H, s, OMe), 5.55 (1H, s, =CH), 6.65 (1H, d, J= 2.6 Hz, ArH), 6.8 (1H, dd, J=8.4, 2.6 Hz, ArH), 7.2 (1H, d, J=8.4 Hz, ArH), *m/z* (FAB): 274 (100%, M^++H), 204 (16), 174 (7) and 162 (12). ν_{max}/cm^{-1} (solid) 3192, 3126, 3006, 2980, 2844, 2501, 2084, 1888, 1720 (CO), 1593, 1495, 1459, 1391, 1366, 1275, 1260, 1112, 1044, 1011, 975, 857, 812, 766, 748, 727, 704, 653, 584, 567, 553, 512 and 466.

The anilide (0.50 g, 1.83 mmol) was reacted according to the general procedure to give the product (**1i**) (0.38 g, 82%), which crystallised from petroleum ether as colourless needles, mp 76–78 °C. Found: C, 61.00; H, 4.80; N, 5.20; $C_{13}H_{12}F_3NO$ requires C, 61.20; H, 4.70; N, 5.50%. δ_H (250 MHz, $CDCl_3$) 2.7, 2.8 (2×3H, 2×s, 2×Me), 3.95 (3H, s, OMe), 6.9 (1H, d, J=8.0 Hz, ArH), 7.5 (1H, d, J= 8.0 Hz, ArH), 7.65 (1H, s, ArH), *m/z* (FAB): 255 (100%, M^+). ν_{max}/cm^{-1} (solid) 2978, 2923, 2851, 1607, 1581, 1513, 1471, 1388, 1343, 1257, 1155, 1140, 1099, 959, 879, 823 and 803.

2.4. General procedure for the synthesis of 8-methylquinoline palladacycles[16]

The quinoline (**1a**–**j**) (2.50 mmol) was added to a solution of palladium acetate (0.51 g, 2.27 mmol) in acetic acid (12 mL) and the reaction mixture was heated to 100 °C for 2 h. Once cooled to room temperature DCM (10 mL) and then water (10 mL) were added. The layers were separated and two more portions of DCM were used to extract the product. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered and the filtrate concentrated. The residue was crystallised from DCM/petroleum ether to give the product.

2.4.1. Di(μ-aceto)bis[8-methylquinoline]dipalladium (2a). 8-Methylquinoline (0.34 mL) was reacted by the general procedure. The product (1.11 g, 72% yield) was obtained as orange prisms as a 4:1 mixture of trans and cis-isomers. mp >200 °C. Found: C, 47.20; H, 3.80, N, 4.30; $C_{24}H_{22}N_2O_4Pd_2$ requires C, 46.90; H, 3.60; N, 4.60%, δ_H (250 MHz): 2.11 (6H, s, Me), 2.52 (2H, d, J=13.8 Hz, CH_2), 3.43 (2H, d, J=13.8 Hz, CH_2), 6.69 (2H, dd, J=1.1, 7.1 Hz, ArH), 6.88 (2H, t, J=7.2 Hz, ArH), 6.97–7.03 (2H, m, ArH), 7.21–7.22 (2H, m, ArH), 7.85 (2H, dd, J=1.4, 8.3 Hz, ArH), 8.51 (2H, dd, J=1.4, 5.0 Hz, ArH), *m/z* (%) (FAB): 616 (M^+, 23), 557 (37), 458 (19), 414 (69), 389 (41), 354 (49), 248 (100), 142 (73), ν_{max}/cm^{-1} (GG): 1412.1 (m, C=N), 1504.7 (s, aromatic ring), 1568.3 (s, aromatic ring).

2.4.2. Di(μ-aceto)bis[5-nitro-8-methylquinoline]dipalladium (2b). 5-Nitro-8-methylquinoline (0.47 g) was reacted by the general procedure. The product (1.20 g, 68% yield) was obtained as black prisms as a 2.3:1 mixture of trans and cis-isomers. mp >200 °C. Found: C, 41.70; H, 2.85; N, 8.20; $C_{24}H_{20}N_4O_8Pd_2$ requires: C, 41.85; H, 2.85; N, 7.95%, δ_H (300 MHz): 2.15 (6H, s, Me), 2.36 (2H, d, J=15.0 Hz, CH_2), 3.56 (2H, d, J=15.0 Hz, CH_2), 6.75 (2H, d, J= 8.0 Hz, ArH), 7.60 (2H, dd, J=5.0, 8.8 Hz, ArH), 7.85 (2H, d, J=8.0 Hz, ArH), 8.71 (2H, dd, J=1.3, 5.0 Hz, ArH), 8.97 (2H, dd, J=1.3, 8.8 Hz, ArH), *m/z* (%) (FAB): 706 (M^++H, 18), 647 (23), 295 (27), 189 (52), 149 (100), ν_{max}/cm^{-1} (GG): 1336.8 (s, CNO_2), 1414.0 (s, C=N), 1502.7 (s, CN=O), 1505.8 (m, aromatic ring), 1568.3 (s, CNO_2), 1570.4 (s, aromatic ring).

2.4.3. Di(μ-aceto)bis[5-fluoro-8-methylquinoline]dipalladium (2c). 5-Fluoro-8-methylquinoline (0.40 g) was reacted by the general procedure. The product (1.16 g, 71% yield) was obtained as orange prisms as a 4:1 mixture of trans and cis-isomers. mp >200 °C. Found: C, 44.05; H, 3.40; N, 4.15; $C_{24}H_{20}F_2N_2O_4Pd_2$ requires: C, 44.25; H, 3.10; N, 4.30%, δ_H (300 MHz): 2.13 (6H, s, Me), 2.44 (2H, d, J=14.8 Hz, CH_2), 3.48 (2H, d, J=14.8 Hz, CH_2), 6.61–6.80 (4H, m, ArH), 7.34 (2H, dd, J=5.1, 8.6 Hz, ArH), 8.13 (2H, dd, J=1.2, 5.1 Hz, ArH), 9.06 (2H, d, J=8.6 Hz, ArH), *m/z* (%) (FAB): 651 (M^+, 8), 591 (10), 391 (100), 326 (37), 279 (27), 266 (50), ν_{max}/cm^{-1} (GG): 1140.1 (m, C–F), 1408.2 (m, C=N), 1475.7 (w, aromatic ring), 1570.2 (m, aromatic ring).

2.4.4. Di(μ-aceto)bis[5-trifluoromethyl-8-methylquinoline]dipalladium (2d). 5-Trifluoromethyl-8-methylquinoline (0.53 g) was reacted by the general procedure. The product (1.41 g, 75% yield) was obtained as red prisms as a 2.3:1 mixture of trans and cis-isomers. mp >200 °C. Found: C, 41.45; H, 2.75; N, 3.55, $C_{26}H_{20}F_6N_2O_4Pd_2$ requires: C, 41.55; H, 2.70; N, 3.75%, δ_H (300 MHz): 2.15 (6H, s, Me), 2.36 (2H, d, J=14.6 Hz, CH_2), 3.48 (2H, d, J=14.6 Hz, CH_2), 6.67 (2H, d, J=7.6 Hz, ArH), 7.26–7.27 (2H, m, ArH), 7.48 (2H, dd, J=5.0, 8.7 Hz, ArH), 8.28 (2H, d, J=8.7 Hz, ArH), 8.67 (2H, dd, J=1.3, 5.0 Hz), *m/z* (%) (FAB): 752 (M^++H, 13), 693 (19), 524 (24), 421 (27), 391 (23), 315 (100), 210 (29), 149 (29), ν_{max}/cm^{-1} (GG): 781.3 (m, C–F), 884.9 (m, aromatic ring), 1317.5 (s, C–F), 1414.0 (m, C=N), 1510.4 (m, aromatic ring), 1570.2 (s, aromatic ring).

2.4.5. Di(μ-aceto)bis[5-methoxy-8-methylquinoline]dipalladium (2e). 5-Methoxy-8-methylquinoline (0.43 g) was reacted by the general procedure. The product (1.25 g, 74% yield) was obtained as orange prisms as a 9:1 mixture of trans and cis-isomers. mp >200 °C. Found: C, 46.05; H, 4.10; N, 3.90; $C_{26}H_{26}N_2O_6Pd_2$ requires C, 46.20; H, 3.90; N, 4.10%, δ_H (300 MHz): 2.13 (6H, s, Me), 2.47 (2H, d, J=12.4 Hz, CH_2), 3.35 (2H, d, J=12.4 Hz, CH_2), 3.85 (6H, s, OMe), 6.28 (2H, d, J=7.9 Hz, ArH), 6.57 (2H, d, J=7.9 Hz, ArH), 7.17 (2H, dd, J=5.0, 8.4 Hz, ArH), 8.17 (2H, dd, J=1.4, 8.4 Hz, ArH), 8.53 (2H, dd, J=1.4, 5.0 Hz, ArH), *m/z* (%) (FAB): 675 (M^+, 9), 616 (15), 448 (24), 278 (37), 172 (100), 149 (47), ν_{max}/cm^{-1} (GG): 771.6 (m, aromatic ring), 806.3 (aromatic ring), 1479.6 (m, C=N), 1574.1 (s, aromatic ring), 1614.6 (m, aromatic ring), 2841.6 (w, O–Me).

2.4.6. Di(μ-acetato)-bis[(2,4,5,8-tetramethylquinoline)]dipalladium (2f). 2,4,5,8-Tetramethylquinoline (0.93 g, 5.0 mmol) was reacted by the general procedure. The product (1.1 g, 68%) was obtained as a yellow amorphous solid, mp 160 °C (dec.), which comprised a ca. 6:1 mixture of trans and cis-isomers. Found: C, 51.70; H, 5.05; N, 3.70; $C_{30}H_{34}N_2O_4Pd_2$ requires C, 51.60; H, 4.90; N, 4.00%. δ_H (300 MHz, $CDCl_3$) 1.92* (6H, s, 2Me), 2.01 (6H, s, 2Me), 2.08*, 2.1*, 2.3* (3×6H, 3×s, 3×2Me), 2.6, 2.65, 2.67 (3×6H, 3×s, 3×2Me), 2.8 (2H, d, J=13.5 Hz, CH_2), 3.26* (2H, d, J=12.1 Hz, CH_2), 3.53 (2H, d, J=13.5 Hz, CH_2), 3.7* (2H, d, J=12.1 Hz, CH_2), 6.5–6.6 (4H, br, ArH), 6.75* (2H, s, ArH), 6.8 (2H, s, ArH, *indicates minor isomer. *m/z* (FAB): 704–694 (M^+, Pd isotope cluster, 700, 10%), 643 (7), 473 (15), 395 (20), 292 (65), 184 (100), 123 (65) and 105 (73). ν_{max}/cm^{-1} (solid) 3055, 2978, 2933, 2888, 1694, 1575, 1417, 1276, 1261, 1032, 851, 824, 763, 750 and 726.

2.4.7. Di(μ-acetato)-bis[(7-fluoro-2,4,8-trimethylquinoline)]dipalladium (2g). 7-Fluoro-2,4,8-trimethylquinoline (0.75 g, 4.0 mmol) was reacted by the general procedure. The product (0.40 g, 60%) was obtained as a yellow amorphous solid, mp 165 °C (dec.), which comprised a ca. 7: 1 mixture of trans and cis-isomers. Found: C, 47.90; H, 4.05; N, 3.70; $C_{28}H_{28}N_2O_4F_2Pd_2$ requires C, 47.60; H, 4.00; N, 4.00%. δ_H (300 MHz, $CDCl_3$) 2.0, 2.4 (2×6H, 2×s, 2×2Me), 2.65 (2H, d, J=13.8 Hz, CH_2), 2.7 (6H, s, 2Me), 2.9* (2H, d, J=13.3 Hz, CH_2), 3.2 (2H, d, J=13.8 Hz, CH_2) 3.5* (2H, d, J=13.3 Hz, CH_2), 6.6 (2H, t, J=8.7 Hz, ArH^c) (J H^c–$H^b \approx J$ H^c–^{19}F), 6.7* (2H, t, J=8.7 Hz, ArH^c) (J H^c–$H^b \approx J$ H^c–^{19}F), 6.9 (2H, s, ArH^a), 6.95* (2H, s, ArH^a), 7.1 (2H, dd, J=8.7, 5.1 Hz, ArH^b, H^b couples with H^c and F), 7.15* (2H, dd, J=8.70, 5.1 Hz, ArH^b, H^b couples with H^c and F). *Indicates minor isomer. *m/z* (FAB): 712–702 (M^+, Pd isotope cluster, 707, 10%), 648 (15), 413 (28), 391 (40), 294 (41), 188 (35), 167 (25), 149 (100), 132 (52) and 113 (25). ν_{max}/cm^{-1} (solid) 2988, 2918, 2883, 1718, 1583, 1514, 1407, 1275, 1261, 1099, 1043, 863, 812, 764 and 750.

2.4.8. Di(μ-acetato)-bis[(2,4,7,8-tetramethylquinoline)]dipalladium (2h). 2,4,7,8-Tetramethylquinoline (0.93 g, 5.0 mmol) was reacted by the general procedure. The product (1.1 g, 68%) was obtained as a yellow amorphous solid, mp 147 °C (dec.), which comprised a ca. 6.5:1 mixture of trans and cis-isomers. Found: C, 51.70; H, 4.85; N, 4.00; $C_{30}H_{34}N_2O_4Pd_2$ requires C, 51.60; H, 4.90; N, 4.00%. δ_H (300 MHz, $CDCl_3$) 1.95* (6H, s, 2Me), 2.0, 2.05 (2×6H, 2×s, 2×2Me), 2.1*, 2.15* (2×6H, 2×s, 2×2Me), 2.35 (6H, s, 2Me), 2.4* (6H, s, 2Me), 2.7 (6H, s, 2Me), 2.8 (2H, d, J=13.3 Hz, CH_2), 3.25* (2H, d, J=12.8 Hz, CH_2), 3.35 (2H, d, J=13.3 Hz, CH_2), 3.6* (2H, d, J=12.8 Hz, CH_2), 6.5* (2H, s, ArH), 6.7 (2H, d, J=8.7 Hz, ArH), 6.75 (2H, s, ArH), 6.95 (2H, d, J=8.7 Hz, ArH), 7.0* (2H, d, J=8.2 Hz, ArH), *indicates minor isomer. *m/z* (FAB): 704–694 (M^+, Pd isotope cluster, 700, 10%), 641 (25), 557 (22), 395 (16), 292 (67), 184 (100) and 115 (12). ν_{max}/cm^{-1} (solid) 3051, 2973, 2925, 2855, 1704, 1583, 1519, 1411, 1344, 1175, 1066, 1027, 856, 779 and 720.

2.4.9. Di(μ-acetato)-bis[(5-methoxy-2-trifluoromethyl-4,8-dimethyl quinoline)]dipalladium (2i). 5-Methoxy-4,8-dimethyl-2-(trifluoromethyl)quinoline (0.25 g, 1.0 mmol) was reacted by the general procedure. The product (0.42 g, 50%) was obtained as a orange amorphous solid, mp 157 °C (dec.), which comprised a ca. 12:1 mixture of trans and cis-isomers. Found: C, 42.60; H, 3.45; N, 3.10; $C_{30}H_{28}N_2O_6F_6Pd_2$ requires C, 42.90; H, 3.35; N, 3.30%. δ_H (300 MHz, $CDCl_3$) 2.0 (6H, s, 2Me), 2.1* (6H, s, 2Me), 2.73 (2H, d, J=12.5 Hz, CH_2), 2.85 (6H, s, 2OAc), 2.9* (6H, s, 2OAc), 3.33* (2H, d, J=12.5 Hz, CH_2), 3.47 (2H, d, J=12.5 Hz, CH_2) 3.73* (2H, d, J=12.5 Hz, CH_2), 3.79* (6H, s, 2OMe), 3.82 (6H, s, 2OMe), 6.38 (2H, d, J=8.1 Hz, ArH), 6.63 (2H, d, J=8.1 Hz, ArH), 6.98* (2H, d, J=8.5 Hz, ArH), 7.15* (2H, d, J=8.5 Hz, ArH), 7.42 (2H, s, ArH), 7.62* (2H, s, ArH), *indicates minor isomer. *m/z* (FAB): 844–832 (M^+, Pd isotope cluster, 839, 7%), 780 (13), 610 (8), 525 (14), 465 (17), 359 (35) and 254 (100).

ν_{max}/cm^{-1} (solid) 2951, 2887, 2849, 1708, 1675, 1612, 1575, 1515, 1472, 1403, 1342, 1327, 1166, 1141, 1087, 975, 948, 828, 751 and 685.

2.4.10. General procedure for the Heck reaction. Palladacycle (**2a–j**) was added to a stirred solution of iodobenzene or 4-bromoacetophenone (1.0 mmol), *n*-butylacrylate (2.0 mol equiv) or benzyl acrylate (2.0 mol equiv) and metal acetate (2.0 mol equiv) or potassium carbonate (2.0 mol equiv) in DMF (GPR grade 10 mL). The reaction mixture was heated at 140 °C (oil bath) for 16–96 h (see Table 1). After cooling to room temperature water (10 mL) was added and the mixture extracted with ether (2×20 mL). The combined organic layer was washed with water (2× 20 mL), dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure to give the crude product as a light yellow oil. The conversion was determined by ^{1}H NMR spectroscopy comparing the ratio of the integrals of iodobenzene (7.1 ppm, 2H, t, J=7.5 Hz, ArH) or 4-bromoacetophenone (2.6 ppm, 3H, s, MeC=O) and that of butyl (2*E*)-3-phenylacrylate (4.21 ppm, t, 2H, J=6.6 Hz, OCH_2; 6.44 ppm, 1H, d, J=16.0 Hz, PhCH=C*H*; 7.7, 1H, d, J= 16.0 Hz, PhC*H*=CH) or that of butyl (2*E*)-3-(4-acetylphenyl)acrylate (2.62 ppm, s, 3H, MeC=O; 4.22 ppm, t, J=6.6 Hz, 2H, OCH_2; 6.53 ppm, 1H, d, J=16.0 Hz, PhCH=C*H*; 8.0 ppm, 1H, d, J=16.0 Hz, PhC*H*=CH).

2.5. General procedure for termolecular cascade involving arylhalide, allene and *N*-nucleophiles

A mixture of palladacycle (**2d**, **e** or **2i**) (0.25–1.0 mol%), iodobenzene or 4-bromoacetophenone (0.20 g, 1.0 mmol), morpholine or piperidine (1.2 mol equiv) and potassium carbonate (0.27 g, 2.0 mol equiv) in DMF (GPR grade, 10 mL) was stirred for 15 min in a Schlenk tube. The mixture was then degassed, frozen, evacuated and filled with allene gas (1 bar). After warming to room temperature, it was heated at 80–120 °C (Table 4) in an oil bath for 24 h. The reaction mixture was cooled to room temperature, excess allene vented, water (10 mL) added and the mixture extracted with ether (2×20 mL). The combined organic layer was washed with water (2×20 mL), dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.

2.5.1. 1-(2-Phenylprop-2-enyl)piperidine (3a). Synthesised by the general procedure from iodobenzene (0.21 g, 1.0 mmol), piperidine (0.12 mL, 1.2 equiv) and allene (1 bar). Purification by column chromatography eluting with 9:1 v/v petroleum ether–EtOAc gave the product (0.17 g, 92%) (R_f 0.11) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 1.4–1.45 (2H, m, piperidinyl H), 1.5–1.6 (4H, m, piperidinyl H), 2.35–2.4 (4H, m, piperidinyl H), 3.3 (2H, d, J=0.8 Hz, CH_2), 5.25 (1H, d, J=1.5 Hz, C=CH_2), 5.45 (1H, d, J=1.5 Hz, C=CH_2), 7.2–7.45 (3H, m, ArH), 7.5 (2H, dd, J=6.70, 1.60 Hz, ArH), *m/z* (EI) 177 (100%, M^+).

The ^{1}H NMR and mass spectroscopic data of the compound **3a** are in full agreement with those reported in the literature.[29]

2.5.2. 4-(2-Phenylprop-2-enyl)morpholine (3b). Synthesised by the general procedure from iodobenzene (0.21 g, 1.0 mmol), morpholine (0.11 mL, 1.2 equiv) and allene (1 bar). Purification by column chromatography eluting with 4:1 v/v petroleum ether–Et_2O gave the product (0.15 g, 75%) (R_f 0.10) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 2.45–2.5 (4H, m, morpholinyl H), 3.0 (2H, d, J= 0.8 Hz, CH_2), 3.65–3.7 (4H, m, morpholinyl H) 5.25 (1H, d, J=1.4 Hz, C=CH_2), 5.5 (1H, d, J=1.4 Hz, C=CH_2), 7.25–7.35 (3H, m, ArH), 7.55 (2H, dd, J=7.5, 1.0 Hz, ArH), *m/z* (EI) 203 (17%, M^+), 144 (13), 118 (48), 100 (100), 91 (24), 77 (7), 56 (30), and 42 (21).

The ^{1}H NMR and mass spectroscopic data of the compound **3b** are in full agreement with those reported in the literature.[29]

2.5.3. 1-{4-[1-(Morpholin-4-ylmethyl)vinyl]phenyl}ethanone (3c). Synthesised by the general procedure from 4-bromoacetophenone (0.20 g, 1.0 mmol), morpholine (0.11 mL, 1.2 equiv) and allene (1 bar). Purification by column chromatography eluting with 4:1 v/v petroleum ether–Et_2O gave the product (0.18 g, 73%) (R_f 0.08) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 2.45–2.50 (4H, m, morpholinyl H), 2.6 (3H, s, Me), 3.35 (2H, d, J=0.6 Hz, CH_2), 3.65–3.7 (4H, m, morpholinyl H) 5.35 (1H, d, J= 1.1 Hz, C=CH_2), 5.6 (1H, d, J=1.1 Hz, C=CH_2), 7.6 (2H, d, J=8.5 Hz, ArH), 7.9 (2H, d, J=8.5 Hz, ArH), *m/z* (EI) 245 (26%, M^+), 186 (15), 160 (20), 145 (37), 115 (47), 100 (100), and 56 (50).

The ^{1}H NMR and mass spectroscopic data of the compound **3c** are in full agreement with those reported in the literature.[29]

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Efficient palladium catalysts for the amination of aryl chlorides: a comparative study on the use of phosphium salts as precursors to bulky, electron-rich phosphines

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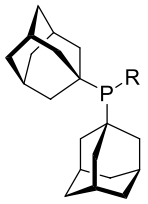
Abstract—Alkyl-di-(1-adamantyl)phosphonium salts are practical ligand precursors for the palladium-catalyzed amination of aryl chlorides. In the presence of typically 0.5 mol% $Pd(OAc)_2$ and 1 mol% of ligand precursor a variety of activated and deactivated aryl chlorides can be aminated in good to excellent yield (73–99%). Applying optimized conditions catalyst turnover numbers up to 10,000 have been achieved.

1. Introduction

The palladium-catalyzed C–N bond formation of aryl halides (Buchwald–Hartwig reaction) is a rapidly developing field of interest due to the importance of anilines and amino-substituted heteroarenes as natural products, drugs, agrochemicals, and fine chemicals.[1] In order to apply such reactions in the fine chemical industry significant cost reduction of a typical lab-scale synthesis is an important requirement. Efforts to substitute costly starting materials such as aryl iodides or triflates by economically more attractive chloro- and bromoarenes, reduction of catalyst concentration, etc. are to be seen in this respect. Despite numerous advances in C–N cross coupling processes,[2] an important factor for industrial applications of palladium-catalyzed amination reactions is the development of more efficient and economically attractive catalysts. Important criteria for such improved catalysts include (1) no special handling of metal complexes and ligands, (2) broad substrate scope, as well as (3) ability to operate under mild reaction conditions and at low catalyst concentration. In this respect there exists still a need for easy-to-use ligands, which lead to highly active catalyst systems, are easily tunable and allow for scale-up.

Herein, we report a novel catalytic system based on phosphonium salts, that meets the above mentioned criteria. Noteworthy are the high catalyst productivity, and the air stability of the ligand precursors, which makes them easy to operate.

Previously we demonstrated, that basic, sterically demanding phosphines with 1-adamantyl substituents[3] (Fig. 1) are suitable ligands for palladium-catalyzed C–C, C–N, and C–O bond forming reactions. Among the various aryl-[4] and alkyl-di-(1-adamantyl)phosphines[5] (cata*CX*ium® A ligands)[6] prepared especially di-(1-adamantyl)-*n*-butylphosphine (**1**) and di-(1-adamantyl)benzylphosphine (**7**) showed good to excellent catalyst performance for different functionalization reactions of aryl chlorides.[7] Very recently, we also reported on the preparation of the respective phosphonium salts via alkylation of di-(1-adamantyl)-phosphine with alkyl or benzyl halides.[8] In this regard it is noteworthy that phosphonium salts of sterically hindered alkylphosphines became interesting as ligand precursors for palladium-catalyzed coupling reactions due to their



1: R = *n*-butyl
2: R = *i*-butyl
3: R = *i*-propyl
4: R = methyl
5: R = allyl
6: R = 2-methoxyethyl
7: R = benzyl

Figure 1. Selected examples of alkyl-di-(1-adamantyl)phosphines (cata*CX*ium® A ligands).

Keywords: Amination; Anilines; Aryl chlorides; Palladium; Phosphines.
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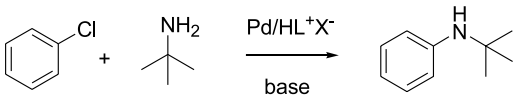


Scheme 1. Coupling reaction of chlorobenzene and *tert*-butylamine.

Table 1. Variation of ligands for the coupling reaction of chlorobenzene and *tert*-butylamine

Entry	Ligand precursor	Conv. (%)[a]	Yield (%)[a]
1	**1**	100	89
2	**H1**$^+$**I**$^-$	100	94
3	**H2**$^+$**I**$^-$	88	69
4	**H3**$^+$**I**$^-$	100	90
5	**H4**$^+$**I**$^-$	26	26
6	**H5**$^+$**Br**$^-$	100	84
7	**H6**$^+$**Br**$^-$	100	88
8	**H7**$^+$**Br**$^-$	63	59

[a] Average of two runs, determined by GC using hexadecane as internal standard.

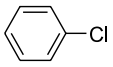
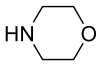
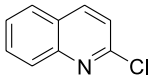
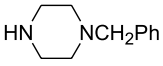
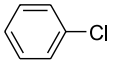
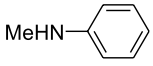
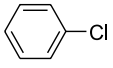
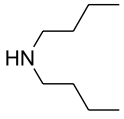
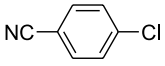
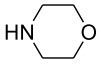
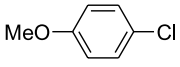
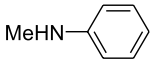
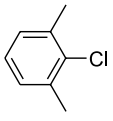
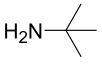
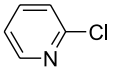
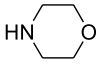
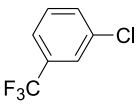
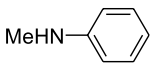
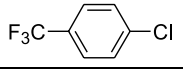
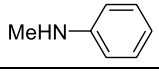
increased stability against air and moisture.[9] However, to the best of our knowledge phosphonium salts have not been tested as ligands in the amination of aryl chlorides.

2. Results and discussion

As a starting point of our investigations we examined the amination of chlorobenzene as an example of a non-activated aryl chloride, with a slight excess of the sterically hindered *tert*-butylamine (Scheme 1, Table 1).

At first the influence of the ligand structure was studied in the presence of 0.5 mol% $Pd(OAc)_2$ and 1 mol% of phosphonium salt with 1.2 equiv NaO*t*Bu as the base in toluene at 120 °C in a sealed tube. These are typical reaction conditions, which have been often used for C–N coupling reactions. Selected results are summarized in Table 1. Interestingly, the variation of the alkyl group has a significant effect on the coupling reaction. Thus, the modular synthesis of cata*CX*ium® A ligands should allow for an easy fine tuning of the ligand properties for other substrates, too.

Table 2. Palladium-catalyzed coupling of aryl chlorides and amines in the presence of **H1**$^+$**I**$^-$ and **H5**$^+$**Br**$^-$[a]

Entry	Aryl chloride	Amine	**H1**$^+$**I**$^-$		**H5**$^+$**Br**$^-$	
			Conv. (%)[b]	Yield (%)[b]	Conv. (%)[b]	Yield (%)[b]
1			100	95	100	99
2[c]			100	99	100	90
3			100	93	100	93
4			100	73	100	87
5			100	75	100	62
6			100	93	100	93
7			100	99	100	79
8			100	95	100	97
9			100	99	100	99
10			100	99	100	99

[a] Conditions: 5 mmol aryl chloride, 6 mmol amine, 6 mmol NaO*t*Bu, 0.5 mol% $Pd(OAc)_2$, 1 mol% ligand, 5 mL toluene, 120 °C, 20 h.
[b] Average of two runs, determined by GC using hexadecane or diethyleneglycol di-*n*-butyl ether as internal standard.
[c] Reaction was carried out on 2 mmol scale.

Control experiments with the free *n*-BuPAd$_2$ ligand (**1**, Table 1, entry 1) indicated that the corresponding phosphonium salt **H1**$^+$**I**$^-$ can be used without any problem (Table 1, entry 2). Good conversion for our model reaction is also observed for di-(1-adamantyl)-*iso*-propyl- (**H3**$^+$**I**$^-$), di-(1-adamantyl)-allyl- (**H5**$^+$**Br**$^-$), and di-(1-adamantyl)-(2-methoxyethyl)phosphonium salts (**H6**$^+$**Br**$^-$, Table 1, entries 4, 6, 7).

Next, the general usefulness of our ligands was examined and is shown in Table 2. Due to the ease of synthesis and the catalytic performance in the model reaction we selected di-(1-adamantyl)-*n*-butyl- and di-(1-adamantyl)-allyl-phosphonium salts (**H1**$^+$**I**$^-$, **H5**$^+$**Br**$^-$) for more detailed studies.

Various secondary amines and *tert*-butylamine can be coupled with different aryl chlorides to give the desired products in high yields. Reactions of chlorobenzene with secondary amines (acyclic, cyclic and aromatic amines) occurred in yields of more than 87% (Table 2, entries 1, 3, 4). In general, the amination of acyclic secondary amines with aryl halides is more challenging than similar reactions with cyclic secondary amines. Nevertheless the di-(1-adamantyl)-allylphosphonium salt is quite effective in the coupling of di-*n*-butylamine and chlorobenzene (Table 2, entry 4). In most of our examples we could not observe a strong dependence of the product yield from donor or acceptor substitution of the chloroarene. For example, electron-rich chloroanisole as well as the electron-poor trifluoromethyl-substituted chlorobenzenes react cleanly with *N*-methylaniline (Table 2, entries 6, 9 and 10). On the other hand, despite favourable electronic conditions, reaction of 4-chlorobenzonitrile with morpholine gave a lower yield of 75% due to side reactions of the nitrile group (Table 2, entry 5).

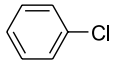
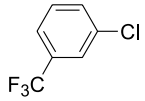
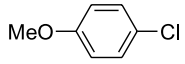
In addition to simple aryl chlorides, also heterocyclic chloroarenes such as 2-chloropyridine and 2-chloroquinoline react well with different amines and demonstrate the scope of our catalyst system (Table 2, entries 2, 8). Furthermore, sterically hindered 2,2′-dimethyl substituted anilines can be obtained in quantitative yield (99%) in the presence of 0.5 mol% palladium catalyst (Table 2, entry 7).

By comparing the performance of the *n*-butyl-substituted phosphonium salt **H1**$^+$**I**$^-$ with the allyl-substituted derivative **H5**$^+$**Br**$^-$ it is obvious that the former one is the (slightly) better ligand precursor in most reactions. However, in case of the arylation of di-*n*-butylamine **H5**$^+$**Br**$^-$ gave reproducibly better results. The reasons for this behaviour are so far unclear, but it suggests that optimized yields can be obtained by further variation of the alkyl group.

Normally, we carried out our catalytic experiments using a standard procedure (see Section 3) with 0.5 mol% Pd(OAc)$_2$ and 1 mol% of phosphonium salt. Clearly, this is a sufficient small amount for lab-scale syntheses of substituted anilines. However, it is well-known that catalyst turnover numbers (TONs) of around 1000–10,000 are required to consider larger scale applications.[10] Therefore, it is surprising that only little attention has been paid to the efficiency (productivity) of the respective palladium catalyst in amination reactions.[11] In general, TONs in the range of 100 are obtained. However, Hartwig et al. have demonstrated very recently that bidentate electron-rich phosphines with a ferrocene backbone lead to highly active and productive catalysts for the amination of aryl chlorides with primary amines.[12]

The results of our study with lower catalyst concentrations are summarized in Table 3. Reactions of *N*-methylaniline with chlorobenzene, 3-chlorobenzotrifluoride and 4-chloroanisole proceed with very good yield (89–94%; TONs 8900–9400) in the presence of only 0.01 mol% Pd(OAc)$_2$ and 0.02 mol% of di-(1-adamantyl)-*n*-butyl-phosphonium iodide at 120 °C.

Table 3. Reaction of aryl chlorides with *N*-methylaniline at low catalyst concentration[a]

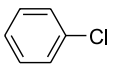
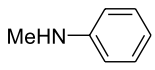
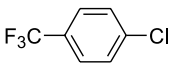
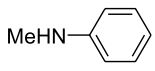
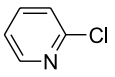
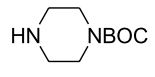
Entry	Aryl chloride	Conv. (%)[b]	Yield (%)[b]
1		100	94
2		100	89
3		100	93

[a] Reaction conditions: 5 mmol aryl chloride, 6 mmol *N*-methylaniline, 6 mmol NaO*t*Bu, 0.01 mol% Pd(OAc)$_2$, 0.02 mol% **H1**$^+$**I**$^-$, 5 mL toluene, 120 °C, 20 h.
[b] Average two runs, determined by GC using diethyleneglycol di-*n*-butyl ether as internal standard.

On the other hand only low conversion and yield is detected under these conditions for the reaction of morpholine with 2-chloropyridine (5–10% yield; TON 500–1000).

Finally, we investigated aminations of various aryl chlorides at lower temperatures (60–80 °C). In order to achieve faster conversion a catalyst concentration of 1 mol% Pd(OAc)$_2$ has been used. As shown in Table 4 reactions of chlorobenzene and 4-chlorobenzotrifluoride with *N*-methylaniline gave 71 and 73% yield, respectively, (Table 4, entries 1–2), which indicates that the amination proceeds

Table 4. Amination of aryl chlorides at lower temperature[a]

Entry	Aryl chloride	Amine	Temp. (°C)	Yield (%)[b]
1			60	71
2			60	73
3			80	98

[a] Reaction conditions: 5 mmol aryl chloride, 6 mmol amine, 6 mmol NaO*t*Bu, 1 mol% Pd(OAc)$_2$, 2 mol% **H1**$^+$**I**$^-$, 5 mL toluene, 120 °C, 20 h.
[b] Average two runs, determined by GC using hexadecane or diethyleneglycol di-*n*-butyl ether as internal standard.

significantly slower at this temperature. Nevertheless, in some cases the use of lower reaction temperatures can be reasonable if one or both of the substrates contain sensitive groups. As an example the amination of 2-chloropyridine with *N*-(*tert*-butoxycarbonyl)piperazine is presented, which gave an excellent yield (98%) at 80 °C (Table 4, entry 3).

In summary, we have shown that phosphonium salts of alkyl-di-(1-adamantyl)phosphines allow for an efficient synthesis of a variety of substituted anilines from aryl or heteroaryl chlorides and amines. Good to excellent yields (75–99%) are obtained at comparatively low catalyst concentration (0.5 mol% $Pd(OAc)_2$; 120 °C). By simply reducing the metal and ligand amount optimized catalyst turnover numbers up to ca. 10,000 have been observed. In addition, the coupling reactions proceed under milder conditions (60–80 °C), albeit with higher catalyst loading.

An important advantage of the presented method is the easy handling of catalyst and ligand precursors. Hence, it is not necessary to exclude strictly air or moisture. Due to the modular synthesis of cata*CX*ium® A ligands a fine tuning of the ligand properties for other substrates is easily possible and should lead to further improved catalyst performance.

3. Experimental

Chemicals were obtained from Aldrich, Fluka and Merck KGaA and used without further purification. Solvents were dried according to standard procedures. ^1H and ^{13}C NMR chemical shifts refer to tetramethylsilane (0 ppm) and $CDCl_3$ (77.0 ppm), respectively. Column chromatography was carried out using silica gel 60 (0.063–0.2 mm Fluka).

3.1. General procedure (Buchwald–Hartwig amination)

A 30 mL pressure tube was loaded with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), the ligand precursor (0.050 mmol), and NaO*t*Bu (577 mg, 6.0 mmol) and was purged with argon. Then, toluene (5 mL), the aryl chloride (5.0 mmol), and the amine (6.0 mmol) were added successively. The mixture was stirred for 20 h at 120 °C. After cooling to room temperature the mixture was diluted with diethyl ether (5 mL) and washed with water (10 mL). The organic phase was dried over $MgSO_4$, concentrated under vacuum and the product was isolated by column chromatography (ethyl acetate/*n*-hexane or acetone/*n*-hexane). Alternatively, diethyleneglycol di-*n*-butyl ether or hexadecane was added as internal standard and quantitative analysis was done by gas chromatography. The commercially available products were identified by comparison of their GC/MS data with the data of authentic samples, known products were characterized by NMR and mass spectroscopy (for more data see Ref. 4c and cited literature there).

3.1.1. *N*-Phenylmorpholine. MS (EI, 70 eV): *m*/*z* (%): 163 [M^+], 105, 77.

3.1.2. Methyldiphenylamine. MS (EI, 70 eV): *m*/*z* (%): 183 [M^+], 167, 104, 77.

3.1.3. *N*,*N*-Di-*n*-butylaniline. MS (EI, 70 eV): *m*/*z* (%): 205 [M^+], 162, 120, 105, 77.

3.1.4. *N*-*tert*-Butyl-2,6-dimethylaniline. MS (EI, 70 eV): *m*/*z* (%): 177, 162, 121.

3.1.5. *N*-(4-Cyanophenyl)morpholine. MS (EI, 70 eV): *m*/*z* (%): 188 [M^+], 130, 102.

3.1.6. *N*-(4-Methoxyphenyl)-*N*-methylaniline. MS (EI, 70 eV): *m*/*z* (%): 213 [M^+], 198, 77.

3.1.7. *N*-Methyl-*N*-[4-(trifluoromethyl)phenyl]aniline. MS (EI, 70 eV): *m*/*z* (%): 251 [M^+], 77.

3.1.8. *N*-Methyl-*N*-[3-(trifluoromethyl)phenyl]aniline. MS (EI, 70 eV): *m*/*z* (%): 251 [M^+], 145, 77.

3.1.9. *N*-(2-Pyridyl)morpholine. MS (EI, 70 eV): *m*/*z* (%): 164 [M^+], 133, 107, 79.

3.1.10. *N*-Benzyl-*N*′-(2-quinolyl)piperazine. Yellow solid; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, $^3J(H,H) = 9.1$ Hz, 1H), 7.61 (d, $^3J(H,H) = 8.5$ Hz, 1H), 7.50 (d, $^3J(H,H) = 8.3$ Hz, 1H), 7.45 (m, 1H), 7.21 (m, 6H), 6.87 (d, $^3J(H,H) = 9.3$ Hz, 1H), 3.68 (t, $^3J(H,H) = 5.1$ Hz, 4H), 3.49 (s, 2H), 2.51 (t, $^3J(H,H) = 5.1$ Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 157.9$, 148.3, 137.8, 129.9, 129.7, 128.7, 127.6, 127.0, 123.5, 122.7, 109.9, 63.6, 53.5, 44.5; MS (EI, 70 eV): *m*/*z* (%): 303 [M^+], 157, 128, 91.

3.1.11. *N*-*tert*-Butoxycarbonyl-*N*′-(2-pyridyl)piperazine. Yellow solid; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 8.18$ (m, 1H), 7.48 (m, 1H), 6.63 (m, 2H), 3.52 (s (br), 8H), 1.47 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 159.3$, 154.8, 148.0, 137.6, 113.6, 107.2, 79.9, 45.1, 43.3 (br), 28.4; MS (EI, 70 eV): *m*/*z* (%): 263 [M^+], 190, 120, 107, 78.

Acknowledgements

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On the efficiency of two-coordinate palladium(0) *N*-heterocyclic carbene complexes in amination and Suzuki–Miyaura reactions of aryl chlorides

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Abstract—The catalytic activity of novel two-coordinate palladium *N*-heterocyclic carbene complexes that differ in their steric and electronic properties is compared in catalytic amination and Suzuki–Miyaura cross-couplings.

1. Introduction

Palladium-catalysed carbon–carbon and carbon–nitrogen bond forming reactions are widely employed methods in modern organic chemistry.[1] The use of such catalytic procedures has found application in the preparation of many natural products,[2] as well as in materials science[3] and the agrochemical industry.[4] Whilst phosphine-based ligands are still commonly used in Pd-catalysed chemical reactions, *N*-heterocyclic carbenes (NHCs)[5] have become attractive alternatives.[6] Many protocols purportedly involving NHC ancillary ligands use the corresponding imidazolium salt and deprotonate in situ, which negates the problems associated with handling the air- and moisture-sensitive carbene. In these procedures the catalytically active species, that is, the species to which the organic electrophile oxidatively adds, is thought to be a NHC-ligated Pd(0) complex. A number of groups, including our own, have shown that such discrete complexes are indeed active catalysts in C–C and C–N bond forming reactions.[7–11] However, the activity of these complexes varies greatly and we have found that the outcome of the reaction is extremely sensitive to alterations in the steric and electronic properties of the ligand.

Such differences have been illustrated by work carried out in our group comparing the catalytic activity of various Pd(0) catalysts, including homoleptic two-coordinate palladium–carbene complexes and heteroleptic phosphine/NHC complexes, in amination reactions.[7] It was found that employing a sterically encumbered homoleptic complex containing diisopropylphenyl-substituted NHC ligands **1** (Fig. 1) led to higher levels of conversion for a wider variety of amines than the unsaturated bis(1,3-bis(*t*-butyl)imidazol-2-ylidene)palladium(0) **2**. These complexes differ both sterically and electronically, and it is therefore not apparent which of these factors, if either, is the most significant for successful catalysis.

We herein report the synthesis of a novel homoleptic Pd(0) NHC complex, and make a comparison of its catalytic activity with other closely related complexes, which differ in the nature of the nitrogen substituent and the degree of backbone saturation in the ligand.

2. Results and discussion

Compounds **1**,[7] **2**[8] and **3**[9] have been previously reported; however, for a complete comparison of the differing steric

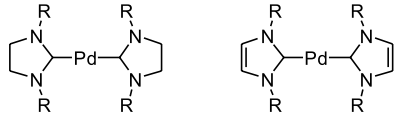

Figure 1. Two-coordinate palladium(0)–carbene complexes.

Keywords: Suzuki–Miyaura reactions; *N*-Heterocyclic carbene; Amination reactions.
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and electronic properties, the synthesis of **4** was necessary. The saturated NHC ligand of complex **4** has been synthesised by Denk et al. via reductive desulfurisation from the corresponding thiourea.[12] However, we have previously synthesised NHCs via deprotonation of the corresponding imidazolium chloride with KO*t*-Bu and NaH,[13] thus, we sought to synthesise the free carbene from the chloride salt, 1,3-bis(*t*-butyl)imidazolinium chloride (SI*t*-Bu·HCl). Initial attempts to synthesise this salt following the procedure developed by Arduengo and co-workers were problematic, as the necessary imine precursor could not be formed.[14] Therefore, the commercially available free amine was used and treated with HCl to form the hydrochloride salt, which was then cyclised to produce the corresponding imidazolinium salt with triethyl orthoformate, according to Arduengo's procedure (Scheme 1).[14]

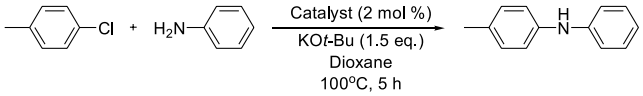
SI*t*-Bu·HCl was deprotonated with NaH and catalytic amounts of KO*t*-Bu to yield 1,3-bis(*t*-butyl)imidazolin-2-ylidene (SI*t*-Bu), which was used in subsequent reactions as a solution of known concentration in THF.

Successful preparation of **4** was achieved using the procedure developed by this group involving nucleophilic attack on [{Pd(η^3-C_4H_7)Cl}$_2$] by sodium dimethylmalonate in the presence of carbene (Scheme 2).[8]

It has been previously established that **1** is a more active catalyst in amination reactions than **2**.[7] This was especially evident when comparing the reaction of 4-chlorotoluene and aniline, where the yields of isolated product differed by 72%. New complexes **3** and **4** were tested in this amination and also displayed markedly different activities (Table 1).

Evident from Table 1 is the reduction in catalytic activity when an unsaturated NHC ligand is used instead of a saturated one. This is illustrated by the superior catalytic efficiency of saturated complex **1** compared to its unsaturated analogue **3** (entries 1 and 3) and also by the varying activities of saturated **4** and unsaturated **2**. Also apparent is the enhanced catalytic activity that is obtained when a more sterically encumbered NHC ligand is used; hence, diisopropylphenyl-substituted complex **1** is a more

Table 1. Amination reaction using different bis-carbene complexes



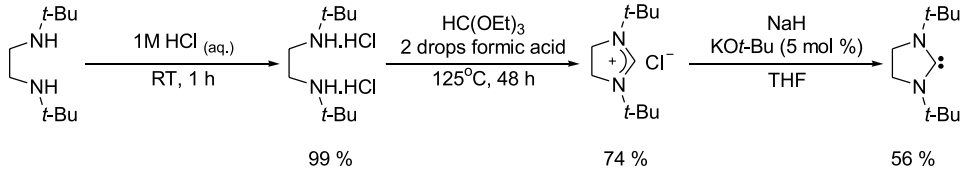
Entry	Catalyst	Yield (%)[a]
1	**1**	91
2	**2**	19
3	**3**	52
4	**4**	30

[a] Isolated yields, average of two runs.

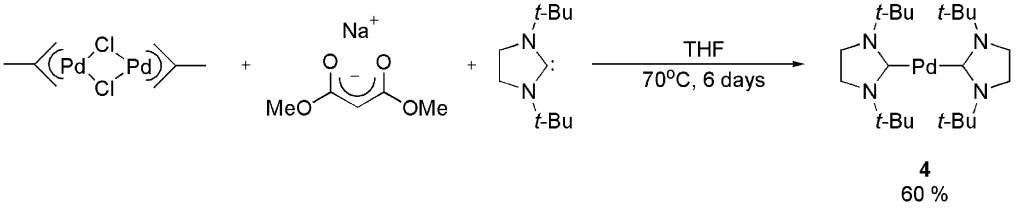
effective catalyst than the *t*-butyl substituted derivative **4** and likewise for the unsaturated variants **3** and **2**. These results suggest that an optimal catalyst for amination reactions would contain both bulky substituents and good electron-donating capabilities, as is epitomised by the sterically hindered, electron-rich complex **1**.

As complexes **1**–**4** are air- and moisture-sensitive, they are not as user-friendly as in situ protocols employing imidazolium salts and an air stable Pd(0) or Pd(II) source. Therefore, the amination reaction in Table 1 was repeated using a $Pd_2(dba)_3$/imidazolium chloride catalytic system (Table 2).

For all imidazolium salts used, a greater yield was obtained using the in situ conditions compared to the corresponding bis-carbene complex in the same reaction time. The difference between the yields could indicate that the amination proceeds in a faster reaction time in the in situ reactions. This is similar to the results obtained by us when performing catalytic aminations using microwave irradiation, where greater yields were achieved with the in situ protocol than when the bis-carbene complex **1** was used.[15] Kinetic studies carried out in these laboratories have shown that for amination reactions using a Pd(NHC)$_2$ catalyst, it is a mono-ligated Pd(0) species that undergoes oxidative addition with the aryl chloride.[16] The data was consistent with a rate-limiting oxidative addition, which requires ligand dissociation from the bis-ligated pre-catalyst to a mono-ligated species. Therefore, it is feasible that when the $Pd_2(dba)_3$/imidazolium salt protocol is used, the mono-ligated, catalytically active species can be formed without

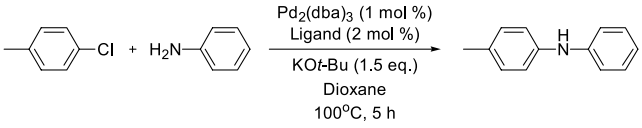


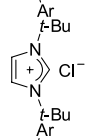
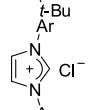
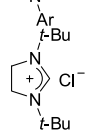
Scheme 1. Synthesis of SI*t*-Bu.



Scheme 2. Synthesis of bis-carbene complex **4**.

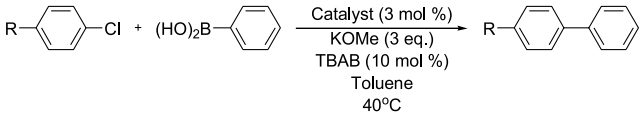
Table 2. Amination reaction using a Pd/imidazolium salt protocol



Entry	Ligand[a]	Yield (%)[b]
1		99
2		26
3		85
4		39

[a] Ar: (2,6-*i*-Pr-C_6H_3).
[b] Isolated yields.

Table 3. Suzuki–Miyaura reactions using different catalysts



Entry	R	Catalyst	Time (h)[a]	Yield (%)[b]
1	MeO	$Pd(dba)_2$/IPr·HCl[c]	6	75[d]
2	MeO	**1**	22	68
3	MeO	**2**	23	0
4	MeO	**3**	23	65
5	MeO	**4**	24	60
6	Me	$Pd(dba)_2$/IPr·HCl[c]	24	75[d]
7	Me	**1**	48	75
8	Me	**2**	48	62
9	Me	**3**	48	74
10	Me	**4**	48	63
11	COOMe	$Pd(dba)_2$/IPr·HCl[c]	5	99[d]
12	COOMe	**1**	16	77
13	COOMe	**2**	16	0
14	COOMe	**3**	16	65
15	COOMe	**4**	16	0

[a] Reaction time not optimised.
[b] Isolated yield, average of two runs.
[c] $Pd(dba)_2$ (3 mol%), 3 mol% IPr·HCl.
[d] Results from Ref. 9.

first forming the two-coordinate palladium–carbene complex. This would negate the requirement for Pd–NHC dissociation, thus circumventing the apparently slow step when using the bis-ligated complex.

In light of the differences in the catalytic activity for the complexes **1** to **4** in the amination reaction detailed above, it was desirable to discover whether the same pattern would occur in the Suzuki–Miyaura reaction. The Suzuki–Miyaura reaction between an organic electrophile and an organoboron reagent is one of the most popular palladium-catalysed cross-coupling processes,[17] owing, in part, to the tolerance of the reaction to a wide range of functional groups on both substrates and the ease of removal of the non-toxic boron-containing by-product.

We have previously published a protocol for Suzuki–Miyaura reactions using $Pd(dba)_2$ and the imidazolium salt, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) as the catalytic system.[9] This protocol is also valid when complex **3** was used as the reaction promoter; however, longer reaction times were needed to achieve similar levels of conversion. Table 3 demonstrates that this was also the case with other $Pd(NHC)_2$ complexes, where a variety of electron-rich (entries 1–5), electron neutral (entries 6–10) and electron-deficient (entries 11–15) aryl chlorides were tested.

For each aryl chloride tested, the yields reached with the in situ Pd/IPr·HCl protocol were higher than the corresponding bis-carbene complexes and reaction times were shorter. Amongst the bis-carbene complexes, the results indicate that the less sterically crowded *t*-butyl substituted **2** and **4** are less effective catalysts than the bulkier complexes **1** and **3**, giving lower levels of conversion for all aryl chlorides tested. In fact, for the coupling of electron-deficient methyl-4-chlorobenzoate, the use of the less sterically hindered **2** and **4** led to no product formation (entries 13 and 15). This trend is similar to that found in the amination reaction. The degree of backbone saturation, and hence, electron donating capability, of the complexes also appears to play a role in the complex's catalytic activity, as with the amination reaction; however, the extent to which it effects catalytic outcome is not as great. Between the two diisopropylphenyl-substituted complexes, the levels of conversion for the different aryl chlorides are similar, with the only notable difference being with the coupling of electron-deficient methyl-4-chlorobenzoate to phenylboronic acid where **1** is the better catalyst (entries 12 and 14). *t*-Butyl substituted **2** and **4** show similar yields for the cross-coupling of electron-neutral 4-chlorotoluene (62 and 63%, respectively) and both show no catalytic activity for methyl-4-chlorobenzoate. It is, therefore, surprising that such a large difference is observed when 4-chloroanisole is the coupling partner, with **4** giving a yield of 60% and its unsaturated analogue giving no product at all.

These results confirm our earlier observation that the steric and electronic effects of the NHC greatly affect the catalytic performance of their corresponding bis-carbene complexes. As with the amination reaction, it is the bulkier complexes **1** and **3** that are more effective and it also appears to be the case that the more electron-donating complexes are more effective catalysts than the unsaturated species. This is in agreement with work by Herrmann and co-workers who have utilized the properties of a sterically encumbered, unsaturated bis-carbene complex bearing adamantyl substituents to affect Suzuki–Miyaura reactions of aryl chlorides at room temperature.[11a] Unfortunately, and somewhat surprisingly, in our hands an in situ protocol using an adamantyl-substituted imidazolium salt was not viable.[9] Fürstner and Leitner have reported that the unsaturated imidazolium salt IPr·HCl is more effective than its saturated analogue in facilitating the coupling of aryl chlorides to sp^3-hybridised borane derivatives.[18] Nolan et al. have also used the salt IPr·HCl to affect Suzuki–Miyaura reactions of

aryl chlorides, and its activity compared more favourably to a mesityl-substituted imidazolium salt.[19] This indicates that the steric and electronic requirements for imidazolium salts when used in cross-coupling reactions are different to bis-carbene complex pre-catalysts.

3. Conclusion

In summary, we have isolated a novel bis-carbene complex and determined its activity in both an amination reaction and Suzuki–Miyaura reactions. We have also tested different two-coordinate palladium–carbene complexes with varying steric and electronic properties in amination and Suzuki–Miyaura reactions and have found that the more sterically encumbered complexes are more effective, as are complexes that possess ligands that are more electron-rich.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon or dinitrogen in oven-dried glassware. Glovebox manipulations were performed in a Miller Howe glovebox under an atmosphere of dry dinitrogen. Solvents were purchased from Fischer and either used as received or were pre-dried over sodium wire, followed by heating at reflux over potassium or sodium in a solvent still under an atmosphere of dinitrogen and were stored over 4 Å molecular sieves or potassium mirror under argon. Anhydrous dioxane was purchased from Aldrich and stored in an ampoule under argon over 4 Å molecular sieves. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates and was visualized using standard procedures. Column chromatography purifications were carried out using Fisher Matrex silica gel 60 (35–70 μm), Biotage KP-SIL, 60 Å (32–63 μm) or Merck 60 silica gel (70–240 μm). ^{1}H NMR were recorded at 300 MHz on a Bruker 300DPX spectrometer operating at 300.13 MHz. ^{13}C NMR were recorded on a Bruker 300DPX spectrometer operating at 75 MHz. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to the residual signals of the internal deuterated solvent. Mass spectra were obtained on a VG autospec Fisons instrument, KRATOS MS80F and MS25, Bruker Daltronics, FT Apex III, ESI. All melting points are uncorrected. *N*,*N*′-Bis(*t*-butylamine)ethane was purchased from Lancaster and used as received. Aryl chlorides were purchased from Aldrich and were degassed prior to use; aniline was distilled at reduced pressure. KO*t*-Bu was purchased from Aldrich and was sublimed twice at 157 °C, 1×10^{-5} mbar. The imidazolium salts 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride,[14] IPr·HCl,[14] and 1,3-bis(*t*-butyl)imidazolium chloride[20] were prepared according to literature procedures, as were the complexes **1**,[7] **2**,[8] and **3**.[9] Bis(methallyl)dichlordipalladium(II) was also prepared according to the literature procedure.[21]

4.1.1. *N*,*N*′-Bis(*t*-butylamine)ethane dihydrochloride. To *N*,*N*′-bis(*t*-butylamine)ethane (5 mL, 23.24 mmol) was added 1 M HCl (47 mL, 46.48 mmol) in portions. The resulting colourless solution was left to stir for 1 h. After this time, the colourless solution was concentrated on a rotary evaporator. The white solid, which precipitated when the majority of the solvent had been removed, was collected by filtration, washed with diethyl ether and then dried under vacuum at 40 °C for 16 h. This yielded 5.65 g (99%) of the title compound as a white crystalline solid. Mp: 278–280 °C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz): δ 9.60 (br s, 1H), 3.31 (s, 4H), 1.33 (s, 18H). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz): δ 56.9 (NCH_2CH_2N), 37.8 ($C(CH_3)_3$), 25.3 (CH_3). HRMS *m*/*z* (ESI) Calcd for $C_{10}H_{25}N_2$ [M^+]: 173.2012. Found: 173.2017.

4.1.2. 1,3-Bis(*t*-butyl)imidazolinium chloride (SI*t*-Bu·HCl). A white suspension of triethyl orthoformate (14.5 mL, 87.18 mmol), *N*,*N*′-bis(*t*-butylamine)ethane dihydrochloride (2.14 g, 8.72 mmol) and formic acid (2 drops) was heated to reflux for 48 h. After 48 h, the pale yellow solution was cooled to ambient temperature and concentrated slightly in vacuo. The precipitated white solid was then collected by filtration and dried at 70 °C under vacuum for 5 h. This afforded the title compound as a white solid (1.42 g, 74%). Mp: 209 °C. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz): δ 8.27 (s, 1H), 3.94 (s, 4H), 1.36 (s, 18H). ^{13}C NMR ($(CD_3)_2SO$, 75 MHz): δ 153.5 (NCHN), 56.3 (NCH_2CH_2N), 45.1 ($C(CH_3)_3$), 27.8 (CH_3). HRMS *m*/*z* (ESI) Calcd for $C_{11}H_{23}N_2$ [M^+]: 183.1856. Found: 183.1862.

4.1.3. 1,3-Bis(*t*-butyl)imidazolin-2-ylidene (SI*t*-Bu). To 1,3-bis(*t*-butyl)imidazolinium chloride (595 mg, 2.72 mmol) in a Schlenk tube was added NaH (261 mg, 10.88 mmol) and KO*t*-Bu (15 mg, 0.136 mmol) in a glovebox. THF (10 ml) was then transferred via cannula. The white reaction mixture was stirred at room temperature for 16 h, after, which time the white mixture was filtered through flame-dried Celite. The filtrate was transferred to a distillation apparatus and the THF was then removed by distillation at atmospheric, oil-bubbler pressure. The colourless residue was washed into a second, smaller distillation apparatus with the minimum of pentane. The pentane was then removed at atmospheric pressure, leaving the title product as a colourless oil. Some residual THF was present in the ^{1}H NMR and the calculated yield was 56%. ^{1}H NMR (C_6D_6, 300 MHz): δ 3.58 (THF), 3.04 (s, 4H), 1.41 (THF), 1.33 (s, 18H). ^{13}C NMR (C_6D_6, 75 MHz): δ 218.7 (*C*:), 67.9 (THF), 54.0 (NCH_2CH_2N), 44.6 ($C(CH_3)_3$), 30.1 (CH_3), 25.9 (THF). HRMS *m*/*z* (ESI) Calcd for $C_{11}H_{22}N_2$ $(M+H)^+$: 183.1861. Found: 183.1869.

4.1.4. Bis(1,3-bis(*t*-butyl)imidazolin-2ylidene)palladium(0) (4). Sodium dimethyl malonate was synthesised by treating a solution of NaH (12 mg, 0.508 mmol) in THF (2 mL) with dimethyl malonate (58 μL, 0.508 mmol) at 0 °C. The solution was allowed to warm to ambient temperature and was stirred for a further 30 min until the evolution of H_2 had ceased and the solution was no longer cloudy. The sodium dimethyl malonate solution (0.508 mmol) was transferred to an ampoule charged with bis(methallyl) dichlorodipalladium(II) (100 mg, 0.254 mmol) and 1,3-bis(*t*-butyl)imidazolin-2-ylidene (185 mg, 1.015 mmol). The pale yellow solution was stirred at 65 °C for 6 days. The resultant orange solution was filtered through flame-dried Celite. The orange filtrate was concentrated in vacuo and petroleum ether (30 mL) was transferred to the residues.

This suspension was sonicated (3×15 min) and the supernatant was then removed by filter cannula. After concentrating the filtrate in vacuo, the title compound was precipitated from THF at −45 °C (143 mg, 60%). ^{1}H NMR (C_6D_6, 300 MHz): δ 2.95 (s, 8H), 1.97 (s, 36H). ^{13}C NMR (C_6D_6, 75 MHz): δ 219.7 (Pd–*C*), 55.4 (N*C*H$_2$*C*H$_2$N), 45.6 (*C*(CH$_3$)$_3$), 31.2 (*C*H$_3$). LRMS *m/z* (EI) 470 [M$^+$], 183 [M$^+$−Pd{*cyclo*-C[N(*t*-Bu)CH$_2$]$_2$}]. Anal. Calcd for $C_{22}H_{44}N_4Pd$: C, 56.10; H, 9.42; N, 11.89. Found: C, 55.94; H, 9.60; N, 11.72.

4.1.5. General procedure for amination of 4-chlorotoluene with aniline. An ampoule was charged with catalyst (0.016 mmol) and KO*t*-Bu (133 mg, 1.19 mmol). Dioxane (4 mL) was added, followed by aniline (87 μL, 0.95 mmol) and 4-chlorotoluene (93 μL, 0.79 mmol). The reaction mixture was stirred at 100 °C for 5 h. After this time, the mixture was cooled to room temperature, diluted with diethyl ether and filtered through a small amount of silica gel. The insoluble residues were washed with diethyl ether. The solvent was removed in vacuo and the crude product was purified by column chromatography (petroleum ether/ethyl acetate 95:5). This yielded the product, phenyl-*p*-tolylamine, as an off-white solid. Mp: 82–84 °C (lit. mp 88–88.5 °C).[22] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10 (d, 2H), 7.00 (d, 2H), 6.95–6.85 (m, 5H), 6.75 (t, 1H), 5.50 (br s, 1H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.3 (*C*$_{ar}$), 140.7 (*C*$_{ar}$), 131.3 (*C*$_{ar}$), 130.3 (*C*H$_{ar}$), 129.7 (*C*H$_{ar}$), 120.7 (*C*H$_{ar}$), 119.3 (*C*H$_{ar}$), 117. 3 (*C*H$_{ar}$), 21.1 (*C*H$_3$). LRMS *m/z* (EI) 183 [M$^+$], 167 [M$^+$−CH$_3$]. Spectroscopic data corresponds to that reported in the literature.[23]

4.2. Suzuki–Miyaura reactions of aryl chlorides using bis-carbene palladium complex catalysts

General procedure. To an ampoule charged with phenylboronic acid (67 mg, 0.550 mmol) and tetra-*n*-butylammonium bromide (TBAB) (16 mg, 0.050 mmol) was added the catalyst (0.015 mmol) and KOMe (105 mg, 1.50 mmol). Toluene (3 mL) was then transferred to the ampoule. After the addition of the aryl chloride (0.50 mmol), the reaction mixture was stirred at 40 °C. The reaction was monitored by TLC to check for the disappearance of the aryl chloride. The solution was cooled to ambient temperature and ethyl acetate (10 mL) and sodium hydroxide (1 M, 10 mL) were added. This mixture was filtered and the aqueous phase was removed. The organic layer was washed with sodium chloride (20% w/v, 2×5 mL). The organic layer was then dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography.

4.2.1. 4-Methoxybiphenyl (entries 1–5). The coupling of 4-chloroanisole and phenylboronic acid was complete after 22–23 h. The crude residue was purified by column chromatography, eluting with petroleum ether/ethyl acetate 97:3, to furnish the title compound as an off-white powder. Mp: 86 °C (lit. mp 91 °C).[24] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50–7.45 (m, 2H), 7.37–7.31 (m, 2H), 7.16 (d, J=9.7 Hz, 2H), 6.90 (m, 1H), 6.75 (d, J=9.0 Hz, 2H), 3.70 (s, 3H). LRMS *m/z* (EI) 184 [M$^+$], 169 [M$^+$−CH$_3$]. Spectroscopic data corresponds to that reported in the literature.[24]

4.2.2. 4-Phenyltoluene (entries 6–10). The coupling of 4-chlorotoluene and phenylboronic acid was complete after 48 h. The crude residue was purified by column chromatography (petroleum ether) to furnish an off-white solid. Mp: 42 °C (lit. mp 49 °C).[24] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (d, J=7.5 Hz, 2H), 7.41 (d, J=8.1 Hz, 2H), 7.34 (t, J=7.5 Hz, 2H), 7.24 (t, J=7.2 Hz, 1H), 7.16 (d, J=7.7 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.1 (*C*$_{ar}$), 137.3 (*C*$_{ar}$), 136.0 (*C*$_{ar}$), 128.4 (*C*H$_{ar}$), 127.7 (*C*H$_{ar}$), 125.9 (*C*H$_{ar}$), 28.7 (*C*H$_3$). Spectroscopic data corresponds to that reported in the literature.[24]

4.2.3. Methyl-(4-phenyl)-benzoate (entries 11–15). The coupling of methyl-4-chlorobenzoate and phenylboronic acid was complete after 16 h. After cooling the reaction mixture to ambient temperature, it was diluted with diethyl ether and filtered through a small amount of silica gel. The insoluble residues were washed with diethyl ether. The solvent was removed in vacuo and the crude product was purified by column chromatography (petroleum ether/ethyl acetate 90:10). This afforded the title compound as a white solid. Mp: 109 °C (lit. mp 117–118 °C).[25] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, J=8.6 Hz, 2H), 7.61–7.52 (m, 4H), 7.43–7.29 (m, 3H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4 (*C*OOMe), 146.1 (*C*$_{ar}$), 140.4 (*C*$_{ar}$), 130.1 (*C*H$_{ar}$), 129.3 (*C*H$_{ar}$), 129.3 (*C*$_{ar}$), 128.5 (*C*H$_{ar}$), 127.7 (*C*H$_{ar}$), 127.6 (*C*H$_{ar}$), 52.6 (O*C*H$_3$). LRMS *m/z* (EI) 212 [M$^+$], 181 [M$^+$−OCH$_3$]. Spectroscopic data corresponds to that reported in the literature.[25]

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Synthesis of novel (NHC)Pd(acac)Cl complexes (acac = acetylacetonate) and their activity in cross-coupling reactions

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Abstract—The synthesis and characterization of two new complexes (IPr)Pd(acac)$_2$ (**1**) and (IPr)Pd(acac)Cl (**2**) (IPr = (*N*,*N*'-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene, acac = acetylacetonate) are described. Complex **2** can be prepared in a one-pot protocol in high yield. A study detailing the versatility of **2** to effectively catalyze a series of cross-coupling reactions is discussed.

1. Introduction

Research focusing on palladium compounds and their use in catalysis at both industrial and laboratory scales has exponentially increased during the last 10 years.[1,2] Although, ligandless systems are also known,[2a] it is well understood that the ancillary ligation to the metal center plays a crucial role in dictating the efficiency of a catalytic system.[3] Bulky, electron-rich phosphines ligands such as P(*t*-Bu)$_3$ are now commonly used to stabilize the Pd(0) intermediates thereby avoiding the precipitation of the metal in homogeneous catalysis.[4] However, the most common phosphine ligands possess several drawbacks: (1) they often are prone to air oxidation and therefore, require air-free handling, (2) when these ligands are subjected to higher temperatures, significant P–C bond degradation occurs and require the use of an excess of the phosphine and (3) they often react with Pd precursors such as Pd(OAc)$_2$ in a reduction process forming Pd(0)P$_n$ and phosphine oxide.[5]

N-Heterocyclic carbenes (NHC)[6] have become increasingly popular in the last few years as they represent an attractive alternative to tertiary phosphines in homogeneous catalysis. The NHC exhibit reaction behavior different than phosphine especially displaying high thermal stability and tolerance to oxidation conditions. We have developed several systems based on the combination of imidazolium salts (air-stable precursors for NHC) and Pd(0) or Pd(II) sources to generate catalytically active species in situ and these mediate numerous organic reactions, principally cross-coupling reactions.[7] These preliminary systems by us and others[8] showed the importance of the NHC/Pd ratio on the efficiency of the reactions, pointing to an optimum 1:1 ligand to metal ratio in most cases. From there, we aimed our efforts on the development of monomeric NHC-bearing Pd(II) complexes and the study of their catalytic activity. Generally, shorter reaction times are observed in these well-defined systems, since the carbene is already coordinated to the palladium center. Also, the use of a well-defined pre-catalyst allows for a better knowledge of the amount of ligand-stabilized palladium species in solution, by reducing the possibility of side reactions leading to ligand or palladium precursor decomposition prior to the coordination of the ligand.

We have reported on the synthesis of monomeric (NHC)Pd(allyl)Cl complexes[7f,9] and (NHC)Pd(carboxylate) complexes[10] among many architectures,[11] and have studied activation mechanisms and catalytic activities. The synthesis of most of these complexes is directly related to successful in situ systems involving the use of NHC and the corresponding palladium source. We reported on a catalytic system for the Heck reaction involving the use of diazabutadiene ligands and Pd(OAc)$_2$, that also could use Pd(acac)$_2$ as palladium precursor.[12] Using the same approach as for (IPr)Pd(OAc)$_2$, we decided to test whether analogous species using Pd(acac)$_2$ as starting material was possible. We report here the synthesis of (IPr)Pd(acac)$_2$ (**1**) and (IPr)Pd(acac)Cl (**2**) (IPr = (*N*,*N*'-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene) complexes and preliminary

Keywords: *N*-Heterocyclic carbenes; Palladium; Aryl amination; Ketone arylation.
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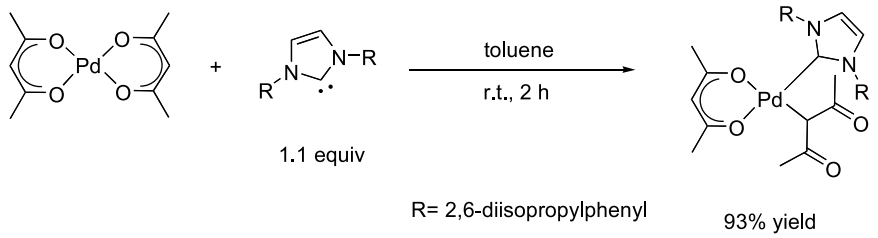


Scheme 1. Synthetic path leading to (IPr)Pd(acac)$_2$.

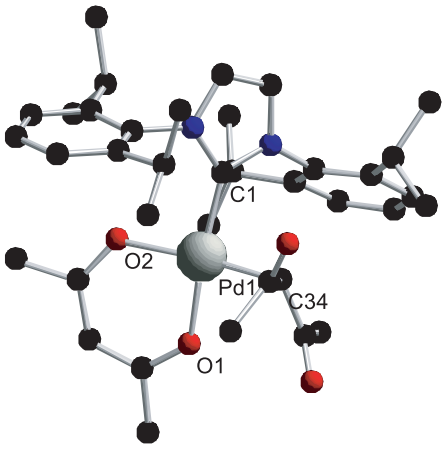


Figure 1. Ball and stick representation of (IPr)Pd(acac)$_2$ (hydrogens omitted for clarity). Selected bond distances (Å): Pd1–C1: 1.982(6), Pd1–C34: 2.073(6), Pd1–O1: 2.038(4), Pd1–O2: 2.081(4). Selected angles (deg): O2–Pd1–O1: 90.70(15), O1–Pd1–C34: 86.4(2), C34–Pd1–C1: 90.4(2), C1–Pd1–O2: 93.2(2).

studies on their catalytic activity in the Buchwald–Hartwig aryl amination reaction and the α-ketone arylation reaction.

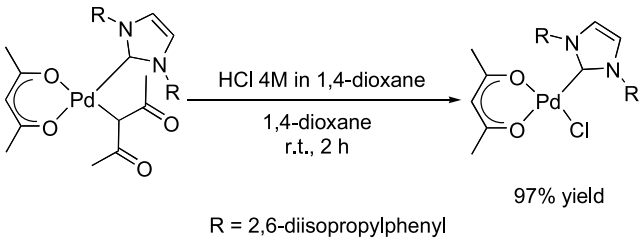
2. Results and discussion

2,4-Pentadione (acetylacetonate, acac) and other β-carbonyl compounds are very versatile and common ligands in transition metal chemistry.[13] 2,4-Pentadione typically binds metal ions in a η^2-*O*,*O* fashion, although some other coordination modes have been observed in platinum (II) and palladium(II) complexes.[14,15] Previous work by Kawaguchi and co-workers focused on the reactivity of palladium(II) acetylacetonate and related compounds with phosphines leading to new complexes, but no catalytic applications were reported.[16] Recently, Shmidt and co-workers have performed a very extensive research on the use of such type of complexes as hydrogenation catalysts.[17]

We have synthesized a NHC-bearing analogue to the reported (PPh$_3$)Pd(acac)$_2$[16a] following a similar procedure (Scheme 1). Direct reaction of the free carbene IPr with Pd(acac)$_2$ at room temperature in anhydrous toluene yielded (IPr)Pd(acac)$_2$ (**1**) in very high yield as a yellow powder. The presence of one oxygen-chelating ligand and one C-bound ligand in the complex was apparent by both ^{13}C and ^{1}H NMR. In the ^{13}C NMR spectrum, 6 different signals above 160 ppm: 207.5 (C-bound acac), 192.9, 188.1, 185.6, 183.3 (carbonyl carbons), and 161.2 (carbenic carbon) were observed. In the ^{1}H NMR spectrum, four methyl-proton singlet signals were observed each at 2.63, 2.01, 1.63, and 1.31, together with two signals at 5.90 and 4.78 ppm. The lowest-field methyl peaks are assigned to the carbon-bonded acac, together with the lowest-field methenic hydrogen, while the other three signals are assigned to the oxygen-chelating ligand. It is of note that the PPh$_3$ analogue showed only one peak for the methyls of the carbon bound ligand, due to free rotation.[18] Clearly, the sterically demanding IPr ligand inhibits this rotation. The disposition of the ligands was unequivocally assigned when the crystal structure was resolved by X-ray diffraction (Fig. 1). A square planar configuration around the palladium center can be observed, with nearly no distortion. As expected, the Pd–C$_{carbenic}$ distance is in the range of a single Pd–C bond. The Pd–O bond opposite to the NHC is elongated compared to the other Pd–O bond due to a strong trans effect.

Preliminary tests on the activity of **1** for the Buchwald–Hartwig reaction using KO*t*Bu as base and DME as solvent at 50 °C for the coupling of 4-chlorotoluene and morpholine showed a moderate activity (43% product in 1 h with 1 mol% catalyst loading). The same moderate activity was observed for the coupling of 4-chlorotoluene and propiophenone using NaO*t*Bu as base and toluene as solvent at 60 °C. The reaction required 2 h to reach completion using 1 mol% catalyst loading. We decided on modifying the complex with the idea of increasing the activity in catalysis.

Kawaguchi reported on the reaction of (PPh$_3$)Pd(acac)$_2$ with benzoyl chloride to yield the new species(PPh$_3$)Pd(acac)Cl, proposing a sequence of oxidative addition–reductive elimination reactions.[16a] In a similar way, compound **1** reacts with 1 equiv of HCl at room temperature to produce the new species (IPr)Pd(acac)Cl (**2**) as a yellow powder in nearly quantitative yield (Scheme 2). The loss of the C-bound ligand is again clearly evidenced by NMR. In ^{13}C NMR, only two carbonyl carbons (187.1, 184.1 ppm) and the carbenic carbon (156.4 ppm) appear, whereas in ^{1}H NMR, only one acac ligand can be assigned: singlet at 5.12 ppm, accounting for one hydrogen, and two methylic singlets (1.84, 1.82 ppm). Again, the structural features



Scheme 2. Synthetic path leading to (IPr)Pd(acac)Cl.

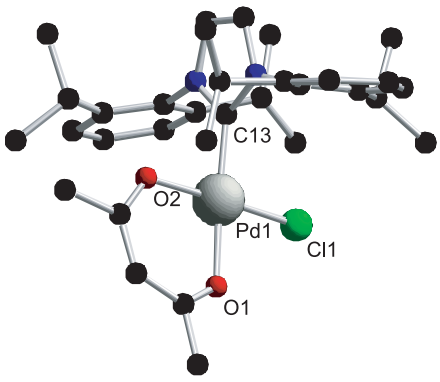
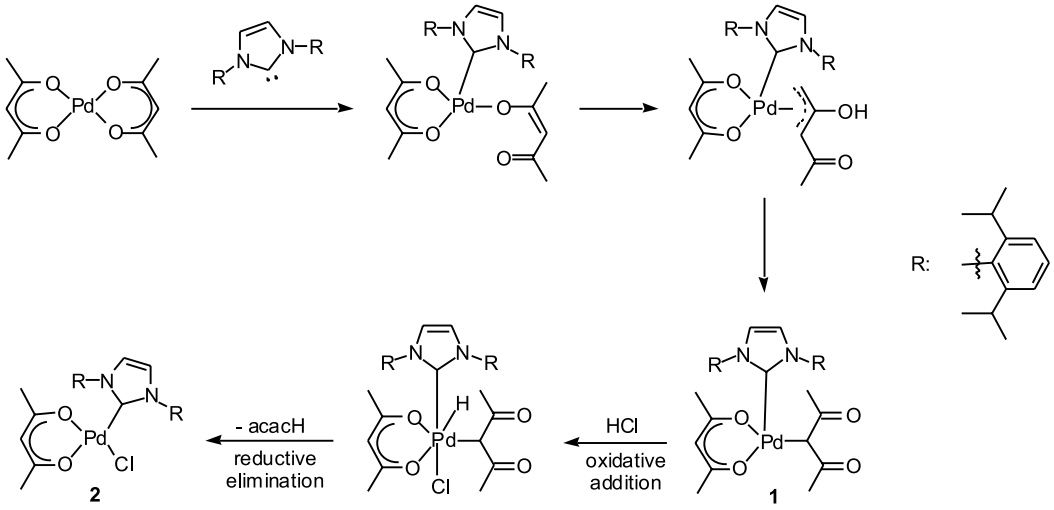


Figure 2. Ball and stick representation of (IPr)Pd(acac)Cl (hydrogens omitted for clarity). Selected bond distances (Å): C13–Pd1: 1.9694(17), Pd1–O2: 2.0362(15), Pd1–O1: 2.0439(14), Pd1–C13: 2.2820(6). Selected angles (deg): O2–Pd1–O1: 92.89(6), O1–Pd1–Cl1: 87.35(4), Cl1–Pd1–C13: 93.89(5), C13–Pd1–O2: 86.21(2).

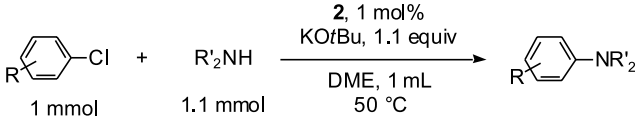
were unequivocally assigned when the structure was determined by single crystal X-ray diffraction (Fig. 2). For this complex, the Pd–O distances are more similar (2.036, 2.044 Å), whereas the square planar coordination around the palladium center becomes slightly more distorted.

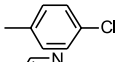
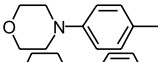
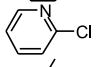
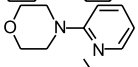
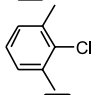
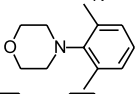
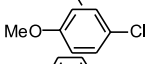
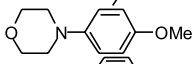
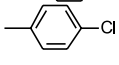
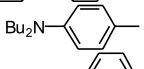
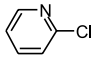
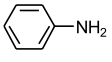
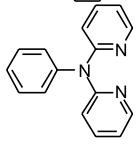
The formation of **1** and subsequently **2** can be postulated to occur by the pathway illustrated in Scheme 3. The coordination of the sterically demanding IPr by palladium is accompanied by the transition of one acac ligand from the η^2-*O*,*O*-chelate to the *O*-monodentate form, with subsequent transformation to the π-hydroxoallyl form and further to the C-bonded form. A similar pathway has been proposed by Shmidt for the phosphine analogues.[17b] Oxidative addition of HCl followed by reductive elimination of acacH yields **2**.



Scheme 3. Proposed mechanism for the formation of **1** and **2**.

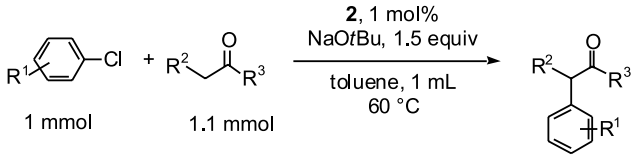
Table 1. Buchwald–Hartwig aryl amination of aryl chlorides using **2**

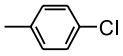
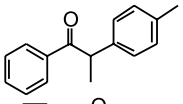
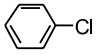
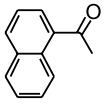
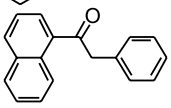
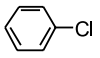
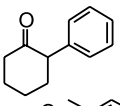
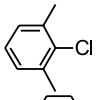
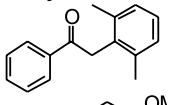
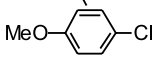
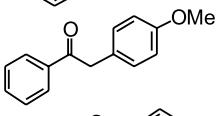
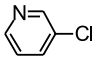
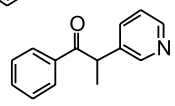


Entry	Aryl chloride	Amine	Product	Time (h)	Yield (%)[a]
1				0.5	97
2				0.5	98
3				1.5	90
4				4	99
5		Bu_2NH		6	95
6				10	93[b]

[a] Isolated yields, average of two runs.
[b] 2.1 equiv of aryl chloride were used.

Table 2. α-Ketone arylation with aryl chlorides using **2**



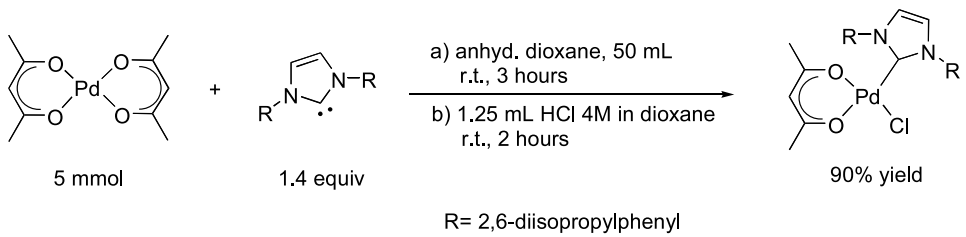
Entry	Aryl chloride	Ketone	Product	Time (h)	Yield (%)[a]
1				1	97
2				10	70
3				2	86
4				1	95
5				1.5	92
6				2	89

[a] Isolated yields, average of two runs.

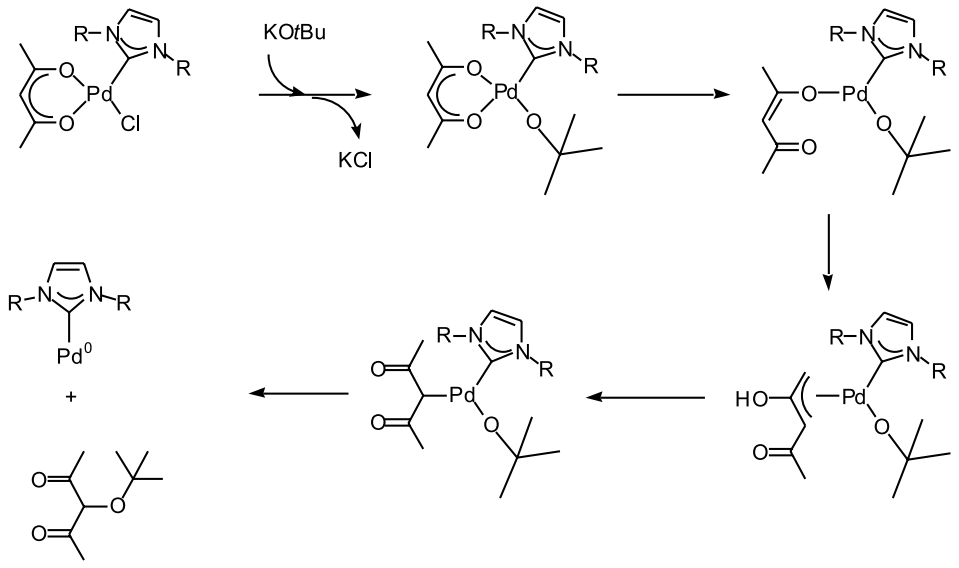
The activity of complex **2** for the Buchwald–Hartwig coupling reaction of morpholine and 4-chlorotoluene in the previously mentioned conditions was then tested. Using 1 mol% of **2**, the coupling occurred in 97% yield in only 30 min (entry 1, isolated yield). It is remarkable that the product could be obtained in good yield using low catalyst loading (0.1 mol%) or at room temperature if the reaction time was increased. Results for the amination of aryl chlorides using **2** as catalyst are shown in Table 1. Various substrates were examined: heteroaromatic (entry 2), sterically demanding (entry 3) and deactivated chlorides (entry 4). The coupling of the sterically demanding dibutylamine with 4-chlorotoluene required a longer time (entry 5), and was the only reaction, in which dehalogenation of the aryl chloride was observed (3% by GC). As the synthesis of unsymmetrical tertiary amines starting from primary amines remains a challenge,[19] we investigated the reaction between aniline and 2-chloropyridine. One-pot syntheses of *N*,*N*-bis(2-pyridyl)amino ligands, especially with aryl chlorides,[20] are attractive due to the number of applications in which these compounds can take part: C–C bond formation,[21] homogeneous and heterogeneous catalysis,[22] DNA binding[23] and nonlinear optical materials.[24] The formation of the double pyridilation product was observed in good yield when 2.1 equiv of the chloride were used (entry 6).

As for the Buchwald–Hartwig reaction, **2** performed more effectively than **1** for the α-ketone arylation reaction, requiring half the time in the coupling of propiophenone and 4-chlorotoluene (Table 2, entry 1). Using **2**, the system allowed for the coupling of aryl–aryl and aryl–alkyl ketones with a variety of aryl chlorides.

Since **2** displayed a higher activity than **1**, we realized the convenience of synthesizing **2** without the need of isolating the (IPr)Pd(acac)$_2$ intermediate. A one-pot multigram synthesis of **2** is summarized in Scheme 4. Reaction of the free carbene IPr with Pd(acac)$_2$ in anhydrous 1,4-dioxane at room temperature, followed by the addition of an equimolecular amount of HCl, leads to the formation of the desired product.



Scheme 4. One-pot protocol for the synthesis of (IPr)Pd(acac)Cl.



Scheme 5. Proposed mechanism for the activation of (IPr)Pd(acac)Cl.

A possible mechanism for the activation of **2** is depicted in Scheme 5.

The activation pathway involves the chloride/*tert*-butoxide anion exchange in a metathetical process followed by a rearrangement of the acac moiety prior to a reductive elimination step that yields the catalytically active [(IPr)Pd(0)] species. Recently, Hartwig reported that sterically demanding ancillary ligands promote the rearrangement of the κ^2-*O*,*O*-bound ligands to the C-tautomers in Pd(II) complexes with malonate or acetylacetonate anions.[25] It was also proposed that only complexes with these ligands in a C-bound mode are able to undergo reductive elimination in high yield. This fact not only supports the need of this rearrangement for the activation of **2**, but also for the formation of **1** and its later transformation into **2** by the addition of HCl (Scheme 3).

We have described the synthesis of two new NHC-bearing palladium complexes using $Pd(acac)_2$ as the Pd precursor. Complex **2** displays high activity for the Buchwald–Hartwig reaction and α-ketone arylation in short reaction times and very mild conditions. Both complexes are air- and moisture-stable and can be prepared on multigram scale in high yields. Studies focusing on the synthesis of related NHC-bearing complexes and their activity in homogeneous catalysis are currently ongoing in our laboratories.

3. Experimental

3.1. General remarks

^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$ (Cambridge Isotope Laboratories, Inc), unless otherwise noted. Elemental analyses were performed at Robertson Microlit Laboratories, Inc., Madison, NJ. IPr·HCl was synthesized according to literature procedures but is also now commercially available from Strem Chemicals Inc or Sigma/Aldrich.[26]

3.2. Synthesis of complexes

3.2.1. (IPr)Pd(acac)$_2$ (1). In a glovebox, a Schlenk flask equipped with a magnetic bar was loaded with free carbene IPr (855 mg, 2.2 mmol), $Pd(acac)_2$ (609 mg, 2 mmol) and anhydrous toluene (30 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and THF (25 mL) was added. The solution was filtered and the solid washed with THF (2×5 mL). The solvent was evaporated in vacuo; the complex was then triturated with cold pentane (25 mL) and the yellow precipitate was collected by filtration. Recrystallization from chloroform/pentane (25:75) yielded 1.28 g (93%) of the desired compound as a yellow microcrystalline material. ^1H NMR (400 MHz, C_6D_6): δ 7.28–7.24 (m, 2H), 7.18 (d, J=8.0 Hz, 4H), 6.47 (s, 2H), 5.90 (s, 1H), 4.78 (s, 1H), 2.88 (q, J=6.8 Hz, 4H), 2.63 (d, J=0.8 Hz, 3H), 2.01 (d, J=0.8 Hz, 3H), 1.63 (s, 3H), 1.35 (d, J=6.8 Hz, 12H), 1.31 (s, 3H), 0.97 (d, J=6.8 Hz, 12H). ^{13}C NMR (100 MHz, C_6D_6): 207.5, 192.9, 188.1, 185.6, 183.3, 161.2, 146.9, 135.9, 131.2, 130.4, 125.7, 125.2, 124.7, 124.5, 104.8, 100.3, 47.2, 31.9, 31.5, 29.3, 29.0, 28.9, 28.1, 27.0, 26.5, 26.2, 25.1, 24.0, 23.8, 23.4. Elemental analysis: Anal. Calcd: C, 64.11; H, 7.27; N, 4.04. Found: C, 63.89; H, 7.06; N: 3.86.

3.2.2. One-pot synthesis of (IPr)Pd(acac)Cl (2). In a glovebox, a Schlenk flask equipped with a magnetic bar was loaded with the free carbene IPr (2.73 g, 7 mmol), $Pd(acac)_2$ (1.53 g, 5 mmol) and anhydrous dioxane (50 mL), and sealed with a rubber cap. The mixture was stirred at room temperature for 2 h. After that time, 1.25 mL of HCl 4 M in dioxane was injected in the solution and the mixture allowed stirring at room temperature for another 2 h. The solvent was then evaporated in vacuo and diethyl ether was added until no more solid dissolved (20 mL). The solution was filtered and the solid washed with diethyl ether (2×10 mL). The solvent was evaporated in vacuo and the powder obtained dried under vacuum overnight to yield 2.85 g

(90%) of the desired product as a yellow microcrystalline material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, J=7.6 Hz, 2H), 7.35 (d, J=8.0 Hz, 4H), 7.12 (s, 2H), 5.12 (s, 1H), 2.95 (q, J=6.4 Hz, 4H), 1.84 (s, 3H), 1.82 (s, 3H), 1.34 (d, J=6.4 Hz, 12H), 1.10 (d, J=6.4 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 187.1, 184.1, 156.4, 147.0, 135.5, 134.8, 130.9, 125.7, 124.7, 124.6, 99.9, 29.1, 30.0, 27.6, 26.8, 23.7, 23.5. Elemental analysis: Anal. Calcd: C, 61.05; H, 6.88; N, 4.45. Found: C, 60.78; H, 7.15; N: 4.29.

3.3. Crystallographic data

3.3.1. (IPr)Pd(acac)$_2$ (1). Single crystals were grown by slow evaporation at room temperature of a concentrated methylene chloride/hexanes solution. $C_{37}H_{50}N_2O_4Pd$, M=693.2. Orthorhombic, space group $P2_12_12_1$, a=11.7529(6) Å, b=13.3836(7) Å, c=22.6493(12) Å, V=3562.6(3) Å^3; $D_c(Z=4)$=1.292 g cm^{-3}; μ_{Mo}=0.560 mm^{-1}; specimen: 0.6×0.5×0.3 mm; $T_{min/max}$=0.88; $2\theta_{max}$=40°; N_t=22450, N_o=3318; R=0.0340, R_w=0.0737.

3.3.2. (IPr)Pd(acac)Cl (2). Single crystals were grown by slow evaporation at room temperature of a concentrated methylene chloride/hexanes solution. $C_{32}H_{43}N_2O_2Pd$, M=629.53. Monoclinic, space group $P2_1/c$, a=10.957(2) Å, b=17.431(3) Å, c=16.814(3) Å, β=106.162(4) V=3084.4(10) Å^3; $D_c(Z=4)$=1.356 g cm^{-3}; μ_{Mo}=0.718 mm^{-1}; specimen: 0.6×0.6×0.4 mm; $T_{min/max}$=0.77; $2\theta_{max}$=45°; N_t=30901, N_o=4006; R=0.0259, R_w=0.0576.

CCDC reference numbers 263919-263920.

See http://www.rsc.org/suppdata/dt/b4/b4125540a/ for crystallographic data in CIF or other electronic format.

3.4. Cross-coupling reactions

3.4.1. Buchwald–Hartwig reaction of aryl chlorides with primary and secondary amines. *General procedure*: In a glovebox, **2** (1 mol%, 6 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg) and DME (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl chloride (1 mmol) were injected in turn through the septum. The vial was then placed in an oil bath at 50 °C and the mixture stirred on a stirring plate. The reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion could be observed, the vial was allowed to cool down to room temperature. Water was added to the reaction mixture; the organic layer was extracted with diethyl ether and dried over magnesium sulfate. The solvent was then evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel (pentane/ethyl acetate: 9:1). Reported yields are the average of two runs:

3.4.1.1. 4-(4-Methylphenyl)morpholine (Table 1, entry 1).[27] The procedure afforded 171 mg (97%) of the title compound.

3.4.1.2. 4-(2-Pyridinyl)morpholine (Table 1, entry 2).[28] The procedure afforded 160 mg (98%) of the title compound.

3.4.1.3. 4-(2,6-Dimethylphenyl)morpholine (Table 1, entry 3).[29] The procedure afforded 170 mg (90%) of the title compound.

3.4.1.4. 4-(4-Methoxyphenyl)morpholine (Table 1, entry 4).[30] The procedure afforded 190 mg (99%) of the title compound.

3.4.1.5. *N*,*N*-Dibutyl-*p*-toluidine (Table 1, entry 5).[31] The procedure afforded 207 mg (95%) of the title compound.

3.4.1.6. *N*-Phenyl-*N*-(pyridin-2-yl)pyridin-2-amine (Table 1, entry 6).[32] The procedure with 2-chloropyridine (2.1 mmol, 200 μL), aniline (1.0 mmol, 93 μL), KO*t*Bu (2.2 mmol, 248 mg), (IPr)Pd(acac)Cl (1.0 mol%, 12.6 mg) and DME (2 mL) afforded 230 mg (93%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.22 (d, J=4 Hz, 2H), 7.61 (m, 2H), 7.38 (t, J=8.1 Hz, 2H), 7.24–7.16 (m, 3H), 7.00 (d, J=8.4 Hz, 2H), 6.97–6.94 (m, 2H). ^{13}C NMR (100 MHz, $((CD_3)_2CO)$): 159.5 (C), 149.4 (CH), 146.6 (C), 138.6 (CH), 130.7 (CH), 128.9 (CH), 126.6 (CH), 119.3 (CH), 118.0 (CH). Elemental analysis: Anal. Calcd for $C_{16}H_{13}N_3$ (M_W 247.29): C, 77.71; H, 5.30; N, 16.99. Found: C, 77.79; H, 5.57; N, 16.93.

3.4.2. α-Ketone arylation of alkyl or aryl ketones

General procedure: In a glovebox, **2** (1 mol%, 6 mg), sodium *tert*-butoxide (1.5 mmol, 144 mg) and toluene (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the ketone (1.1 mmol) and the aryl chloride (1.0 mmol) were injected in turn through the septum. The vial was then placed in an oil bath at 60 °C and the mixture stirred on a stirring plate. The reaction was monitored by gas chromatography. When reaction reached completion, or no further conversion could be observed, the vial was allowed to cool to room temperature. Water was added to the reaction mixture; the organic layer was extracted with diethyl ether and dried over magnesium sulfate. The solvent was then evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel (pentane/ethyl acetate: 9:1). The reported yields are the average of two runs:

3.4.2.1. 2-(4-Methylphenyl)-1-phenyl-1-propanone (Table 2, entry 1).[33] The procedure afforded 216 mg (97%) of the title compound.

3.4.2.2. 1-(Naphthyl)-2-phenylethanone (Table 2, entry 2).[34] The procedure afforded 173 mg (70%) of the title compound.

3.4.2.3. α-Phenylcyclohexanone (Table 2, entry 3).[35] The procedure afforded 150 mg (86%) of the title compound.

3.4.2.4. 2-(2,6-Dimethylphenyl)-1-phenylethanone (Table 2, entry 4). The procedure afforded 212 mg (95%) of the title compound as a white compound. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.09 (d, J=7.2 Hz, 2H), 7.64 (t, J=7.2 Hz, 1H), 7.54 (t, J=8.0 Hz, 2H), 7.14–7.06 (m, 3H), 4.40 (s, 2H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, CD_2Cl_2):

197.5 (C), 137.7 (C), 133.7 (CH), 133.4 (C), 129.2 (CH), 128.5 (CH), 128.3 (CH), 127.3 (CH), 114.0 (C), 40.2 (CH_2), 20.6 (CH_3). Elemental analysis: Anal. Calcd for $C_{16}H_{16}O$ (M_W 224.30): C, 85.68; H, 7.19. Found: C, 85.36; H, 7.23.

3.4.2.5. 2-(*p*-Methoxyphenyl)-acetophenone (Table 2, entry 5).[36] The procedure afforded 208 mg (92%) of the title compound.

3.4.2.6. 1-Phenyl-2-(3-pyridinyl)-1-propanone (Table 2, entry 6).[37] The procedure afforded 188 mg (89%) of the title compound.

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Towards the rational design of palladium-*N*-heterocyclic carbene catalysts by a combined experimental and computational approach

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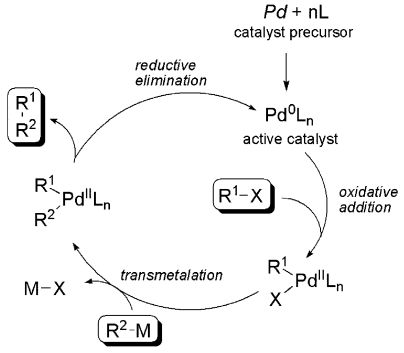
Abstract—A combined experimental and computational approach towards the development of Pd–NHC catalysts is described. A range of benzimidazolylidinium ligands incorporating electron-rich and electron-poor substituents were prepared and evaluated in the Suzuki reaction. The most electron-rich ligand showed the highest catalytic activity. Based on this information, the first alkyl–alkyl Negishi cross-coupling reaction protocol was developed. Evaluation of *N*,*N*′-diaryl-(4,5-dihydro)imidazolylilidinium ligands showed a strong dependence on the steric topography around the metal centre. A computational study of the most active ligand in the Negishi reaction, its Pd(0) and $PdCl_2$-complexes and related structures were modelled at the B3LYP/DZVP and HF/3-21G levels of theory. The potential energy hypersurfaces flattened with increase in ligand size. Binding energies were computed for carbene/Pd(0) adducts (in the range ~31–40 kcal mol^{-1}), roughly double that for PH_3 (~16 kcal mol^{-1}). Weak intramolecular interactions were found using AIM analyses.

1. Introduction

The coupling of organohalides or pseudohalides with organometallic reagents utilising Pd catalysts represents one of the corner stones in modern organic chemistry. The applications of various cross-coupling methodologies are numerous and far ranging, from total synthesis to materials to industrial-scale drug production.[1] The established mechanism (Scheme 1) is believed to proceed through three discrete steps: oxidative addition, transmetalation, and finally, reductive elimination concomitant with regeneration of the Pd(0) species. Oxidative addition is believed to be enhanced by an electron-rich palladium centre, which is facilitated by careful choice of the supporting ligand. The reductive elimination step is primarily affected by the steric topography surrounding the transition metal centre.[2] The linking transmetalation step is unique in its role of delivery of the second coupling partner into the catalytic cycle. The judicious choice of solvents, temperature and transmetalation promoters (e.g., bases, additives) can have a profound effect on the success of the overall cross-coupling process. The continuing quest to improve catalyst performance in recent years has led to significant advancements. The groups of Beller[3] and Buchwald[4] introduced a series of bulky biaryldialkylphosphine derivatives **1–11** for Suzuki and Negishi reactions. Similarly, bulky trialkyl phosphines[5] have proven very effective in these processes (Fig. 1). In addition, numerous palladacycles have been prepared and



Scheme 1. General mechanism of Pd-catalysed cross-coupling reactions.

Keywords: Alkyl–alkyl Negishi cross-coupling reaction; Oxidative addition; Reductive elimination.
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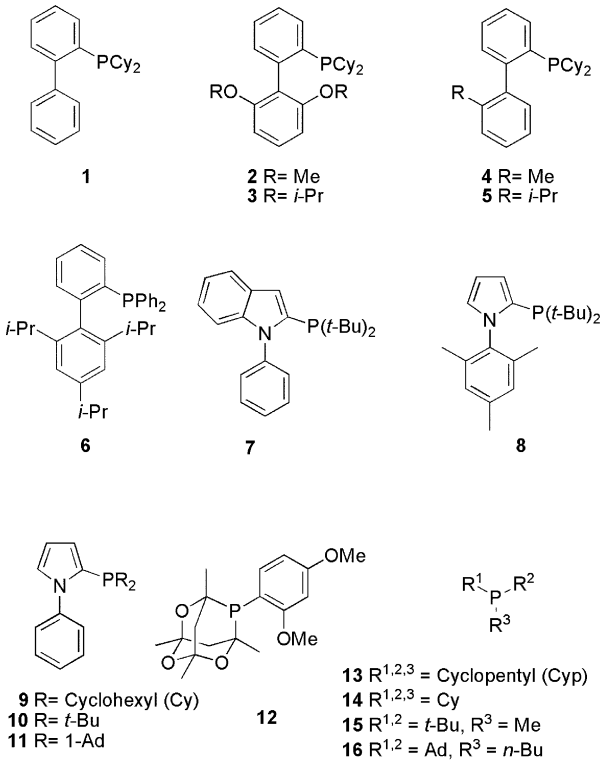


Figure 1. Bulky phosphines used as ligands in Pd-catalysed cross-coupling reactions.

employed as catalysts or pre-catalysts in a variety of Pd-catalysed processes, including cross-coupling reactions.[6]

Arguably, the most challenging cross-coupling is that of an alkyl halide with an alkyl organometallic reagent. The first example of a coupling of alkyl halides (RI) possessing β-hydrogens with alkyl-9-BBN derivatives used $Pd(PPh_3)_4$ as catalyst and appeared in 1992.[7] By changing the phosphine ligand to **14**, Fu and co-workers extended this protocol to alkyl halides (RBr, RCl),[8] while alkyl tosylates required **15**.[9] The latter ligand was also effective in a single example of coupling of an alkyl chloride with *n*-hexylboronic acid.[10] Capretta et al. recently developed a novel phosphine (**12**) for Pd-catalysed cross-coupling of alkyl bromides (primary and secondary), chlorides and tosylates with a range of alkyl-9-BBN derivatives, as well as alkylboronic acids.[11] Building on the pioneering studies by Knochel and co-workers on the Ni-catalysed alkyl–alkyl Negishi cross-coupling reaction,[12] Fu et al demonstrated that **13** formed a competent catalyst for the cross-coupling reaction of primary alkylzinc reagents with primary alkyl chlorides, bromides and tosylates[13] in THF–NMP (2/1) at 75 °C.

Phosphines however, have significant drawbacks particularly the more useful trialkyl derivatives, which are oxygen sensitive, some even pyrophoric, thus requiring special handling. Fu and co-workers employed phosphonium tetrafluoroborate salts as a way to circumvent these issues.[14] Under mild conditions, an exchange of alkyl- and aryl groups from the phosphine to palladium and vice-versa has been observed.[15] Additionally, the fact that phosphines readily dissociate from the metal limits their use in supported synthesis as the metal leaches off the support. In recent years *N*-heterocyclic carbenes (NHCs), previously referred to as 'phosphine mimics', have emerged as effective supporting ligands for palladium catalysed cross-coupling reactions.[16] Efficient protocols for Pd–NHC catalysed reactions have been developed recently that have allowed NHCs protocols to approach the levels of activity attainable with phosphines. Herrmann et al. disclosed a very catalytically active Pd–NHC complex related to **19** for the conversion of aryl chlorides to biaryls in Suzuki reactions.[17] Due to the size of the adamantyl groups, *o*-substituents in both the aryl chloride and the boronic acid were not tolerated. Subsequently, Glorius developed pentacyclic carbenes (e.g., **20**) that overcame this barrier.[18] The authors proposed that the 'flexible steric bulk' of the pentacyclic NHC ligand is largely responsible for the high activity of Pd catalysts based on **20** in the coupling of sterically demanding substrates. Nolan and co-workers have made significant contributions to the field of Pd–NHC catalysis. While their early efforts focused on catalysts prepared in situ based on ligands **17** and **18**,[19] subsequently, isolated Pd complexes (**21**, **22**,[20] **23**, **24**[21] and **25**, **26**[22]) were synthesized and shown to be active in Suzuki cross-couplings of a wide range of aryl chlorides. Beller and co-workers developed a series of dimeric Pd–NHC naphthoquinone complexes (**27**, **28**), which proved to be active in a variety of cross-coupling reactions (Fig. 2). [23]

While phosphines are used in catalysis 'as is', *N*-heterocyclic carbenes are often generated from the corresponding azolium salts by treatment with a strong base.[24] When alkali metal alkoxides are used as bases, an addition–elimination mechanism dominates over direct deprotonation (Fig. 3).[25] Owing to the intrinsic instability and moisture sensitivity of many NHCs, Pd–NHC catalysts are prepared in situ from Pd precursors and azolium salts. The result is that the exact amount and chemical composition of the catalysts is unknown and this is a serious impediment to the interpretation of results. To deal with this problem, well-defined Pd–NHC complexes (e.g., **21**–**26**) have been studied more recently in the context of catalysis.

One area of phosphine based methodology, which hitherto has not been accomplished successfully (in high yield) with NHC protocols are alkyl–alkyl coupling reactions.[26] Beller et al.[27] obtained high yields in the cross-coupling of aryl magnesium bromides with alkyl halides utilising the preformed catalysts **27** and **28**. Fu et al. developed a Pd–NHC/CuI-catalysed Sonogashira coupling of alkyl bromides and iodides.[28] Recently, Caddick, Cloke et al. published the first Pd–NHC (ligand **18**) catalysed alkyl–alkyl Suzuki reaction in low to moderate yields.[29] These examples demonstrate that Pd–NHC complexes are capable of inserting into alkyl–halide bonds.

With all of the above in mind, we initiated a program to develop a high-yielding, practical and efficient protocol(s) for cross-coupling reactions in general, and alkyl–alkyl coupling in particular, utilising Pd–NHC catalyst(s) combining experimental and computational studies in a unified, rational approach.

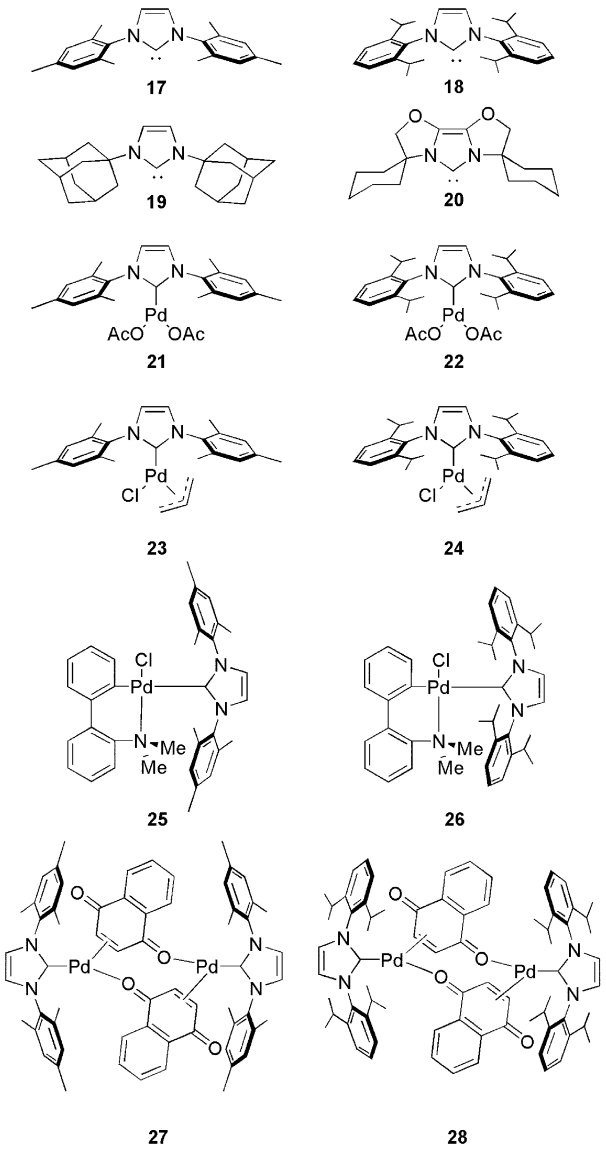


Figure 2. Highly catalytically active NHC ligands and Pd–NHC complexes.

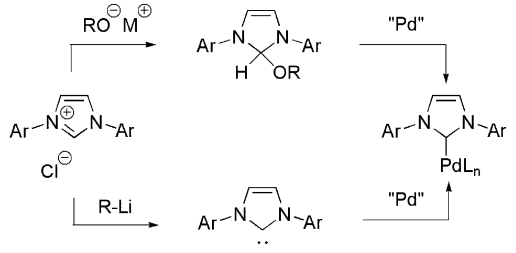


Figure 3. Common ways for preparation of Pd–NHC complexes and catalysts.

2. NHC–Pd catalyst development program overview

Traditionally, catalyst development was based on serendipitous discovery followed by trial and error optimisation. Parallel or combinatorial synthesis of catalyst candidates and subsequent high-throughput screening for activity has improved discovery.[11] A different approach would be the rational design of the catalyst.[30] For this there needs to be at least partial understanding of a number of issues. First and foremost, detailed mechanistic information regarding the steps in the catalytic cycle is necessary as a basis for the design of the ligand. The current accepted cross-coupling mechanism details three distinct steps (Scheme 1): oxidative addition, transmetalation and reductive elimination. These steps pose distinct, and sometimes, even contradictory steric and electronic demands on the catalyst.[1a] Although there is a significant body of literature pertaining to computational studies on Pd-catalysed reactions with phosphines,[31] there is little data available for Pd–NHC complexes.[32] In an attempt to clarify the issues raised above we embarked on computational studies to answer four fundamental questions: (1) what is the 'true' steric and electronic nature of the NHC ligand; (2) how does the NHC ligand's steric and electronic environment affect the Pd metal centre; (3) how do the combined properties of the Pd metal and NHC ligand transmit into the 'catalytic cycle'; (4) how do Pd–NHC and Pd–phosphine catalysts differ with respect of catalytic activity? Nevertheless, computation at present can only provide part of the answer. Therefore, we are putting serious efforts into the synthesis and systematic evaluation of NHC ligands with carefully tuned electronic and steric properties, the structure-activity relationship (SAR) of the NHC ligand platform being the ultimate goal. We assumed this would be led initially by experimental results guided by current literature data and intuition. However, a computation model being developed in parallel will take an ever increasing role in ligand design by elucidating the SAR of the NHC ligand platform. To that end we envisioned preparing transition metal–NHC complexes (e.g., Pd, Ag, Ni or Fe) and characterising the nature of the metal–ligand bond. This will be done by studying the effect of the ligand on the electronic properties of the metal centre using multinuclear NMR. As an additional benefit, such studies will allow the validation of our computational model, bridging the gap between computation and experiment. This paper presents our efforts and places them in context with the current state-of-the-art in the cross-coupling reaction field. First, we will present our experimental findings with respect to ligand design and evaluation, cross-coupling protocol development and its application in synthesis. Computationally we will discuss the steric and electronic nature of NHC ligands **17** and **18** (the most widely employed) and their Pd complexes.

3. Experimental

3.1. Ligand design

Initially, we focused on designing new NHC ligands of varying electronic and steric nature. We hoped to use these ligands to identify cross-coupling reactivity trends to aid further ligand design. We chose the well established, operationally simpler aryl–aryl Suzuki reaction as a tool to elucidate the effects of the electronic and steric features of NHC ligands on the cross-coupling reaction.[33] Even though benzimidazolylidenes have received limited attention as NHC ligands,[34] they provide a suitable platform for tuning the electron density on the carbene carbon. By introducing electronically different substituents at positions 5 and 6 (Fig. 4) we hoped to remotely alter the electronic character of the palladium metal centre without altering the steric

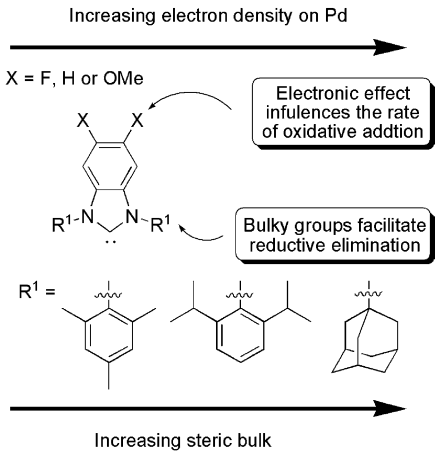
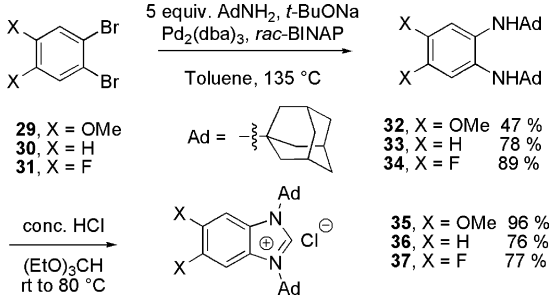


Figure 4. Tuneable benzimidazolylilidinium ligands.

environment at the metal. At the same time, altering the *N*-substituent would allow the topography around the metal to be tuned to ensure the required steric bulk for reductive elimination is in place.

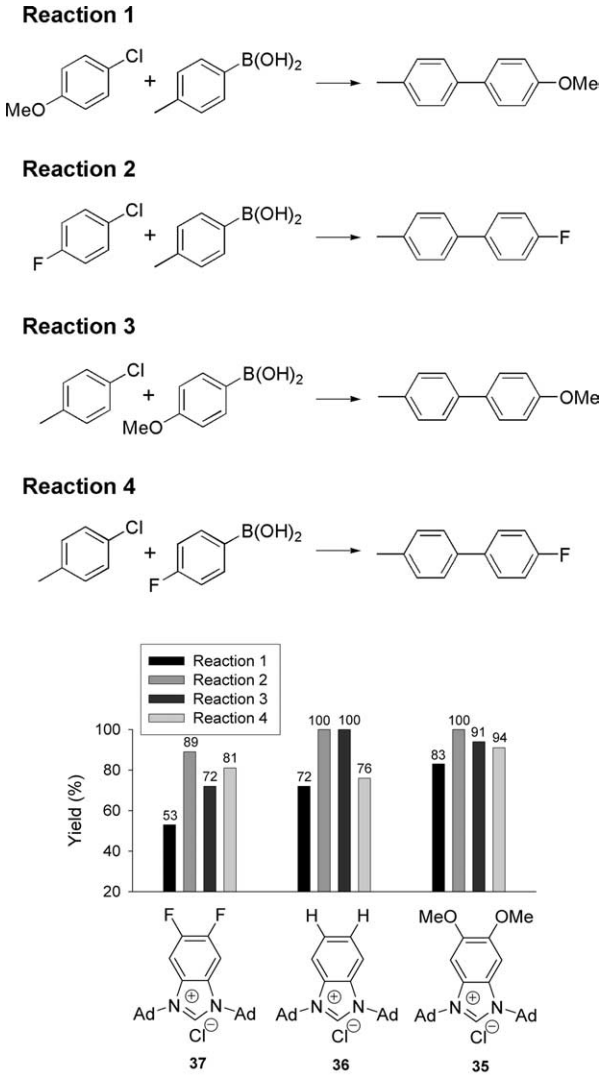
The first step in the benzimidazolium salt synthesis[35] was a Buchwald–Hartwig amination of the required 1,2-dibromoarene (**29**–**31**) with excess 1-adamantylamine and sodium *tert*-butoxide (Scheme 2). This was followed by cyclisation of **32**–**34** with ethyl orthoformate/HCl producing the benzimidazolium chlorides **35**–**37** in good yields. Unfortunately, we were unable to cyclise any of the corresponding aniline derived analogues.



Scheme 2. Synthesis of *N*,*N*-diadamantylbenzimidazolium salts.

We submitted NHC precursors **35**–**37** to the Suzuki reaction conditions.[36] Using an electron-rich (Reaction 1, Graph 1) and an electron-poor (Reaction 2, Graph 1) chloroarene with *p*-tolylboronic acid (an electronically neutral substrate) would allow us to probe the electronic influence of the ligands on oxidative addition. Alternatively, coupling *p*-chlorotoluene (an electronically neutral substrate) with an electron-rich (Reaction 3, Graph 1) and an electron-deficient (Reaction 4, Graph 1) phenylboronic acid would allow us to probe the electronic influence of the ligands on reductive elimination.

Results suggest that the transmetalation and reductive elimination steps are unaffected by the electronic nature of the carbene ligand. However, reactions conducted with the most electron deficient ligand **37** consistently yielded the lowest amount of product whilst the most electron rich ligand **35** was found to give the highest yields. These results



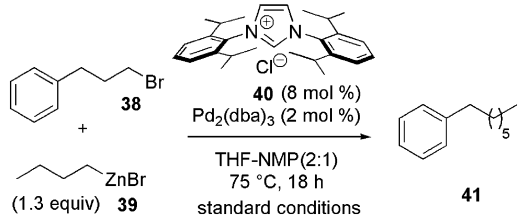
Graph 1. Suzuki cross-coupling reaction of a range of electron-rich and electron-deficient chloroarenes and phenylboronic acids. The most electron rich ligand (**35**) was found to give the highest coupling yields, whilst the most electron-poor (**37**) the lowest, with the electronically neutral ligand (**36**) in-between. The reaction was more sensitive towards electronic perturbance in the chloroarene than in the phenylboronic acid, suggesting that the oxidative addition is affected mostly by electronic effects, while steric bulk played the dominant role during the reductive elimination. Reaction conditions: 4 mol% $Pd(OAc)_2$, 8 mol% **35**–**37**, 0.5 mmol of 4-chlorotoluene, 0.75 mmol of arylboronic acid, 1 mmol Cs_2CO_3, dioxane (1.5 mL), 80 °C, 24 h, in duplicate. The yields were determined by GC/MS against calibrated internal standard (undecane).

indirectly corroborate the theory that the reductive elimination step in Pd–NHC catalysed reactions is primarily governed by the steric nature of the NHC ligand.[2,33] If oxidative addition is the rate-determining step and its rate is increased by an electron rich metal centre,[37] these results can be explained by assuming that rate of oxidative addition of the palladium complexes is in the order **35**>**36**>**37**, which is in agreement with the current mechanistic theory.[1a] Also, insightful work by Fairlamb et al. showed that electron rich *trans*, *trans*-dibenzoylacetone (dba) analogues led to an increase in catalyst efficiency of Pd–NHC (ligand **17**) catalysts when used as co-ligands.[38] These results imply that NHC ligand design should focus on creating an electron rich carbene ligand with a carefully selected steric

environment around the metal centre. While the topography created by the neighbouring *N*-substituents must not retard the oxidative addition, it must be sufficient to ensure rapid elimination of the product and thus, turn-over of the catalyst while avoiding β-hydride elimination.

3.2. Alkyl–alkyl cross-coupling protocol development

Armed with this information we set about the development of an alkyl–alkyl cross-coupling protocol.[39] Since we were unable to synthesize the originally intended ligand set of *N*,*N*′-disubstituted benzimidazolium salts (Fig. 3), we did not have the whole spectrum of ligand topology available. Therefore, **35–37** were not employed in our initial investigations. Also, we had reached an opinion that once a certain 'level' of σ-donating power had been reached by the NHC ligand the steric environment imparted by the ligand was then the most important factor in the development of a successful protocol. Hence, we submitted the bulky imidazolium salt **40** (Fig. 2) to Negishi conditions,[13] assuming that the alkylzinc reagent would facilitate the formation of active catalyst. We were delighted to find that cross-coupling occurred in high yield (Scheme 3, Table 1, entry 1). An earlier report indicated that the addition of *N*-methylimidazole (NMI) in alkyl–alkyl Negishi cross-coupling reactions catalysed by Pd/**13** leads to higher yields. This was attributed to



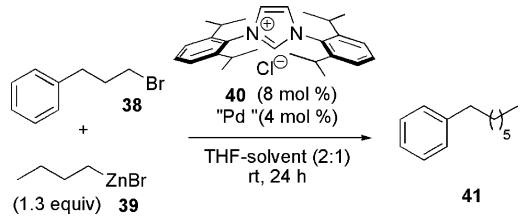
Scheme 3. Alkyl–alkyl Negishi cross-coupling reaction—initial optimization.

Table 1. Effect of reaction conditions on the yield of alkyl–alkyl Negishi coupling

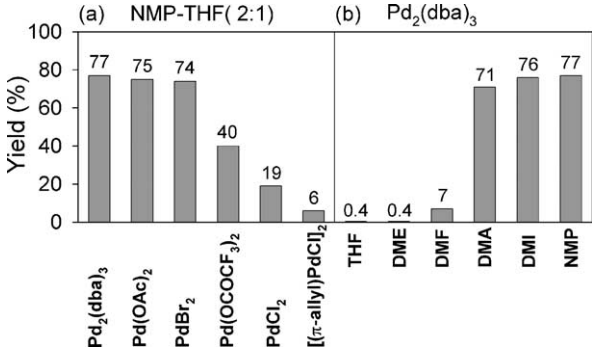
Entry	Change from standard conditions	Yield (%)[a]
1	None	75
2	No ligand (1)	0.3
3	No $Pd_2(dba)_3$	0.0
4	Add NMI (1.2 equiv)	75
5	55 °C	70
6	Room temperature, 24 h	77

[a] GC yield against a calibrated internal standard (undecane); reactions were performed in duplicate and the average yield reported.

activation of the organozinc reagent.[13] In contrast, we found that NMI is not beneficial for achieving a high cross-coupling yield in the Pd–NHC protocol (Scheme 3, Table 1, entry 4). Furthermore, the reaction proceeded with equal efficiency at 55 °C and room temperature (Scheme 3, Table 1, entries 6 and 7). Further evaluation of palladium precatalysts at room temperature demonstrated that $Pd_2(dba)_3$, $Pd(OAc)_2$ and $PdBr_2$ were equally successful, while other Pd precursors were less effective (Scheme 4, Graph 2a). Finally, a solvent study revealed a dependence on polar amide solvents (DMA, DMI, NMP, but not DMF)



Scheme 4. Alkyl–alkyl Negishi cross-coupling reaction—source of Pd and temperature study.



Graph 2. Optimisation of catalyst composition: (a) assessment of commercially available Pd-precatalysts; (b) assessment of co-solvents. We determined that $Pd_2(dba)_3$, $Pd(OAc)_2$ and $PdBr_2$ were optimal (74–77% yield), as were amide solvents (NMP, DMI, DMA, but not DMF, 71–77% yield).

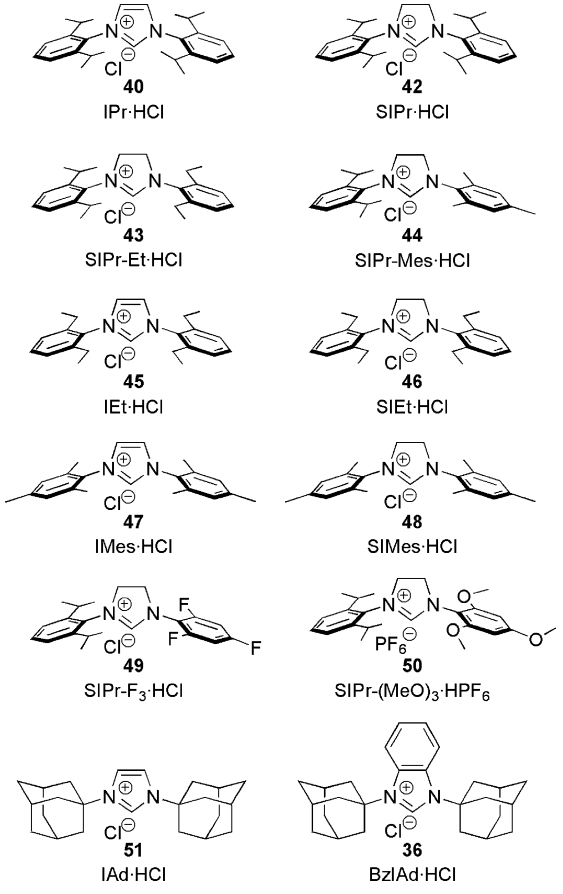
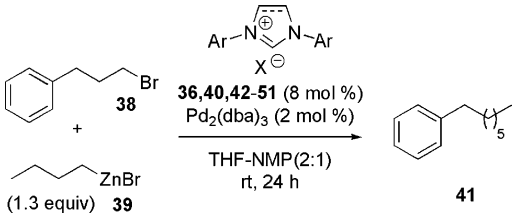


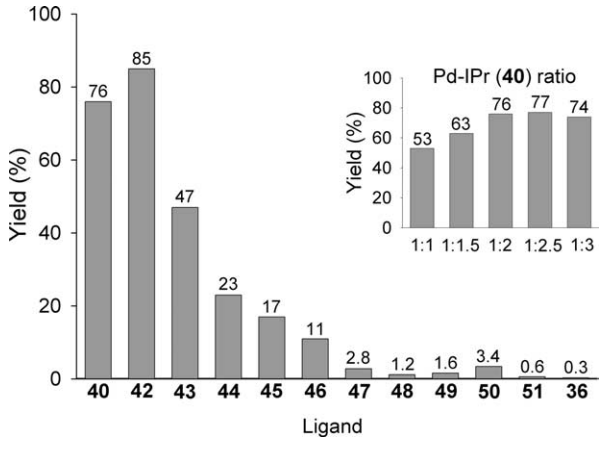
Figure 5. Imidazolium and 4,5-dihydroimidazolium NHC ligand precursors.

to achieve high yields (Graph 2b), similar to earlier reports.[12,13] However, ether solvents (THF, DME) proved ineffective (Scheme 4, Graph 2b).

Following our initial success, we conducted a detailed evaluation of a series of imidazolium and 4,5-dihydroimidazolium salts (Fig. 5, Scheme 4, Graph 3). We observed a very strong dependence on the steric bulk of the substituents on the nitrogen atoms of the five-membered ring (Graph 3) (Scheme 5). The 2,6-diisopropylphenyl substituent was required for high coupling yields, irrespective of the nature of the carbene, imidazolium (**40**) versus 4,5-dihydroimidazolium (**42**). The corresponding ethyl analogues **43**[40] and **44** were much less active and the mesityl carbenes derived from **47** and **48** were ineffective.[8a,13] The most sterically demanding adamantyl carbenes derived from **51** and **36** did not yield any cross-coupling product. Whether this failure was due to the different topology imparted by adamantyl groups (compared to the 2,6-dialkylphenyl) or lack of Pd–NHC complex formation remains unclear at this point. Intrigued by the effect of the bulky 2,6-diisopropylphenyl substituent, we decided to evaluate a range of unsymmetrical 4,5-dihydroimidazolium salts. One 2,6-diisopropylphenyl substituent was retained and either a 2,6-disubstituted or 2,4,6-trisubstituted aryl moiety bearing a range of alkyl groups, electron-donating (OMe) or electron-withdrawing substituents (F) was introduced on the other nitrogen. We observed that ligand precursor **43**, possessing the most sterically hindered arene substituents (2,6-diisopropylphenyl and 2,6-diethylphenyl) yielded 47% of product compared to 11% for the symmetrical diethyl analogue (**46**). An analogous yield increase was observed for the 2,6-diisopropylphenyl-mesityl derivative (**44**) compared to the symmetrical mesityl NHC precursor (**47**). In contrast, even though the *o*-methoxy groups in **50** are similar in size to the ethyl groups in **45**, very little product was observed. Similarly, the 2,4,6-trifluoroanalogue **49** was ineffective. Finally, an investigation of the Pd:NHC (precursor **40**) ratio confirmed that a 1:2 ratio was optimal (Graph 3). Only slight variations in yield were observed when the Pd:**40** ratio was increased from 1:1 to 1:3. This suggests that only one catalytically active species was formed and the variation in yield was due to differing amounts of the active catalyst being produced in situ. We propose this to be a monoligated Pd–NHC species.[35a,41]



Scheme 5. Alkyl–alkyl Negishi cross-coupling reaction—ligand evaluation.



Graph 3. Evaluation of ligand structure (Fig. 5). The symmetrical 2,6-diisopropylphenyl substituted salts (**40**, **42**) yielded the most cross-coupling product (76 and 85%), irrespectively of the nature of the carbene backbone (unsaturated vs saturated). We also observed slight dependency on Pd–IPr ratio, inferring that a monoligated Pd–IPr species is the active catalyst. We observed a direct correlation between the size of the flanking aryl substituents and cross-coupling yield. Electron-withdrawing (**49**) or electron-donating (**50**) substituents were detrimental regardless of substituents size. Similarly, the adamantyl-substituted ligands **51** and **36** were not effective.

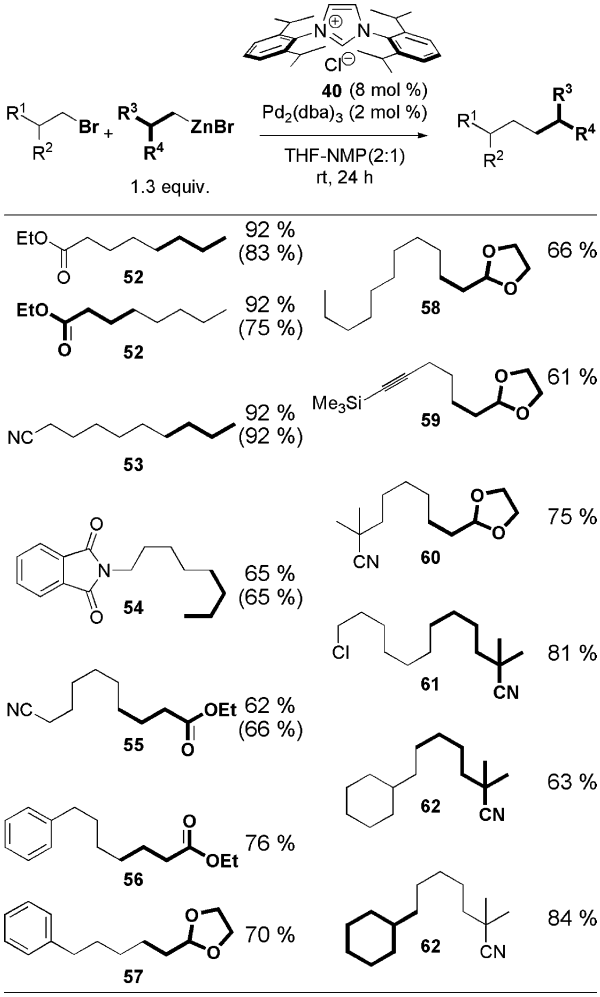


Figure 6. Room temperature Negishi cross-coupling reactions of unactivated alkyl bromides with alkyl zinc reagents. The alkyl fragment from the organozinc reagent is shown in bold. Conditions: $Pd_2(dba)_3$ (2 mol%), IPr·HCl (8 mol%), *n*-butylzinc bromide (0.5 M in THF, 12 mol%) stirred for 1 h, alkyl bromide (0.5 mmol), alkylzinc reagent (0.5 M in THF, 0.65 mmol) in THF–NMP (2/1), room temperature, 24 h, in duplicate. Average isolated yield at room temperature; isolated yield at 75 °C in parentheses.

3.3. Synthetic applications of the alkyl–alkyl Negishi cross-coupling protocol

Under optimised conditions, a variety of substrates were coupled in good to excellent yields at room temperature (Fig. 6). The results indicate that a number of functional groups (esters, nitriles, amides, alkynes and acetals) were tolerated. It is noteworthy that the yields at room temperature were generally higher than when performed at 75 °C. The addition of a small amount (12 mol%) of *n*-butylzinc bromide ensured reproducible catalyst formation. Of particular interest is the coupling of β-substituted alkyl bromides and alkylzinc reagents to produce products such as **62**. Moreover, we observed that alkyl chlorides were unreactive under these conditions as we were able to activate selectively an alkyl bromide in the presence of an alkyl chloride (product **61**).

4. Computation and models

4.1. General computational methods

The GAUSSIAN 98 (G98) program package[42] was used for all computations in this work. Common convergence criteria of 3.0×10^{-4}, 4.5×10^{-4}, 1.2×10^{-3} and 1.8×10^{-3} were used for the gradients of the root mean square (RMS) force, maximum force, RMS displacement and maximum displacement vectors, respectively. Model carbene and saturated-carbene structures were constructed from existing and pre-computed molecular structures. In order to meet the 'design criteria' for a scalable ab initio 'building block' approach, a modular construct was employed that allowed for addition and/or removal of any portion of the model, without gross perturbation to the remainder. This was achieved via a numerical definition of the relative spatial orientation of all constituent atoms, affording explicit control over all degrees of freedom, allowing for perturbation of the existing precomputed data.[43] Although all assemblies of pre-computed building blocks must still be geometry optimised, the use of pre-optimised portions allow for an overall increase in computational efficiency as well as theoretical accuracy and precision.[44] Utilising existing Unix-shell and practical extraction and report language (PERL) scripts,[45] computation, data and networking management were optimised. Computations were performed on distributed and algorithm-specific hardware arrays. All results were housed in a growing database of computed structures.[44,46] The rsync option[47] was used to continually and accurately update the database. Each structure was initially geometry optimised using the ab initio[48] Hartree-Fock (HF) method,[49] employing the STO-3G[50] and split-valence 3-21G basis sets.[51] The results of the HF/3-21G computations were used as input in a theoretical refinement, using the B3LYP density functional theory (DFT) method.[52] Mathematical amelioration of the models was subsequently achieved through the use of the DZVP basis set.[53] The structural results of the B3LYP/3-21G level were used as starting structures in the B3LYP/DZVP computations. All structures were confirmed as residing at minima on their respective potential energy hypersurfaces (PEHS) using frequency calculations. Structures were visualised using the Molekel software package.[54]

4.2. Atoms in molecules (AIM) method

For the weak interactions including hydrogen-bond interaction, studies that use the theory of atoms in molecules (AIM),[55] based on both theoretical[56] and experimental[57,58] electron densities have drawn considerable interest recently. Different types of hydrogen bonding and weak interactions have been studied to describe the nature of these interactions. The topological properties of electron density distribution of a molecular system are based on the gradient vector field of the electron density $\rho(r)$ and on the Laplacian distribution of the electron density $\nabla^2\rho(r)$.[55,58] In the light of the AIM approach, critical points (CPs) of rank 3 were identified in the electron densities, both theoretical and experimental. There are bond critical points (BCPs), ring critical points (RCPs) and cage critical points (CCPs). The existence of a BCP between two atoms in an equilibrium molecular geometry is the necessary condition for two atoms that are bonded to one another. The pairs of gradient paths that originate at a BCP and terminate at neighbouring nuclei define a line through which electron distribution, $\rho(r)$, is a maximum with respect to any lateral displacement. In this paper, BCP properties were obtained using AIMPAC[59] and AIM98PC.[60] The molecular graphs studied were calculated and plotted using AIM2000.[61] In order to obtain meaningful data from AIM calculations it is essential to use all-electron wavefunctions; for this reason it was necessary to use the computationally time-consuming DZVP basis set and not resort to computationally more viable effective core potential calculations (ECP).

4.3. Background

Intrigued by the very different activities of IPr (**18**) and IMes (**17**) in the alkyl–alkyl cross-coupling Negishi reaction, we decided to model these ligands and their monoligated Pd(0) and Pd(II) complexes (Fig. 7). To increase computational efficiency, standardised numeric descriptions of the structures, intramolecular degrees of freedom, may be constructed and applied in computation. The atoms in a molecular structure may be numbered and thus, the intramolecular degrees of freedom defined in a systematic and modular way. Automation of input structure construction, computation, level augmentation, result extraction and theoretical reproduction is facilitated using standardised and numeric structural descriptions. Therefore, for the sake of

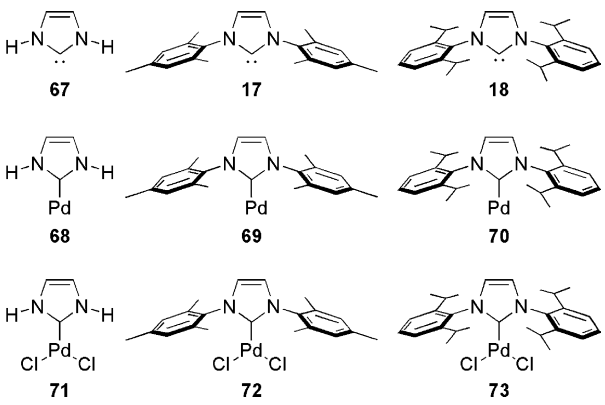


Figure 7. Computed NHC ligands and their Pd(0) and Pd(II) complexes

reproducibility and computational efficiency, the relative spatial orientation of all constituent atoms in the ligand and Pd-complex structures were defined in a standardised, numeric and modular fashion. Simple Unix-shell and PERL[45] scripts may be employed and visualisation tools are not required during computation.

All systems were constructed numerically (without visualisation) and geometry optimised at the HF/STO-3G level of theory. The geometry optimised structures from this level were used as input for the HF/3-21G level. Due to computational demands of the Pd-containing systems, the Pd–NHC systems were only geometry optimised to the HF/3-21G level of theory. The NHC and NHC–$PdCl_2$ systems were brought up to the more accurate B3LYP/DZVP level of theory, through subsequent theoretical refinement steps, via the B3LYP/3-21G level:

HF/STO-3G → HF/3-21G → B3LYP/3-21G → B3LYP/DZVP

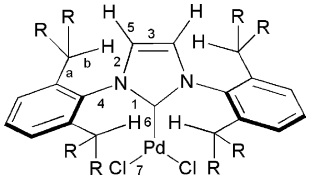


Figure 8. Bond lengths (Table 2).

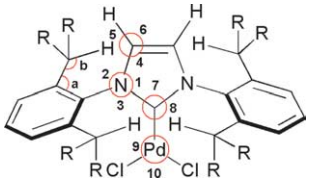


Figure 9. Bond angles (Table 3).

4.4. Geometry

All carbene structures retained C_2 symmetry and thus all bond lengths, bond angles and dihedrals angles (Fig. 8, (Table 2), Fig. 9 (Table 3), Fig. 10 (Table 4), Fig. 11 and Fig. 12) presented are almost identical on either side of the axis going through the metal–carbene bond; consequently only the values from one side are listed in Tables 2 and 3. From the selected results listed in Table 2, it is clear that all of the reported geometric parameters differ only by a very small relative amount and there is a marked conservation of geometry throughout all the structures. The carbene ring has a nearly identical structure in all cases and remains perfectly planar with all dihedral angles $<0.1°$, thus only one column is used to report all carbene-ring dihedral angles. The Pd–C–N–C dihedral angle and thus, the geometric relation of the metal to the carbene ring remains in the *anti* conformation and thus, in-plane with the five-membered ring for both dihedral angles (Pd–C–N–C vs Pd–C–N′–C′).

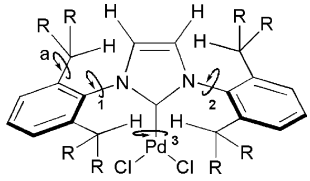


Figure 10. Dihedral angles (Table 4).

Table 2. Selected bond lengths (Å) for structures **17**, **18**, **67–73**, geometry optimised at the HF/3-21G and B3LYP/DZVP levels of theory, corresponding to the bond lengths outlined in Figure 8

Structure	Level	Bond lengths (Å)								
		1	**2**	**3**	**4**	**5**	**6**	**7**	**a**	**b**
67	B3LYP/DZVP	1.372	1.395	1.361	1.010	1.081	n/a	n/a	n/a	n/a
17	B3LYP/DZVP	1.374	1.398	1.359	1.440	1.081	n/a	n/a	1.512	1.095
18	B3LYP/DZVP	1.375	1.397	1.359	1.443	1.081	n/a	n/a	1.526	1.093
68	HF/3-21G	1.361	1.401	1.332	0.992	1.063	2.082	n/a	n/a	n/a
69	HF/3-21G	1.366	1.407	1.329	1.430	1.063	2.124	n/a	1.514	1.083
70	HF/3-21G	1.367	1.407	1.329	1.434	1.063	2.198	n/a	1.524	1.080
71	B3LYP/DZVP	1.349	1.387	1.365	1.019	1.080	1.970	2.357	n/a	n/a
72	B3LYP/DZVP	1.359	1.393	1.357	1.451	1.080	1.982	2.344	1.511	1.094/1.096[a]
73	B3LYP/DZVP	1.360	1.393	1.356	1.456	1.079	1.977	2.338	1.527	1.092

[a] Two values are presented for the two side chain H atoms for structure **72**, as they differ slightly in geometry indicative of an interaction.

Table 3. Selected bond angles (degrees) for structures **17**, **18**, **67–73**, geometry optimised at the HF/3-21G and B3LYP/DZVP levels of theory, corresponding to the bond lengths outlined in Figure 9

Structure	Level	Bond angles (degrees)											
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**a**	**b**
67	B3LYP/DZVP	114.3	124.3	121.4	105.5	123.8	130.7	100.4	n/a	n/a	n/a	N/a	n/a
17	B3LYP/DZVP	113.0	123.5	123.5	106.1	123.0	131.0	101.8	n/a	n/a	n/a	121.0	110.7/111.8[a]
18	B3LYP/DZVP	113.0	123.4	123.6	106.1	123.0	130.9	101.7	n/a	n/a	n/a	122.3	107.9
68	HF/3-21G	112.8	125.0	122.2	106.2	123.1	130.7	101.9	129.0	n/a	n/a	n/a	n/a
69	HF/3-21G	112.0	123.8	124.3	106.7	122.1	131.2	103.0	128.6	n/a	n/a	120.3/120.8[a]	108.6/110.2[a]
70	HF/3-21G	112.1	123.2	124.7	106.6	122.0	131.4	103.0	128.7	n/a	n/a	121.2	108.3
71	B3LYP/DZVP	110.9	128.6	120.6	106.4	122.7	130.9	105.5	127.2	91.6	176.8	n/a	n/a
72	B3LYP/DZVP	109.7	123.1	127.2	107.1	121.5	131.4	106.4	126.8	96.2	167.6	122.2	111.3/111.7[a]
73	B3LYP/DZVP	109.6	122.7	127.7	107.2	121.6	131.2	106.4	126.8	95.5	169.0	123.1	108.2

[a] Two values are presented for the two side chain H atoms for structures **17**, **69** and **72**, as they differ slightly in geometry indicative of an interaction.

Table 4. Selected bond angles (degrees) for structures **17**, **18**, **67–73**, geometry optimised at the HF/3-21G and B3LYP/DZVP levels of theory, corresponding to the bond lengths outlined in Figure 10

Structure	Level	Dihedral angles (degrees)				
		Ring	**1**[a]	**2**[a]	**3**	**a**
67	B3LYP/DZVP	0.0	N/a	n/a	n/a	n/a
17	B3LYP/DZVP	0.0	89.8/−90.2	n/a	n/a	58.5/−60.5[b]
18	B3LYP/DZVP	0.0	90.0/−90.1	n/a	n/a	9.7
68	HF/3-21G	0.0	n/a	n/a	n/a	n/a
69	HF/3-21G	0.0	74.3/−106.6	−106.5/74.3	n/a	n/a
70	HF/3-21G	0.0	90.5/−90.6	−90.5/90.5	n/a	n/a
71	B3LYP/DZVP	0.0	n/a	0.1/179.9	0.0/179.9	n/a
72	B3LYP/DZVP	0.0	91.6/−92.3	−90.7/89.4	−90.7/89.3	52.1/−68.1[b]
73	B3LYP/DZVP	0.0	92.0/−91.8	−91.8/92.0	−89.9/90.2	−22.9

[a] Two values are presented for the phenyl ring dihedral angle relative to the carbene ring measured using both *o*-carbons.
[b] Two values are presented for the two side chain H atoms for structures **17** and **72**, as they differ slightly in geometry indicative of an interaction.

Table 5. Total energy (Hartree), zero point energy (ZPE) (Hartree) and binding energy (kcal mol^{-1}) computed at the B3LYP/DZVP level of theory

Reaction	Total energy ligand	ZPE ligand	Total energy $PdCl_2$	ZPE $PdCl_2$	Total energy $PdCl_2$-ligand	ZPE $PdCl_2$-ligand	Binding energy
67+$PdCl_2$→**71**	−226.196584	0.070913	−5860.045312	0.001888	−6086.362733	0.076043	73.8
17+$PdCl_2$→**72**	−924.241516	0.396443	−5860.045312	0.001888	−6784.400676	0.401992	69.1
18+$PdCl_2$→**73**	−1160.125480	0.396443	−5860.045312	0.001888	−7020.278419	—	(67.5)[a]

[a] Value in parentheses due to ZPE not included.

Table 6. Total energy (Hartree), zero point energy (ZPE) (Hartree) and binding energy (kcal mol^{-1}) computed at the HF/3-21G level of theory

Reaction	Total energy ligand	ZPE ligand	Total energy Pd	ZPE Pd	Total energy Pd–ligand	ZPE Pd–ligand	Binding energy
67+Pd(0)→**68**	−223.523397	0.077109	−4915.067168	0.000000	−5138.638258	0.078773	28.9
17+Pd(0)→**69**	−912.976187	0.427118	−4915.067168	0.000000	−5828.094484	0.429031	30.9
18+Pd(0)→**70**	−1145.885268	0.612974	−4915.067168	0.000000	−6061.015022	0.616391	41.4
PH_3+Pd→Pd(PH_3)	−340.704519	0.024686	−4915.067168	0.000000	−5255.799862	0.026506	16.5

The length of the Pd–carbene bond was ∼2.0 Å and varies by ∼+0.150 and ∼−0.030 Å at most (Table 2, column 6). Apparently, this distance has little dependence on the formal charge on the palladium. The bond angles of the carbene ring vary little, with the H-substituted carbene showing the 'tightest' N–C–N angle. All carbene angles conserve their geometry upon metal-binding. The phenyl rings in **17**, **18**, **69–73** are essentially perpendicular to the carbene ring. The two chlorides attached to the Pd in **72** and **73** adopt a geometry perpendicular to the carbene ring. The conformational space is quite restricted in these systems. In **18**, **70** and **73**, each structure optimised to a geometry where the IPr-sidechain oriented with the isopropyl C–H oriented inwards over the π-system of the carbene ring. This suggests that perhaps there is a CH···π interaction, not uncommon in other systems. The PH_3 and Pd–PH_3 structures were easily and quickly geometry optimised at the B3LYP/DZVP level of theory, with geometry and energetic results reported (Fig. 13 and Table 5, respectively).

The majority of the first 10 frequencies for the complexes have very low energies (cm^{-1}) indicative of very flat surfaces with much displacement at little energetic cost. In particular on increasing the size of the *N*-substituent the surface flattens, going from **67/68/71** through **17/69/72** to **18/70/73**. We suspect the flattened nature of the PEHS for the IPr systems is somehow tied to its reactivity; perhaps facilitating small structural perturbations while maintaining a crowded centre.

4.5. Energies

Total energies, zero-point energies (ZPE) and resultant binding energies are reported in Tables 5 and 6. The binding energy of the NHC **67** to Pd(0) is calculated to be 28.9 kcal mol^{-1}, almost twice the value obtained for PH_3 (16.5 kcal mol^{-1}). The binding energy for NHC is large for a neutral complex, almost comparable with the binding energies for mono-positive metal ions with small neutral ligands in the gas phase. Replacement of the hydrogens on the nitrogen atoms with aryl substituents, forming complexes **69** and **70**, results in an increase in the binding energy. The same three NHC ligands when attached to $PdCl_2$ have much higher binding energies (∼70 kcal mol^{-1}). Here, the inclusion of the aromatic rings on nitrogen has the reverse effect of slightly decreasing the binding energy.

4.6. Interactions

There is the question of the role intramolecular interactions play in the stabilisation of the ligands and Pd-ligated complexes. Possible interactions include Pd···ligand, Cl··· ligand and ligand···ligand but may not be characterised solely on geometric threshold separation. The aspect of matching donor- and receiver-orbital energies and

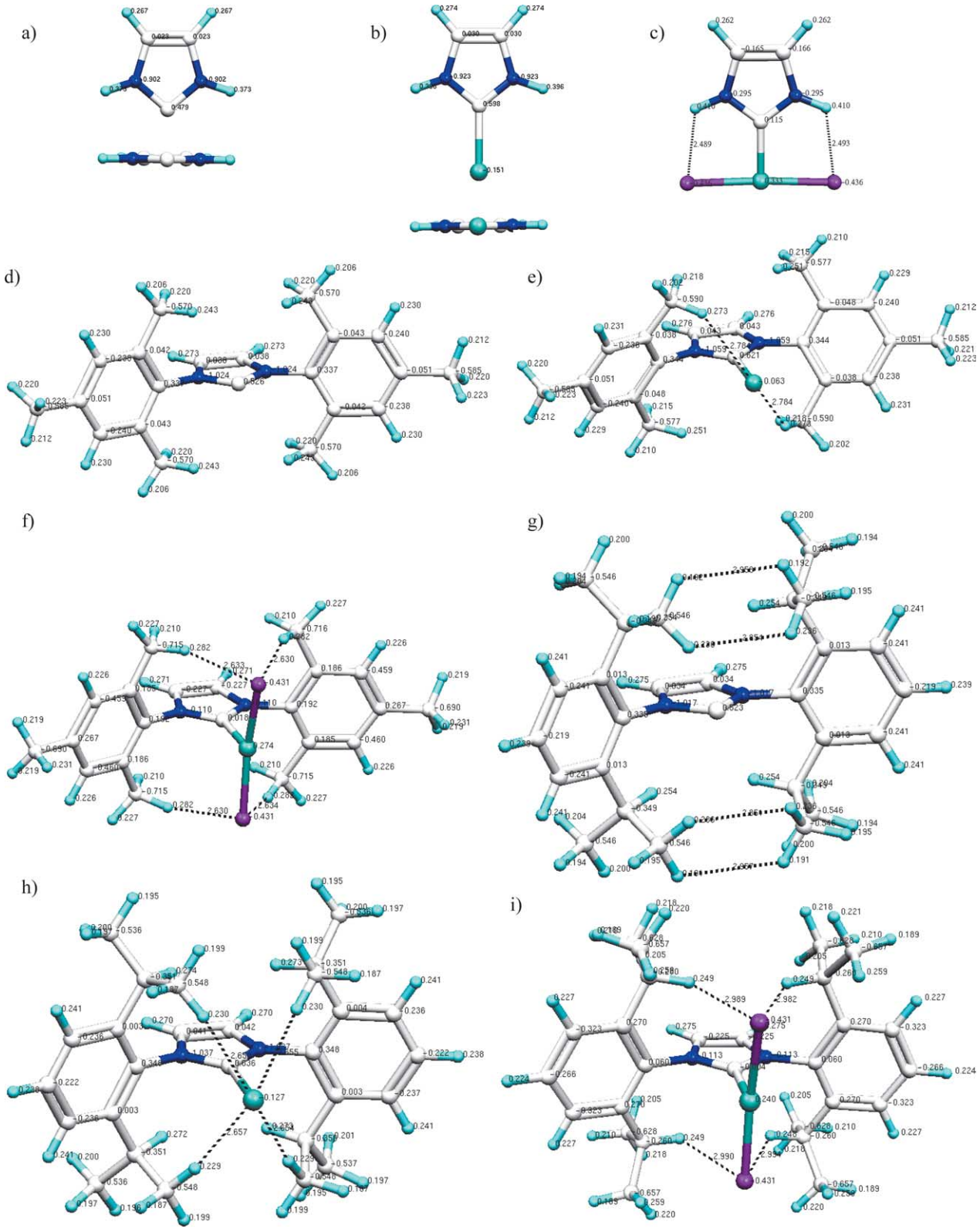


Figure 11. Visual representation of the geometry optimised structures : (a) **67** (b) **68** (c) **71** (d) **17** (e) **69** (f) **72** (g) **18** (h) **70** (i) **73**, with Mulliken charges on each atom. Distances (Å) are shown as dotted lines where there are possible weak intramolecular interactions.

symmetries is an important factor determining whether or not there is an actual interaction, based on sharing or exchange of electron density. This type of analysis is outside of the scope of this paper; however, preliminary AIM analyses show the presence of BCPs between non-covalently bound atoms. In ligand **18**, Me–H···H–Me interactions are observed and have distances of 3.052, 3.054, 3.106, 3.110, respectively, for the inner and outer (relative to the carbene ring) two H's (Fig. 12c). This was not expected until the AIM analysis was completed on the

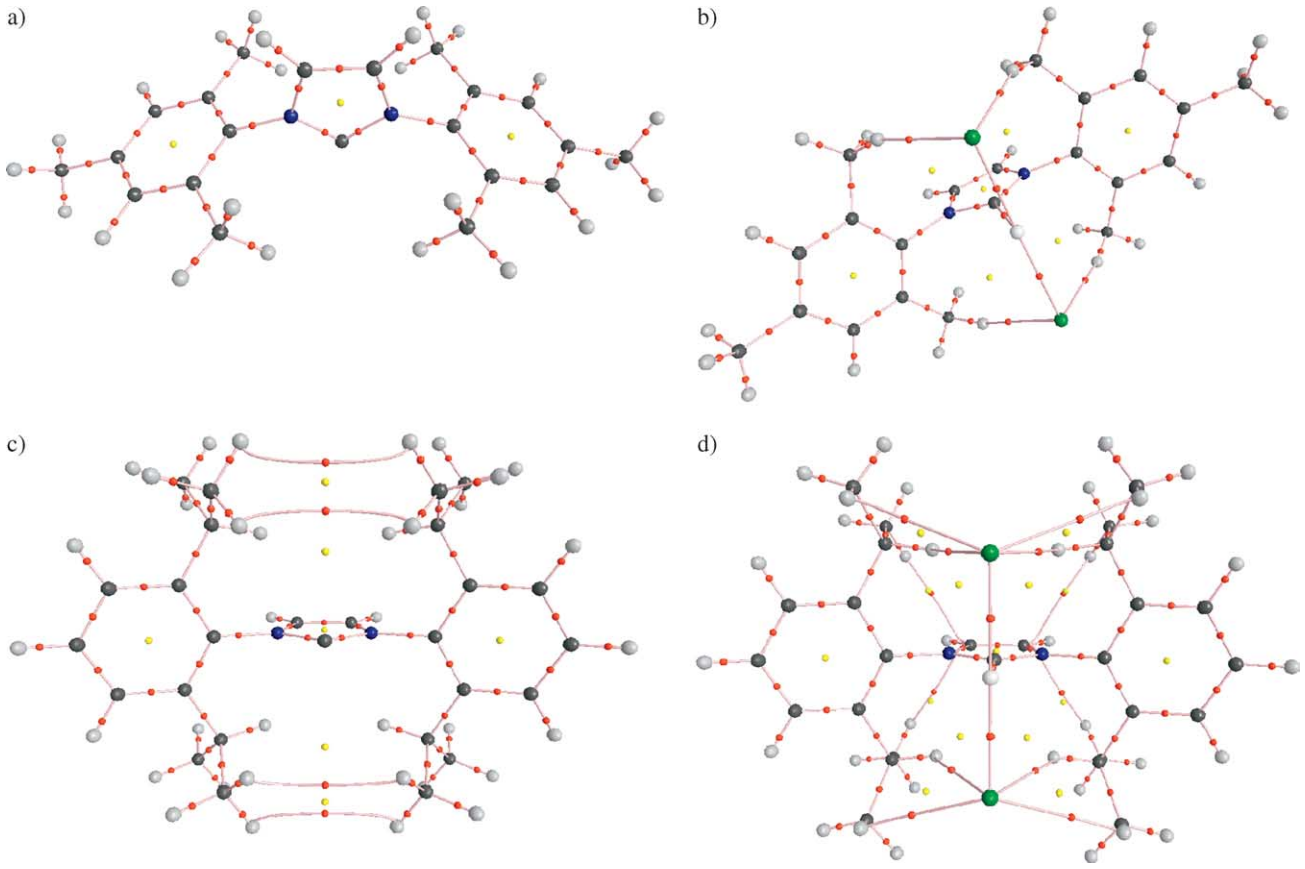


Figure 12. Molecular graphs generated from AIM analyses of the wavefunctions from the geometry optimised structures: (a) **17** (b) **72** (c) **18** (d) **73**, showing bond-critical points (BCPs-red) and ring-critical-points (RCPs-yellow).

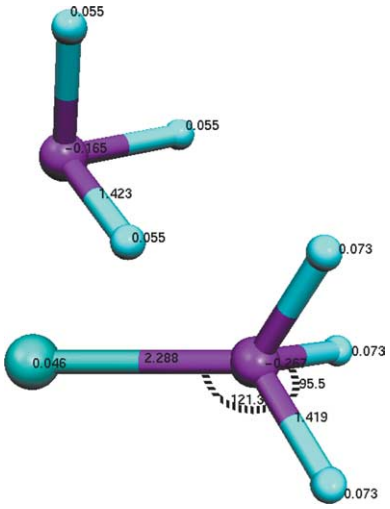


Figure 13. Visual representation of the B3LYP/DZVP geometry optimised PH_3 and Pd–PH_3 structures, showing selected bond lengths (Å), bond angles (degrees) and Mulliken charges.

geometry optimised structure. Although the interaction is expected to be very weak, it is important to note that the methyl groups rotate 60° upon metal-binding from a doubly-bisecting conformation to a singly-bisecting conformation. This observation hints that Pd ligation disrupts some intramolecular interactions in the free ligand. Furthermore, AIM analysis on the NHC-$PdCl_2$ structures all show a Cl···H interaction (Fig. 12b,c). In the monoligated Pd–NHC complexes (**69**, **70**) before the oxidative addition, these interactions are weak. However, as the catalytic cycle proceeds and more substituents are transferred onto the metal centre, such non-bonded interactions may exert a significant contribution to the overall success of the final process.

5. Future direction

The synthetic portion of this paper detailed the development of an alkyl–alkyl Negishi cross-coupling reaction. Future work will be directed towards expanding the scope of the protocol to include aryl, vinyl and alkyl chlorides and sulfonates and more elaborate organozinc reagents. Finally, we envisage that our Negishi protocol will be routinely applied in combinatorial library, parallel and target-oriented synthesis. Concurrently, we are preparing a library of NHC precursors to be evaluated in Suzuki and Negishi reactions with the dual aim of understanding the structure-catalytic activity relationship of the NHC ligand family and expanding the current set of practically useful ligands. Finally, the evaluation of user friendly, easily prepared, highly catalytically active Pd–NHC complexes with broad applicability in cross-coupling reactions is underway.

Computations must be carried out using DFT or post-Hartree-Fock methods, employing higher level basis sets

which include core electrons, in order to achieve satisfactory results to quantitatively align with trends observed experimentally. AIM analysis not only requires core electrons to be included in the basis sets, but is incorrect in their absence or through the use of basis sets employing an effective core potential (ECP) to approximate the influence of the core. The potential energy hypersurface (PEHS) flattens as the size of the ligand increases. Lower energetic barriers of rearrangement of the bulkier ligands could manifest themselves in 'breathing motions' of the *o*-substituents on the benzene ring, that may affect the oxidative addition or reductive elimination stages in the catalytic cycle. Intramolecular interactions show dependence on ligand–metal binding and ligand conformation, subsequently affecting the electron density of both ligand and metal. Therefore, understanding the influence of the conformational character upon the metal at the molecular level and of the metal on ligand conformation may allow for prediction and perhaps optimisation of resultant reactivity and yields. In the more sterically crowded complexes along the reaction profile these types of interactions may be more significant and it is essential to use at least a level of theory allowing for subsequent AIM analyses to characterise bonding and interactions.

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Oxidative addition of *N*-halosuccinimides to palladium(0): the discovery of neutral palladium(II) imidate complexes, which enhance Stille coupling of allylic and benzylic halides

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Abstract—The Stille coupling of organostannanes and organohalides, mediated by air and moisture stable palladium(II) phosphine complexes containing succinimide or phthalimide (imidate) ligands, has been investigated. An efficient synthetic route to several palladium(II) complexes containing succinimide and phthalimide ligands, has been developed. *cis*-Bromobis(triphenylphosphine)(*N*-succinimide)palladium(II) [$(Ph_3P)_2Pd(N\text{-Succ})Br$] is shown to mediate the Stille coupling of allylic and benzylic halides with alkenyl, aryl and allyl stannanes. In competition experiments between 4-nitrobromobenzene and benzyl bromide with a *cis*-stannylvinyl ester, $(Ph_3P)_2Pd(N\text{-Succ})Br$ preferentially cross-couples benzyl bromide, whereas with other commonly employed precatalysts 4-nitrobromobenzene undergoes preferential cross-coupling. Furthermore, preferential reaction of deactivated benzyl bromides over activated benzyl bromides is observed for the first time. The type of halide and presence of a succinimide ligand are essential for effective Stille coupling. The type of phosphine ligand is also shown to alter the catalytic activity of palladium(II) succinimide complexes.

1. Introduction

Great progress has been made in the development of transition metal-catalysed processes for the formation of carbon–carbon bonds.[1] Palladium-catalyzed processes, to date, represent the most frequently applied of these reactions and are increasingly being employed in synthetic routes to complex biological targets and therapeutic agents.[2] The Stille coupling reaction between organohalides and organostannanes, mediated by palladium, has attracted considerable attention and has been used as a 'test-bed' for the development of highly active palladium catalysts.[3,4] The broad utility of the Stille reaction is primarily due to the accessibility of a diverse range of organostannanes, their air and moisture stability and their excellent functional group compatibility, although the toxicity of organotin compounds can present problems. The scope of the Stille reaction has been substantially expanded recently, through state-of-the-art developments in the creation of highly active catalysts that operate under mild conditions.[5] Room temperature protocols for reactions employing organobromides, including hindered derivatives, are now available. Coupling of deactivated substrates such as aryl chlorides, not possible prior to 1998, is facilitated by electron rich bulky two-electron donor ligands such as $t\text{-}Bu_3P$[6] and *N*-heterocyclic carbenes.[7] The importance attached to the use of an activating donor ligand (strong σ-donor) derives from promotion of the oxidative addition process. Steric and electronic properties of ligands also produce pronounced effects, usually by influencing the intrinsic stability/reactivity of the palladium intermediates throughout the catalytic cycle.[8] The use of co-catalysts/additives and variation of the solvent can also be employed to optimize the efficiency of Stille coupling processes.[9]

Halide counterions are also known to play an important role in palladium-mediated cross-coupling processes, as well as in other transition metal-mediated reactions.[10] Pseudohalides (OAc, OTf) can also be influential: for example, in studies by Bedford and co-workers using palladacycles as pre-catalysts, the catalyst activity and lifetime, were dependent on the nature of the pseudohalide.[11] Comprehensive support for the involvement of halide/pseudohalide anions in palladium-catalysed cross-coupling reactions has been elegantly demonstrated by Amatore and Jutand.[12] Thus, in the presence of halides, the existence of an

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alternative catalytic cycle involving tricoordinated anionic complexes such as $L_2Pd(0)Cl^-$ and $L_2Pd(0)OAc^-$ has been demonstrated. Dimeric anionic palladium–halide complexes such as $[Pd_2I_6][Y_2]$, where $Y=DMFH^+$ or Et_3NH^+, have also been detected.[13] In addition, when palladium(II) precursors, for example, $Pd(Ph_3P)_2Cl_2$ or $Pd(OAc)_2$, are employed in coupling reactions, it has been proposed that anionic complexes are active catalysts as well as low-ligated, palladium '$L_nPd(0)$' (L is usually R_3P and $n=1$ or 2). Importantly, the nature of the halide or pseudohalide influences the reactivity of these palladium intermediates. In the absence of halide, the reduced species undergoes rapid reaction to form metallic palladium, which is clearly a limitation. Halide binding serves to stabilize the $L_nPd(0)$ complex. The halide could also stabilize palladium clusters or colloids, which act as a reservoir[14] of active catalytic Pd(0) species (neutral or anionic).

We have been interested in harnessing halide and pseudohalide effects in the design of improved catalysts for Stille coupling, as this is a potentially tunable property that could be exploited in increasing reactivity and substrate scope, but might also produce selective processes. This interest has been driven by our recent finding that succinimide, a pseudohalide, shows intriguing effects in the Stille reaction.[15] At the present time, it has not been established how this ligand exerts its effect, but it is clearly more than just a simple halide mimetic. Mechanistic studies are ongoing but in this paper, the preparation and application of Pd(II) succinimide and phthalimide complexes are discussed.

2. Results

2.1. The initial observation

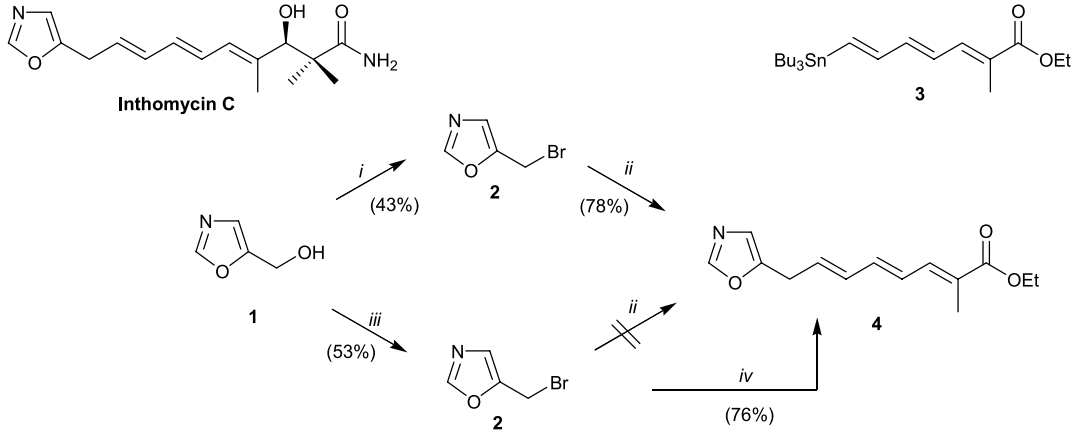
During the course of synthetic studies towards inthomycin C, a Stille coupling of oxazole bromide **2** with *E*,*E*,*E*-triene **3** was investigated (**2**+**3**→**4**, Scheme 1).

Bromide **2** was initially obtained from alcohol **1** using *N*-bromosuccinimide (NBS)/triphenylphosphine.[16] However, it proved to be sensitive to light, temperature, moisture and prolonged chromatography (although at −20 °C in the dark it was largely unchanged after one month); it was therefore semi-purified by passage through a very short silica column. In this form, **2** underwent efficient Stille coupling with organostannane **3** and catalytic $(PPh_3)_4Pd$ to give **4** in 78% yield. As large quantities of **4** were required, the use of CBr_4/Ph_3P[17] was investigated in order to improve the yield of bromide **2**. However, when **2** prepared via this route, was subjected to the Stille reaction as before, no coupling was observed. The reaction was repeated many times without success (purification of solvents/reagents and the use of freshly prepared $(Ph_3P)_4Pd$ did not alter the outcome).

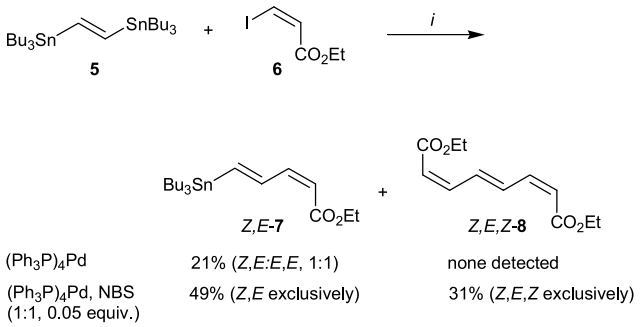
This surprising result led us to compare the two procedures. It seemed likely that traces of an 'impurity' were being carried through undetected with **2**; that is, something remaining from the NBS method could be acting to promote the coupling process or something from the CBr_4 method could be inhibiting coupling. The CBr_4/Ph_3P method produces Ph_3PO and $CHBr_3$, but excess starting reagents could also be present. However, $CHBr_3$ might be expected to enhance the Stille reaction as $CHBr_3$ is known to react with Pd_2dba_3/t-Bu_3P to give a palladium(I) dimer $[Pd_2(\mu\text{-}Br)_2(t\text{-}Bu_3P)_2]$,[18] which is a highly active catalyst for cross-coupling (amination)[19] and an excellent source of mono-ligated palladium(0) 't-Bu_3P-Pd(0)'.

Given that Ph_3P and Ph_3PO are present in both methods, attention was turned to the importance of the NBS. It seemed possible that trace amounts of NBS could be carried through the silica column with **2**, then activating the subsequent Stille coupling in a manner yet to be revealed. Indeed, on closer examination of the ^1H NMR spectrum of **2** used in the successful coupling process, a small singlet was observed at δ 2.7 ($CDCl_3$, 400 MHz), which corresponds to NBS. We therefore repeated the Stille coupling reaction of **2**, formed using the CBr_4 method, with stannane **3** but on this occasion added an equimolar amount of NBS with respect to the $(Ph_3P)_4Pd$. We were delighted to observe that this formerly unsuccessful process, now proceeded to give **4** in 76% yield.

In order to establish that the above observation had some generality, we studied its value in another problematic process investigated during the inthomycin programme (Scheme 2).



Scheme 1. i, Ph_3P, NBS, THF, 25 °C, 1 h; ii, **3** (1.05 equiv), $Pd(Ph_3P)_4$ (0.05 equiv), toluene, reflux, 20 h; iii, Ph_3P, CBr_4, CH_2Cl_2, 0 °C; iv, as for ii with added NBS (0.05 equiv).



Scheme 2. i, Toluene, reflux, 3 h.

Reaction of *E*-bis-1,2-(tributylstannyl)ethene **5**, with ethyl 2-iodo-2*Z*-propenoate **6** using $(Ph_3P)_4Pd$ had been shown to give 11% of the mono-coupled product *Z*,*E*-**7** and 10% of the corresponding *E*,*E*-isomer. Repeating the reaction but with addition of an equimolar amount of NBS with respect to the $(Ph_3P)_4Pd$, resulted in the formation of 49% of *Z*,*E*-**7** and 31% of *Z*,*E*,*Z*-**8**. The stereoselectivity observed in the NBS-modified process was noteworthy, as was the improvement of the overall yield from 21 to 80%.

The results shown in Schemes 1 and 2 indicated that the combination of NBS and $(Ph_3P)_4Pd$ had generated a highly active palladium catalyst. A search of the literature revealed that the oxidative addition of NBS to palladium(0) and platinum(0) precursors to give air and moisture stable complexes *cis*-$(Ph_3P)_2M(N\text{-Succ})Br$ (M=Pd or Pt), had been reported by Serrano and co-workers, although the catalytic properties of these complexes were not studied.[20] We therefore, decided to prepare such complexes and investigate their value in Stille coupling reactions.

2.2. Preparation of Pd(imidate)$(Ph_3P)_2$X complexes (X= halide or imidate; imidate=succinimide or phthalimide)

The published procedure for the preparation of *cis*-$(Ph_3P)_2$-Pd(*N*-Succ)Br **9** utilised Pd_2dba_3 dba (dba=*E*,*E*-dibenzylidene acetone) and NBS in dry CH_2Cl_2 at ambient temperature, followed by addition of 2 equiv of Ph_3P. In our hands **9** was obtained in low yields (~10%) with another palladium complex being isolated as a yellow precipitate in 30–40% yields, whose formation was dependent on a number of variables (vide infra). Recrystallisation of this major product followed by X-ray crystallography (Fig. 1), allowed identification as *trans*-$(Ph_3P)_2PdBr_2$ (^{31}P NMR, 202 MHz, CD_2Cl_2, δ 21.93). Changing to $(Ph_3P)_4Pd$ as the palladium(0) source, resulted in a rapid initial reaction but low conversion, as the additional phosphine removes NBS from the system as the phosphonium salt: addition of excess NBS (~3 equiv) pushes the reaction to completion, but the yield of **9**, although improved, was modest (31%).

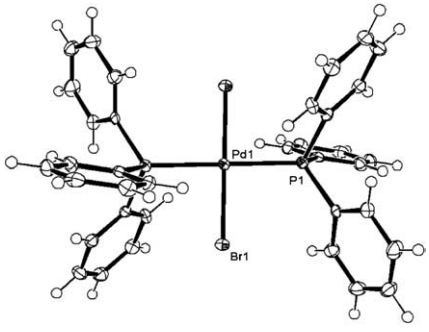
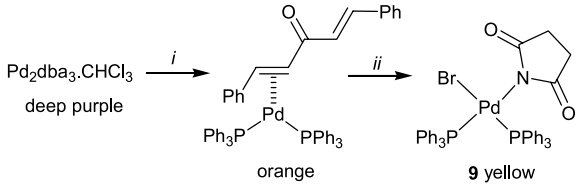


Figure 1. X-ray crystal structure of $(Ph_3P)_2PdBr_2$. Thermal ellipsoids are shown at 50% probability level.

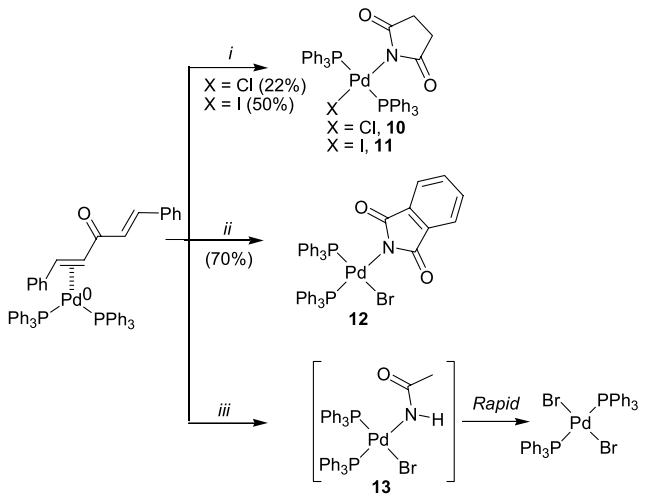
We discovered that improved yields of **9** could be obtained from Pd_2dba_3 dba simply by reversing the order of addition of reagents given in the published procedure.[20] Reaction of Pd_2dba_3 dba (1 equiv) with Ph_3P (4 equiv) in CH_2Cl_2 produced an intense orange colour, which can be attributed to the formation of '$(Ph_3P)_2Pd(0)$-η^2-dba' (Scheme 3).[21] Addition of a solution of NBS in CH_2Cl_2 at 21 °C after 0.15 h caused the reaction mixture to change to a bright yellow colour. The small amount of precipitate, which is *trans*-$(Ph_3P)_2PdBr_2$ is then removed by filtration. Addition of petroleum ether to the resultant filtrate produced a creamy yellow precipitate of **9** in yields, which varied between 20 and 52%. However, switching to $Pd_2dba_3\cdot CHCl_3$ as the palladium source resulted in an improvement to 74% yield. Complex **9** was crystallised from CH_2Cl_2/diethyl ether (1:5, 24 h, −20 °C) to give fine yellow crystals, which were characterised by X-ray diffraction and NMR spectroscopic studies.[15a]



Scheme 3. i, $Pd_2dba_3\cdot CHCl_3$ (0.5 equiv), Ph_3P (2 equiv), CH_2Cl_2, 25 °C, 0.2 h; ii, NBS (1 equiv), 0.2 h.

Related palladium complexes such as $Pd_2dba_3\cdot$solvent; solvent=benzene, toluene or CH_2Cl_2, can also be used to prepare **9**, as can $Pd_2[3,5,3',5'\text{-}(MeO)_4\text{-dba}]_3\cdot CH_2Cl_2$.[22] In this complex, the electron-rich dba dissociates more rapidly from palladium(0) than unsubstituted dba, increasing the relative rate of the oxidative addition process.[23] Using this precursor, a yield of 82% of **9** was attained. It should be noted that small quantities of *trans*-$(Ph_3P)_2PdBr_2$ were obtained if the reaction concentration exceeded 11 mM. Increasing the reaction temperature also leads to increasing amounts of *trans*-$(Ph_3P)_2PdBr_2$ but keeping the reaction temperature in the range 15–21 °C avoids the problem. It is believed that *trans*-$(Ph_3P)_2PdBr_2$ is formed via a bridged halide intermediate species, produced by dimerisation/disproportionation of two molecules of **9**.

We next examined whether other *N*-halo-succinimides, phthalimides and acetamides could used to prepare similar complexes to **9**. Using the optimum procedure for **9**, but employing *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS), gave the chloro- **10** and iodo- **11** analogues in ca. 22, and 50% yields, respectively, (Scheme 4). The lower yields are again due to the formation of complexes of the type $(Ph_3P)_2PdX_2$ (X=Cl, I). In fact, it was not possible to isolate **10** in pure form due to this impurity. Complexes **10** and **11** exhibit a *trans*-geometry around the palladium(II)



Scheme 4. Synthesis of other imidato palladium(II) complexes. i, $Pd_2dba_3\cdot CHCl_3$ (0.5 equiv), Ph_3P (2.0 equiv), CH_2Cl_2, 25 °C, 0.2 h, then NBS, NCS or NIS (1 equiv), 0.2 h; ii, as for i, but using NBP (1 equiv); iii, as for i, but using NBA (1 equiv).

centre (based on a singlet signals observed by ^{31}P NMR spectroscopy). On steric grounds, one might predict such a geometry for iodide **11**, but the fact that the NBS reaction gave *cis*-**9**, led us to predict that **10** might be *cis* as well. We presume that for **10** the *trans*-geometry is best rationalised by the relatively strong π-donor nature of chlorine—and with succinimide being a good π-acceptor, the *trans*-effect dominates.

It was not possible to obtain an X-ray crystal structure of chloride **10** but the X-ray structure of **11** was solved, confirming the *trans*-geometry and indicating extensive π-stacking interactions between the phosphorus aryl substituents and the succinimide methylene groups (Fig. 2). This interaction appears to shield both faces of the succinimide ring, but as two signals are observed for the succinimide methylene protons in $CDCl_3$, it would appear that the faces are differentially shielded.

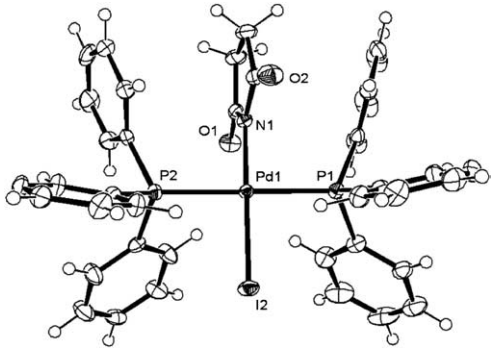
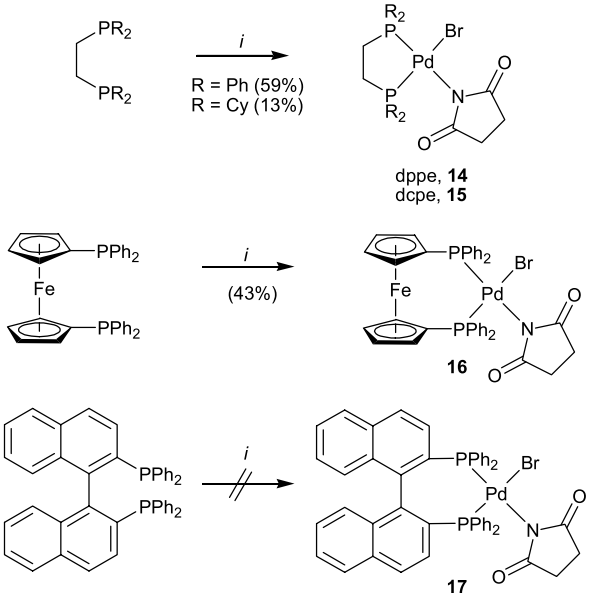


Figure 2. X-ray structure of **11**. Thermal ellipsoids are shown at 50% probability level.

The oxidative addition of *N*-bromophthalimide (NBP) to $Pd_2dba_3\cdot CHCl_3$ proceeded in a similar manner to the reaction with NBS, providing **12** in 70% yield (Scheme 4). The *cis*-geometry was confirmed by two inequivalent phosphorus signals as doublets at δ 24.89 and 33.80. The two-bond phosphorus–phosphorus coupling constant ($^2J_{PP}=8.39$ Hz) is similar to that seen in **9** ($^2J_{PP}=8.49$ Hz). Interestingly, the formation of $(Ph_3P)_2PdBr_2$ is not observed in this reaction. On the other hand, the oxidative addition of *N*-bromoacetamide (NBA) to $Pd_2dba_3\cdot CHCl_3$ to yield **13** was unsuccessful, affording $(Ph_3P)_2PdBr_2$ in 49% yield.

2.3. Preparation of succinimide complexes containing bidentate ligands

Reaction of $Pd_2dba_3\cdot CHCl_3$ with bidentate ligands, followed by oxidative addition with NBS was achieved using 1,2-bis(diphenylphosphino)ethane (dppe), 1,2-bis(dicyclohexylphosphino)ethane (dcpe) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) (Scheme 5). For dppe, **14** was isolated in 59% yield (δ 23.95, br s; and 61.87, br s; ^{31}P NMR, 161.2 MHz, $CDCl_3$), whereas the more electron rich and bulky dcpe ligand gave **15** in a poor 13% yield (δ 88.68, d, $^2J_{PP}=8.39$ Hz; and δ 91.30, d, $^2J_{PP}=8.39$ Hz; ^{31}P NMR, 202 MHz, CD_2Cl_2). The ferrocenyl ligand, dppf, also underwent reaction giving **16** in 43% yield (δ 24.52, br s; and δ 35.10, d, $^2J_{PP}=5.95$ Hz; ^{31}P NMR, 202 MHz, $CDCl_3$). In all three cases the products were formed as the *cis*-isomers. The reaction of (±)-BINAP was also attempted, but the expected complex **17** was not formed (several species were shown to be present by ^{31}P NMR spectroscopy).

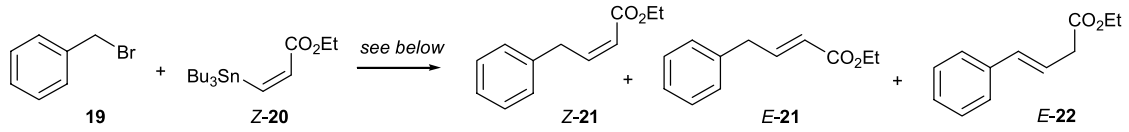


Scheme 5. i, $Pd_2dba_3\cdot CHCl_3$ (0.5 equiv), ligand (1.0 equiv), CH_2Cl_2, 25 °C, 0.2 h, then add NBS (1 equiv), 0.2 h. dppe = 1,2-bis(diphenyl phosphino)ethane, dcpe = 1,2-bis(dicyclohexylphosphino)ethane and dppf = 1,1′-bis(diphenylphosphino)ferrocene.

2.4. Stille coupling of allylic and benzylic substrates

With several palladium(II) imidate complexes in hand, we moved on to study their catalytic properties. The Stille coupling of benzyl bromide **19** with *Z*-organostannane **20** at 60 °C to give *Z*-**2** was used as the benchmark reaction (the reactions proceed significantly slower at temperatures <50 °C). The reactions mediated by our novel palladium imidate catalyst systems and a range of related catalysts/

Table 1. Comparison of various palladium complexes in the benchmark Stille coupling reaction[a]



19 *Z*-**20** *Z*-**21** *E*-**21** *E*-**22**

Entry	Complex	Time/h	Isolated yields/%[b]		
			Z-**21**	*E*-**21**	**22**
1	$(Ph_3P)_4Pd$[c]	18	17	—	—
2	$Pd(OAc)_2$, Ph_3P[d]	18	16	25	5
3	$Pd_2(dba)_3$.dba, Ph_3P[e]	18	13	28	—
4	$(Ph_3P)_2PdBr_2$	18	23	—	—
5	$(Ph_3P)_2Pd(Bn)Br$	18	19	30	5[f]
6	$(Ph_3P)_2Pd(Bn)Cl$	18	66	—	—
7	$(Ph_3P)_4Pd$, NBS[g]	18	83	—	—
8	$(Ph_3P)_4Pd$, NCS[g]	18	61	—	—
9	$(Ph_3P)_4Pd$, NIS[g]	18	33	—	—
10	$Pd_2(dba)_3$.dba, Ph_3P, NBS[g]	18	76	—	—
11	$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	1.5	99	—	—
12	$(Ph_3P)_2Pd$(*N*-succ)I, **11**	18	56	—	—
13	$(Ph_3P)_2Pd$(*N*-phthal)Br,[h] **12**	1.5 (18)	72 (98)	—	—
14	(dppe)Pd(*N*-succ)Br, **14**	18	87	3	—
15	(dcpe)Pd(*N*-succ)Br, **15**	18	43	—	—
16	(dppf)Pd(*N*-succ)Br, **16**	18	64	—	—
17	$(Ph_3P)_2Pd(N\text{-succ})_2$, **23**	48	10	—	—
18	$(Ph_3P)_2Pd(N\text{-phthal})_2$, **24**	48	11	—	—
19	NBS with no added palladium[i]	3	2	—	—

[a] Reaction conditions: benzyl bromide **19** (1 equiv), organostannane *Z*-**20** (1.2 equiv), [Pd] (0.05 equiv), toluene, 60 °C.
[b] Isolated yield after KF work-up and chromatography. Note: A DBU/I_2/Et_2O work-up for this specific reaction results in rapid regio- and stereo-isomerisation (<2 min).
[c] Freshly prepared from $(Ph_3P)_2PdCl_2$, NH_2NH_2 in EtOH at 120 °C.
[d] 3 equiv of Ph_3P were used w.r.t. to Pd.
[e] 2 equiv of Ph_3P were used w.r.t. to Pd.
[f] A mixture of stereoisomers were observed (*E*:*Z*, 1:0.9).
[g] 1 equiv of the *N*-halosuccinimide was added w.r.t. to Pd.
[h] Numbers in brackets are the time after 18 h reaction and the corresponding yield, respectively.
[i] NBS (5 mol%) was added under the reaction conditions described in *a*—but in the absence of palladium (new glassware was employed for this reaction).

precatalysts are summarised in Table 1. The known catalysts/precatalysts $(Ph_3P)_2PdBr_2$, $(Ph_3P)_2Pd(Bn)Br$, $(Ph_3P)_2PdCl_2$ and $(Ph_3P)_4Pd$ are commercially available and $(Ph_3P)_2Pd(Bn)Br$ **18**, was prepared by a reported procedure.[24]

With $(Ph_3P)_4Pd$ alone, a 17% yield of *Z*-**21** was obtained after 24 h (entry 1). Use of a $Pd(OAc)_2/Ph_3P$ combination gave a mixture of the stereoisomers, *Z*-**21** and *E*-**21**, and the regioisomer *E*-**22**, in overall 46% yield (entry 2). Another classic combination is Pd_2dba_3 dba/Ph_3P (entry 3). A mixture of *Z*-**21** and *E*-**21** was obtained in this reaction, which favoured the latter compound, but the overall yield was again modest (41%). The reaction mediated by $(Ph_3P)_2PdBr_2$ gave only a 23% yield of *Z*-**21**, albeit exclusively (entry 4). The neutral oxidative addition intermediate, in Stille couplings mediated by Pd/Ph_3P catalyst systems with benzyl bromide, is $(Ph_3P)_2Pd(Bn)Br$. The use of this complex or $(Ph_3P)_2Pd(Bn)Cl$ in the benchmark reaction gave reasonable yields (entries 5 and 6). However, the former showed poor selectivity, whereas the latter gave *Z*-**21**, exclusively in 66% yield (entry 6).

Having obtained results for comparison, we then examined succinimide-based catalysts. Catalysts formed in situ were examined first (entries 7–10). The addition of NBS to $(Ph_3P)_4Pd$ gave *Z*-**21** as the sole product in an excellent 83% yield (entry 7). Other *N*-halosuccinimides, NCS and NIS, also promoted the reaction, but to a lesser extent (61 and 33%, respectively, entries 8 and 9). The use of the catalyst formed by the addition of NBS to Pd_2dba_3 dba/Ph_3P provided *Z*-**21** exclusively in 76% yield (entry 10).

We then moved on to investigate pre-prepared complexes (entries 11–18). $(Ph_3P)_2Pd$(*N*-succ)Br **9** exhibited the best result by some margin (entry 11). The reaction was complete after 1.5 h and gave a 99% isolated yield of **21** (confirmed by several runs: Lowest yield 92%). The iodo relative, $(Ph_3P)_2Pd$(*N*-succ)I **11** gave a 56% yield, highlighting the importance of the halide (entry 12). It was anticipated that $(Ph_3P)_2Pd$(*N*-phthal)Br **12** would show similar catalytic activity to $(Ph_3P)_2Pd$(*N*-succ)Br **9**, and so it was compared (entry 13). Although the yield was good (72%) after 1.5 h, a reaction time of 18 h was needed for the reaction to reach completion indicating a clear difference between the two imidate ligands.

The bidentate ligand complexes (dppe)Pd(*N*-succ)Br **14**, (dcpe)Pd(*N*-succ)Br **15** and (dppf)Pd(*N*-succ)Br **16** were studied next (entries 14–16); all promoted the reaction but all required longer reaction times than $(Ph_3P)_2Pd$(*N*-succ)Br **9**. For completeness, the $(Ph_3P)_2Pd(N\text{-succ})_2$[15c] **23** and $(Ph_3P)_2Pd(N\text{-phthal})_2$[25] **24** relatives were screened to assess the importance of the halide in the palladium complex (entries 17 and 18). In stark contrast to the other catalysts containing imidate ligands, very poor yields were observed after 48 h (10 and 11% yield, respectively). It is clear that

the presence and nature of the halide are important for the efficacy of this reaction. In the absence of Pd, catalytic NBS (5 mol%), under the same reaction conditions, shows negligible conversion (2% yield, entry 19), confirming the importance of Pd.

It should be noted that when using many of the standard palladium complexes (Table 1, entries 1–6), a precipitate of palladium black is observed whereas with $(Ph_3P)_2Pd$(*N*-succ)Br **9**, the reaction remains yellow (in the absence of air and moisture) at the completion of the coupling process and no precipitate is observed. Also noteworthy is the fact that elevated temperatures can lead to additional isomerisation. For example, coupling using $(Ph_3P)_2Pd$(*N*-succ)Br **9**, which was stereoselective at 60 °C (entry 11), gave isomeric mixtures (*E*:*Z*=80:20) when the reaction was carried out at reflux. We established that this process was mediated by palladium by carrying out control experiments. Thus, pure *Z*-**21** was refluxed in toluene, in the presence and absence of $(Ph_3P)_2Pd$(*N*-succ)Br **9**. In the presence of $(Ph_3P)_2Pd$(*N*-succ)Br after 0.5 h at reflux, *cis–trans* isomerisation was observed by ^1H NMR analysis (*E*:*Z*=35:65) whereas in the absence of palladium, no stereoisomerisation was detected (even after 24 h).

We next carried out experiments to compare coupling reactions of a range of allylic and benzylic substrates using $(Ph_3P)_2Pd$(*N*-succ)Br **9** and other typical catalysts (Table 2). Thus, geranyl bromide **25** underwent coupling with *Z*-stannyl ester *Z*-**20** to give adduct **26** (entry 1). As can be seen, with $(Ph_3P)_2Pd$(*N*-succ)Br **9**- product *E*,*Z*-**26** was obtained in 67% yield, with complete preservation of alkene stereochemistry, whereas the other catalysts gave much lower yields with evidence of product isomerisation.

For the related *E*-stannyl ester *E*-**20** coupling with geranyl bromide **25**, all catalysts gave similar yields, although $(Ph_3P)_2Pd$(*N*-succ)Br **9** was again the catalyst of choice (entry 2). For the coupling between *Z*-**20** and cinnamyl bromide to give *E*,*Z*-**28** (entry 3), the best yield (86%) was again obtained using $(Ph_3P)_2Pd$(*N*-succ)Br **9**. Comparable results were seen in the coupling of *E*-**20** with cinnamyl bromide *E*-**27** (entry 4). Again, complete stereoselectivity was observed in these processes.

The corresponding coupling of benzyl bromide **19** and *E*-**20** was investigated next and predicted to give similar results to the corresponding benchmark study involving benzyl bromide and *Z*-**20** (Table 1), but this turned out not to be the case (entry 5). With all catalysts, the yields were good to excellent (>90% using $(Ph_3P)_2Pd$(Bn)Cl and $(Ph_3P)_2Pd$(*N*-succ)Br **9**). Interestingly, it was noted that the reaction time for the coupling of benzyl bromide **19** and *E*-**20** with $(Ph_3P)_2Pd$(*N*-succ)Br **9** as catalyst was much longer (5 h vs 1.5 h) than that corresponding with *Z*-**20** (Table 2, entry 5 vs Table 1, entry 11). The reaction of phenylstannane **29** with **19** to give **30**, proceeded well with all four catalysts (entry 6).

To assess the substrate scope in benzylic/allylic Stille reactions mediated by $(Ph_3P)_2Pd$(*N*-Succ)Br **9**, several other reactions were studied (Table 3). All but one of the examples gave good yields, with high regio- and stereo-selectivity observed throughout the series. The exception was the reaction of geranyl bromide *E*-**25** with phenylstannane **29**, which give *E*-**37** in only 34% yield after 18 h (entry 4).

Thus, with a range of benzylic (entry 1) and allylic bromides, vinylstannanes **31** and **33**, and phenylstannane **29**, undergo efficient coupling (entries 2,3, 5–7). The reaction of an allylstannane **41** with *E*-cinnamyl bromide *E*-**27**, which is formally an sp^3–sp^3 type of coupling process, also proceeds efficiently (entry 8). Benzyl chloride also underwent efficient coupling reactions (entries 9–10), the reaction with *Z*-**20** at 60 °C giving *Z*-**21** in 81% yield (entry 9). However, 48 h at 60 °C was required for complete consumption of benzyl chloride **43**: Increasing the reaction temperature to 110 °C reduced the reaction time to 18 h (isomerisation is observed if longer reflux times are employed at this temperature). The reaction of *E*-**20**, under the same reactions conditions with elevated temperature, gave *E*-**21** in 68% yield after 18 h (entry 10). A literature survey reveals that few Stille couplings of benzyl chloride have been reported,[4b,15b] and the majority of reactions require harsh conditions or toxic additives, for example, HMPA.

2.5. Stille coupling of aryl substrates

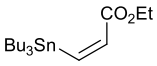
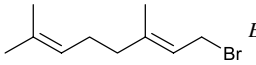
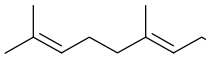
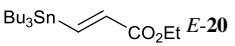
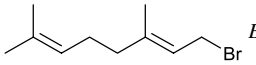
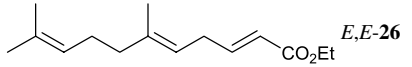
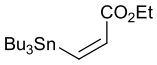
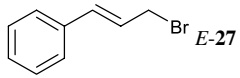
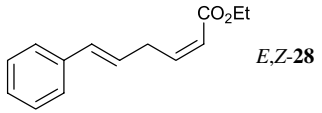
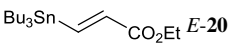
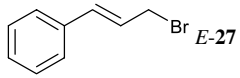
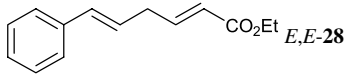
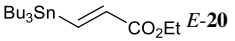
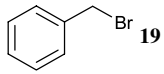
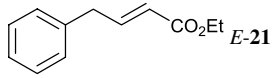
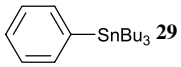
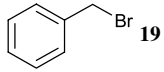
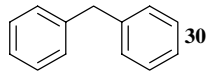
Having established that $(Ph_3P)_2Pd$(*N*-succ)Br **9** is an efficient catalyst for the Stille coupling of allyl and benzylic substrates, coupling reactions with aryl substrates were investigated. 4-Nitrobromobenzene **44** was selected as the model substrate, as it is known to be one of the most active electrophilic substrates for Stille coupling.[5] Tributylvinyltin **33** was chosen as the coupling partner (Scheme 6 and Table 4).

After 5 h at reflux, $(Ph_3P)_4Pd$ gave the coupled product in 65% yield (entry 1). Higher yields were obtained using $(Ph_3P)_2Pd$(Bn)Cl and $(Ph_3P)_2Pd$(Bn)Br (entries 2 and 3, respectively). However, when the reaction was carried out in the presence of the $(Ph_3P)_4Pd$/NBS combination (entry 4), the yield dropped to 35% (after 24 h), showing for the first time that this system could be less active than $(Ph_3P)_4Pd$ alone! $(Ph_3P)_2Pd$(*N*-succ)Br **9** gave an improved yield (66%), but a substantially longer reaction time was required (24 h, entry 5). Thus, for a typical aryl halide Stille coupling, standard catalyst systems are more efficient than both the $(Ph_3P)_4Pd$/NBS combination and $(Ph_3P)_2Pd$(*N*-succ)Br **9**. Similar results were obtained using bromobenzene as the substrate.

2.6. Competition Stille coupling reactions

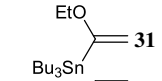
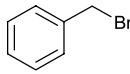
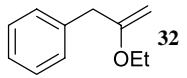
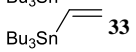
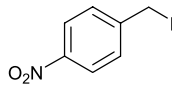
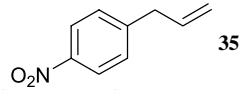
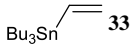
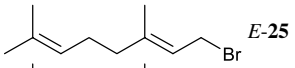
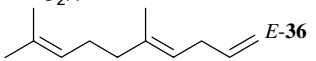
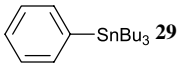
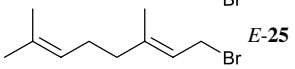
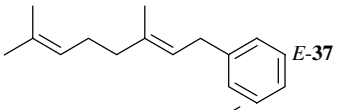
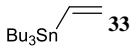
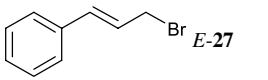
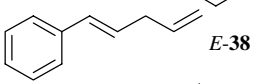
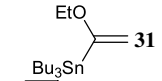
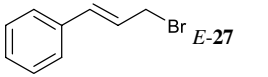
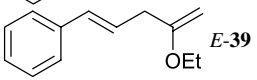
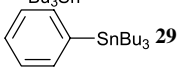
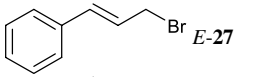
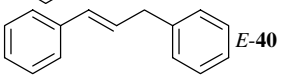
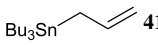
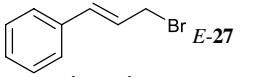
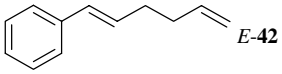
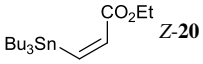
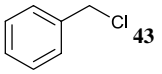
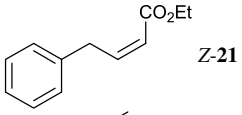
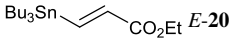
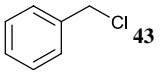
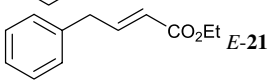
The efficiency of $(Ph_3P)_2Pd$(*N*-succ)Br **9** as a catalyst for allylic/benzylic halide coupling reactions, compared to its low reactivity for the coupling of aryl halides was of some interest. Several competition experiments were therefore devised to evaluate the substrate scope against different palladium catalyst systems. In the first example, bromobenzene **46**, benzyl bromide **19** and *Z*-vinylstannane **20** (in a 1:1:1 ratio) were subjected to the reaction conditions outlined in Scheme 7 and Table 5. Two major products

Table 2. Stille coupling reactions mediated by a range of palladium sources[a]

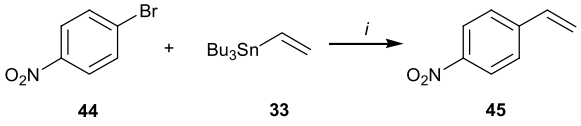
Entry	Organostannane	Organohalide	Catalyst	Time/h	Cross-coupled product	Yield/%[b]
1	 *Z*-**20**	 *E*-**25**	$(Ph_3P)_4Pd$	24	 *E,Z*-**26**	11
			$(Ph_3P)_2Pd(Bn)Br$	24		30[c]
			$(Ph_3P)_2Pd(Bn)Cl$	24		32[c]
			$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	24		67
2	 *E*-**20**	 *E*-**25**	$(Ph_3P)_4Pd$	24	 *E,E*-**26**	51
			$(Ph_3P)_2Pd(Bn)Br$	24		55
			$(Ph_3P)_2Pd(Bn)Cl$	24		49
			$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	24		56
3	 *Z*-**20**	 *E*-**27**	$(Ph_3P)_4Pd$	24	 *E,Z*-**28**	56
			$(Ph_3P)_2Pd(Bn)Br$	20		78
			$(Ph_3P)_2Pd(Bn)Cl$	20		71
			$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	13		86
4	 *E*-**20**	 *E*-**27**	$(Ph_3P)_4Pd$	23	 *E,E*-**28**	56
			$(Ph_3P)_2Pd(Bn)Br$	18		77
			$(Ph_3P)_2Pd(Bn)Cl$	24		58
			$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	13		81
5	 *E*-**20**	 **19**	$(Ph_3P)_4Pd$	24	 *E*-**21**	73
			$(Ph_3P)_2Pd(Bn)Br$	5		97
			$(Ph_3P)_2Pd(Bn)Cl$	24		71
			$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	5		95
6	 **29**	 **19**	$(Ph_3P)_4Pd$	24	 **30**	90
			$(Ph_3P)_2Pd(Bn)Br$	24		97
			$(Ph_3P)_2Pd(Bn)Cl$	24		90
			$(Ph_3P)_2Pd$(*N*-succ)Br, **9**	24		93

[a] Reaction conditions: allylic/benzylic bromide (0.25 mmol), organostannane (0.3 mmol), $C_6H_5CH_3$ (2.5 mL) at 60 °C, under an inert atmosphere of N_2.
[b] Isolated yields after KF work-up and chromatography.
[c] ~1% of the *E*-isomer was detected by ^1H NMR spectroscopy.

Table 3. Products from the Stille coupling of allylic or benzylic substrates with organostannanes, mediated by $(Ph_3P)_2Pd(N\text{-Succ})Br$, **9**[a]

Entry	Organostannane	Organohalide	Coupled product	Yield/%[b]	Reaction time/h
1	 **31**	 **19**	 **32**	84	20
2	 **33**	 **34**	 **35**	67	6
3	 **33**	 *E*-**25**	 *E*-**36**	78	18
4	 **29**	 *E*-**25**	 *E*-**37**	34	18
5	 **33**	 *E*-**27**	 *E*-**38**	92	18
6	 **31**	 *E*-**27**	 *E*-**39**	79	20
7	 **29**	 *E*-**27**	 *E*-**40**	79	18
8	 **41**	 *E*-**27**	 *E*-**42**	70	24
9	 *Z*-**20**	 **43**	 *Z*-**21**	81[c]	48
10	 *E*-**20**	 **43**	 *E*-**21**	68[d]	18

[a] Reaction conditions: allylic/benzylic bromide (0.25 mmol), organostannane (0.3 mmol), $C_6H_5CH_3$ (2.5 mL) at 60 °C, under an inert atmosphere of N_2.
[b] Isolated yields after KF workup and column chromatography.
[c] 79% after 18 h when reaction conducted at 110 °C.
[d] Reaction conducted at 110 °C.



Scheme 6. Stille coupling of 4-nitrobromobenzene **44** with tributylvinyltin **33**. i, [Pd] (0.05 equiv.), toluene, reflux, 6 h (for details, see Table 4).

Table 4. Stille coupling of a vinylstannane with 4-nitrobromobenzene

Entry	Complex	Time/h	Isolated yield/ %
1	$(Ph_3P)_4Pd$	5	65
2	$(Ph_3P)_2Pd(Bn)Cl$	5	80
3	$(Ph_3P)_2Pd(Bn)Br$	5	86
4	$(Ph_3P)_4Pd+NBS$	24	35
5	$(Ph_3P)_2Pd$(*N*-succ)Br **9**	24	66

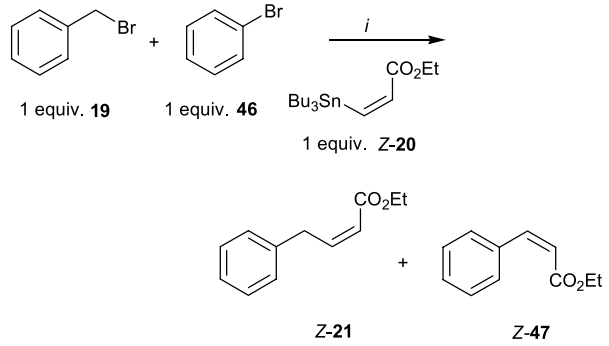
were expected from this reaction, namely *Z*-**21** from benzyl bromide **19**, and *Z*-**47** from bromobenzene **46**.

In the reactions mediated by $(Ph_3P)_4Pd$ and $(Ph_3P)_2PdBr_2$, *Z*-**21** was not detected, the only product isolated being the bromobenzene adduct *Z*-**47**, along with the corresponding *E*-isomer (entries 1 and 2). The use of $(Ph_3P)_2Pd(Bn)Br$ promoted some coupling with benzyl bromide, but again the coupling with bromobenzene **46** predominated (entry 3). A major switch in selectivity was observed when $(Ph_3P)_2$ Pd(*N*-succ)Br was employed as catalyst (entry 4). In this reaction, no aryl coupling was observed, only coupling with benzyl bromide giving *Z*-**21** (86%). The major difference between this catalyst system and $(Ph_3P)_2Pd(Bn)Br$ or $(Ph_3P)_2PdBr_2$ is the presence of the succinimide ligand, as opposed to the benzyl or bromide ligands, respectively. It seemed possible that a bromide salt could influence selectivity. Addition of lithium bromide to the $(Ph_3P)_2Pd$ (*N*-succ)Br coupling competition reaction had a profound effect, causing a large reduction in the selectivity, although *Z*-**21** still predominated (entry 5). The results in Table 5 clearly demonstrate the importance of the succinimide ligand for selectivity (which we will now refer to as the succinimide effect).

The effect of electron-releasing and withdrawing groups in the benzylic coupling partner, relative to benzyl bromide itself, was evaluated in a second competition study with stannane *Z*-**20** (Scheme 8). The outcome from these experiments was once again surprising. 4-Nitrobenzyl bromide **48** was expected to react faster than benzyl bromide **19** but actually the benzyl bromide adduct *Z*-**21** was produced in 36% yield, compared to only 14% of *Z*-**49** (Eq. 1, Scheme 8). In a reaction containing 4-methoxybenzyl bromide **50** and benzyl bromide **19** itself, the product that predominated (*Z*-**51**) was derived from the methoxylated substrate (Eq. 2, Scheme 8). These results exhibit a reversal of the expected reactivity.

In the third competition experiment, the coupling reaction of stannane *Z*-**20** with 4-nitrobromobenzene **40** and 4-nitrobenzyl bromide **36** was compared (Scheme 9).

No selectivity was observed in this reaction, where **51** and **48** reacted equally well to give the cross-coupled products *Z*-**49** and *Z*-**52** in 48% and 49% yield, respectively,



Scheme 7. Competition experiment between aryl and benzylic bromides. i, [Pd] (0.05 equiv), toluene, reflux, 18 h (for details, see Table 5).

Table 5. Competition study between benzyl bromide and bromobenzene

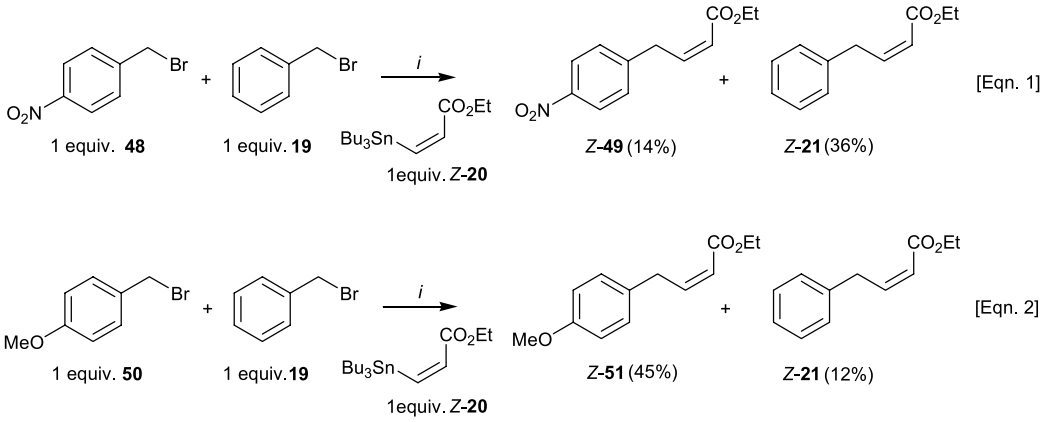
Entry	Complex	Isolated yield/%	
		Z-**21**	*Z*-**47** (*E*-**47**)
1	$(Ph_3P)_4Pd$	0	39 (9)
2	$(Ph_3P)_2PdBr_2$	0	21 (15)
3	$(Ph_3P)_2Pd(Bn)Br$	16	36
4	$(Ph_3P)_2Pd$(*N*-succ)Br	86	0
5	$(Ph_3P)_2Pd$(*N*-succ)Br+LiBr	45	22

indicating that there is essentially no difference in the reactivity of either substrate in coupling reactions mediated by $(Ph_3P)_2Pd$(*N*-Succ)Br **9**. The complete consumption of *Z*-**20** demonstrates the efficiency of these reactions.

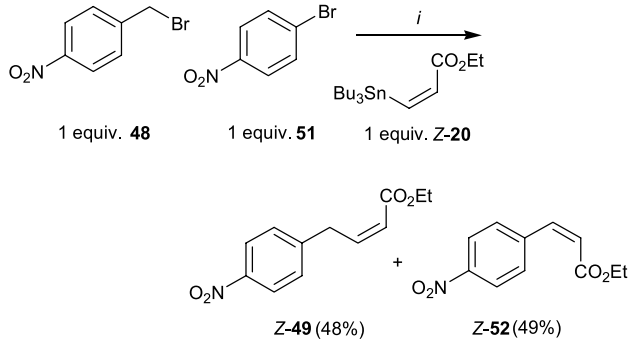
3. Discussion and conclusions

The results above indicate that $(Ph_3P)_2Pd$(*N*-Succ)Br **9** is an effective mediator of Stille coupling reactions involving allylic and benzylic halides. At the present time, we cannot state unambiguously whether $(Ph_3P)_2Pd$(*N*-Succ)Br **9** is a catalyst or precatalyst. A more thorough investigation into the mechanism of Stille coupling reactions mediated by $(Ph_3P)_2Pd$(*N*-Succ)Br is required before a detailed proposal can be made. Important observations have, however, been made in the present study: (1) that in allylic/benzylic Stille processes, increased yields and higher catalytic activity are observed for succinimide-containing palladium complexes, when compared to related palladium(II) complexes containing only Ph_3P as the donor ligand; (2) the increased reactivity of stannnane *Z*-**20** compared to its *E*-isomer in Stille couplings mediated by $(Ph_3P)_2Pd$(*N*-Succ)Br **9**; (3) the preferential Stille coupling of electron-rich benzyl bromides versus electron poor benzyl bromides with stannane *Z*-**20**; (4) the benzylic versus aryl selectivity observed for $(Ph_3P)_2Pd$(*N*-Succ)Br **9** compared to common palladium catalysts/precatalysts.

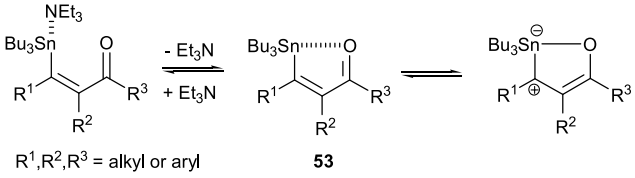
To elaborate on the second point. In reactions mediated by $(Ph_3P)_2Pd$(*N*-Succ)Br **9** the increased reactivity demonstrated by stannane *Z*-**20** over *E*-**20** with respect to benzyl bromide **19** and geranyl bromide *E*-**25** is an intriguing observation. In related studies, Takeda and co-workers showed that β-tributylstannyl-α,β-unsaturated ketones were relatively poor nucleophiles in Stille coupling—coordination of the oxygen lone pair electrons to the Bu_3Sn group



Scheme 8. Competition reactions employing electron-rich and electron-poor benzyl bromides. i, $(Ph_3P)_2Pd(N\text{-succ})Br$ (0.05 equiv), toluene, 60 °C, 18 h.



Scheme 9. Competition between nitro-substituted aryl and benzylic bromide substrates.

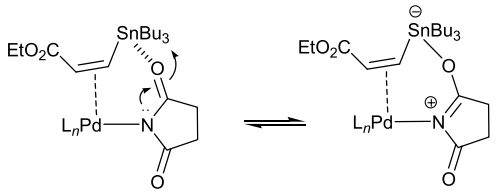


Scheme 10. Activation at tin by Et_3N and deactivation by O→Sn coordination.

deactivating the *cis*-vinyl stannane towards transmetallation (Scheme 10).[26]

In Takeda's study, copper(I) and triethylamine (Et_3N) were required to activate stannane **53** to Stille coupling reactions with benzylic and aryl halides. The former was used to promote the transmetallation step, either by scavenging excess phosphine ligands or by becoming involved in a Sn/Cu pre-transmetallative process (the vinylcuprate is more reactive). It was proposed that the amine donor ligand disrupted O→Sn coordination to give an activated stannane (through Et_3N→Sn coordination). The higher reactivity of stannane *Z*-**20** over *E*-**20** observed in Stille reactions mediated by $(Ph_3P)_2Pd(N\text{-Succ})Br$ **9** is therefore surprising.

Further, analysis of the coupling of *E*-**25** with both *Z*-**20** and *E*-**20** shows a unique trend (entries 1 and 2, Table 2). For *Z*-**20**, deactivation is clearly seen using $(Ph_3P)_4Pd$, $(Ph_3P)_2Pd(Bn)Br$ and $(Ph_3P)_2Pd(Bn)Cl$, whereas a good yield was obtained for $(Ph_3P)_2Pd(N\text{-Succ})Br$ **9**. In contrast to this observation, negligible differences were seen for *E*-**20** with these palladium complexes (entry 2, Table 2; also entries 4 and 5). For *Z*-**20**, there is a possibility that the succinimide ligand is activating tin intramolecularly, as shown in Scheme 11 (intermolecular activation is also possible but seems less likely). It is known that there is significant electron repulsion between the nitrogen lone pair electrons and the d_π electrons of palladium(II).[27] This promotes electron delocalisation onto the carbonyl substituent. η^2-Alkene coordination of *Z*-**20** to the palladium centre facilitates *O*-coordination, and hence activation, from a neighbouring succinimide ligand (a chelation-controlled activation process). We presume that the *trans*-stannane *E*-**20**, does not experience the same activation, possibly due to the incorrect orientation of the Bu_3Sn group (and ester group).



Scheme 11. Activation at tin by the succinimide ligand.

To summarise, the preparation of $(Ph_3P)_2Pd(N\text{-Succ})Br$ **9** and several other novel succinimide and phthalimide-containing palladium complexes, has been described. The complex $(Ph_3P)_2Pd(N\text{-Succ})Br$ **9** has been shown to be an efficient catalyst for the Stille coupling reactions of a range of allylic and benzylic halides with different vinylstannanes. In a number of these reactions, a comparison of the catalytic activities of several different palladium complexes has been carried out. Competition reactions and preliminary mechanistic observations have been reported herein, which indicate the novel selectivity of $(Ph_3P)_2Pd(N\text{-Succ})Br$ **9** and lead to the proposal of a succinimide effect in Stille coupling reactions. Further synthetic studies, as well as mechanistic investigations concerning the oxidation states and geometries of key palladium intermediates (neutral or anionic), possibly involving radicals, in the catalytic cycle, are continuing in our laboratories.

4. Experimental

4.1. General details

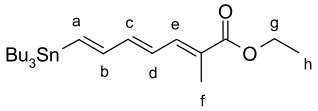
See reference for general experimental information.[15c]

The following routine compounds show comparable characterisation data according to literature precedent: 1, 3-oxazol-5-ylmethanol (**1**),[28] *E*-bis-1,2-tributylstannylethene (*E*-**5**),[29] ethyl 3-iodo-2*Z*-propenoate (*Z*-**6**),[30] ethyl 3-(tributylstannyl)-2*Z*-propenoate (*Z*-**20**), ethyl 3-(tributylstannyl)-2*E*-propenoate (*E*-**20**),[45] ethyl (2*Z*)-4-phenyl-2-butenoate (*Z*-**21**),[31] ethyl (2*E*)-4-phenyl-2-butenoate (*E*-**21**),[32] ethyl (3*E*)-4-phenyl-3-butenoate (*E*-**22**),[33] diphenylmethane (**30**),[34] 2-ethoxy-3-phenylpropene (**31**),[35] 1-allyl-4-nitrobenzene (**35**),[36] (2*E*)-3,7-dimethyl-1-phenyl-2,6-octadiene (*E*-**37**),[37] (1*E*)-1,4-pentadienylbenzene (*E*-**38**),[38] 1,3-diphenylpropene (*E*-**40**),[39] 1*E*-phenyl-1,5-hexadiene (*E*-**42**),[40] 1-nitro-4-vinylbenzene (**45**),[41] ethyl (2*Z*)-3-phenyl-2-propenoate (*Z*-**47**)[42] and ethyl (2*E*)-3-phenyl-2-propenoate (*E*-**47**).[42]

4.1.1. 5-(Bromomethyl)-1,3-oxazole (2). *Method A*.[36] NBS (recrystallised from H_2O) (0.237 g, 1.33 mmol) was added to a solution of **1** (0.12 g, 1.21 mmol) and Ph_3P (0.35 g, 1.33 mmol) in CH_2Cl_2 (4 mL). The reaction was stirred at ambient temperature for 1 h then concentrated in vacuo and passed directly through a short plug of silica using PE–EtOAc (1:1, v:v) as the eluent. This afforded the title compound **2** as a colourless oil (0.058 g, 30%). The compound was extremely unstable, but it may be stored in the freezer at −20 °C. R_f=0.37 (PE–EtOAc, 1:1); R_f=0.26 (CH_2Cl_2); δ_H (270 MHz; $CDCl_3$) 2.85 (1H, br s, OH^d), 4.68 (2H, s, CH_2^c), 7.00 (1H, s, CH^b), 7.85 (1H, s, CH^a) (consistent with data previously reported).[36]

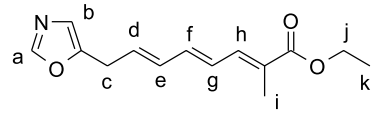
Method B.[43] Carbon tetrabromide (0.68 g, 2.0 mmol) was added to a solution of **1** (0.169 g, 1.7 mmol) and Ph_3P (0.58 g, 2.2 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C. The reaction was stirred at 0 °C for 1 h, concentrated in vacuo and passed directly through a short plug of silica using PE–EtOAc (1:1, v:v) as the eluent, giving the title compound **2** as a colourless oil (0.148 g, 54%).

4.1.2. Ethyl (2*E*,4*E*,6*E*)-2-methyl-7-(tributylstannyl)-2,4,6-heptatrienoate (*E*,*E*,*E*-3).



TPAP (0.024 g, 0.007 mmol) was added to a cooled mixture (0 °C) of (2*E*,4*E*)-5 (tributylstannyl)-2,4-pentadien-1-ol (0.50 g, 1.34 mmol), powdered 4 Å molecular sieves (0.50 g) and NMO (0.24 g, 2.0 mmol) in CH_2Cl_2 (10 mL). The green solution was stirred for 90 min, then the solvent was removed in vacuo. Subsequent purification by column chromatography using CH_2Cl_2 as the eluent afforded (2*E*,4*E*)-5-(tributylstannyl)-2,4- pentadienal as a pale yellow oil, which was used directly in the following reaction: KHMDS (0.5 M in toluene, 4.0 mL, 2.0 mmol) was added dropwise to a stirred solution of ethyl 2-(diethoxyphosphoryl) propenoate (0.43 mL, 2.0 mmol) in THF (25 mL) at −78 °C. After 15 min, the aldehyde (prepared above) in THF (25 mL) was added. The reaction was stirred at −78 °C for 1 h before addition of saturated aq NH_4Cl (10 mL), whereupon it was warmed to ambient temperature. The resulting mixture was extracted with Et_2O (3×10 mL), the combined organic extracts dried over Na_2SO_4 and the solvent removed in vacuo. Purification by column chromatography using PE–EtOAc–TEA, (97:2:1) afforded the title compound (0.35 g, 58%) as a pale yellow oil. R_f=0.74 (CH_2Cl_2); δ_H (270 MHz, $CDCl_3$) 0.87–0.96 (18H, m, Bu+CH_3^h), 1.25–1.38 (6H, m, Bu), 1.43–1.56 (6H, m, Bu), 1.97 (3H, d, ^4J=1.0 CH_3^f), 4.20 (2H, q, J=7.0 Hz, CH_2^g), 6.37–6.55 (2H, m, CH^{c+d}), superimposed by 6.49 (1H, d, ^3J=11.5 Hz, CH^a), 6.64 (1H, dd, ^3J=11.5, 9.0 Hz, CH^b), 7.21 (1H, d, ^3J=8.5 Hz, CH^e); δ_C (67.9 MHz, $CDCl_3$) 9.7 (CH_2), 12.8 (CH_3), 13.8 (CH_3), 14.4 (CH_3), 27.4 (CH_2), 29.2 (CH_2), 60.6 (CH_2), 126.6 (CH), 127.6 (C), 138.3 (CH), 140.7 (CH), 141.8 (CH), 146.5 (CH), 168.5 (C); ν_{max} (neat, cm^{-1}) 2925, 2854, 1705, 1618, 1454, 1367, 1277, 1232, 1113, 1095, and 1000 cm^{-1}; *m*/*z* (CI), 457 (MH^+, 84%), 399 (58), 308 (100), 167 (35); [HRMS (CI): calcd for $C_{22}H_{41}O_2{}^{116}Sn$, 453.2124. Found: MH^+, 453.2119 (1.0 ppm error)]. Stereochemistry of new double bond confirmed by quantitative NOE measurements (500 MHz): 3.8% NOE observed between CH_3^f and CH^d.

4.1.3. Ethyl (2*E*,4*E*,6*E*)-2-methyl-8-(1,3-oxazole-5-yl)-2,4,6-octatrienoate (*E*,*E*,*E*-4).



$(Ph_3P)_4Pd$ (5.0 mg, 0.05 equiv, 5 mol%) was added to a solution of 3 (0.40 g, 0.79 mmol) and 2 (0.122 g, 0.75 mmol) (synthesised by method A) in dry degassed toluene (5 mL) and heated to reflux in the dark for 20 h. After this time, the reaction was cooled to ambient temperature, then the solvent removed in vacuo. The resulting syrup was purified by column chromatography using PE–EtOAc (1:1) as the eluent. This afforded the title compound as a bright yellow oil (0.152 g, 82%). R_f=0.31 (PE–EtOAc, 1:1, v:v); δ_H (270 MHz, $CDCl_3$) 1.27 (3H, t, ^3J=7.5 Hz, CH_3^k), 1.92 (3H, s, CH_3^i), 3.50 (2H, d, ^3J=7.0 Hz CH_2^c), 4.18 (2H, q, ^3J=7.5 Hz, CH_2^j), 5.89 (1H, dt, ^3J=15.0, 7.0 Hz, CH^d), 6.24 (1H, dd, ^3J=15.0, 11.5 Hz, CH^e), 6.49 (2H, m, CH^{f+g}), 6.79 (1H, s, CH^b), 7.19 (1H, d, ^3J=12.0 Hz, CH^h), 7.78 (1H, s, CH^a); δ_C (67.9 MHz, $CDCl_3$) 12.6 (CH_3), 14.2 (CH_3), 28.8 (CH_2), 60.5 (CH_2), 122.7 (CH), 127.5 (CH), 127.6 (CH), 130.8 (CH), 132.9 (CH), 137.6 (CH), 138.0 (CH), 150.2 (C), 150.4 (C), 168.2 (C); ν_{max} (film) 2956, 2929, 1701, 1614, 1510, 1464, 1367, 1257, 1225, 1103, 991 and 964 cm^{-1}; *m*/*z* (CI), 248 (MH^+, 100%), 234 (10), 174 (7), 82 (6); [HRMS (CI): calcd for $C_{14}H_{18}O_3N$, 248.1287. Found: MH^+, 248.1287 (0.2 ppm error)]. Stereochemistry of new double bond confirmed by a quantitative an NOE experiment 4.5% NOE observed between CH_3^f and CH^e.

4.1.4. Ethyl (2*Z*,4*E*)-5-(tributylstannyl)penta-2,4-dienoate (*Z*,*E*-7) and diethyl octa-2*Z*,4*E*,6*Z*-triendioate (*Z*,*E*,*Z*-8). The palladium catalyst (0.05 equiv, 5 mol%) was added

to a solution of *E*-**5** (1.0 g, 1.65 mmol) and *Z*-**6** (0.36 g, 1.6 mmol) in dry degassed toluene (10 mL). The reaction was heated to reflux for 3 h. The reaction was allowed to cool to ambient temperature, whereupon a saturated aq KF (10 mL) was added. The mixture was stirred vigorously for 1 h, then filtered through Celite®, and the residue rinsed with Et_2O (2×10 mL). The filtrate was washed with saturated aq NaCl and then dried (Na_2SO_4). Subsequent purification by column chromatography, using PE–EtOAc–TEA (97:2:1) as the eluent, afforded the title compounds as pale yellow oils, in yields specified in the text. Data for ethyl (2*Z*,4*E*)-5-(tributylstannyl)penta-2,4-dienoate (*Z*,*E*-**7**): obtained as a yellow oil. R_f=0.60 (PE–EtOAc, 9:1, v:v); δ_H (270 MHz, $CDCl_3$) 0.86–0.98 (15H, m, Bu), 1.24–1.38 (9H, m, CH_2 of Bu and CH_3^f), 1.24–1.38 (6H, m, Bu), 4.20 (2H, q, ^3J=7.0 Hz, CH_2^e), 5.58 (1H, dd, ^3J=11.5 Hz, ^4J=1.0 Hz CH^d), 6.50 (1H, ddd, ^3J=11.5, 10.5 Hz, ^4J=1.0 Hz, CH^c) 6.75 (1H, dd, ^3J=19.0 Hz, ^4J=1.0 Hz, CH^a) 7.81 (1H, ddd, ^3J=19.0, 10.5 Hz, ^4J=1.0 Hz, CH^b); δ_C (67.9 MHz, $CDCl_3$), 9.6 (CH_2), 13.6 (CH_3), 14.3 (CH_3), 27.2 (CH_2), 20.0 (CH_2), 59.9 (CH_2), 115.9 (CH), 142.5 (CH), 146.5 (CH), 147.8 (CH), 166.2 (C); ν_{max} (neat, cm^{-1}) 2958, 1718, 1616, 1550 and 1162; *m*/*z* (CI), 417 (MH^+, 17%), 308 (100); [HRMS (CI): calcd for $C_{19}H_{37}O_2^{116}Sn$, 413.1807. Found: MH^+, 413.1811 (1.1 ppm error)]. Data for diethyl octa-2*Z*,4*E*,6*Z*-triendioate (*Z*,*E*,*Z*-**8**): obtained as a white solid; R_f=0.34 (PE–EtOAc, 9:1, v:v); mp 53.0–53.5 °C; δ_H (270 MHz, $CDCl_3$) 1.30 (3H, t, ^3J=7.5 Hz, CH_3^a), 4.20 (2H, q, ^3J=7.5 Hz, CH_2^b), 5.81 (1H, d, ^3J=11.0 Hz, CH^c), 6.71 (1H, ddd, ^3J=11.0, 10.5,^4J=3.0 Hz, CH^d), 7.76 (1H, dd, ^3J=10.5, 3.0 Hz, CH^e); δ_C (67.9 MHz, $CDCl_3$), 14.2 (CH_3), 60.2 (CH_2), 120.7 (CH), 135.9 (CH), 143.38 (CH), 166.1 (C); ν_{max} (nujol, cm^{-1}) 1718, 1616 and 1165; *m*/*z* (EI) 224 (M^+, 53%), 195 (91), 167 (70), 149 (100); [HRMS (EI): calcd for $C_{12}H_{16}O_4$, 224.1049. Found: M^+, 224.1043 (2.5 ppm error)].

4.1.5. *cis*-Bromobis(triphenylphosphine)(succinimide) palladium(II) (*cis*-9). To a Schlenk tube containing vacuum dried $Pd_2dba_3{\cdot}CHCl_3$ (100 mg, 0.097 mmol) and Ph_3P (101.4 mg, 0.387 mmol) in dry CH_2Cl_2 (7 mL) at 21 °C under N_2, was stirred for 0.2 h, after, which time an orange colour persisted. A solution of recrystallised *N*-bromosuccinimide (34.5 mg, 0.194 mmol) in dry CH_2Cl_2 (2 mL) was added in one portion and the mixture stirred for 0.2 h. If a precipitate is observed, filter off—this is $(Ph_3P)_2PdBr_2$). The resulting yellow solution was concentrated in vacuo to a third of its original volume and petroleum ether added to precipitate the complex. The creamy yellow solid was filtered and washed with small quantities of hexane, which is the title compound (104 mg, 74% yield). A small quantity of *cis*-**9** was recrystallised by slow vapour diffusion of Et_2O in a CH_2Cl_2 solution of the complex (5:1) at 0 °C for 2 days. ν_{max} (CH_2Cl_2, cm^{-1}) 1631 (C=O); δ_H (500 MHz, CD_2Cl_2) 1.59 (2H, dd, $^2J_{HaHa'}$=16.5 Hz, $^3J_{HaHb'}$=4.1 Hz, CH_A and $CH_{A'}$), 2.20 (2H, dd, $^2J_{HbHb'}$=16.5 Hz, $^3J_{HbHa'}$=4.5 Hz, CH_B and $CH_{B'}$), 7.1–7.6 (30H, m, Ph–H); δ_P (202 MHz, CD_2Cl_2) 23.96 (1P, d, $^2J_{PP}$=8.49 Hz, $P1_{(cis)}$) and 32.91 (1P, d, $^2J_{PP}$=8.49 Hz, $P2_{(trans)}$); *m*/*z* (FAB), 810 (MH^+, 4), 710 (29), 629 (17), 339 (100), 263 (Ph_3PH^+, 28), 183 (43), 154 (79). Anal. Calcd for $C_{40}H_{34}BrNO_2P_2Pd{\cdot}½\ CH_2Cl_2$, C, 57.36; H, 4.23; N, 1.63. Found C, 57.49; H, 3.99; N, 1.66.

4.1.6. *trans*-Chlorobis(triphenylphosphine)(succinimide) palladium(II) (*trans*-10). Following a similar procedure to *cis*-**9**. To a Schlenk tube containing vacuum dried $Pd_2dba_3{\cdot}CHCl_3$ (104 mg, 0.1 mmol) and Ph_3P (105 mg, 0.4 mmol) in dry CH_2Cl_2 (8 mL) at 21 °C under N_2, was stirred for 0.2 h, after, which time an orange colour persisted. Then *N*-chlorosuccinimide (NCS) (0.018 g, 0.25 mmol) (recrystallised from H_2O and dried under high vacuum) in CH_2Cl_2 (2 mL), was added in one portion. The solution went pale orange. The mixture was stirred for 0.5 h. The solution was reduced to a third of its original volume in vacuo and then petroleum ether (2 mL) added to precipitate the complex. This gave the title compound as a cream solid (0.033 g, 22%). ν_{max} ($CHCl_3$, cm^{-1}) 1633 (C=O); δ_H (270 MHz, $CDCl_3$, selected data) 1.32 (2H, br s, CH_{2A}), 1.69 (2H, br s, CH_{2B}), 7.26–7.62 (18H, m, Ph–H), 7.70–7.91 (12H, m, Ph–H); δ_P (109.1 MHz, $CDCl_3$) 23.45 (2P, s, P1–P2); *m*/*z* (FAB), 764 (MH^+, 2), 728 (12), 629 (5), 339 (100).

4.1.7. *trans*-Iodobis(triphenylphosphine)(succinimide) palladium(II) (*trans*-11). Following a similar procedure to *cis*-**9**. To a Schlenk tube containing vacuum dried $Pd_2dba_3{\cdot}CHCl_3$ (104 mg, 0.1 mmol) and Ph_3P (105 mg, 0.4 mmol) in dry CH_2Cl_2 (8 mL) at 21 °C under N_2, was stirred for 0.2 h, after, which time an orange colour persisted. Then, *N*-iodosuccinimide (NIS) (0.056 g, 0.25 mmol) in CH_2Cl_2 (2 mL) was added in one portion. The solution went yellow immediately. A small amount of a precipitate (0.028 g) was formed ($(Ph_3P)_2PdI_2$), which was filtered. The solution was reduced to a third of its original volume in vacuo and then petroleum ether (2 mL) added to precipitate the complex. This gave the title compound as a cream solid, which was crystallised from a layered solvent system (CH_2Cl_2/hexane, 1/4, *c* 0.1 M) by slow evaporation in air (0.086 g, 50%). Mp 197–199 °C (decomp.); δ_H (400 MHz, $CDCl_3$) 1.32 (2H, s, CH_{2A}), 1.62 (2H, s, CH_{2B}), 5.30 (1H, s, ½CH_2Cl_2 of recrystallization), 7.37–7.47 (18H, m, Ph–H), 7.78–7.82 (12H, m, Ph–H); δ_P (161 MHz, $CDCl_3$) 21.65 (2P, s, P1–P2); ν_{max} ($CHCl_3$, cm^{-1}) 1631 (C=O); *m*/*z* (FAB), 764 (MH^+, 1), 728 (M–Cl. 16), 665 (8), 629 (58), 495 (50); [HRMS (FAB): 100% rel. abundance, $MH^+C_{40}H_{35}NO_2P_2^{105}PdI$=856.024].

4.1.8. *cis*-Bromobis(triphenylphosphine)(*N*-phthalimide) palladium(II) (*trans*-12). Following a similar procedure to *cis*-**9**. To a Schlenk tube containing vacuum dried $Pd_2dba_3{\cdot}CHCl_3$ (104 mg, 0.1 mmol) and Ph_3P (105 mg, 0.4 mmol) in dry CH_2Cl_2 (8 mL) at 21 °C under N_2, was stirred for 0.2 h, after, which time an orange colour persisted. Then, *N*-bromophthalimide (57 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added in one portion. The solution went yellow immediately. The solution was reduced to a third of its original volume in vacuo and then diethyl ether (2 mL) added to precipitate the complex. This gave the title complex as a pale yellow solid (0.120 g, 70%). Mp 199–203 °C (decomp.); (270 MHz, $CDCl_3$) 5.30 (2H, s, CH_2Cl_2 of recrystallization), 7.12–7.42 (27H, m, Ph–H), 7.62–7.86 (7H, m, Ph–H); δ_P (109.1 MHz, $CDCl_3$) 33.80 (1P, d, $^2J_{PP}$=8.39 Hz), 24.89 (1P, $^2J_{PP}$=8.39 Hz); ν_{max} ($CHCl_3$, cm^{-1}) 1651 (C=O), 1628 (C=C); *m*/*z* (FAB), 858 (MH^+, 4%), 776 (21), 711 (25), 629 (15), 332 (100); [HRMS (FAB): 100% rel. abundance, $MH^+C_{44}H_{35}NO_2P_2^{81}BrPd$= 858.036].

4.1.9. *cis*-Bromobis(1,2-bis(diphenylphosphino)ethane) (succinimide)palladium(II) (*cis*-14). Following a similar procedure to *cis*-**9**. To a Schlenk tube containing vacuum dried $Pd_2dba_3 \cdot CHCl_3$ (104 mg, 0.1 mmol) and 1,2-bis(diphenylphosphino)ethane (104 mg, 0.26 mmol) in dry CH_2Cl_2 (8 mL) at 21 °C under N_2, was stirred for 0.2 h, after, which time an orange colour persisted (0.25 h). A solution of recrystallised *N*-bromosuccinimide (46 mg, 0.26 mmol) in dry CH_2Cl_2 (2 mL) was added in one portion. The solution rapidly turned to a yellow colour. The solution was reduced to half of its original volume in vacuo and then petroleum ether (2 mL) added to precipitate the complex. This gave the title compound as a cream solid (209 mg, 59%). δ_H (270 MHz, $CDCl_3$) 2.09–2.16 (4H, br, $2\times CH_2$ dppe backbone), 2.24–2.29 (4H, m, $2\times CH_2$ of succinimide), 5.30 (1H, s, $\frac{1}{2}CH_2Cl_2$ of recrystallization), 7.15–7.68 (30H, m, phenyl groups); δ_P (161.2 MHz, $CDCl_3$) 23.95 (1P, br s), 61.87 (1P, br s) (consistent with data previously reported).[44]

4.1.10. *cis*-Bromobis(1,2-bis(dicyclohexylphosphino) ethane) (succinimide)palladium(II) (*cis*-15). Following a similar procedure to *cis*-**9**. To a Schlenk tube containing vacuum dried $Pd_2dba_3 \cdot CHCl_3$ (41 mg, 39.6 μmol) and 1,2-bis(dicyclohexylphosphino)ethane (34 mg, 793 μmol) in dry CH_2Cl_2 (4 mL) at 21 °C under N_2, was stirred for 0.5 h, after, which time an orange colour persisted. A solution of recrystallised *N*-bromosuccinimide (14 mg, 79.3 μmol) in dry CH_2Cl_2 (1 mL) was added in one portion. The solution rapidly turned a red colour. The solution was reduced to half of its original volume in vacuo and then petroleum ether (2 mL) added to precipitate the complex. This gave the title compound as a pale red solid (7.3 mg, 13%). δ_H (500 MHz, $CDCl_3$) 1.24–1.55 (24H, br, Cy–H), 1.65–1.96 (20H, br, Cy–H), 1.41 (2H, br s, CH_A and $CH_{A'}$), 2.15 (2H, br s, CH_B and $CH_{B'}$), 2.47 (2H, br s, CH_2 dcpe backbone), 2.69 (2H, br s, CH_2 dcpe backbone), 7.41–7.43 (12H, m, Ph–H), 7.64 (8H, m, Ph–H). δ_P (202 MHz, $CDCl_3$) 88.68 (1P, br s), 91.30 (1P, d, $^2J_{PP}=8.39$ Hz) (pure to the limits of detection). *m*/*z* (FAB) 708 (MH^+, 9), 626 (M–Br, 21), 528 (32), 423 (100), 341 (21) (the correct isotopic distribution was observed for the molecular ion of this complex).

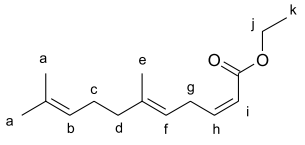
4.1.11. *cis*-Bromobis(1,1′-bis(diphenylphosphino)ferrocene) (succinimide)palladium(II) (*cis*-16). Following a similar procedure to *cis*-**9**. To a Schlenk tube containing vacuum dried $Pd_2dba_3 \cdot CHCl_3$ (60 mg, 58 μmol) and 1,1′-bis(diphenylphosphino)ferrocene (67.5 mg, 0.12 mmol) in dry CH_2Cl_2 (8 mL) at 21 °C under N_2, was stirred for 0.2 h, after, which time an orange colour persisted. A solution of recrystallised *N*-bromosuccinimide (21.6 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) was added in one portion. No obvious colour change was observed. The solution was reduced to half of its original volume in vacuo and then petroleum ether (2 mL) added to precipitate an orange complex. This gave the title compound as an orange solid (48 mg, 49%). δ_H (500 MHz, $CDCl_3$) 1.56 (2H, m, CH_A and $CH_{A'}$), 2.22 (2H, m, CH_B and $CH_{B'}$), 3.37 (1H, m, Cp–H), 4.16 (1H, m, Cp–H), 4.60 (1H, m, Cp–H), 5.20 (1H, m, Cp–H), 7.20–8.21 (20H, br. m, Ph–H). δ_P (202 MHz, $CDCl_3$) 24.57 (1P, d, $^2J_{PP}=6.36$ Hz), 35.13 (1P, d, $^2J_{PP}=6.36$ Hz) (pure to the limits of detection). *m*/*z* (FAB) 840 (MH^+, 3), 760 (M–Br, 15), 741 (M–*N*-Succ, 2), 555 (32) (the correct isotopic distribution was observed for the molecular ion of this complex).

4.1.12. *trans*-Bis(triphenylphosphine)palladium(II) (benzyl) bromide (*trans*-18). Prepared by an alternative procedure to that reported.[45] To a Schlenk tube containing vacuum dried $Pd_2dba_3 \cdot CHCl_3$ (100 mg, 0.097 mmol) in dry CH_2Cl_2 (3 mL), under N_2, was added a solution of PPh_3 (101.4 mg, 0.387 mmol) in dry CH_2Cl_2 (2.5 mL). The mixture was stirred for 0.2 h, after, which time an orange colour persisted. A solution of benzyl bromide in CH_2Cl_2 (2 mL) was added in one portion. The mixture turned a yellow colour after a few minutes, although stirring was continued for 0.5 h. The solution was concentrated in vacuo to a third of its original volume and petroleum ether added to precipitate the complex, *trans*-$Pd(Bn)(PPh_3)_2Br$. The yellow solid was filtered and washed with diethyl ether (117 mg, 76%); mp 124–125 °C (decomp.), lit.124–130 °C;[45] δ_H ($CDCl_3$, 300 MHz) 2.73 (2H, br s, CH_2), 7.37–7.70 (35H, m, Ph–H). δ_P ($CDCl_3$, 121 MHz) 23.26 (2P, s, P1–P2). A broad signal at δ 30.43 (s) is also observed.

4.2. General Stille coupling procedure

To a solution of the organohalide (0.25 mmol, 1 equiv) and the organostannane (0.3 mmol, 1.2 equiv) in dry degassed (freeze–pump–thaw cycles) toluene (2.5 mL), was added the palladium catalyst (0.0125 mmol, 0.05 equiv). The mixture was placed under a dry N_2 atmosphere and heated to 60 °C in the dark (flask was covered with domestic foil) for the specified time. All reactions were followed by TLC, GC or GC/MS analysis. On completion, the reaction was cooled to ambient temperature, then saturated aqueous KF (2.5 mL) was added and the mixture stirred vigorously for 1 h. The mixture was filtered through Celite®, and the residue rinsed with Et_2O (2×5 mL), washed with saturated aqueous NaCl (2×2.5 mL) and dried ($MgSO_4$). Concentration in vacuo and subsequent purification by column chromatography (using EtOAc–hexane or PE mixtures) gave the products as oils.

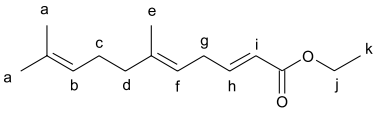
4.2.1. Ethyl (2*Z*,5*E*)-6,10-dimethyl-2,5,9-undecatrienno-ate (*Z*,*Z*-26).



The title compound was obtained as a pale yellow oil. $R_f=0.50$ (PE–EtOAc, 9:1); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, $^3J=7.5$ Hz CH_3^k), 1.59 (6H, s, CH_3^a), 1.67 (3H, s CH_3^e), 1.98–2.10 (4H, m, CH_2^{c+d}), 3.36 (2H, dd, $^3J=7.5$, 7.5 Hz, CH_2^g), 4.17 (2H, q, $^3J=7.5$ Hz, CH_2^j), 5.09 (1H, tt, $^3J=6.5$ Hz, $^4J=1.0$ Hz, CH^b), 5.16 (1H, td, $^3J=7.5$ Hz, $^4J=1.0$ Hz, CH^f), 5.74 (1H, dm, $^3J=11.5$ Hz, CH^i), 6.13 (1H, dt, $^3J=11.5$, 7.5 Hz, CH^f); δ_C (100.6 MHz, $CDCl_3$), 14.4 (CH_3), 16.3 (CH_3), 17.8 (CH_3), 25.8 (CH_3), 26.6 (CH_2), 28.2 (CH_2), 39.7 (CH_2), 60.0 (CH_2), 119.0 (CH), 120.6 (CH), 124.2 (CH), 128.7 (CH), 131.6 (C), 137.6 (C), 166.6 (C). ν_{max} (neat, cm^{-1}) 2981, 2938, 1717, 1644, 1450, 1373, 1268,

1182, 1095 and 1032; *m/z* (CI), 254 (MNH_4^+, 26%), 237 (MH^+, 100), 191 (28), 163 (53), 123 (86), 69 (58) 41 (34); [HRMS (CI): calcd for $C_{15}H_{25}O_2$, 237.1855. Found: MH^+, 237.1855 (0.8 ppm error)].

4.2.2. Ethyl (2*Z*,5*E*)-6,10-dimethyl-2,5,9-undecatriennoate (*E*,*E*-26).



The title compound was obtained as a colourless oil. R_f=0.44 (PE–EtOAc, 9:1); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, ^3J=7.0 Hz CH_3^k), 1.59 (6H, s, 2×CH_3^a), 1.68 (3H, s, CH_3^e, NB. Isomerisation to cis observed as a singlet at 1.72), 2.00– 2.11 (4H, m, 2×CH_2^{c+d}), 2.88 (2H, app. br. t, dd, ^3J=7.5, 6.0 Hz, CH_2^g), 4.18 (2H, q, ^3J=7.0 Hz, CH_2^j), 5.06 (1H, m, CH^b), 5.13 (1H, br. t, ^3J=7.5 Hz, CH^f), 5.79 (1H, dt, ^3J=15.5 Hz, ^4J=2.0 Hz, CH^i), 6.92 (1H, dt, ^3J=15.5, 6.0 Hz, CH^h); δ_C (100.6 MHz, $CDCl_3$), 14.2 (CH_3), 16.0 (CH_3), 17.6 (CH_3), 25.6 (CH_3), 26.4 (CH_2), 30.6 (CH_2), 39.6 (CH_2), 60.1 (CH_2), 118.9 (CH), 120.9 (CH), 124.0 (CH), 131.6 (C), 138.3 (C), 147.7 (CH), 166.7 (C); ν_{max} (neat, cm^{-1}) 2967, 2926, 1722, 1651, 1448, 1370, 1321, 1266, 1172, 1094 and 1043; *m/z* (CI), 254 (MNH_4^+, 10%), 237 (MH^+, 77), 191 (46), 163 (100), 123 (45); [HRMS (CI): calcd for $C_{15}H_{25}O_2$, 237.1854. Found: MH^+, 237.1849 (2.2 ppm error)].

4.2.3. Ethyl (2*Z*,5*E*)-6-phenyl-2,5-hexadienoate (*E*,*Z*-28).

The title compound was obtained as a colourless yellow oil. R_f=0.36 (PE–EtOAc, 9:1, v:v); δ_H (270 MHz, $CDCl_3$) 1.28 (3H, t, ^3J=7.0 Hz CH_3^g), 3.55 (2H, dd, ^3J=6.5, 7.5 Hz, CH_2^c), 4.17 (2H, q, ^3J=7.0 Hz, CH_2^f), 5.82 (1H, dt, ^3J=11.5 Hz, ^4J=1.5 Hz, CH^e), 6.19 (1H, dt, ^3J=16.0, 6.5 Hz CH^f), 6.25 (1H, dt, ^3J=11.5, 7.5 Hz CH^d), 6.43 (1H, d, ^3J=16.0 Hz, CH^g), 7.14–7.33 (5 H, m, Aryl); δ_C (67.9 MHz, $CDCl_3$), 14.2 (CH_3), 32.3 (CH_2), 59.9 (CH_2), 120.2 (CH), 126.0 (CH), 126.8 (CH), 127.1 (CH), 128.5 (CH), 131.4 (CH), 137.3 (C), 146.8 (CH), 166.3 (C); ν_{max} (film, cm^{-1}) 3028, 2982, 1717, 1642, 1448, 1413, 1199, 1168, 034, 966, 823, 744 and 694; *m/z* (CI), 243 (MNH_4^+, 25%), 217 (MH^+, 100); 188 (12), 169 (16), 143 (22), 125 (12), 112 (7), 106 (12); [HRMS (CI): calcd for $C_{14}H_{17}O_2$, 217.1229. Found: MH^+, 217.1230 (0.5 ppm error)].

4.2.4. Ethyl (2*E*,5*E*)-6-phenyl-2,5-hexadienoate (*E*,*E*-28).

The title compound was obtained as a pale yellow oil. R_f= 0.20 (PE–EtOAc, 9:1); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, ^3J=7.0 Hz CH_3), 3.00 (2H, ddd, ^3J=6.5, 6.5 Hz, ^4J=1.5 Hz, CH_2), 4.09 (2H, q, ^3J=7.0 Hz, CH_2), 5.80 (1H, dt, ^3J=15.5 Hz, ^4J=1.5 Hz, CH), 6.08 (1H, dt, ^3J=16.0, 6.5 Hz CH), 6.34 (1H, d, ^3J=16.0 Hz CH), 6.94 (1H, dt, ^3J=15.5, 6.5 Hz, CH), 7.14 (1H, m, aromatic CH), 7.19–7.26 (4H, m, Ph–H); δ_C (100.6 MHz, $CDCl_3$), 14.2 (CH_3), 35.2 (CH_2), 60.2 (CH_2), 122.4 (CH), 125.5 (CH), 126.2 (CH), 127.5 (CH), 128.7 (CH), 132.6 (CH), 137.2 (C), 146.6 (CH), 166.6 (C); ν_{max} (film, cm^{-1}) 3058, 3027, 2982, 2934, 2903, 1719, 1652, 1448, 1367, 1322, 1267, 1201, 1159, 1092, 1042 and 967; *m/z* (CI), 234 (MNH_4^+, 22%), 217 (MH^+, 100); 171 (6), 143 (16), 128 (11), 115 (6); [HRMS (CI): calcd for $C_{14}H_{20}NO_2$, 234.1494. Found: MNH_4^+, 234.1496 (0.7 ppm error)].

4.2.5. (4*E*)-5,9-Dimethyl-1,4,9-decatriene (*E*-36).

The title compound was obtained as a colourless oil. R_f=0.73 (PE–EtOAc, 9:1) on alumina; δ_H (270 MHz, $CDCl_3$) 1.61 (6H, s, CH_3^a), 1.69 (3H, s, CH_3^e), 1.99–2.10 (4H, m, CH_2^{c+d}), 2.75 (2H, app. br. t, dd, ^3J=7.0, 6.5 Hz, CH_2^g), 4.96 (1H, dd, ^3J=15.5 Hz, ^2J=1.0 Hz, $CH_2^{i\ cis}$), 5.01 (1H, dd, ^3J=19.5 Hz, ^4J=1.0 Hz, $CH_2^{i\ trans}$), 5.08– 5.19 (2H, m, CH's$^{f\ and\ b}$), 5.80 (1H, m, CH^h); δ_C (100.6 MHz, $CDCl_3$), 23.4, 25.7, 267 31.9, 32.2, 39.7, 114.0, 114.2, 121.3, 122.3, 124.3, 137.5; *m/z* (EI), 164 [M^+] (2%), 149 (5), 123 (10), 94 (14), 69 (100), 41 (57); [HRMS (EI): calcd for $C_{12}H_{20}$, 164.1565. Found: M^+, 164.1561 (2.2 ppm error)].

4.2.6. Ethoxy-5-phenyl-(1,4*E*)-pentadiene (*E*-39).

The title compound was obtained as a colourless oil. R_f= 0.73 (PE–EtOAc, 9:1) on alumina; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, ^3J=7.0 Hz CH_3^f), 2.91 (2H, dd, ^3J=7.0 Hz, CH_2^c), 3.67 (2H, q, ^3J=7.0 Hz, CH_2^e), 3.83 (1H, d, ^3J=2.0 Hz, $CH_2^{d,\ trans}$), 3.84 (1H, d, ^3J=2.0 Hz, $CH_2^{d\ cis}$), 6.19 (1H, dt, ^3J=16.0, 7.0 Hz CH^b), 6.36 (1H, d, ^3J=16.0 Hz, CH^a), 7.10–7.15 (1H, m, CH^3), 7.16– 7.23 (2H, m, CH^1), 7.23–7.30 (2H, m, CH^2); δ_C (100.6 MHz, $CDCl_3$), 14.5 (CH_3), 38.7 (CH_2), 62.9 (CH_2), 81.4 (CH_2), 126.1 (CH), 126.6 (CH), 127.1 (CH), 128.4 (CH), 131.6 (CH), 137.5 (C), 161.7 (C); ν_{max} (film, cm^{-1}) 3028, 2978, 2927, 1653, 1599, 1496, 1448, 1425, 1385, 1294, 1277, 1227, 1192, 1117, 1070, 966, 800, 744 and 692; *m/z* (CI), 189 (MH^+, 100%), 143 (11); [HRMS (CI): calcd for $C_{13}H_{17}O_1$, 189.1279. Found: MH^+, 189.1278 (0.8 ppm error)].

4.2.7. Ethyl (2*Z*)-4-(4-nitrophenyl)-2-butenoate (*Z*-49).

The title compound was obtained as a pale yellow oil. R_f= 0.30 (PE–EtOAc, 9:1); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, ^3J=7.0 Hz CH_3), 4.14 (2H, d, ^3J=7.5 Hz, CH_2), 4.21 (2H, q, ^3J=7.0 Hz, CH_2), 5.95 (1H, dd, ^3J=11.5 Hz, ^4J=1.0 Hz, CH), 6.31 (1H, dt, ^3J=11.5, 7.5 Hz, CH), 7.40 (2H, d, ^3J=8.5 Hz CH), 8.17 (2H, d, ^3J=8.5 Hz, CH); δ_C (100.6 MHz, $CDCl_3$), 14.2 (CH_3), 38.4 (CH_2), 60.2 (CH_2), 122.3 (CH), 126.3 (CH), 128.7 (CH), 137.8 (C), 147.2 (CH), 166.5 (C), 171.6 (C); ν_{max} (neat, cm^{-1}) 2957, 2925, 2854, 1716, 1682, 1645, 1600, 1521, 1346, 1206, 1167 and 1037; *m/z* (CI), 253 (MNH_4^+, 53%), 223, (16), 216 (25), 206 (100), 199 (21); [HRMS (CI): calcd for $C_{12}H_{17}O_4N_2$, 253.1188. Found: MNH_4^+, 253.1188 (0.2 ppm error)].

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Catalytic activity of η^2-(olefin)palladium(0) complexes with iminophosphine ligands in the Suzuki–Miyaura reaction. Role of the olefin in the catalyst stabilization

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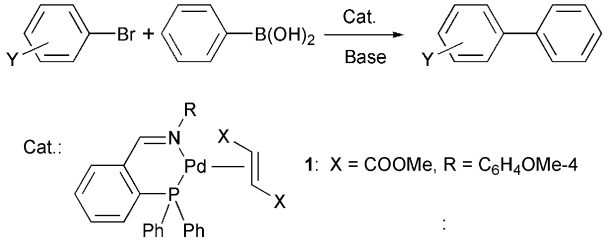
Abstract—The catalytic activity of η^2-(olefin)palladium(0)(iminophosphine) complexes in the Suzuki–Miyaura coupling is strongly dependent on the reaction conditions and on the nature of the ligands. The reaction is at the best carried out in aromatic solvents in the presence of K_2CO_3 at 90–110 °C. Higher reaction rates are obtained when the R substituent on the *N*-imino group is an aromatic group of low steric hindrance and the olefin is a moderate π-accepting ligand such as dimethyl fumarate. At temperatures lower than 90 °C, a self-catalyzed process leading to catalyst deactivation becomes predominant. Preliminary mechanistic investigations indicate that the oxidative addition of the aryl bromide to a Pd(0) species is the rate determining step in the catalytic cycle and that the olefin plays a key role in catalyst stabilization. Systems in situ prepared by mixing $Pd(OAc)_2$ or $Pd(dba)_2$ with 1 equiv of iminophosphine appear substantially less active than the preformed catalysts.

1. Introduction

The Suzuki–Miyaura reaction (Scheme 1) is one of the most powerful and versatile synthetic methods for the formation of carbon–carbon bonds.[1] In particular, this reaction is finding increasing application in the synthesis of biaryls,[1,2] which are key intermediates in fine chemistry (pharmaceuticals, agrochemicals) as well as in advanced material chemistry (dendrimers, polymers and nanostructured materials).



Scheme 1.

Recently, we have reported that iminophosphine–palladium(0) complexes of type **1** (Scheme 1) catalyze the coupling of aryl bromides with boronic acids with high efficiency allowing to obtain turnover numbers of up to $10^5\ h^{-1}$ (turnover number: mol of substrate converted/mol of catalyst).[3] Among the most interesting features of these catalysts, is to mention: (i) the relative insensitivity to the presence of deactivating groups on the aryl bromide, (ii) the almost complete conversion attainable with a wide variety of substrates upon a suitable choice of the reaction conditions and (iii) the good stability under aerobic conditions.[3]

These results prompted us to investigate more deeply the catalytic activity of complexes of type **1** in order to optimize the reaction conditions and understand the factors, which control the catalytic activity. In particular, we thought it interesting to study the effects brought about by the nature of the imino substituent and of the olefin. Furthermore, we have checked if a comparable catalytic efficiency can be obtained using catalysts prepared in situ by reacting some palladium(0) catalyst precursors with an iminophosphine.

2. Results and discussion

A wide variety of solvents and bases are commonly used in

Keywords: Suzuki–Miyaura reaction; Iminophosphine complexes; Palladium; Arylboronic acids; Biaryls; Cross-coupling.
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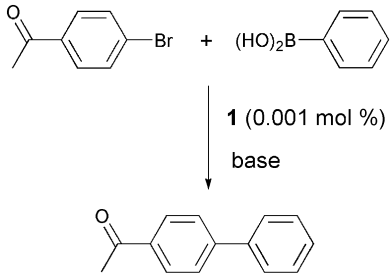
the Suzuki coupling. Inspection of the literature reveals that there is not a set rule and that each catalyst needs a specific solvent and a certain base to attain the highest efficiency.

The coupling of 4-bromoacetophenone with phenylboronic acid (Scheme 2) was used as the model reaction in order to highlight the influence of the solvent and of the base on the catalytic activity. The relevant results are reported in Tables 1 and 2, respectively. The reaction appears to be quite sensitive to the nature of the solvent. In general, in solvents of moderate or low polarity such as aromatic hydrocarbons or even alkanes (entries 1–4) the reaction proceeds faster, the highest rate being observed in toluene at 110 °C.



Scheme 2.

Table 1. Influence of the solvent[a]

Entry	Solvent	*T* (°C)	Yield (%)[b]	TON[c] ($\times 10^{-3}$)
1	Toluene	110	82	164
2	*n*-Dodecane	110	30	60
3	*n*-Tetradecane	110	25	50
4	1,3,5-Trimethylbenzene	110	20	11
5	*N*-Methylpirrolidinone	110	0	0
6	*N*,*N*-Dimethylformamide	110	10	20
7	Dimethyl sulfoxide	110	0	0
8	*N*,*N*-Dimethylacetamide	110	30	60
9	*o*-Xylene	140	70	140
10	*m*-Xylene	140	56	112
11	*p*-Xylene	140	45	90
12	*o*-Dichlorobenzene	140	56	112
13	1,2-Dimethoxyethane	140	9	18

[a] Reaction conditions. Solvent: 12 mL; *t*: 2 h; catalyst: complex **1** (2×10^{-5} mmol); 4-bromoacetophenone: 4.0 mmol; phenylboronic acid: 6.0 mmol; base: K_2CO_3 (8.0 mmol); [ArBr]/[**1**]=200,000; [acid]/[ArBr]=1.5; base/ArBr=2.0 (mol/mol).
[b] GLC with *n*-undecane as internal standard.
[c] Mol of substrate converted/mol of catalyst.

Table 2. Influence of the base[a]

Entry	Base	pK_a[b]	Yield (%)[c]
1	CH_3COONa	4.76	3
2	Piperidine	11.1	0
3	Na_2CO_3	10.3	26
4	K_2CO_3	10.3	30
5	Cs_2CO_3	10.3	17
6	K_3PO_4	12.3	12

[a] Reaction conditions. Solvent: *N*,*N*-dimethylacetamide (12 mL); *T*: 110 °C; *t*: 2 h; catalyst: complex **1** (2×10^{-5} mmol); 4-bromoacetophenone: 4.0 mmol; phenylboronic acid: 6.0 mmol; [ArBr]/[**1**]=200,000; [acid]/[ArBr]=1.5; base/ArBr=2.0 (mol/mol).
[b] The values refer to dilute aqueous solutions, data from Ref. 5.
[c] GLC with *n*-undecane as internal standard.

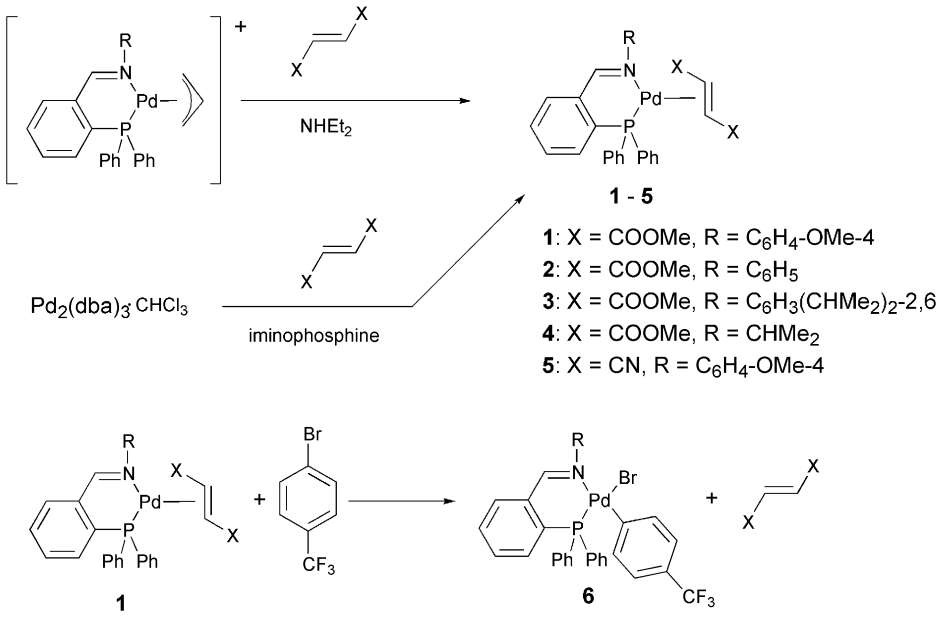
In highly polar solvents the catalytic activity is lower, possibly owing to the coordinating properties of these solvents. Toluene appears superior to other more substituted aromatics as demonstrated by the low activity of 1,3,5-trimethylbenzene (entry 4) and xylenes even at higher temperatures (entries 9–11). It is interesting to observe that since the catalyst is not able to promote the coupling of aryl chlorides with boronic acids[3] it is possible to carry out the reaction in *o*-dichlorobenzene at 140 °C with fairly good yields.

As far as the nature of the base is concerned, it is generally accepted that the use of stronger bases leads to higher yields in the Suzuki coupling.[4] The data obtained using complex **1** in *N*,*N*-dimethylacetamide in the presence of some different bases are reported in Table 2. The experiments do not reveal a plain connection between the catalytic activity and the strength of the base. Indeed, in the presence of organic bases such as the weak base sodium acetate or the stronger base piperidine, the reaction proceeds sluggishly. This behavior is likely due to the coordinating properties of these bases, which may compete with the substrates for the coordination to the metal center. The use of inorganic bases such as carbonates or phosphates allows to obtain much higher reaction rates, but still there is not a plain relationship between the base strength and the catalytic activity, since the best activity is achieved employing the lesser basic carbonates. In this connection, it is worth noting that the best reaction rates are obtained using the inexpensive sodium or potassium carbonates.

As a further step of our investigations we have studied the influence brought about by the R substituent on the iminophosphine and by the olefin coordinated to palladium. To this purpose, we have examined the catalytic activities of the iminophosphine–palladium complexes **1**–**6** (Scheme 3).

Complexes **1**–**5** were prepared either by reacting the corresponding cationic η^3-(allyl) complexes with diethylamine in the presence of the appropriate olefin[6] or by reacting $Pd(dba)_3CHCl_3$ (dba=dibenzylideneacetone) with the appropriate iminophosphine and olefin.[7] Complex **6** was synthesized by reacting **1** with 4-(trifluoromethyl)bromobenzene as described in Section 4. The coordination geometry of **6** with the aryl ligand trans to the imino nitrogen is based on trans influence considerations, the aryl group and the phosphorus atom being the strongest donors,[8] and X-ray structural analyzes of related complexes [PdI(Ph)(P–N)] (P–N=iminophosphine).[9]

The data of entries 1–5 in Table 3 show that the highest reaction rates are observed when R is an aromatic group of low steric requirements, such as C_6H_4OMe-4 or C_6H_5. The catalytic activity decreases considerably when R is the more sterically demanding $C_6H_3(CHMe_2)_2$-2,6 group (complex **3**, entry 3), and even more when R is an electron-donating substituent such as the isopropyl group (complex **4**, entry 4). The catalytic activity is also influenced by the π-accepting properties of the η^2-bound olefin, as indicated by the significant drop in the reaction rate on going from the dimethyl fumarate complex **1** to the analogous complex **5** containing the much stronger π-accepting olefin



Scheme 3.

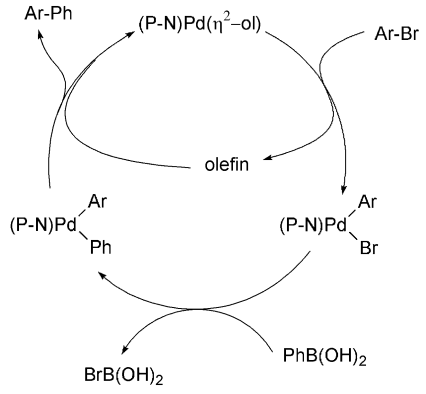
Table 3. Influence of the catalyst structure[a]

Entry	Catalyst	Yield (%)[b]
1	**1**	82
2	**2**	78
3	**3**	33
4	**4**	11
5	**5**	54
6	**6**	17

[a] Reaction conditions. Solvent: toluene (12 mL); *T*: 110 °C; *t*: 2 h; catalyst: complex **1** (2×10^{-5} mmol); 4-bromoacetophenone: 4.0 mmol; phenylboronic acid: 6.0 mmol; base: K_2CO_3 (8.0 mmol); [ArBr]/[**1**]=200,000; [acid]/[ArBr]=1.5; base/ArBr=2.0 (mol/mol).
[b] GLC with *n*-undecane as internal standard.

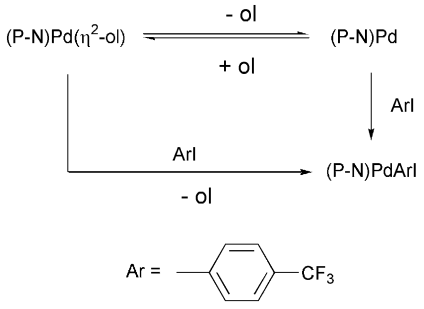
fumaronitrile. Similar effects are seen in $Pd(dba)_n$ complexes described by Fairlamb and co-workers.[10]

The commonly accepted mechanism for the Suzuki reaction involves the initial oxidative addition of the aryl halide to a zerovalent palladium species, followed by transmetalation and reductive elimination to give the coupling product and restore the catalytically active palladium(0) species (Scheme 4).[11]



Scheme 4.

A mechanistic study on the single steps of the catalytic cycle is currently in progress.[12] Preliminary results indicate that (i) with the complexes **1**–**5** the rate-determining step of the catalytic cycle is the oxidative addition of the aryl bromide and that (ii) the rate of the oxidative addition of 4-(trifluoromethyl)bromobenzene to complexes **1**–**5** decreases in the order **1**≈**2**>**3**>**4** ≫**5**. This reactivity order closely parallels that found for the oxidative addition of 4-(trifluoromethyl)iodobenzene to complexes **1**, **4**, and **5** for which the observed reaction rates decrease in the order **1**>**4**≫**5**.[7] The two parallel pathways depicted in Scheme 5 are operative and the much lower reactivity of complex **5** is explained on the basis of the greater π-accepting properties of fumaronitrile, which (i) increase the strength of the palladium–olefin bond thus lowering the concentration of the highly reactive (P–N)Pd species and (ii) reduce the electron density on the metal making the (P–N)Pd(η^2-ol) complex less susceptible of oxidative addition by the aryl halide.



Scheme 5.

However, at the light of the reactivity order **1**≈**2**>**3**>**4**>**5** found for the oxidative addition of 4-(trifluoromethyl)bromobenzene to complexes **1**–**5**, the fairly good catalytic activity of complex **5** is somewhat outstanding, as it appears from the data of Table 3, which show the catalytic activity to be decreasing in the order **1**≈**2**>**5**>**3**>**4**.

To further explore the role played by the olefin coordinated to the metal center we have carried out some experiments using complex **6** as the catalyst. Indeed, we deemed it interesting to evaluate the catalytic efficiency of this Pd(II) species since being the product of the oxidative addition of 4-(trifluoromethyl)bromobenzene to **1** it is one of the key intermediates of the catalytic cycle. In absence of any olefin, its catalytic activity should be that of a 'naked' (P–N)Pd fragment and, hence, comparable if not superior to that of **1**. Unpredictably, the experiments reveal that **6** is much less active than both **1** and **5**.

The observation that during the synthesis of complex **6** we detected the formation of significant amounts of metallic palladium helps to rationalize this result, suggesting that the low product yield observed using **6** should be attributed to a short life of the catalytic species rather than to an intrinsic low activity.

From these findings it emerges that the olefin has an important role in catalysis as its presence contributes to stabilize the catalytically active species. Accordingly, the fairly good activity of **5** is better interpreted in terms of a greater stabilization of the (P–N)Pd fragment by the strongly π-accepting fumaronitrile ligand. Such stabilizing effect is substantiated by the observation that when a toluene solution of **1** is heated at 90 °C in the presence of phenylboronic acid and K_2CO_3 (**1**/$PhB(OH)_2$/K_2CO_3 molar ratio=1:10:15) extensive decomposition to metallic palladium is detected. Under the same experimental conditions, a slight decomposition occurs also for complex **5**, but at a much lower rate.

Catalyst deactivation has been previously noticed in the Suzuki coupling by several authors and, in particular, Bedford has pointed out the importance of the catalyst longevity in order to achieve high substrate conversions and product yields.[4,13]

The occurrence of catalyst deactivation is further supported by the issues of the studies of the temperature influence on the catalysis.

The use of mild reaction conditions is essential with substrates bearing thermally unstable functional groups, and therefore the development of systems active at low temperatures is of great relevance. Accordingly, we have investigated the influence of the temperature on the catalytic activity of complex **1**. The relevant data (Table 4) show that on lowering the temperature to 90 °C the rate of the model reaction is approximately halved so that using an aryl bromide/catalyst molar ratio of 80,000:1 only a 55% conversion is obtained after 2 h. In order to obtain an almost quantitative yield in 2 h it is necessary to double the amount of the catalyst employed.

When the reaction temperature is further decreased to 70 °C, a lower, but still good catalyst activity is observed (25% substrate conversion after 2 h, entry 4 of Table 4). However, when the reaction time is increased up to 24 h, the product yield increases only to 27% (entry 5 of Table 4), indicating that after 2 h at this temperature the catalyst loses its activity.

Catalyst deactivation is commonly accompanied by the formation of metallic palladium.[4,13] During our experiments we did not observe the formation of palladium black; however, this can be ascribed either to the use of a minute amount of complex **1** in the presence of a huge amount of potassium carbonate or to the formation of colloidal palladium, which may be hardly visible to the naked eye. In this connection, it is to remind that in the synthesis of complex **6** a significant amount of metallic palladium is also formed.

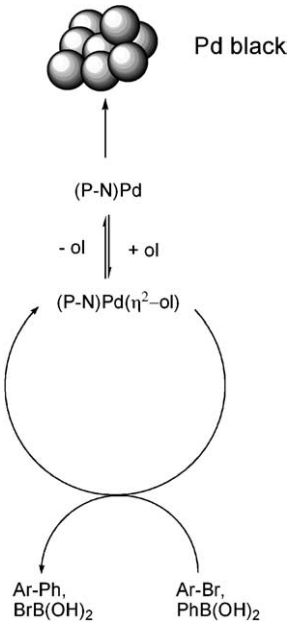
In order to increase the product yield, some reactions at increasing catalyst concentrations were carried out. A series of isochronous experiments at 70 °C reveals that the substrate conversion does not increase linearly with the amount of the employed catalyst (entries 4, 6–8, Table 4). On the contrary, by taking into account the turnover numbers it appears that the catalyst efficiency decreases with increasing its concentration. Summing up, the experiments at low temperature reveal that (i) under 90 °C catalyst deactivation becomes much more significant, and (ii) that its rate increases with increasing the catalyst concentration, that is, the deactivation process is self-catalyzed.

Also these findings can be explained by taking into account the stability of the coordinatively unsaturated and highly reactive (P–N)Pd fragment, which forms in the reductive elimination step at the end of the catalytic cycle. To enter a new catalytic cycle the (P–N)Pd fragment must add an aryl bromide molecule. This productive process is in competition with a second one, which leads to the formation of metallic palladium particles inactive in catalysis (Scheme 6).

Table 4. Influence of the temperature and of the catalyst concentration[a]

Entry	*T* (°C)	**1** (mmol)	[ArBr]/[**1**]	*t* (h)	Yield (%)[b]	TON[c]
1	110	5×10^{-5}	80,000	2	99	80,000
2	90	5×10^{-5}	80,000	2	55	44,000
3	90	1×10^{-4}	40,000	2	96	38,400
4	70	5×10^{-5}	80,000	2	25	20,000
5	70	5×10^{-5}	80,000	24	27	21,600
6	70	1×10^{-4}	40,000	2	40	16,000
7	70	2×10^{-4}	20,000	2	51	10,000
8	70	4×10^{-4}	10,000	2	57	5,700

[a] Reaction conditions. Solvent: toluene (12 mL); ArBr: 4-bromoacetophenone (4.0 mmol); base: K_2CO_3 (8.0 mmol); phenylboronic acid: 6.0 mmol; [acid]/[ArBr]=1.5; base/ArBr=2.0 (mol/mol).
[b] GLC with *n*-undecane as internal standard.
[c] Mol of substrate converted/mol of catalyst.



Scheme 6.

When the oxidative addition is too slow owing to the low reaction temperature, or when at high catalyst loadings the palladium metal forming process is very fast owing to its self-catalytic nature, the formation of metallic palladium becomes the predominant process leading to the removal of all the active species from the catalytic cycle.

During our investigation on the catalytic activity of iminophosphine palladium(0) complexes of the type **1** in the Stille reaction, we observed that the activity of these species can be further enhanced by the addition of 1 equiv of free iminophosphine.[14] Moreover, it was found that a comparable catalytic efficiency can be obtained by in situ combining $Pd(OAc)_2$ or $Pd(dba)_2$ (dba=dibenzylideneacetone) with 2 equiv of iminophosphine. Therefore, we have investigated if also in Suzuki reaction it is possible to employ such in situ systems instead of the preformed catalysts of the type **1**. At first, in order to determine the optimal Pd/iminophosphine ratio we studied the activity of the system obtained by mixing complex **1** with an equivalent of free ligand in the coupling of 4-bromoacetophenone with phenylboronic acid. The experiment shows that the addition of 1 equiv of the free P–N ligand to complex **1** has almost no effect on the reaction rate (compare entries 1 and 2 of Table 5). This result is confirmed by the observation that the oxidative addition of an excess of $BrC_6H_4CF_3$-4 to the complex **1** or to an equimolar mixture **1**/iminophosphine proceeds at comparable rate in toluene at 90 °C, with a $BrC_6H_4CF_3$-4/**1** molar ratio of 10:1. As indicated by the IR spectra at different times, the reaction goes to completion in about 15 min in both cases.

This result contrasts with what we found for complex **1** in the Stille reaction where the addition of 1 equiv of free iminophosphine to complex **1** leads to an approximate doubling of the reaction rate. Possibly, the different behavior is to be attributed to the quite different experimental conditions (solvent, temperature, substrate/catalyst molar ratio) employed in the two reactions. Consequently, we extended our investigation to the systems $Pd(OAc)_2$/P–N and $Pd(dba)_2$/P–N (P–N=2-$(PPh_2)C_6H_4$-1-CH=NC_6H_4OMe-4) with a Pd/P–N molar ratio of 1:1.

The activity of the catalyst prepared by combining $Pd(OAc)_2$ with 1 equiv of iminophosphine turns out to be much lower than that of complex **1** (entries 3 and 1 of Table 5). Moreover, almost the same catalytic activity is obtained when $Pd(OAc)_2$ is combined with 2 equiv of iminophosphine, thus confirming that the presence of a second P–N ligand has no effect on the catalytic system (compare entries 3 and 4 of Table 5). On the other hand, the system obtained by combining $Pd(dba)_2$ with one iminophosphine ligand appears significantly more active than the analogous one prepared using $Pd(OAc)_2$ (entries 5 and 3 of Table 5) although somewhat less efficient than complex **1**. In keeping with what found with complex **1** and $Pd(OAc)_2$, the addition of a second iminophosphine ligand does not change the catalytic activity. It is also interesting to note that the reactivity of the system

Table 5. Comparison of the catalytic activity of **1** with some in situ catalysts[a]

Entry	Catalyst	Aryl bromide	Equivalents of added ligand[b]	Total P/Pd ratio	Yield (%)[c]
1	Complex **1**	4-$CH_3COC_6H_4Br$	—	1:1	82
2	Complex **1**	4-$CH_3COC_6H_4Br$	1	2:1	84
3	$Pd(OAc)_2$	4-$CH_3COC_6H_4Br$	1	1:1	20
4	$Pd(OAc)_2$	4-$CH_3COC_6H_4Br$	2	2:1	17
5	$Pd(dba)_2$	4-$CH_3COC_6H_4Br$	1	1:1	52
6	$Pd(dba)_2$	4-$CH_3COC_6H_4Br$	2	2:1	53
7	Complex **1**	4-$CF_3C_6H_4Br$	—	1:1	95
8	$Pd(OAc)_2$	4-$CF_3C_6H_4Br$	1	1:1	42
9	$Pd(dba)_2$	4-$CF_3C_6H_4Br$	1	1:1	50
10	Complex **1**	C_6H_5Br	—	1:1	80
11	$Pd(OAc)_2$	C_6H_5Br	1	1:1	18
12	$Pd(dba)_2$	C_6H_5Br	1	1:1	27
13	Complex **1**	4-$CH_3OC_6H_4Br$	—	1:1	68
14	$Pd(OAc)_2$	4-$CH_3OC_6H_4Br$	1	1:1	22
15	$Pd(dba)_2$	4-$CH_3OC_6H_4Br$	1	1:1	28

[a] Reaction conditions. Solvent: toluene (12 mL); *T*: 110 °C; *t*: 2 h; catalyst: complex **1** (2×10^{-5} mmol); aryl bromide: 4.0 mmol; phenylboronic acid: 6.0 mmol; base: K_2CO_3 (8.0 mmol); [ArBr]/[Pd]=200,000; [acid]/[ArBr]=1.5; base/ArBr=2.0 (mol/mol).
[b] Ligand=2-$(PPh_2)C_6H_4$-1-CH=NC_6H_4OMe-4.
[c] GLC with *n*-undecane as internal standard.

$Pd(dba)_2$/iminophosphine is very close to that displayed by complex **5** (compare entry 5 of Table 3 with entry 5 of Table 5).

This quite remarkable reactivity pattern is not due to the particular substrate used in these reactions as shown by the experiments carried out with other activated or deactivated aryl bromides (see Table 5).

These investigations confirm the important role played by the olefin in stabilizing the Pd(P–N) fragment, which forms in the last step of the catalytic cycle. In fact, the data of Table 5 show a catalytic activity decreasing in the order **1** > $Pd(dba)_2$/P–N > $Pd(OAc)_2$/P–N, which can be rationalized on the basis of the following considerations. When no olefin is present, as in the case of the system $Pd(OAc)_2$/P–N, the lack of stabilization brings about a lower catalytic activity due to decomposition of the Pd(P–N) fragment to inactive palladium metal particles. In this connection, it is worth noting that the activity of the system $Pd(OAc)_2$/P–N is quite close to that of complex **6** under the same experimental conditions (compare entry 3 of Table 5 with entry 6 of Table 3). The activity increases moderately for the $Pd(dba)_2$/P–N system due to the presence of dibenzylideneacetone, which is an olefin of moderate π-accepting ability, and much more for the complex **1** due to the better π-accepting properties of dimethyl fumarate.[15]

3. Conclusive remarks

Our investigations indicate that the catalyst activity is significantly affected by its composition and the reaction conditions. In particular, it emerges that a key role is played by the olefin bound to palladium in order to assure a long life to the catalytically active species. This appears of primary importance because the Suzuki–Miyaura reaction is currently used as a key step in the synthesis of valuable fine chemicals. While the here reported catalytic and preliminary mechanistic studies suggest that the commonly accepted catalytic cycle is operative and that oxidative addition of the aryl bromide to a palladium(0) species is the rate determining step, some peculiar effects such as that of the nature of the base and of the solvent deserve further mechanistic investigations, which are currently in progress.

4. Experimental

4.1. General methods

All reactions, unless otherwise stated, were carried out under an inert atmosphere (argon). Commercial solvents (Aldrich or Fluka) were purified before the use according to standard procedures.[16] Bromobenzene, 4-bromoanisole, 1-bromo-4-trifluoromethylbenzene, and piperidine (Aldrich) were distilled before the use. 4-Bromoacetophenone (Aldrich) was recrystallized from methanol.[16] Anhydrous sodium acetate, anhydrous potassium carbonate, anhydrous sodium carbonate, and cesium carbonate (p.a.) were obtained from Aldrich. Complexes **1**–**5** were prepared as described in the literature.[6,7] The coupling products were identified by their GC–MS and ^{1}H NMR spectra. GLC analyzes were performed on a Agilent 6850 gas chromatograph; GC–MS analyzes were performed on a HP 5890 series II gas chromatograph interfaced to a HP 5971 quadrupole mass-detector. ^{1}H and ^{31}P NMR spectra were registered on a Bruker Avance 300 NMR spectrometer operating at 300.11 and 121.49 MHz, respectively. The IR spectra were recorded on a Perkin-Elmer 983G spectrophotometer using KBr cells.

4.2. Catalytic experiments

The coupling reactions were carried out in a magnetically stirred glass reactor (50 mL) having an inert gas inlet and a side arm closed with a rubber septum for the withdrawing of GLC samples. In a typical experiment (entry 1 of Table 1), the reactor was charged with 4-bromoacetophenone (0.80 g, 4.0 mmol), phenylboronic acid (0.73 g, 6.0 mmol), K_2CO_3 (1.10 g, 8.0 mmol), complex **1** (0.013 mg, 2.0×10^{-5} mmol) and 12 mL of toluene (freshly distilled from sodium/benzophenone). The mixture was heated under stirring at 110 °C for 2 h and then cooled to rt. After filtration on Celite the raw reaction mixture was analyzed by GLC using *n*-undecane as internal standard.

4.2.1. [PdBr($C_6H_4CF_3$-4)(2-(PPh_2)C_6H_4-1-CH=NC_6H_4-OMe-4)] (6). Complex **1** (0.646 g, 1 mmol) and 4-(trifluoromethyl)bromobenzene (2.55 g, 10 mmol) were dissolved in dry toluene (40 mL). The mixture was heated at 110 °C (5 min) under N_2 atmosphere. Despite the short reaction time, some decomposition to metallic palladium took place. The solvent was then removed at reduced pressure, and the solid residue was extracted with CH_2Cl_2. After addition of charcoal and filtration, the resulting clear solution was evaporated to ca. 3 mL and diluted with Et_2O to precipitate a yellow solid. Recrystallization from CH_2Cl_2/Et_2O afforded analytically pure complex **6** (0.480 g, 66% yield); Analytical data: found: C 52.54, H 3.96, N 2.11%. $C_{33}H_{26}F_3BrNOPPd$ requires C 52.74, H 3.66, N 2.20%; IR (Nujol): ν(C=N) at 1611 cm^{-1} *m*. ^{1}H NMR ($CDCl_3$, δ): 8.21 (1H, s, N=CH), 7.80–7.26 (18H, m, aryl protons), 6.96–6.81 (4H, m, *m*-H of $C_6H_4CF_3$-4 and C_6H_4OMe-4), 3.83 (3H, s, OCH_3); ^{31}P NMR ($CDCl_3$): 28.3 (s).

4.3. Studies of the oxidative addition reaction

The reactions of 4-(trifluoromethyl)bromobenzene with complexes **1**–**5** were carried out in dry toluene at 90 °C under a N_2 atmosphere. The initial complex concentration was 1×10^{-2} mol/L and the aryl bromide/complex molar ratio was 10:1; in the experiments carried out in the presence of added iminophosphine, the same initial complex concentration was used and the aryl bromide/iminophosphine/complex molar ratios were 10:1:1. The course of the reaction was monitored by IR spectroscopy of the reacting mixtures either following the intensity of the ν(C=O) band at 1725 cm^{-1} relevant to free dimethyl fumarate (reactions of the complexes **1**–**4**), or the intensity of the ν(C≡N) band at 2204 cm^{-1} (reaction of complex **5**).

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Use of a bulky phosphine of weak σ-donicity with palladium as a versatile and highly-active catalytic system: allylation and arylation coupling reactions at 10^{-1}–10^{-4} mol% catalyst loadings of ferrocenyl bis(difurylphosphine)/Pd

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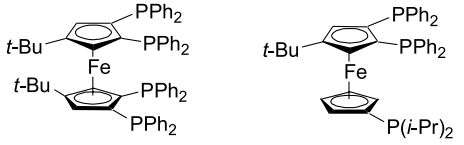
Abstract—Carbon–carbon(sp^2–sp^2 and sp^1–sp^2) and carbon–nitrogen (nucleophilic allylation) coupling processes are promoted by a catalytic system containing $[PdCl(\eta^3\text{–}C_3H_5)]_2$ with the new ferrocenyl bis(difurylphosphine) 1,1′-bis[di(5-methyl-2-furyl)phosphino] ferrocene, $Fc[P(Fu^{Me})_2]_2$. Starting from aryl bromides or allylic acetates this versatile catalyst system may be used at low palladium loadings (10^{-1}–10^{-4} mol%) in some Heck, Suzuki, Sonogashira and allylic amination reactions to give cross-coupled products in excellent yield. Remarkably high activity is obtained in allylic substitution reactions, providing a significant impetus for the development of bulky phosphines possessing weak σ-donicity for this particular reaction.

1. Introduction

Palladium-catalysed carbon–carbon and carbon–heteroatom bond formations represent important catalytic processes with extensive scope in contemporary synthetic chemistry. The progress made since the late 1960's, following the seminal studies by Heck, Sonogashira, Suzuki, Tsuji and others,[1] provides a variety of protocols for the production of organic building blocks of prodigious interest in material science, medicine or agronomy. Some practical problems exist, which will require addressing for these reactions to move from academic laboratories to industrial processes.[2] Indeed, until very recently reported catalytic systems were most often used at 1–10 mol% palladium loadings at best, which is non-efficient in terms of turnover number and sometimes of turnover frequency. Concomitantly, such high catalyst loadings impose financial constraints on scaling up reactions, or at least in problems associated with catalyst removal. The necessity to provide catalytic systems minimising the consumption of expensive transition-metals can be fulfilled through the synthesis of accessible, efficient and inexpensive ligands. The new bis(difurylphosphino)-ferrocene ligand **1** presented herein was developed following this objective, and pertains to a family of highly efficient catalytic auxiliaries based on ferrocenyl poly-phosphines, which we have synthesized (**2a** and **2b** Scheme 1).[3–6]



$Fc(P)_4{}^tBu$, **2a** $Fc(P)_2{}^tBu(P^iPr)$, **2b**

Scheme 1.

Keywords: Catalysis; Palladium; Ferrocenylphosphine; Furyl; Allylic substitution; Cross-coupling; Ligand effect.
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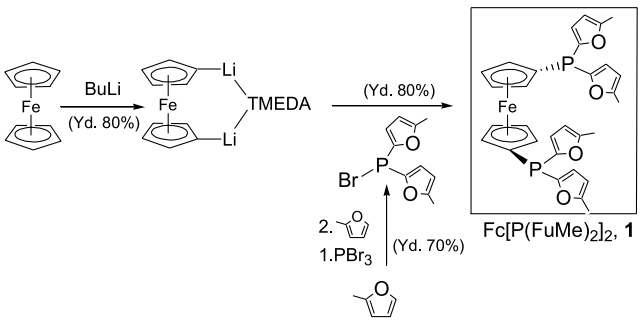
2. Results and discussion

2.1. Preparation and characterization of the ligand 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene

A literature survey from the last 20 years concerning palladium-catalysed cross-coupling reactions clearly shows that much progress in this field was accomplished from the synthesis/identification of efficient auxiliary ligands. Such species not only allowed a wide range of synthetic advances but moreover, provided interesting mechanistic investigations. Amongst these auxiliaries, bulky phosphines with high σ-donicity emerged as powerful ligands.[7–15] Their efficiency was initially surprising since strong σ-donor ligands would not be expected to facilitate the crucial transmetalation[16] and reductive elimination steps,[17] but rather would be assumed to be powerful inhibitors. These results indicated the importance associated with the often rate-limiting oxidative-addition step, particularly with substrates containing strong carbon-halide bonds. Additionally, the success of bulky phosphines has been suggested to be derived from the ability of these ligands to promote geometrically driven coordinative unsaturation and palladium reactivity (mainly due to steric hindrance[2,18,19] and/or cone/bite angle[20]). These geometric features appear to be important to transmetalation[2] and reductive elimination[21] steps, when utilising strongly electron-donating ligands. Finally, investigations on ligands exhibiting both pronounced electronic and steric properties, contribute to synthetic advances, as well as to mechanistic understanding.

As a consequence of the complexity in the prediction of a rate-limiting step,[20] it did not appear unreasonable to us to test, in more depth, a range of cross-coupling reactions using a comparatively 'forgotten' strongly electron-withdrawing bulky phosphine ligand.[22] We choose to build a weakly σ-donor phosphine on the robustness of the ferrocenic backbone.[3] Ferrocenic phosphines with phosphorus bearing heterocyclic substituents[23] are notably less developed than the corresponding ferrocenyl diphosphines bearing aryl or alkyl substituents.[14,24–26] Nevertheless, the new ligand 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene, **1**, is obtained pure in 80% isolated yield from reaction of lithiated ferrocene with the bis(5-methyl-2-furyl)bromophosphine $BrP(Fu^{Me})_2$ (Scheme 2). Compound **1** was isolated in pure form on a 10 g scale, as a crystalline orange powder, insensitive to air and moisture, easy to handle and crystallise. This synthesis is different to that previously reported for the parent compound: 1,1′-bis[di(-2-furyl)-phosphino]ferrocene, available by reaction of bis(dichlorophosphino)ferrocene with 2-lithiofuran.[23]



Scheme 2.

Table 1 summarizes some of the ^{31}P NMR chemical shifts recorded for ferrocenyl heteroannular diphosphines, including the data for **1**, which displays a noticeable high-field signal. The electronic difference expected between the phosphorus atoms of **1** and the related ferrocenyl diphosphines incorporating aryl or alkyl substituents was confirmed. Evidence concerning the intrinsic low Lewis-basicity of phosphorus bearing 2-furyl substituents have been collected and reported.[27]

Table 1. ^{31}P NMR chemical shifts for ferrocenyl heteroannular diphosphines

$Fe[\eta_5\text{-}C_5H_4(PR_2)]_2$	^{31}P NMR (ppm)/solvent
R = *t*-Bu	27.1[14]/C_6D_6
R = *i*-Pr	−0.2[25]/C_6D_6
R = Cy	−9.7[26]/$CDCl_3$
R = Ph	−17.2[28]/$CDCl_3$
R = Menthyl	−24.1[25]/$CDCl_3$
	−25.2[25]/C_6D_6
R = 5-Me-2-furyl	−63.8/$CDCl_3$
R = 2-Furyl	−64.9[23]/$CDCl_3$

The molecular structure of $Fc[P(Fu^{Me})_2]_2$ shows that in the solid state the cyclopentadienyl rings adopt an eclipsed conformation (Fig. 1). In contrast to dppf (dppf = 1,1′-bis[diphenylphosphino]ferrocene), for which the phosphorus atoms point away from each other (C_{p1}–CNT1–CNT2–C_{p2} torsion angle 180°, antiperiplanar staggered conformation), in **1** a 72° only torsion angle is observed for C_{p1}–CNT1–CNT2–C_{p2} (synclinal eclipsed).[29] We did not detect any noticeable ordered crystalline arrangement or hydrogen bonding, which would explain such a geometry. Bond angles and distances are within the expected values.

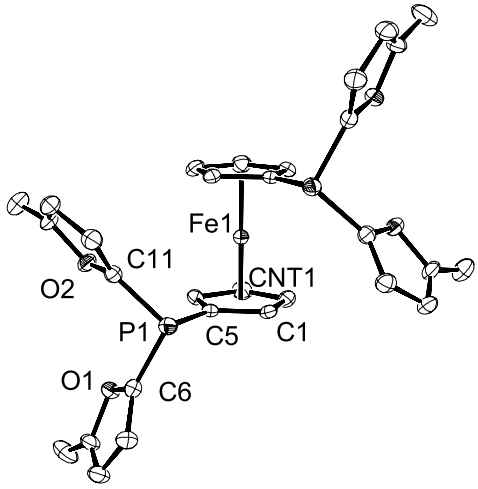


Figure 1. Molecular structure of **1**. Selected bond lengths (Å) and angles (°): Fe(1)–CNT(1) 1.655(2), P(1)–C(5) 1.812(2), P(1)–C(6) 1.804(2), P(1)–C(11) 1.803(2), O(1)–C(6) 1.385(3), O(2)–C(11) 1.385(3), CNT(1)–Fe(1)–CNT(2) 178.18(14), C(11)–P(1)–C(5) 103.80(10), C(11)–P(1)–C(6) 102.77(10), O(1)–C(6)–P(1) 121.77(16), O(2)–C(11)–P(1) 103.80(10).

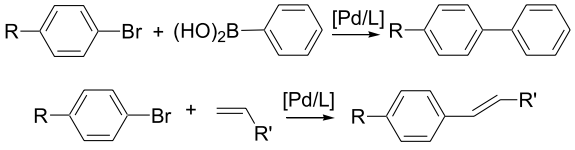
2.2. Catalytic results in 'Suzuki', 'Heck' and 'Sonogashira' cross-coupling reactions

To evaluate the ligand properties in cross-coupling reactions systematically, we first tested the performance of **1** in Suzuki–Miyaura cross-coupling reactions using the activated substrate 4-bromoacetophenone with phenylboronic acid, following previously reported procedures.[3] The reaction of aryl halide (10 mmol), aryl boronic acid (20 mmol) at 130 °C during 20 h in dry xylene or DMF, under argon, affords the corresponding products in presence of palladium/phosphine catalysts and K_2CO_3. Surprisingly, regarding the low basicity of phosphorus, a high turnover number (TON) of 100,000 with a complete conversion was obtained in presence of 10^{-3} mol% catalyst (Table 2, entry 1), a result equivalent to that obtained with the more electron-rich tetraphosphine **2a** under identical conditions.[3] A conversion of 18% is obtained in the presence of 10^{-4} mol% catalyst (TON 180,000, entry 2) after 20 h. Nevertheless, this facile coupling-reaction is to be used as a guide and not as a stern benchmark to screen new Pd-catalysts.[9] We tested a more demanding substrate, the deactivated and electron-rich organohalide, 4-bromoanisole. Complete conversion was obtained in the presence of 10^{-2} mol% catalyst (TON 10,000, entry 3), but disappointingly a lower concentration produces no cross-coupled product (entry 4). Under identical conditions the tetraphosphine **2a** facilitated a TON of 77,000, in the presence of 10^{-3} mol% catalyst.[3]

The preliminary experiments on the Heck alkenylation reaction were conducted using 4-bromoanisole with *n*-butyl acrylate without addition of tetraalkyl ammonium salts, which are often used to delay palladium black formation. Here, excellent conversions were obtained in the presence of 10^{-1} and 10^{-2} mol% catalyst (entries 5–6, TON 10,000), but lowering the concentration inhibits completely the reaction. At this stage, the results obtained without any further optimization,[30] that meet the definition of high-turnover catalysts (HTC) proposed by Farina[2] (a catalyst that can lead to quantitative conversion of starting materials at a load of 0.1 mol% or less), however did not completely satisfy our activity criteria for the Suzuki–Miyaura cross-coupling and Heck alkenylation reaction.

We next, compared the activity of **1** in the Sonogashira arylation of phenylacetylene with the activated and deactivated substrates: 4-bromoacetophenone and 4-bromoanisole, respectively. Using 4-bromoacetophenone in the presence of 10^{-4} mol% catalyst, a TON of 920,000, among the highest reported,[4,31] was obtained (Table 3, entry 10). 4-Bromoanisole, as expected was quantitatively converted (at 10^{-1} mol% catalyst concentration) at a lower TON of 1000. Note that under the same reactions conditions (i.e., using K_2CO_3 as base and 10^{-1} mol% catalyst) the absence of ligand lead to no conversion.[31] In the presence of a large excess of PPh_3, 5% conversion was observed, 3% with P(*o*-tol)$_3$ and 50% maximum using an excess of 1,4-bis(diphenylphosphino)butane (dppb). With a more demanding substrate such as an activated aryl chloride: 4-chloroacetophenone; no coupling product was obtained, even at 0.4 mol% catalyst loading, whereas under the same

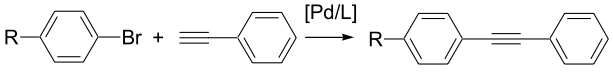
Table 2. Suzuki and Heck reactions catalysed by the Fc[P(Fu^{Me})$_2$]$_2$/palladium system



Entry	Aryl bromide	Aryl boronic acid or alkene	Ratio substrate/catalyst	Yield%
1	4-MeCOC$_6$H$_4$Br	PhB(OH)$_2$	100,000	100
2			1,000,000	18
3	4-MeOC$_6$H$_4$Br	PhB(OH)$_2$	10,000	100
4			100,000	0
5	4-MeOC$_6$H$_4$Br	^{n}BuOCOCH=CH$_2$	1000	100
6			10,000	99
7			100,000	0

Conditions: catalyst [PdCl(η^3–C$_3$H$_5$)]$_2$/**1**: ½. Suzuki: ArBr 1 equiv, ArB(OH)$_2$ 2 equiv, K_2CO_3 2 equiv, 20 h, 130 °C, xylene. Heck: ArBr 1 equiv, alkene 2 equiv, K_2CO_3 2 equiv, 20 h, 130 °C, dimethylformamide (DMF).

Table 3. Sonogashira reaction catalysed by the Fc[P(Fu^{Me})$_2$]$_2$/palladium system



Entry	Aryl halide	Alkyne	Ratio substrate/catalyst	Yield%
8	4-MeCOC$_6$H$_4$Br	PhC≡CH	10,000	100
9			100,000	100
10			1,000,000	92
11	4-MeOC$_6$H$_4$Br	PhC≡CH	250	100
12			1000	100
13			10,000	Traces

Conditions: catalyst [PdCl(η^3-C$_3$H$_5$)]$_2$/**1**: ½. ArBr 1 equiv, alkyne 2 equiv, K_2CO_3 2 equiv, CuI 0.05 equiv, 20 h, 130 °C, DMF.

reactions conditions the triphosphine ligand **2b** leaded to 82% conversion.[4]

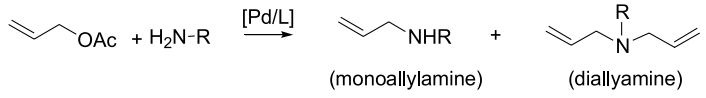
In the reactions conducted with **1**, very high TONs were obtained when activated substrates were used, and comparatively disappointing results were observed from more demanding aryl halides. From these results in C–C cross-coupling reactions, several conclusive trends, which are discussed in Section 2.4, led us to focus our further catalytic investigations on the allylic amination reaction.

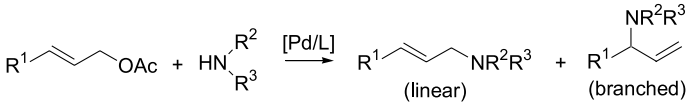
2.3. Catalytic results in 'Tsuji-Trost' allylic amination

Allylamines are important building blocks in modern chemistry and their preparation is a key synthetic and industrial goal.[32] The allylamine fragment is found in many natural products, and can undergo a range of different chemical processes on the C=C bond (functionalization, oxidation, etc.). One of the most attractive and preferred ways to form allylamines is by palladium-catalysed nucleophilic allylic substitution, in the presence of a stabilising ligand, mostly phosphines. In this field, a large number of research groups have mainly focused on the development of chiral catalysts, inducing enantioselectivity in allylic alkylation reactions in general. Some of these complexes have been applied to allylic amination.[32,33] Consequently, even in the achiral form of the reaction, the catalytic systems reported, to date, are generally used at 1–5 mol%. The knowledge related to more efficient catalytic systems in terms of scope and catalyst economy (reduction of the loading of the expensive catalytic metal, of sophisticated ligands and of polluting additives) is very limited, the reported examples being rare.[34–36]

The results obtained in allylic amination with various allylic acetate and amine substrates are summarised in Table 4. To evaluate the scope and limitation of the system Pd/**1**, allyl acetate was reacted with primary and secondary aliphatic and cyclic amines of various steric and nucleophilic features. We were delighted to see that without optimisation procedures our system allowed to reach the best turnover frequencies (TOFs) reported to date, and this at rt, in the absence of base[37] or any additive and in the presence of as little as 0.01 mol% catalyst. A complete conversion was obtained from the primary amine aniline with a satisfactory selectivity of 96% in monoallylaniline (Table 4 entry 14, TOF 10,000 h^{-1}).[38] An excellent 98% conversion was also achieved from the cyclic secondary amine pyrrolidine (entry 15, TOF 4900); we verified the facile access to the product (pure) after classical work-up procedures, with an isolated yield of 88%. Interestingly, only a slightly decreased 85% conversion was obtained with the less nucleophilic cyclic morpholine (entry 16, TOF 4250 h^{-1}) under the same conditions; morpholine can be quantitatively converted in 3 h at rt. The coupling of primary amine benzylamine appeared more difficult and less selective (entry 17, TOF 1825 h^{-1} for a 75% selectivity in monoallylation product). In addition to primary amines and cyclic secondary amines, also more challenging aliphatic secondary amines such as *n*-dioctylamine, can be coupled efficiently. A complete conversion of the sterically demanding diisopropylamine was obtained at 80 °C in the presence of 0.1 mol% catalyst

Table 4. Allylic amination reaction catalysed by the Fc[$P(Fu^{Me})_2$]$_2$**1**/palladium system





Entry	Allylic acetate	Amine	Ratio substrate/catalyst	Reaction conditions	Yield%	Selectivity %
14	Allyl acetate	H_2NPh	10,000	rt,[a] 1 h	100	96/4 (mono/di)
15	Allyl acetate	$-(CH_2)_4HN-$	10,000	rt,[a] 2 h	98	100
16	Allyl acetate	$-[O(CH_2)_4]HN-$	10,000	rt,[a] 2 h	85	100
17	Allyl acetate	H_2NCH_2Ph	10,000	rt,[a] 4 h	73	75/25 (mono/di)
18	Allyl acetate	HN(*n*-octyl)$_2$	1000	rt, 20 h	100	100
19			10,000		45	100
20			100,000		5	100
21	Allyl acetate	HN(*i*-propyl)$_2$	1000	80 °C,[a] 2 h	96	100
22	3-Phenylallyl acetate	$HNEt_2$	1000	rt, 20 h	100	94/6 (lin/brch)
23			10,000		76	94/6
24	3-Phenylallyl acetate	$-(CH_2)_4HN-$	1000	50 °C, 20 h	100	94/6 (lin/brch)
25			10,000		26	94/6
26	3-Phenylallyl acetate	$-[O(CH_2)_4]HN-$	1000	50 °C, 20 h	100	93/7 (lin/brch)
27			10,000		48	93/7
28	*E*-Hex-2-en-1-yl acetate	$HNEt_2$	250	50 °C, 20 h	100	99/1 (lin/brch)
29			1000		76	99/1
30	*E*-Hex-2-en-1-yl acetate	$-(CH_2)_4HN-$	1000	50 °C, 20 h	100	94/6 (lin/brch)
31	*E*-Hex-2-en-1-yl acetate	$-[O(CH_2)_4]HN-$	1000	50 °C, 20 h	98	94/6 (lin/brch)
32	*E*-Hex-2-en-1-yl acetate	HN(*n*-octyl)$_2$	250	50 °C, 20 h	59	100
33			1000		11	100

Conditions: catalyst [$PdCl(\eta^3$-$C_3H_5)]_2$/**1**: ½. No base. Allylic acetate 1 equiv, amine 2 equiv, tetrahydrofuran.
[a] Carried out in toluene. For 100% conversion in 20 h the reaction time was not minimised.

in 2 h (entry 21, TOF 480 h^{-1}),[36] and of the long alkyl chain-bearing dioctylamine at rt after a longer period (entries 18–20, best TOF 250 h^{-1}).

This new catalytic system was also found to be remarkably active and selective for the more difficult amination of substituted allylic acetates. Using the same pool of amines, we focused our catalytic investigations on coupling reaction of 3-phenylallyl acetate and *E*-hex-2-en-1-yl acetate at 0.1 and 0.01 mol% Pd/**1**, at moderate temperature on a short period of time. Starting from diethyl amine, pyrrolidine and morpholine a complete conversion was obtained from 0.1 mol% catalyst (entries 22, 24 and 26). Lowering the catalyst loading to 0.01 mol% resulted in TONs of 7600, 2600 and 4800, respectively (entries 23, 25 and 27). In each case, good regioselectivity was observed for the linear product (93–94%), especially concerning the primary amine: $HNEt_2$; for which monoallylation occurs exclusively (for primary amines, theoretically five different products could be obtained: linear/branched mono or diallylic product combinations). The selectivity is even higher in linear monoallylamine for the coupling of $HNEt_2$ to the *E*-hex-2-en-1-yl acetate (99%, entries 28, 29). For the cyclic secondary amines these coupling reactions proceeded in >90% yield using as little as 0.1 mol% catalyst (94% selectivity in linear product, entries 30, 31). Finally, only in the course of the addition of dioctylamine, lower TONs and TOFs were observed, since to reach 60% conversion in 20 h at 50 °C, 0.4 mol% catalyst was required (entries 32, 33).

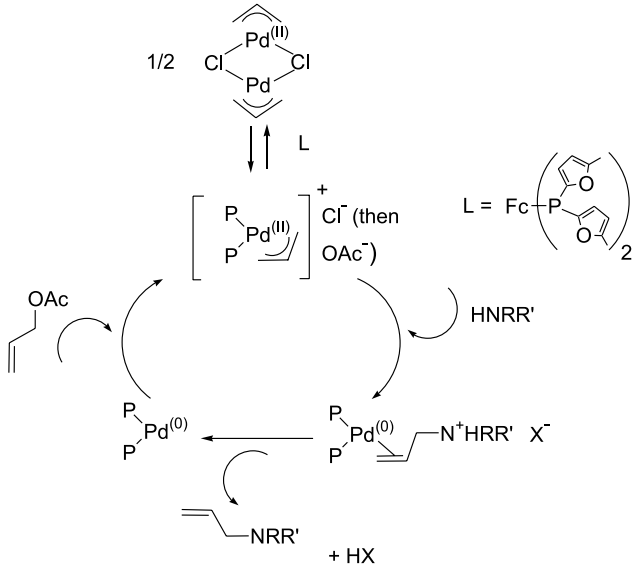
2.4. Discussion

To the best of our knowledge, only a few reports exist on the use of HTC incorporating very poor σ-donating phosphine ligands in Suzuki–Miyaura cross-coupling reactions.[22,39,40] Our experiments from coupling aryl bromide with phenyl boronic acid, confirmed the early investigations by Albisson et al. using a system Pd/triaryl phosphite catalyst system.[39,40] Under the reactions conditions, which are rather close to those used herein (toluene, 110 °C, K_2CO_3 as a base), the authors obtained complete conversion of the activated 4-bromoacetophenone with a turnover number of 10^6, while the complete conversion for the deactivated 4-bromoanisole was obtained at a 10^3 TON. Whereas comparisons between different systems must be treated with some caution, it is worth noting that for the same reactions, we obtained complete conversion from 4-bromoacetophenone with a TON of 10^5 and complete conversion from bromoanisole at 10^4 TON. Under similar conditions, the Pd/**1** catalyst combination shows an order of magnitude weaker activity for the electron-rich substrate and an order of magnitude higher activity for the electron-poor substrate. Our system, as in the Pd/triaryl phosphite combination, exhibits no propensity to couple even electronically-activated aryl chlorides such as 4-chloroacetophenone. A rather simple explanation of this noticeable parallel behaviour could be linked to the subtle changes depending on the substrate of the rate determining-step: thus, for more demanding substrates, the oxidative addition is rate-determining (and severely disfavoured by poor σ-donating ligands). In contrast, for strongly activated substrates (aryl iodides and activated bromides) where the oxidative addition is comparatively facile, the same ligands would multiply the rates of transmetalation and reductive elimination, steps which would become determining.[41] This hypothesis is consistent with the early results from Farina and Krishnan,[16] on the use of trifurylphosphine and triphenylarsine (ligands of weaker basicity compared to PPh_3) in the Stille coupling reaction with substrates capable of undergoing fast oxidative addition (aryl iodides for instance); the Stille coupling of organostannanes being a reaction, for which transmetalation is decisive and possibly rate-determining.[42–44]

Nevertheless, the present tendency in cross-coupling reactions to use the cheaper aryl chlorides (very reluctant to oxidative addition)[45,46] with a view to industrial applications, leaves only a small place to the development of weakly σ-donating ligands,[47] except if other strategies are proposed like the systems developed by Bedford using mixed ligand systems such as bulky σ-acceptor/σ-donor ligands (Pd/{di-*tert*-butylphenyl}phosphite/tricyclohexylphosphine).[48,49]

The tendencies, discussed above, are somewhat confirmed by the results obtained in Heck alkenylation and Sonogashira cross-coupling reactions. The system Pd/**1** gave a TON of 10^4 for the Heck reaction of the deactivated 4-bromoanisole and *n*-butylacrylate, while the Pd/triarylphosphite system reported by Albisson et al. gave complete conversion[50] at a TON of 440–500 (again for less demanding substrates TONs above 10^6 are reported). Finally, consistent with our hypothesis of the changes of the rate determining-step, depending on the substrate, an extremely high TON of 920,000 (with almost complete conversion) was obtained for 4-bromoacetophenone (facile oxidative addition, the rate-determining step being reductive elimination or transmetalation), while when 4-bromoanisole was used a TON of 10^2 was reached (rate-determining step is thus, oxidative addition). Clearly these hypotheses require further comparative kinetics studies to be confirmed.

To demonstrate the potential and catalytic utility of bulky



Scheme 3.

phosphines of weak σ-donicity we choose to apply the Pd/**1** catalytic system to a reaction where the possible determining-step required an electrophilic metallic transition-state: for instance the palladium-catalysed allylic amination with the nucleophilic attack on the allyl ligand (Scheme 3).[51]

The recent mechanistic studies on allylic amination by Kuhn and Mayr provided meaningful kinetic evidence.[52] Indeed, in this relevant work, the use of various amines (diethylamine, piperidine) and 3-phenylallyl acetate (cinnamyl acetate) in presence of either PPh_3 or the less electron-donor $P(OPh)_3$ conducted to global reaction rates two orders of magnitude higher in favour of $P(OPh)_3$. The excellent results obtained with our system could be rationalized through the catalytic cycle depicted in Scheme 3. Relevant reports discuss the general rate-determining step in the soft nucleophilic allylic substitutions.[51–57] We propose that, as anticipated, that the high TOFs and good TONs reported herein are the result of the ability of the ligand **1** to electronically increase the electrophilicity of the Pd(II)/allyl transient species (accelerating the nucleophilic attack, which seems to be the rate-determining step) and to sterically stabilize the Pd(0) complex resulting from product elimination. This is in agreement with the early work of Åkermark and co-workers.[51]

3. Conclusion

In summary, the synthesis, characterisation and catalytic behaviour of the new bulky ferrocenic ligand of low σ-donicity, 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene **1**, has been reported. In cross-coupling reactions and Heck alkenylation processes starting from aryl bromides, the system using Pd/**1** allows high turnover catalysis ($\leq$0.1 mol% catalyst) since a total conversion is obtained for the model substrates: 4-bromoacetophenone and 4-bromoanisole. However, more demanding substrates (aryl chlorides) are not turned-over in the presence of low concentrations of catalyst. In contrast, the ligand is revealed to be among one of the more efficient auxiliaries for palladium-catalysed allylic substitution processes. Facile and convenient reaction conditions were employed in allylic amination, since most of the screened substitution reactions were conducted: (i) from acetates in the absence of base (neutral conditions);[37] (ii) at 20 or 50 °C temperatures; (iii) in less than 24 h; (iv) in the presence of 0.1–0.01 mol% catalyst. Thus, a subtle combination of electronic and steric properties of the ligand produces a highly active catalyst for allylic amination. In particular, the ligand is expected to substantially enhance the rate of nucleophilic attack on the palladium(II)allyl species. Further studies will address and enlarge the scope of the present system in allylic substitutions.

4. Experimental

4.1. General procedures

All reactions and workup procedures were performed under an inert atmosphere of argon using conventional vacuum-line and glasswork techniques. Solvents were dried and freshly distilled under argon. Reagents were purchased from commercial suppliers. $CDCl_3$ and CD_2Cl_2 degassed and stored over molecular sieves under argon were used for NMR studies. Xylene and DMF analytical grade (98%) were not distilled before use. Potassium carbonate (99+%) was used without drying. Except for the diphosphine ligand and for some of the aryl halides and amines, which were distilled before use, the organic and organometallic products were received from commercial sources, and used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). Elemental analyses, ^{1}H, ^{31}P and ^{13}C NMR were performed in our laboratories (on Bruker 300). The evolution of catalyzed reactions was followed by GC (or GC/MS) and NMR for high boiling point substrates, and by GC for low boiling point substrates. For the X-ray diffraction structure of **1**, data were collected on a Nonius Kappa CDD (Mo Kα) diffractometer at 110 K. The structure was solved by a Patterson search program and refined by full-matrix least-squares methods based on F^2 using SHELX97 with the help of the WinGX program at the 'Université de Bourgogne'.

4.2. Synthesis of 1,1′-bis[di(5-methyl-2-furyl)phosphino] ferrocene, $Fc[P(Fu^{Me})_2]_2$, 1

The starting products $BrP(Fu^{Me})_2$ and $FeCp_2Li_2$-TMEDA were synthesised in high yield following procedures described in the literature.[58,59] To a stirred suspension of 6.78 g (21.61 mmol) of $FeCp_2Li_2$-TMEDA in 60 mL of hexane was added dropwise a solution of 11.8 g (43.22 mmol) $BrP(Fu^{Me})_2$ in 25 mL hexane. After 2 h stirring at rt, 20 mL of degassed water was added. An orange powder was obtained, which was washed three times with hexane and then dried under vacuum. Purification was carried out by dissolution in chloroform and filtration on silica gel. 9.86 g of **1** were obtained (17.30 mmol, yield 80%). The product was recrystallised from a chloroform/hexane mixture.

4.2.1. Spectroscopic and single X-ray characterization of the ligand $Fc[P(Fu^{Me})_2]_2$. ^{1}H NMR ($CDCl_3$, 300.13 MHz, δ in ppm): δ=2.33 (s,12H, ^{Me}Fu); 4.15 and 4.30 (m, 8H, Cp) 5.96 and 6.52 (m, 4H, *H*Fu); ^{31}P {H} NMR ($CDCl_3$, 121.49 MHz): δ=−63.8 (s); ^{13}C {^{1}H} NMR (CD_2Cl_2, 75.47 MHz): δ=12.95 (s, 4C, ^{Me}Fu), 71.02 (d, 4C, $^{2}J_{CP}$=5.4 Hz, CpCH), 73.18 (d, 4C, $^{3}J_{CP}$=17.2 Hz, CpCH), 73.02 (d, 2C, $^{1}J_{CP}$=3.6 Hz, Cp), 105.80 (d, 4C, $^{2}J_{CP}$=5.7 Hz, C=C(O)Me), 119.75 {d, 4C, $^{3}J_{CP}$=21.7 Hz, sp^2 CH=C(O)}, 149.45 (d, 4C, $^{1}J_{CP}$=4.1 Hz, P–C(O)=C), 155.47 (d, 4C, $^{4}J_{CP}$=2.3 Hz, Me–C(O)=C). Anal. Calcd. for $C_{30}H_{28}FeP_2O_4$: C 63.17, H 5.20. Found C 63.05, H 4.95. Crystal data for **1**. $C_{30}H_{28}FeO_4P_2$, M=570.32, orthorhombic, space group *Pbcn*, a=8.1795(2) Å, b=12.9172(4) Å, c=24.9485(9) Å, Z=4, V=2635.96(14) Å^3, D_c=1.437 g/cm^3, Mo Kα radiation (λ=0.71073 Å), μ=0.729 mm^{-1}, crystal dimensions 0.25×0.15×0.05 mm^3, T=110(2) K. From 12136 reflections, 3014 were unique (R_{int}=0.0771). 1956 with $I>2s(I)$ were used in refinement. Data parameters ratio 3014/170, R=0.0404, $R\omega$=0.0761.

4.3. Catalytic reactions procedures

Cross-coupling and Heck reactions were carried out following reported procedures.[3,4] In a typical procedure for allylic amination, with a ratio substrate/catalyst = 10,000, the palladium/ferrocenyl furylphosphine catalyst was prepared by stirring a mixture of the diphosphine **1** (0.04 mmol, 22.8 mg) with $[Pd(\eta\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 3.65 mg) in 10 mL toluene, under argon for 30 min. The same batch of catalyst was used for more than a week without any activity decrease (stable in solution in the fridge under argon). One millilitre of the previously prepared catalyst solution (thus, 0.001 mmol Pd) was added to the mixture of allyl acetate and amine (20 mmol) in solvent. The mixture was stirred at fixed temperature for 1–20 h. Pure products are obtained after addition of water, extraction with organic solvents (ether, dichloromethane), separation, drying of the organic phase ($MgSO_4$), concentration, chromatography on silica gel and possibly distillation for oily compounds.

4.4. ^{1}H NMR characterization of some coupling products

References for some of the cross-coupled products are available.[4,36]

4.4.1. 4-Acetyl-1,1′-biphenyl. ^{1}H NMR ($CDCl_3$): δ 8.0 (d, J=8.5 Hz, 2H), 7.67 (d, J=8.5 Hz, 2H), 7.61 (d, J=7.0 Hz, 2H), 7.45 (dd, J=7.5, 7.0 Hz, 2H), 7.37 (t, J=7.5 Hz, 1H), 2.6 (s, 3H). CAS: 92-91-1.

4.4.2. 4-Methoxy-1,1′-biphenyl. ^{1}H NMR ($CDCl_3$): δ 7.54 (d, J=7.4 Hz, 2H), 7.52 (d, J=8.6 Hz, 2H), 7.40 (dd, J=7.4, 7.2 Hz, 2H), 7.29 (t, J=7.4 Hz, 1H), 6.96 (d, J=8.6 Hz, 2H), 3.82 (s, 3H). CAS: 613-37-6.

4.4.3. *E*-Butyl 4-acetylcinnamate (coupling anisole/butyl acrylate). ^{1}H NMR ($CDCl_3$): δ 7.55 (d, J=16.0 Hz, 1H, ArCH=), 7.37 (d, J=8.7 Hz, 2H, Ar), 6.80 (d, J=8.7 Hz, 2H, Ar), 6.21 (d, J=16.0 Hz, 1H, =$CHCO_2Bu$), 4.12 (t, J=6.6 Hz, 2H, $CO_2CH_2CH_2$), 3.69 (s, 3H, OMe), 1.60 (tt, J=6.8, 6.6 Hz, 2H, $CO_2CH_2CH_2$), 1.33 (qt, J=7.3, 6.8 Hz, 2H, CH_2CH_3), 0.87 (q, J=7.3 Hz, 3H, CH_2CH_3). CAS: 173464-57-8.

4.4.4. 4-(2-Phenylethynyl)acetophenone. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J=8.1 Hz, 2H), 7.59 (d, J=8.1 Hz, 2H), 7.53 (m, 2H), 7.35 (m, 3H), 2.58 (s, 3H). CAS: 1942-31-0.

4.4.5. (4-Methoxyphenyl)phenylacetylene. ^{1}H NMR ($CDCl_3$): δ 7.50–7.48 (m, 2H), 7.45 (d, J=8.8 Hz, 2H), 7.32 (m, 3H), 6.86 (d, J=8.8 Hz, 2H), 3.80 (s, 3H). CAS: 7380-78-1.

4.4.6. Allyldioctylamine. ^{1}H NMR δ 5.78 (ddt, 1H, J=16.9, 10.1, 6.6 Hz), 5.06 (d, 1H, J=16.9 Hz), 5.00 (d, 1H, J=10.1 Hz), 3.00 (d, 2H, J=6.6 Hz), 2.5 (t, 4H, J=6.8 Hz), 1.15–1.43 (m, 24H), 0.8 (t, 6H, J=6.3 Hz).

4.4.7. *N*-3-Phenylallylmorpholine. ^{1}H NMR δ 7.35–7.15 (m, 5H), 6.45 (d, 1H, J=16.4 Hz), 6.18 (dt, 1H, J=16.4, 6.8 Hz), 3.65 (t, 4H, J=4.6 Hz), 3.08 (d, 2H, J=6.8 Hz), 2.40 (t, 4H, J=4.6 Hz); ^{13}C NMR δ 136.8, 133.4, 128.6, 127.6, 126.4, 126.1, 67.0. *N*-1-Phenylallylmorpholine was not isolated in pure form. Partial ^{1}H NMR spectra was obtained from the mixture: δ 5.15 (d, 1H, J=17.2 Hz), 5.01 (d, 1H, J=9.9 Hz).

4.4.8. *N*-3-Phenylallylpyrrolidine. ^{1}H NMR δ 7.30–7.10 (m, 5H), 6.50 (d, 1H, J=16.0 Hz), 6.20 (dt, 1H, J=16.0, 6.5 Hz), 3.20 (d, 2H, J=6.5 Hz), 2.50 (t, 4H, J=6.5 Hz), 1.80 (m, 4H); ^{13}C NMR δ 136.8, 133.4, 128.6, 127.6, 126.4, 126.1, 67.0. *N*-1-Phenylallylpyrrolidine was not isolated in pure form. Partial ^{1}H NMR spectra was obtained from the mixture: δ 5.10 (d, 1H, J=17.4 Hz), 5.05 (d, 1H, J=10.0 Hz).

4.4.9. *E*-1-(2-Hexenyl)diethylamine. ^{1}H NMR δ 5.59 (dt, 1H, J=15.4, 6.3 Hz), 5.43 (dt, 1H, J=15.4, 6.6 Hz), 3.11 (d, 2H, J=6.3 Hz), 2.58 (q, 4H, J=7.1 Hz), 1.96 (td, 2H, J=7.3, 6.6 Hz), 1.33 (tq, 2H, J=7.3, 7.3 Hz), 1.02 (t, 6H, J=7.1 Hz), 1.33 (t, 3H, J=7.3 Hz).

4.4.10. *E*-1-(2-Hexenyl)morpholine. ^{1}H NMR δ 5.47 (dt, 1H, J=15.4, 6.3 Hz), 5.35 (dt, 1H, J=15.4, 6.0 Hz), 3.60 (t, 4H, J=4.4 Hz), 2.80 (d, 2H, J=6.3 Hz), 2.31 (d, 4H, J=4.4 Hz), 1.90 (td, 2H, J=7.3, 6.3 Hz), 1.28 (tq, 2H, J=7.3, 7.3 Hz), 0.77 (t, 3H, J=7.3 Hz). 3-(1-Hexenyl) morpholine was not isolated in pure form. Partial ^{1}H NMR spectra was obtained from the mixture: δ 5.15 (dd, 1H, J=17.2, 1.5 Hz), 5.05 (dd, 1H, J=10.0, 1.5 Hz).

4.4.11. *E*-1-(2-Hexenyl)pyrrolidine. ^{1}H NMR δ 5.57 (dt, 1H, J=15.4, 5.8 Hz), 5.45 (dt, 1H, J=15.4, 6.1 Hz), 3.10 (m, 6H), 2.60 (m, 4H), 1.90 (td, 2H, J=7.3, 6.1 Hz), 1.28 (tq, 2H, J=7.3, 7.3 Hz), 0.80 (t, 3H, J=7.3 Hz). 3-(1-Hexenyl)pyrrolidine was not isolated in pure form. Partial ^{1}H NMR spectra was obtained from the mixture: δ 5.15 (dd, 1H, J=17.2, 1.5 Hz), 5.05 (dd, 1H, J=10.0, 1.5 Hz).

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Ferrocenyl-palladium complexes in cross-coupling reactions: a comparative study

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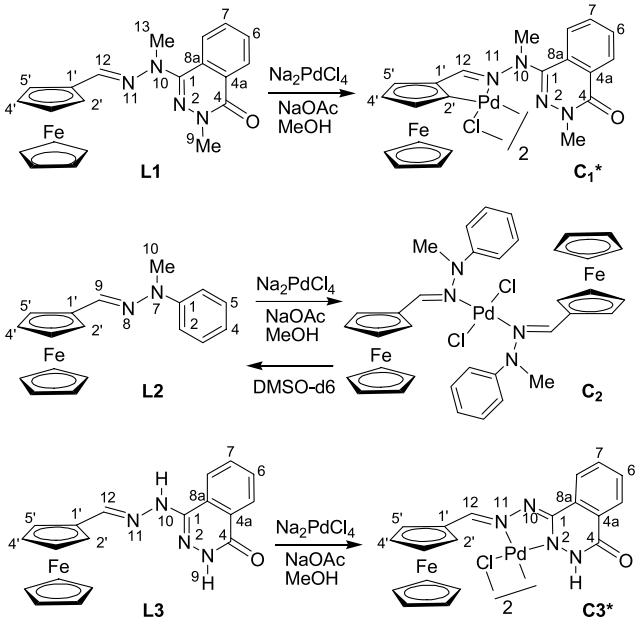
Dedicated to Professor András Lipták on the occasion of his 70th birthday.

Abstract—Ferrocenecarboxaldehyde hydrazones were converted into palladium complexes on treatment with sodium tetrachloropalladate. The substitution pattern of the ferrocenylhydrazones was found to have a marked influence on the mode the palladium was attached to the organic moiety. The catalytic activity of the new palladium complexes in cross-coupling reactions was examined in detail, and it was compared with conventional catalyst systems.

1. Introduction

The identification of cyclopalladated tri-*o*-tolylphosphine as a highly active catalyst in carbon–carbon bond forming reactions[1] has initiated the thorough study of the catalytic activity of palladacycles. These metallacycles, containing a carbon–palladium-heteroatom motif and in certain cases other ancillary ligands, are usually effective catalysts in cross-coupling reactions and a series of highly active systems were reported. The selection of ring heteroatoms includes phosphorous,[1–4] oxygen,[5] nitrogen,[6–9] or sulphur,[10,11] while additional ligands are mostly phosphanes.[12] On the evidence of the accumulated data[13,14] a debate commenced,[15] whether the high catalytic activity of such systems stems from the fact that palladacycles are robust catalysts, or they are merely a source of low-ligated palladium complexes.[16]

Our study was aimed at the synthesis of a series of ferrocene containing palladacycles, hopefully showing high activity, and the study of their catalytic behaviour in cross-coupling reactions. The catalysts were all based on the ferrocenylhydrazone framework, and the model reactions of our choice included the Heck, Suzuki and Sonogashira coupling. Detailed spectroscopic study of the prepared catalyst complexes revealed, that in spite of their similar ligand framework, each ferrocenylhydrazone gave a complex with a considerably different coordination mode. This unexpected finding provided us an additional opportunity to establish the influence of the coordination mode of palladium on its catalytic activity.



Scheme 1. The palladation of ferrocenylhydrazones **L1–L3** with sodium tetrachloropalladate.

Keywords: Palladium complexes; Heck coupling; Tetrachloropalladate.
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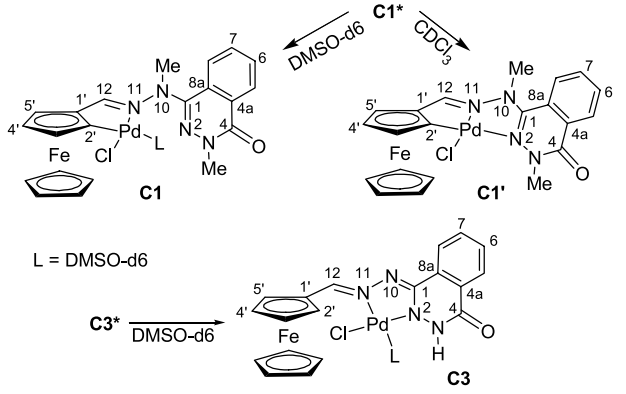
2. Preparation of the ferrocene-based palladium complexes

The studied catalysts were obtained by the treatment of ferrocenylhydrazone type ligands **L1**–**L3** with Na_2PdCl_4 in methanol in the presence of NaOAc at rt (Scheme 1), a procedure widely applied in the synthesis of carbopalladated complexes.[17] Under this condition the chelating phthalazonyl derivatives **L1** and **L3**[18] underwent carbopalladation and azapalladation, respectively, affording chloro-brideged dimers **C1*** and **C3***, while the phenylhydrazone **L2**[19] simply coordinated to $PdCl_2$ to give **C2**. The dimeric structure of **C1*** is stated on the basis of its amide-I IR band (1652 cm^{-1}), which is very similar to that (1659 cm^{-1}) measured for ligand **L1**,[18] suggesting that the proximal nitrogen atom (N2) of the phthalazine ring is not coordinated to the palladium centre. As a consequence of this, we must assume the stabilization of the palladium by the formation of a μ-chloro-bridged dimmer (**C1***). The presence of the Pd–N2 bond in **C3*** in the solid state is clearly reflected in its amide-I frequency (1721 cm^{-1}), which is significantly higher than that of the free ligand **L3** (1652 cm^{-1}).[18] In **C3*** the coordinative saturation of the palladium centre also requires the formation of the μ-chloro-bridged dimer form. The proposed structures for **C1*** and **C3*** are also supported by other physical measurements (see later). The solid structure of **C2** is regarded to be analogous to that reported for the closely related $PdCl_2$ complex of *N*,*N*-dimethyl-ferrocenylhydrazone.[20]

The prepared ferrocenylhydrazone-palladium complexes were also characterized by ^1H, ^{13}C and ^{15}N NMR spectroscopy (Scheme 2). Dissolved in $CDCl_3$ **C1*** was transformed into the pentacyclic chelate **C1′** through the connection of the phthalazine moiety (N2) and the palladium centre, as followed by ^1H-^{15}N-HMBC spectroscopy. The ^{15}N signal of N2 shifts considerably upfield (245 ppm), relative to that measured for the non-coordinated N2 atom in the free ligand **L1** (284 ppm). In DMSO-d_6, representing the more polar conditions of the catalytic reactions, the weak Pd–N2 bond is cleaved by a coordinating solvent molecule as reflected by the downfield shift of the N2 signal to 304 ppm in complex **C1**. Since we were unable to grow crystals that were suitable for X-ray analysis, the relative configuration of the dimeric **C1*** structure (meso or racemic) could not be determined so far.



Scheme 2. The different coordination modes of complexes **C1** and **C3**.

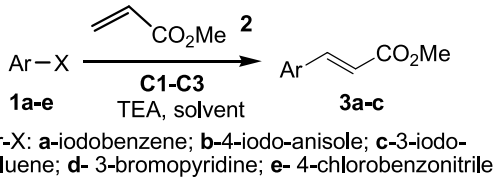
In DMSO-d_6 **C2** gives the ^1H and ^{13}C NMR spectra of **L2** referring to dissociation of both Pd–N bonds. In $CDCl_3$ two isomeric species (in ca. 70 and 30%) were detected, which may differ in the relative orientation of the two ferrocenyl groups (*N.B.* two analogous isomers were identified for the closely related $PdCl_2$ complex of *N*,*N*-dimethyl-ferrocenylhydrazone).[20] The presence of Pd–N bonds in both isomers of **C2** was supported by ^1H ^{15}N HMBC spectroscopy. The ^{15}N signals of N8 shift considerably upfield [234 and 226 ppm for the asymmetric major (**A**) and 229 ppm for the symmetric minor (**B**) component], relative to that measured for the non-coordinated N8 atom in the free ligand **L2** (325 ppm).

Under the same conditions (dissolved in DMSO-d_6) **C3*** presumably undergoes dissociation to **C3** whose strongly coordinated N2 atom has a significant sp^3 character, which is also reflected by its NMR shift of 154 ppm.[21–23] The strong coordination of the sp^2 nitrogen atom (N11) in **C1** and **C3** is evidenced by its signal (274 and 254 ppm, respectively), shifted substantially upfield relative to the free ligands **L1** (330 ppm) and **L3** (316 ppm). In **C3** the H-2′/5′ ^1H NMR signal (5.13 ppm) as well as the C1- and C12 ^{13}C NMR signals (158.2 and 149.2 ppm) are downfield shifted from those of **L3** (4.56 ppm for H-2′/5′, 143.0 ppm for C1 and 143.9 ppm for C12)[18] providing further evidence of the presence of the Pd–N2, and Pd–N11 bonds.

In summary, the formed ferrocenylhydrazone complexes under the conditions, where their catalytic activity is to be tested, contain the palladium centre in a NPdC attachment mode in a palladacycle (**C1**), in a NPdN attachment mode in a palladacycle (**C3**), or as part of a loosely coordinated NPdN complex (**C2**).

3. Catalysis studies

The first model reaction selected was the Heck coupling of different aryl halides and methyl acrylate in the presence of triethylamine as base (Scheme 3). The opening experiments were aimed at establishing the dependence of the catalytic activity of **C1**–**C3** on the reaction media. Iodobenzene was coupled in solvents of different polarity ranging from DCM to water, to find that polar coordinating solvents such as DMF or DMA gave the best results under the applied conditions (Table 1).



Scheme 3. The reactions used to test the catalytic activity of complexes **C1**–**C3** in Heck couplings.

All conversion measurements presented are an average of at least three parallel reactions and the determined values are based on internal standards. The first set of data obtained after running the reaction for 18 h at 50 °C (Table 1) revealed that in DMF and DMA both **C1** and **C2** gave near

Table 1. The catalytic activity of **C1–C3** in the model Heck coupling in various solvents[a,b]

	DCM	THF	MeCN	DMF	H_2O	DMA
C1	11.6	16.9	35.5	99.9	2.8	99.9
	16	*27.3*	*43.8*	*99.9*	*5.1*	*99.9*
C2	7.8	8.8	35.6	98.6	2.1	100
	11.6	*17.9*	*55.2*	*99.5*	*13.2*	*100*
C3	26.6	40.9	65.8	77.6	0.7	94.9
	43.8	*52.3*	*86.6*	*85.1*	*18.9*	*96.5*

[a] Iodobenzene (1 equiv), 1.2 equiv methyl acrylate, 1.4 equiv TEA, 1 ml/mmol solvent, 0.1% **C1**, 0.1% **C2**, or 0.2% **C3**, respectively.
[b] Normal numbers refer to the conversion values determined by GC analysis of the reaction mixtures after 18 h at 50 °C. Italics refer to the conversion values obtained after a further 2 h heating at 70 °C.

complete conversion. **C3** also gave good results, although, it was significantly less reactive. Of the other solvents tested in DCM, THF and MeCN the catalysts showed only mediocre activity, interestingly **C3** being more active than the other complexes (probably **C1*** and **C2***). Increase of the temperature to 70 °C for 2 h led to a considerable improvement of the catalytic activity in all possible cases.

In the first coupling experiments iodobenzene was reacted with methyl acrylate in the presence of the different palladium complexes **C1–C3** (Fig. 1). For the kinetic study of the Heck coupling catalyst loadings of 10^{-2}–$2*10^{-2}$% were found optimal. For comparison the reaction was also run in the presence of 10^{-2}% $Pd(OAc)_2$ with and without $2*10^{-2}$% PPh_3.

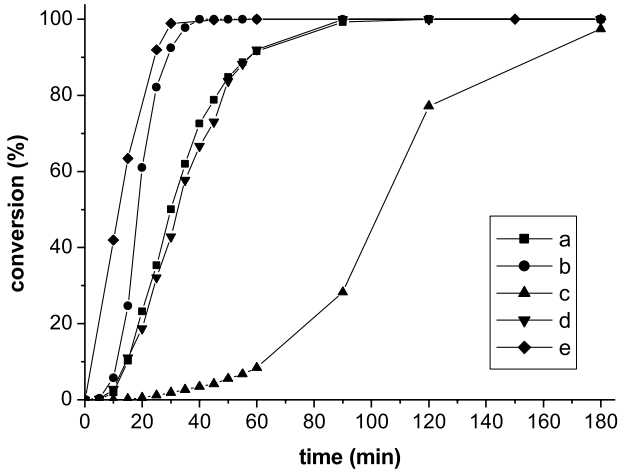


Figure 1. Kinetic study of the catalytic activity of **C1–C3** in the model Heck coupling. (a) 10^{-2}% **C1**; (b) 10^{-2}% **C2**; (c) $2*10^{-2}$% **C3**; (d) 10^{-2}% $Pd(OAc)_2$ and $2*10^{-2}$% PPh_3; (e) 10^{-2}% $Pd(OAc)_2$ at 100 °C.

Table 2. The catalytic efficiency of complexes **C1–C3** in the Heck coupling of different aryl halides (**1a–e**) at 0.05% catalyst loading[a,b]

ArX	C1	C2	C3
1a	100 (82)	100 (51)	100 (73)
1b	100 (93)	100 (99)	100 (98)
1c	100 (97)	100 (95)	100 (96)
1d	0	0	0
1e	0	0	0

[a] Numbers refer to conversion values determined by GC, numbers in parenthesis refer to isolated yields.
[b] Aryl halide (1 equiv), 1.2 equiv methyl acrylate, 1.4 equiv TEA, 1 ml/mmol DMF, 0.05% **C1**, 0.05% **C2** or 0.1% **C3** were heated at 100 °C for 1 h, or until full conversion.

The catalytic activity of **C1**, **C2** and the palladium–triphenylphosphine system were very similar, showing only a brief induction period, with $Pd(OAc)_2$ and **C2** being the most active under the applied conditions. The time-conversion curve of **C3** is significantly different from the other catalyst systems, exhibiting a prolonged induction phase and showing only decreased activity. In the light of the kinetic studies of Pfaltz and Blackmond on the Heck coupling reactions using palladacycles[24] it is probable, that the difference in the activity of the examined catalyst systems originates from the differences in the ease of formation of the catalytically active species.

The scope of the use of catalysts **C1–C3** in Heck couplings on a preparative scale is limited to aryl iodides (Table 2). Using 0.05–0.1% of the catalysts gave appreciable conversion only with iodobenzene (**1a**), 4-iodoanisole (**1b**) and iodotoluene (**1c**). The expected cynnamate derivatives were isolated in good to excellent yields, while less reactive aryl halides, such as 3-brompyridine (**1d**) or 4-chlorobenzonitrile (**1e**) gave no conversion. These results point out, that our catalysts fall into the same category with a series of other complexes, which show acceptable catalytic activity with highly reactive iodoarenes, but are inefficient when the coupling of bromo-, and chloroaromatics are concerned.[16]

The addition of external ligands, such as triphenylphosphine or tri(*tert*-butyl)phosphine has a profound effect on the activity of the catalysts. The coupling of bromobenzene and methyl acrylate catalysed by **C1**, not running in the absence of external ligands, was also tested in the

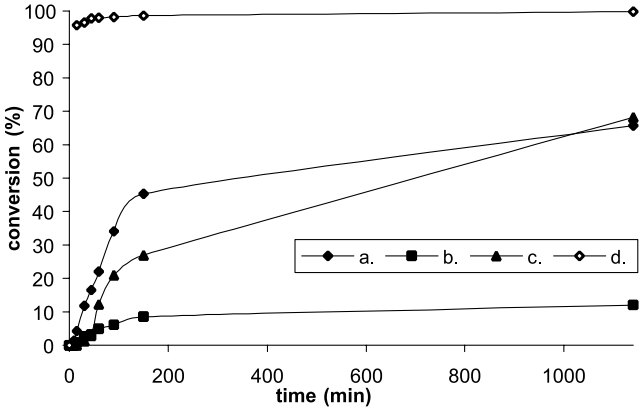


Figure 2. Kinetic study of the catalytic activity of **C1–C3** in the model Heck coupling, when the starting material is bromobenzene (a) 0.5% $Pd(OAc)_2$ and 1% PPh_3; (b) 0.5% **C1** and 0.5% PPh_3; (c) 0.5% **C1** and 1% PPh_3; (d) 0.5% **C1** and 2% P^tBu_3.

presence of added phosphins. For reference the reaction was also run in the presence of $Pd(OAc)_2$–2 PPh_3. The studied reactions revealed (Fig. 2) that the addition of PPh_3 has a marked influence on the catalytic activity of **C1**. Already the addition of 1 equiv PPh_3 to **C1** led to some product formation, and increase of the phosphine–palladium ratio to 2 resulted in a catalytic activity comparable to the $Pd(OAc)_2$–PPh_3 system. The addition of tri(*tert*-butyl)phosphine, as expected, led to the formation of a highly active catalyst species, giving nearly full conversion in 5 min. Tricyclohexylphosphine, although formed an active catalyst, initiated other transformations. The addition of tetrabutylammonium salts to the reaction mixture, or the change of base to *N*-methyl-dicyclohexylamine or sodium acetate had no significant effect on the catalytic activity of **C1**, even when the temperature was raised to 150 °C.

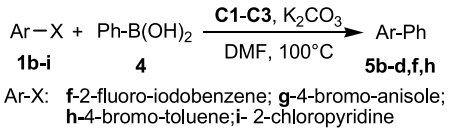
We also determined the longevity parameter (TON) for complexes **C1**–**C3** in the reaction of iodobenzene and methyl acrylate at 10^{-3} and 10^{-4}% catalyst loadings. The determined values, shown in Table 3., correspond to partial conversions, except for 10^{-3}% **C2**, where a near complete conversion was achieved before the catalyst was deactivated. Although, the TON values fall into the same range, a tendency might be observed, with the loosest bonded palladium complex (**C2**) giving the highest number and the complex where palladium is bound the strongest giving the lowest TON.

Table 3. The turnover numbers determined for complexes **C1**–**C3** in the model Heck coupling at 10^{-3} and 10^{-4}% catalyst loadings[a,b]

	C1	C2	C3
TON	62,000 *(48,000)*	92,500 *(96,000)*	23,000 *(35,000)*

[a] Regular numbers refer to values determined at 10^{-3}, and italic numbers to values determined at 10^{-4}% catalyst loading.
[b] Iodobenzene (1 mmol), 1.2 mmol methyl acrylate, 1.4 mmol TEA, 1 ml DMF, and 10^{-3} or 10^{-4}% of the appropriate catalyst (**C1**–**C3**) were heated at 100 °C for a period of time (maximum 72 h), after which no significant conversion was observed.

In the next set of experiments we studied the efficiency of our catalysts **C1**–**C3** in the Suzuki coupling of different aryl halides (**1b**–**i**) and phenylboronic acid (**4**) (Scheme 4). The reaction of 2-fluoro–bromobenzene (**1f**) and **4**, in the presence of potassium carbonate in DMF, was used to establish the kinetic profile of the transformations (Fig. 3).



Scheme 4. The reactions used to test the catalytic activity of complexes **C1**–**C3** in Suzuki couplings.

The ligands **C1** and **C2**, when added in 0.1 mol%, both showed a similar activity, giving acceptable conversions in about 3 h. **C2** was again slightly superior to **C1** (cf. Fig. 1), suggesting that the ease of palladium's release from the starting complex might have a major influence on the catalyst's activity. **C3**, alike in the Heck coupling, showed a prolonged induction period and decreased catalytic activity compared to the other complexes. For comparison the

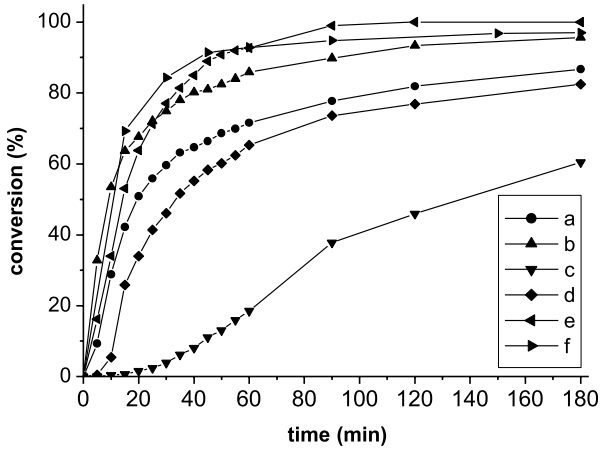


Figure 3. Kinetic study of the catalytic activity of **C1**–**C3** in the model Suzuki coupling. (a) 0.1% **C1**; (b) 0.1% **C2**; (c) 0.2% **C3**; (d) 0.1% **C2** and 0.2% PPh_3; (e) 0.1% $Pd(OAc)_2$ and 0.2% PPh_3; (f) 0.1% $Pd(OAc)_2$.

$Pd(OAc)_2$–PPh_3 and $Pd(OAc)_2$ catalyst systems were also examined under the same conditions (0.1% $Pd(OAc)_2$, 0.2% PPh_3) to reveal these catalysts as the most active of the studied systems. Surprisingly, the addition of triphenylphosphine to the active ferrocene based catalyst, **C2**, unlike in the **C1** catalysed Heck coupling of bromobenzene (Fig. 2), led to a marked decrease in the catalytic activity of the system.

The catalysts **C1**–**C3** were also tested in the Suzuki coupling of other substrates (Table 4). Comparison of the conversion data observed after running the reactions for 4 h are in good agreement with the kinetic measurements.

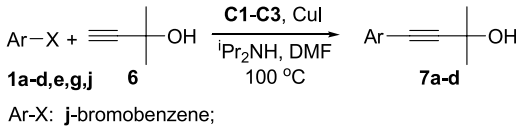
Table 4. The catalytic efficiency of complexes **C1**–**C3** in the Suzuki coupling of different aryl halides (**1b**–**i**) at 0.5% catalyst loading[a,b]

ArX	C1	C2	C3
1b	75 (97)	96	80
1c	89 (71)	99	90
1d	96 (95)	98	71
1e	0	0	0
1f	92 (67)	99	90
1g	21	33	15
1h	14	40	12
1i	0	0	0

[a] Numbers refer to conversion values determined by GC after 4 h, numbers in parenthesis refer to isolated yields after full conversion.
[b] Aryl halide (1 equiv), 1.5 equiv phenylboronic acid, 2 equiv K_2CO_3, 8 ml/mmol DMF, 0.5% **C1**, 0.5% **C2**, or 1% **C3**, respectively, were heated at 100 °C.

In each case, where appreciable conversion was observed (**1b**–**d**,**f**–**h**) **C2** gave the best results and **C3** the lowest conversion values. In case of **C1** the processes were repeated on a preparative scale too, and the products of the couplings were isolated where the conversion values were satisfactory giving the expected biaryls in good to excellent yield. Unlike in the Heck coupling, in these reactions we observed some conversion for bromoaromatics too, although, our catalysts are of limited synthetic value in this respect.

Finally, we also tested the activity of our catalysts in the Sonogashira coupling of different aryl halides (**1a**–**d**,**e**,**g**,**j**) and 2-methyl-3-butyn-2-ol (**6**) (Scheme 5). As it is well



Scheme 5. The reaction used to test the catalytic activity of complexes **C1**–**C3** in Sonogashira coupling.

known, the Sonogashira coupling is more sensitive to the nature and amount of the catalyst used, and we had to increase the loading of **C1**–**C3** a further order of magnitude to obtain reasonable conversions.

Iodobenzene (**1a**) and **6** were reacted in the presence of copper iodide and diisopropylamine in DMF. Addition of the catalysts **C1**–**C3** and $Pd(OAc)_2$ in 2 mol% to the reaction mixture led to no appreciable conversion and it was only after the addition of 4 mol% triphenylphosphine to the mixture that the Sonogashira coupling commenced. Comparison of the activity of **C1**–**C3** and $Pd(OAc)_2$ in the presence of 2 equiv of trihenylphosphine (relative to palladium), shows a picture that is analogous to the previous cases (Fig. 4).

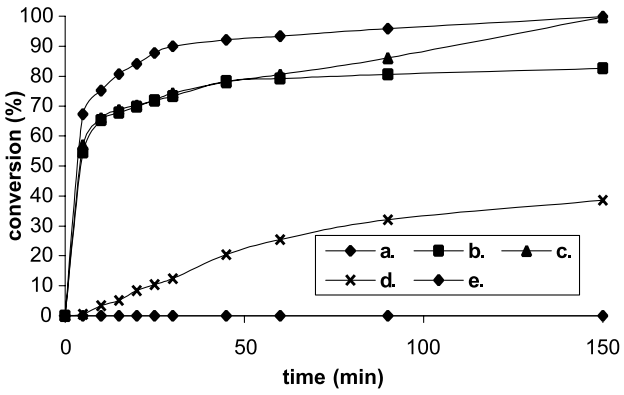


Figure 4. Kinetic study of the catalytic activity of **C1**–**C3** and $Pd(OAc)_2$ in the model Sonogashira coupling. (a) 2% $Pd(OAc)_2$ and 4% PPh_3; (b) 2% **C1** and 4% PPh_3; (c) 2% **C2** and 4% PPh_3; (d) 2% **C3** and 4% PPh_3 (e) 2% $Pd(OAc)_2$.

C1, **C2** and $Pd(OAc)_2$ show a similar activity, with $Pd(OAc)_2$ being slightly more efficient than the ferrocene containing catalysts. The activity of **C3**, as in all other cases, is inferior to the other systems. Of **C1** and **C2** the latter has a longer lifetime, reaching near complete conversion (just as $Pd(OAc)_2$), while **C1** is deactivated at ca. 80% conversion.

The catalysts **C1**–**C3** were also tested in the Sonogashira coupling of other substrates (**1a**–**d**,**e**,**g**,**j**; Table 4). Comparison of the conversion data observed after running the reactions for 4 h are in good agreement with the kinetic measurements. All aryl iodides and the reactive bromopyridine gave near complete conversion with **C2**, while of the other complexes **C1** gave the higher conversion values. The catalysts were also active with bromobenzene (**1j**), while the less reactive bromoanisole (**1g**) was only partially converted and 4-chlorobenzonitrile (**1e**) remained intact. These results are comparable with our recent observations using the Pd/C–PPh_3 catalyst system[25] (Table 5).

Table 5. The catalytic efficiency of complexes **C1**–**C3** in the Sonogashira coupling of different aryl halides (**1a**–**d**,**e**,**g**,**j**) at 2% catalyst loading[a,b]

ArX	C1	C2	C3
1a	99 (56)	99	65
1b	44 (25)	99	26
1c	65 (46)	99	36
1d	100 (89)	99	99
1e	0	0	0
1g	20	30	30
1j	100 (51)	80	65

[a] Numbers refer to conversion values determined by GC after 4 h, numbers in parenthesis refer to isolated yields.
[b] Aryl halide (1 equiv), 1.2 equiv 2-methyl-3-butyn-2-ol, 2 equiv diisopropylamine, 5 ml/mmol DMF, 2% **C1**–**C3**, respectively, and 4% PPh_3 were heated at 100 °C.

The similarity of the catalytic behaviour of complexes **C1** and **C2** in cross-coupling reactions, as well as the resemblance of their activity to palladium acetate suggests, that the active species in these catalytic systems are probably of alike nature. The minor differences might arise from the difference in the way the catalytically active species is formed from the starting complex, and the presence of different loosely coordinating ferrocenylhydrazone moieties in the reaction mixture. In case of complex **C3** we observed a decreased activity in all cases, which might be attributed to the strong coordination of the phtalazolyl moiety to the palladium, hindering the formation of the catalytically active species and leading to an elongated induction period and different kinetic characteristics.

In summary, three palladium complexes were prepared containing similar ferrocenylhydrazone-based ligands in different coordination modes: one a palladacycle, the other a palladium-imine and the third a palladium-amide connection. The catalytic activity of the complexes was compared with the palladium acetate–triphenylphosphine system in cross-coupling reactions. On the basis of the accumulated data it is proposed, that the catalytically active species is of similar nature in most cases, and the differences in the behaviour of the examined complexes originate in the mode and kinetics of the formation of the active species. The weaker the attachment of the palladium to the ligand, the higher the observed activity of the catalyst system. The results suggest that the principal role of the organic backbone (ligand) is to make the palladium available for activation in the reaction media. Although, the described complexes are not highly active, the authors hope that the presented data contributes to the better understanding of catalytic processes and thereby helps in the future to design highly active catalyst systems.

4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Boetius hotplate. The ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded in 5 mm tubes at rt on a Bruker DRX-500 spectrometer at 500 MHz (^{1}H), 125 MHz (^{13}C) and 50 MHz (^{15}N) (for **C1**–**C3**) or on a Bruker DRX-250 spectrometer (**3a**–**c**, **5b**–**h**) at 250 MHz (^{1}H), 62.5 MHz (^{13}C) with the deuterium signal of

the solvent as the lock. In ^{1}H and ^{13}C measurements the residual peaks of the solvent were used as reference, while in the ^{15}N measurements the scale was adjusted to the reference signal of liquid NH_3 ($\delta=0$ ppm). The exact assignment of the ^{1}H, ^{13}C and ^{15}N signals for **C1–C3** were based on 2D-COSY, 2D-HSQC and 2D-HMBC measurements. The IR spectra were obtained on a Bruker IFS-55 FTIR spectrometer. Gas chromatography was carried out on a Hewlett-Packard 5790A instrument. Silica gel (0.04–0.063 mm) was used for flash column chromatography.

4.2. Preparation of complexes C1*, C2 and C3*

A mixture of the corresponding hydrazone (1 mmol), Na_2PdCl_4 (0.294 g, 1 mmol) and NaOAc*3H_2O (0.136 g, 1 mmol) was dissolved in dry methanol (20 mL). The deep red solution was stirred at rt for 1 day. The resulted precipitate was filtered off and the solution was evaporated to dryness. Complex **C2** was purified by washing the precipitate with cold methanol. For the isolation of **C1*** the precipitate was subjected to column chromatography on Silica using chloroform as eluent. The second deep orange band was collected and after the evaporation of the chloroform the oily residue was crystallized with cold methanol. The first orange band consists of the unchanged hydrazone **L1**. For the isolation of **C3*** the residue, obtained by the evaporation of the volatiles from the reaction mixture, was purified by chromatography on Silica using chloroform as eluent. The first deep red band was collected and after the evaporation of the chloroformic solution the oily residue was crystallized with cold methanol–diethylether (3–3 mL).

4.2.1. Description of C1*. Deep red powder; 0.189 g (35%); mp: 213–216 °C (decomp.); IR ν_{max} 1652, 1578, 1540 cm^{-1}; the NMR spectra for **C1′**: δ_H ($CDCl_3$) 8.42 (1H, d, $J=7.8$ Hz, H5), 7.96 (1H, s, H12) 7.97 (1H, d, $J=7.8$ Hz, H8), 7.88 (1H, t, $J=7.8$ Hz, H7), 7.84 (1H, t, $J=7.8$ Hz, H6), 5.30 (1H, br s, H3′), 4.38 (2H, br s, H4′ and H5′), 4.34 (5H, s, Cp ring), 4.03 (3H, s, H9), 3.57 (3H, s, H13); δ_C ($CDCl_3$) 168.4 (C12), 157.8 (C4), 150.2 (C1), 133.6 (C7), 129.0 (C4a), 129.7 (C6), 128.3 (C5), 126.6, (C8a) 126.4 (C8), 100.5 (C2′), 86.5 (C1′), 74.3 (C3′), 71.8 (Cp ring), 69.0 (C4′), 67.0 (C5′), 46.5 (C9), 41.0 (C13); δ_N ($CDCl_3$) 254 (N11), 245 (N2), 178 (N3), 126 (N10); the NMR spectra for **C1**: δ_H (DMSO-d_6) 8.38 (1H, s, H12), 8.27 (1H, d, $J=7.8$ Hz, H5), 8.12 (1H, d, $J=7.8$ Hz, H8), 7.98 (1H, t, $J=7.8$ Hz, H7), 7.85 (1H, t, $J=7.8$ Hz, H6), 5.13 (1H, br s, H3′), 4.43 (1H, br s, H4′), 4.41 (1H, br s, H5′), 4.18 (5H, s, Cp ring), 3.69 (3H, s, H9), 3.20 (3H, s, H13); δ_C (DMSO-d_6) 172.8 (C12), 159.0 (C4), 145.5 (C1), 133.8 (C7), 132.5 (C6), 129.2 (C4a), 127.3 (C5), 127.0, (C8a) 126.5 (C8), 108.5 (C2′), 83.6 (C1′), 75.6 (C3′), 70.9 (Cp ring), 70.0 (C4′), 68.6 (C5′), 40.5 (C13), 39.6 (C9); δ_N (DMSO-d_6) 304 (N2), 274 (N11), 182 (N3), 127 (N10). Anal. Calcd for $C_{21}H_{19}ClFeN_4PdO$ (541.40) C 46.59, H 3.54, N 10.35; Found C 46.50, H 3.60, N 10.38%.

4.2.2. Description of C2. Deep red powder; 0.338 g (83%); mp: 178–184 °C (decomp.); IR ν_{max} 1597, 1495, 1107 and 476 cm^{-1}; (for comparision the IR for **L2**: 1590, 1500, 1112 and 488 cm^{-1}); δ_H (DMSO-d_6) 7.44 (1H, s, H9), 7.29 (2H, d, $J=8.1$ Hz, H2/6), 7.24 (2H, t, $J=8.1$ Hz, H3/5), 6.81 (1H, t, $J=8.1$ Hz, H4), 4.61 (2H, br s, H2′/5′), 4.31 (2H, br s, H3′/4′), 4.15 (5H, s, Cp ring), 3.16 (3H, s, H10); δ_C (DMSO-d_6) 148.5 (C1), 133.4 (C9), 129.8 (C3/5), 120.1 (C4), 115.4 (C2/6), 83.6 (C1′), 69.8 (Cp ring), 69.6 (C3′/4′), 67.2 (C2′/5′), 33.6 (C10) (the spectra are identical with those measured for ligand **L2**): δ_H ($CDCl_3$) 8.26, 7.59 (2×s, H9, **A**), 8.16 (s, H9, **B**), 7.5–7.0 (overlapping m's, H2-6 **A** and **B**), 4.6–4.5 (overlapping m's, H2′-5′, **A**), 4.46 (t, $J=$ 1.8 Hz, H2′/5′, **B**), 4.23 (t, $J=1.8$ Hz, H3′/4′, **B**), 4.31 and 4.20 (2×s, Cp rings, **A**), 4.23 (s, Cp ring, **B**), 3.57 and 3.19 (2×s, H10, **A**), 3.13 (s, H10, **B**); δ_N ($CDCl_3$) 234 and 226 (N8, **A**), 229 (N8, **B**), 130 and 127 (N7, **A**), 125 (N7, **B**). For comparison the ^{15}N NMR data of **L2**: δ_N ($CDCl_3$) 325 (N8), 129 (N7). Anal. Calcd for $C_{36}H_{36}Cl_2Fe_2N_4Pd$ (814.00) C 53.12, H 4.46, N 6.88; Found C 53.05, H 4.55, N 6.81%.

4.2.3. Description of C3*. Deep red powder; 0.140 g (27%); mp: 190–194 °C (decomp.); ν_{max} 1721, 1642, 1571, 1506 cm^{-1}; δ_H (DMSO-d_6) 9.42 (1H, s, H3), 8.18 (1H, d, $J=7.8$ Hz, H5), 8.15 (1H, d, $J=7.8$ Hz, H8), 7.87 (1H, t, $J=7.8$ Hz, H7), 7.80 (1H, t, $J=7.8$ Hz, H6), 7.62 (1H, s, H12), 5.13 (2H, br s, H2′/H5′), 4.55 (2H, br s, H3′/H4′), 4.20 (5H, s, Cp ring); δ_C (DMSO-d_6) 158.2 (C11), 157.1 (C4), 149.2 (C12), 134.5 (C7), 132.2 (C6), 128.0 (C5), 127.6 (C8),125.7 (C8a), 125.5, (C4a), 75.8 (C1′), 72.9 (C3′/C4′), 72.2 (C2′/C5′), 70.2 (Cp ring); δ_N (DMSO-d_6) 254 (N11), 243 (N10), 154 (N2), 134 (N3) (the spectra for **C3**); for comparison the ^{15}N NMR data of **L3**: δ_N (DMSO-d_6) 316 (N11), 261 (N2), 175 (N3), 138 (N10). Anal. Calcd for $C_{19}H_{15}ClFeN_4PdO$ (515.37) C 44.28, H 2.93, N 10.87; Found C 44.35, H 3.00, N 10.82%.

4.3. General conditions for cross-coupling reactions

A mixture of the aryl halide, coupling partner, catalyst, base, internal standard and co-catalyst (where applicable) were taken up in the appropriate solvent in a vial. After flushing with argon and sealing, the vial was placed in a temperated oil bath and the contents were stirred. Samples were taken by a Hamilton syringe and were diluted by DCM before analysis. The work-up of the reactions included the addition of aqueous ammonium chloride, separation, extraction with DCM, drying of the combined organic phases and purification by column chromatography after evaporation of the solvent under reduced pressure.

4.3.1. Component ratios for the coupling reactions and the characterization of isolated products.

4.3.1.1. Heck coupling. Aryl halide (**1a–e**) (1 equiv), 1.2 equiv methyl acrylate (**2**) and 1.4 equiv triethylamine were stirred under argon in 1 mL solvent/1 mmol aryl halide at 70–100 °C.

4.3.1.2. Suzuki coupling. Aryl halide(**1b–i**) (1 equiv), 1.5 equiv phenylboronic acid (**4**), and 2 equiv of K_2CO_3, in 8 mL DMF/1 mmol aryl halide were stirred under argon at 100 °C.

4.3.1.3. Sonogashira coupling. Iodobenzene (**1a**) (1 equiv), 1.2 equiv 2-methylbut-3-yn-2-ol (**6**) and 2 equiv of diisopropylamine were stirred under argon in 5 mL DMF/1 mmol iodobenzene at 100 °C.

4.3.1.4. Methyl cinnamate (3a).[26] Starting from **1a** (302 mg, 1.48 mmol) we obtained 197 mg (82%) **3a**. δ_H ($CDCl_3$) 7.43 (1H, d, $J=16.1$ Hz), 7.20–7.15 (2H, m), 7.07–7.01 (3H, m), 6.17 (1H, d, $J=16.1$ Hz), 3.48 (3H, s); δ_C ($CDCl_3$) 166.4, 144.0, 133.7, 129.6, 128.2, 127.4, 117.2, 50.8 ppm.

4.3.1.5. Methyl 4′-methoxy-cinnamate (3b).[27] Starting from **1b** (346 mg, 1.48 mmol) we obtained 263 mg (93%) **3b**. δ_H ($CDCl_3$) 7.56 (1H, d, $J=16.0$ Hz), 7.40 (2H, d, $J=8.8$ Hz), 6.83 (2H, d, $J=8.8$ Hz) 6.21 (1H, d, $J=16.0$ Hz), 3.76 (3H, s) ppm.

4.3.1.6. Methyl 3′-methyl-cinnamate (3c).[28] Starting from **1c** (323 mg, 1.48 mmol) we obtained 252 mg (97%) **3c**. δ_H ($CDCl_3$) 7.54 (1H, d, $J=16.1$ Hz), 7.42–7. 00 (4H, overlapping m's), 6.30 (1H, d, $J=16.1$ Hz), 3.67 (3H, s), 2.22 (3H, s) ppm.

4.3.1.7. 4-Methoxybiphenyl (5b).[29] Starting from **1b** (61 mg, 0.26 mmol) we obtained 46 mg (97%) **5b**. δ_H ($CDCl_3$) 7.44 (2H, d, $J=7.7$ Hz), 7.41 (2H, d, $J=8.6$ Hz), 7.30 (1H, t, $J=7.7$ Hz), 7.18 (1H, t, $J=7.7$ Hz), 6.86 (2H, d, $J=8.2$ Hz), 3.71 (3H, s); δ_C ($CDCl_3$) 159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.2 ppm.

4.3.1.8. 3-Methylbiphenyl (5c).[30] Starting from **1c** (57 mg, 0.26 mmol) we obtained 31 mg (71%) **3c**. δ_H ($CDCl_3$) 7.56 (2H, d, $J=7.5$ Hz), 7.44–7.26 (6H, overlapping m's), 7.12 (1H, d, $J=7.0$ Hz), 2.38 (3H, s); δ_C ($CDCl_3$) 141.3, 141.2, 138.2, 128.71, 128.65, 127.95, 127.92, 127.20, 127.13, 124.2, 21.5 ppm.

4.3.1.9. 3-Phenylpyridine (5d).[31] Starting from **1d** (41 mg, 0.26 mmol) we obtained 38 mg (95%) **3d**. δ_H ($CDCl_3$) 8.85 (1H, dd, $J=1.6$ Hz), 8.59 (1H, dd, $J=4.7$, 1.2 Hz), 7.86 (1H, d, $J=6.3$ Hz), 7.58 (2H, d, $J=7.6$ Hz), 7.48 (2H, t, $J=7.6$ Hz), 7.42 (1H, t, $J=7.6$ Hz), 7.35 (1H, dd, $J=6.3$, 4.7 Hz), 3.71 (3H, s); δ_C ($CDCl_3$) 148.4, 148.3, 137.7, 126.5, 134.3, 129.0, 128.0, 127.1, 123.5 ppm.

4.3.1.10. 2-Fluorobiphenyl (5f).[32] Starting from **1f** (58 mg, 0.26 mmol) we obtained 30 mg (67%) **3f**. δ_H ($CDCl_3$) 7.54 (2H, d, $J=7.8$ Hz), 7.45–7.40 (3H, overlapping m's), 7.36 (1H, t, $J=7.8$ Hz), 7.29–7.13 (3H, overlapping m's); δ_C ($CDCl_3$) 158.7 (d, $J=227.7$ Hz), 134.8, 129.7 (d, $J=3.3$ Hz), 128.1, 128.0, 127.9, 127.4, 126.6, 123.3 (d, $J=3.7$ Hz) 115.0 (d, $J=22.5$ Hz) ppm.

4.3.1.11. 4-Methylbiphenil (5h).[33] Starting from **1h** (44 mg, 0.26 mmol) we obtained 35 mg (81%) **5h**. δ_H ($CDCl_3$) 7.49 (2H, d, $J=7.7$ Hz), 7.41 (2H, d, $J=8.2$ Hz), 7.36 (1H, t, $J=7.7$ Hz), 7.23 (1H, t, $J=7.7$ Hz), 7.16 (2H, d, $J=8.2$ Hz) 2.31 (3H, s); δ_C ($CDCl_3$) 141.1, 138.3, 137.0, 129.5, 128.73, 128.68, 126.97, 126.95, 21.5 ppm.

4.3.1.12. 2-Methyl-4-phenylbut-3-yn-2-ol (7a).[34] Starting from **1a** (94 mg, 0.462 mmol) we obtained 41 mg (56%) **11**. δ_H ($CDCl_3$) 7.44–7.40 (2H, m), 7.31–7.27 (3H, m), 2.15 (1H, d), 1.62 (6H, s); δ_C ($CDCl_3$) 131.6, 128.2 (two coalesced lines), 122.6, 93.7, 82.1, 65.6, 31.5 ppm.

4.3.1.13. 4-(4′-Methoxyphenyl)-2-methylbut-3-yn-2-ol (7b).[35] Starting from **1b** (108 mg, 0.46 mmol) we obtained 23 mg (25%) **7b**. δ_H ($CDCl_3$) 7.29–7.24 (2H, m), 6.77–6.71 (2H, m), 3.71 (3H, s), 2.19 (1H, s), 1.52 (6H, s); δ_C ($CDCl_3$) 159.47, 133.01, 114.79, 113.82, 92.4, 81.93, 65.57, 55.21, 31.53 ppm.

4.3.1.14. 2-Methyl-4-(3′-methylphenyl)-3-butyn-2-ol (7c).[25] Starting from **1c** (100 mg, 0.46 mmol) we obtained 37 mg (46%) **7c**. δ_H ($CDCl_3$) 7.18–7 (4H, m), 2.42 (1H, br s), 2.31 (3H, s), 1.6 (6H, s) ppm.

4.3.1.15. 2-Methyl-4-(3′-pyridyl)-3-butyn-2-ol (7d).[25] Starting from **1d** (73 mg, 0.46 mmol) we obtained 66 mg (89%) **7d**. δ_H ($CDCl_3$) 8.74 (1H, br s), 8.47 (1H, br s), 7.65 (1H, d, $J=7.9$ Hz), 7.26–7.12 (1H, m), 5.14 (1H, br s), 2.29 (6H, s); δ_C ($CDCl_3$) 151.64, 147.66, 138.75, 123.23, 120.5, 98.53, 78.02, 64.68, 31.23 ppm.

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Pd_2dba_3/P(*i*-BuNCH$_2$CH$_2$)$_3$N: a highly efficient catalyst for the one-pot synthesis of *trans*-4-*N*,*N*-diarylaminostilbenes and *N*,*N*-diarylaminostyrenes

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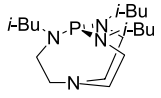
Abstract—A Pd_2dba_3/P(*i*-BuNCH$_2$CH$_2$)$_3$N catalyzed one-pot synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes and both symmetrically and unsymmetrically substituted *N*,*N*-diarylaminostyrene derivatives is reported. The procedure involves two or more palladium catalyzed sequential coupling reactions (an amination and an inter-molecular Heck reaction) in one-pot using the same catalyst system with two different aryl halides, including aryl chlorides and hetero aryl halides as the coupling partners.

1. Introduction

Palladium catalyzed C–C and C-hetero-atom bond forming reactions represent one of the most powerful methods for the synthesis of several complex molecular structures such as gilvocarcines and pradimicines.[1] The scope of these methods has been enhanced by the discovery of new ligands that facilitate coupling reactions more efficiently under mild reaction conditions. In recent years our explorations of the chemistry of commercially available proazaphosphatranes such as **1**, first synthesized in our laboratories,[2] have shown them to be efficient ligands in palladium-catalyzed N-arylation,[3] Suzuki[4] and Stille[5] couplings, including those of neutral as well as electron-rich and electron-deficient aryl chlorides. Moreover, proazaphosphatranes can also function as strong non-ionic stoichiometric bases that facilitate a variety of useful organic transformations.[6] Recently, palladium-catalyzed sequential coupling reactions have emerged as a powerful tool for the synthesis of complex organic molecules from readily available starting materials in a single pot reaction.[7] Among them, the palladium-catalyzed synthesis of *N*-aryl-2-benzylindolines via a sequential N-arylation/cyclization/C-arylation reaction between 2-allylaniline and aryl halides demonstrated the importance of such reactions in modern synthetic chemistry.[8]



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N,*N*-Diarylaminostilbenes are versatile compounds that have found interesting applications in the field of photochemistry as electro photographic photoconductors and photoreceptors.[9] A series of recent reports showed that the fluorescence enhancement of *N*,*N*-diarylaminostilbenes has been achieved by *N*-phenyl substitution[10] and also their use as new ionophores for transition metals.[11] The traditional approaches to the synthesis of these compounds begin from aniline and the corresponding aryl halides via a multi step process.[12] Recently, the synthesis of *trans*-4-*N*,*N*-diarylaminostilbenes from the corresponding halostilbenes or aminostilbenes, using palladium catalyzed amination reactions, has also been reported.[10,11]

Very recently, we disclosed in preliminary form an efficient one-pot procedure for the synthesis of *trans*-4-*N*,*N*-diarylaminostilbenes via a sequential double amination/arylation protocol using Pd_2dba_3/**1** as the catalyst.[13] In this full paper we report the results of our detailed investigation of the one-pot synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes and both symmetrically and unsymmetrically substituted *N*,*N*-diarylaminostyrenes. Furthermore, we report the synthesis of dibenz[*b*,*d*]azepine via a palladium-catalyzed one-pot amination/Suzuki reaction.

Keywords: Proazaphosphatranes; Palladium; Amination; C–C Coupling; *trans*-4-*N*,*N*,-Diarylaminostilbenes; Heck reaction.
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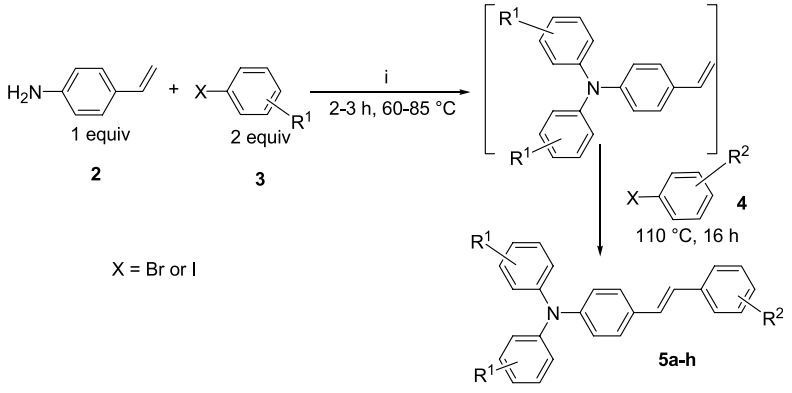
2. Results and discussion

2.1. One-pot synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes (identical aryl groups on the nitrogen)

The optimized reaction conditions for the one-pot synthesis of symmetrically and unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes have previously been reported.[13] From these experiments, it is evident that the title compounds were formed via a double amination, followed by an inter-molecular Heck reaction. Thus, the reaction of **2** with 2 equiv of the first aryl halide **3** completed the double amination as judged by TLC (Scheme 1). The subsequent Heck reaction was initiated by adding 1.2 equiv of the second aryl halide **4** followed by increasing the temperature to 110 °C for an additional 16 h (see Table 1 for details).

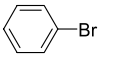
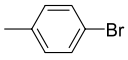
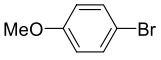
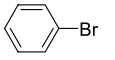
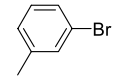
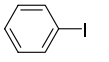
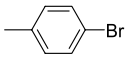
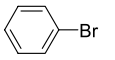
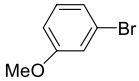
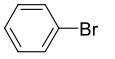
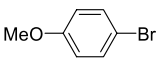
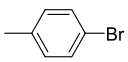
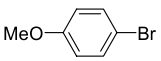
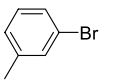
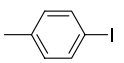
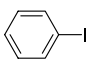
The products in entries 5 and 7 are novel and their structures were confirmed on the basis of their ^{1}H and ^{13}C NMR and their high-resolution mass spectra. The yield for **5a** (86%) is comparable to that reported in a patented procedure (89%) involving the single-step reaction of 4-methyldiethylbenzylphosphonate with 4-*N*,*N*-diphenylaminobenzaldehyde.[14] However, the yield of **5a** is substantially better than that attained in the same patent via the Wittig reaction of 4-methylbenzyltriphenylphosphonium chloride with the aforementioned aldehyde (72%) and also to the overall yield (46%) reported for an earlier three-step synthesis.[14] Although the remaining compounds in entries 2, 3, 4, 6, and 8 were reported earlier,[9,15] no yields were provided. The difference in reactivity of 4-aminostyrene at different temperatures under our reaction conditions allowed us to couple a variety of aryl halides at the nitrogen and the double bond to synthesize unsymmetrically substituted title compounds.



i. $Pd_2(dba)_3$, **1**, NaO-*t*-Bu, dry toluene.

Scheme 1.

Table 1. One-pot synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes

Entry	Aryl halide (**3**)	Time (h)	Temperature *T* (°C)	Aryl halide (**4**)	Yield (%)[a,b]
1		3	60		86 (46)[c]
2		3	60		60[c]
3		2	85		83
4		2	85		91
5		2	85		75
6		3	60		44
7		3	60		43
8		3	60		81

[a] Isolated yield, average of two runs.
[b] Reaction conditions: $Pd_2(dba)_3$ (2 mol%), **1** (4 mol%), NaO-*t*-Bu (3.5 equiv), aryl halide **3** (2 equiv), aryl halide **4** (1.2 equiv), 10 mL of dry toluene, argon atmosphere.
[c] Literature yield.

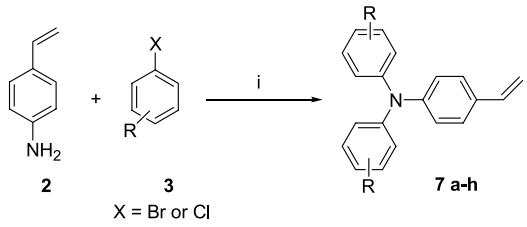
2.2. One-pot synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes (different aryl groups on nitrogen)

Encouraged by the results obtained via Scheme 1, we investigated the reaction of **2** with different aryl halides by changing the mode of coupling, namely, by carrying out mono-amination using the first aryl halide followed by the second amination and inter-molecular Heck reaction, by addition of the second aryl halide and heating at 110 °C for an additional 16 h (Scheme 2). This reaction was also found to be quite general, allowing the synthesis of a variety of the title compounds using the same protocol.

Our yield of 78% for **6a** is lower than that reported in a patent,[9] which involved the reaction of 4-[*N*-(4-methylphenyl)-*N*-phenylamino]benzaldehyde with diethylbenzylphosphonate (91%). It should be noted that the higher literature yield[9] for **6a** was achieved in a single reaction involving two reactants, one of which required prior synthesis. When this requirement is taken into account, the overall literature yield is 50%[16] compared with our one-pot yield of 78%. The compounds in entries 6 and 10 are novel, while the products in entries 4 and 9 were reported previously,[15] although no yield was given. It is also worthy of note that although when the less reactive aryl chlorides were used as the first aryl halide (entries 7, 8, and 9), the yields for the target compounds were still excellent although a higher temperature and longer reaction time was required. It may be noted that while the application of less expensive aryl chlorides further reduces the cost of the total procedure, additional energy costs would be incurred.

2.3. One-pot synthesis of diarylaminostyrenes with identical aryl groups on the nitrogen

As with *N*,*N*-diarylaminostilbenes, *N*,*N*-diarylaminostyrenes have also been used as hole-transport materials for organic electroluminescent devices and electrophotographic photoreceptors.[17] Moreover, this class of compounds serves as a precursor for the synthesis of a variety of photo chemically valuable target molecules such as *N*,*N*-diarylaminostilbenes, which are building blocks for the synthesis of oligo(phenylenevinylene) (OPV) dyes containing diphenylamino substituents.[18] Several methods are available in the literature for the synthesis of *N*,*N*-diarylaminostyrenes possessing identical aryl groups on the nitrogen, but most of these approaches are multi-step procedures.[17b] It is evident from the literature that a simple, mild, and efficient one-pot procedure for the synthesis of these compounds would be very useful. Herein, we report such a protocol using the same catalyst system employed earlier in this paper and the results are collected in Scheme 3 (Table 2).



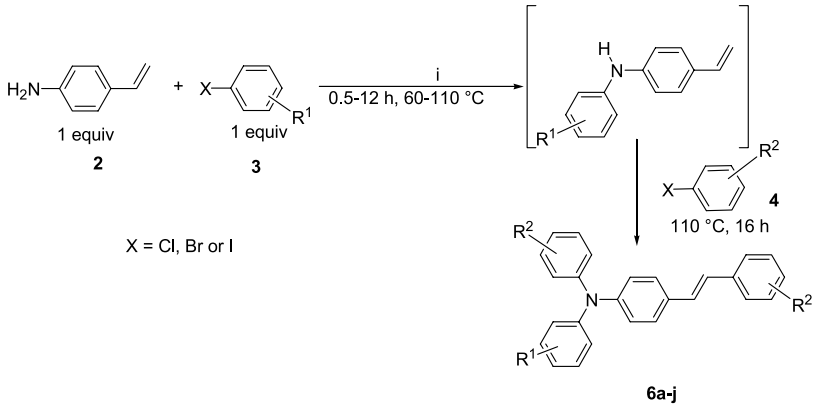
i. $Pd_2(dba)_3$, **1**, NaO-*t*-Bu, dry toluene.

Scheme 3.

The compounds in entries 5 and 6 are novel and the structures of the products were confirmed on the basis of their spectral data. The yields of *N*,*N*-diarylaminostyrenes obtained in entries 1, 2, and 8 using our protocol are better than the two step procedure reported in a patent, which involve a palladium-catalyzed amination to synthesize the corresponding 4-chlorotriphenylamine followed by a Grignard reaction with vinyl chloride.[17b] The products in entries 3 and 7 were reported in patents,[19] but no yields were given. The reaction of less reactive 4-chlorotoluene also afforded **7** in 78% yield, using the same amount of catalyst loading, but an elevated temperature and a longer reaction time was required (Table 3, entry 8).

2.4. One-pot double amination for the synthesis of unsymmetrically substituted *N*,*N*-diarylaminostyrenes

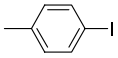
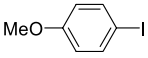
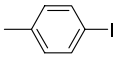
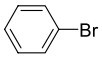
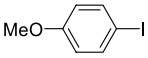
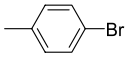
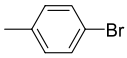
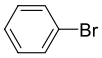
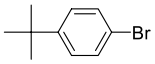
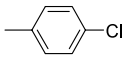
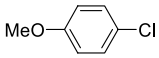
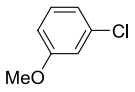
Unlike symmetrically substituted *N*,*N*-diarylaminostyrenes, a general procedure for the synthesis of unsymmetrically substituted *N*,*N*-diarylaminostyrenes is not known in the literature, owing primarily to the difficulty in controlling the mono-amination step in known procedures such as Ullmann coupling followed by a Vilsmeir and Wittig reaction sequence.



i. $Pd_2(dba)_3$, **1**, NaO-*t*-Bu, dry toluene.

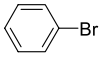
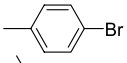
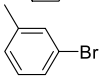
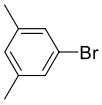
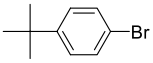
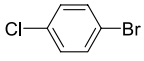
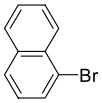
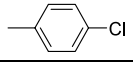
Scheme 2.

Table 2. One-pot synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes

Entry	Aryl halide (**3**)	Time (h)	Temperature *T* (°C)	Aryl halide (**4**)	Yield (%)[a,b]
1		3	60		78 (50)[c]
2		3	60		79
3		3	60		52
4		3	60		81
5		3	85		50
6		3	85		71
7		12	110		44
8		12	110		71
9		12	110		65
10		0.5	110		74

[a] Isolated yield, average of two runs.
[b] Reaction conditions: $Pd_2(dba)_3$ (2 mol%), **1** (4 mol%), NaO-*t*-Bu (3.5 equiv), aryl halide **3** (2 equiv), aryl halide **4** (1.2 equiv), 10 mL of dry toluene, argon atmosphere.
[c] Literature yield.

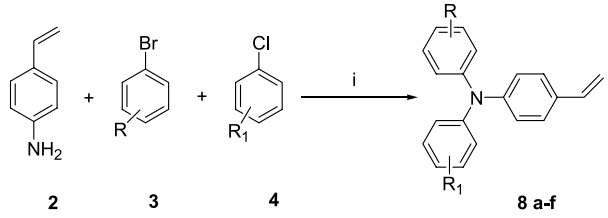
Table 3. One-pot synthesis of symmetrically substituted *N*,*N*-diarylaminostyrenes

Entry	Aryl halide	Time (h)	Temperature *T* (°C)	Yield (%)[a,b]
1		3	60	90 (78)[c]
2		3	85	86 (77)[c]
3		3	85	86[c]
4		3	85	81
5		3	85	91
6		3	85	78
7		12	100	86
8		16	110	78

[a] Isolated yield, average of two runs.
[b] Reaction conditions: $Pd_2(dba)_3$ (2 mol%), **1** (4 mol%), NaO-*t*-Bu (2.5 equiv), aryl halide **3** (2.1 equiv), 10 mL of dry toluene, argon atmosphere.
[c] Literature yield.

We were able to synthesize several derivatives of **8** with two different aryl groups on nitrogen in a one-pot multicomponent reaction using the Pd_2dba_3/**1** as catalyst system, and aryl bromides and aryl chlorides as the two coupling substrates. The success of this reaction relies on the fact that the amination using an aryl bromide was completed in 2–3 h at 60–80 °C, whereas the aryl chlorides required a minimum of 110 °C to couple. In a typical procedure, the reaction of 4-aminostyrene with 1-bromo-4-*tert*-butyl benzene and 4-chlorotoluene afforded product **8a**. The reaction mixture was heated at 85 °C for 2 h, during which time monoamination was completed as judged by TLC. Raising the temperature to 110 °C for another 16 h completed the synthesis of **8a** in 80% yield (entry 1 in Table 4).

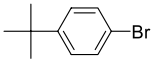
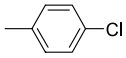
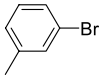
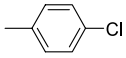
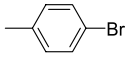
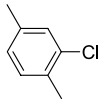
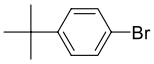
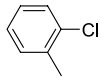
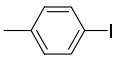
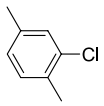
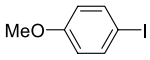
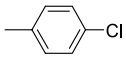
All the products in Table 4 are novel and their structures were assigned on the basis of their ^1H and ^{13}C NMR, and their HRMS spectra. As with other aryl chlorides, sterically hindered examples such as 2-chlorotoluene and 2-chloro-*p*-xylene were equally reactive, affording the coupled products in moderate to good yields (Table 4, entries 3–5) (Scheme 4).



i. $Pd_2(dba)_3$, **1** (4 mol %), NaO-*t*-Bu, dry toluene.

Scheme 4.

Table 4. One-pot synthesis of unsymmetrically substituted *N*,*N*-diarylaminostyrenes

Entry	Aryl halide (**3**)	Aryl halide (**4**)	Yield (%)[a,b]
1			80
2			81
3			66
4			53
5			73
6			68

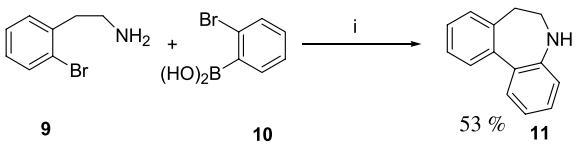
[a] Isolated yield, average of two runs.
[b] Reaction conditions: $Pd_2(dba)_3$ (2 mol%), **1** (4 mol%), NaO-*t*-Bu (2.5 equiv), aryl halide **3** (1 equiv), aryl halide **4** (1.2 equiv), 10 mL of dry toluene, 2 h at 85 °C and then the temperature was raised to 110 °C for 16 h, argon atmosphere.

2.5. Synthesis of 5,6-dihydro-7*H*-dibenz[*b*,*d*]azepine

To test a different application of proazaphosphatranes as ligands in one-pot multi-component reactions, we tried a one-pot amination/Suzuki sequence for the synthesis of 5,6-dihydro-7*H*-dibenz[*b*,*d*]azepine (**11**). Apart from an isolated literature report for the synthesis of **11** in 48% yield, via a trifluoromethanesulfonic acid-catalyzed cyclization of *N*-aminophenethylaniline,[20] no other descriptions for the synthesis of this compound were found in the literature. Although a single report of a one-pot amination/Suzuki reaction was found for the synthesis of 1,3-diphenylindazoles; this protocol required a bi-catalytic system.[21]

The reaction of 2-bromophenethylamine with 2-bromophenylboronic acid in the presence of 4 mol% of $Pd(OAc)_2$ and 8 mol% of **1** at 110 °C for 24 h afforded **11** in 53% isolated yield (Scheme 5).

Although, possible side reactions such as inter and intra molecular amination[22] and Suzuki coupling could be expected under our experimental conditions, we were able to isolate the expected product in somewhat better yield than that reported earlier.[20] The product was characterized by its ^1H and ^{13}C NMR and high-resolution mass spectra. Further elaboration of the methodology depicted in Scheme 5 to synthesize more complex molecules using one-pot sequential reactions is underway.



i. $Pd(OAc)_2$ (4 mol %), **1** (8 mol %), Cs_2CO_3 (4 equiv), 10 mL of dry toluene, 110 °C, 24 h., argon atmosphere.

Scheme 5.

3. Conclusion

The Pd_2dba_3/**1** ligand system has been shown to be useful for the one-pot synthesis of a variety of symmetrically and unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes and for *N*,*N*-diarylaminostyrenes. Interestingly, the same catalyst system is used for both the amination and the inter-molecular Heck coupling with a catalyst loading that is relatively low (2 mol% of $Pd_2(dba)_3$ and 4 mol% of the ligand). Using 4 mol% of $Pd(OAc)_2$ and 8 mol% of **1**, 5,6-dihydro-7*H*-dibenz[*b*,*d*]azepine was synthesized in moderate yield in a one-pot amination/Suzuki reaction.

4. Experimental

4.1. General considerations

All reactions were performed under an atmosphere of argon in oven dried glassware. Toluene was collected from a Grubbs type solvent purification system (Innovative Technologies) and stored over 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on Varian VXR 300 MHz and Bruker 400 MHz NMR spectrometers. NMR spectra were obtained using $CHCl_3$-*d* as solvent. Chemical shifts are given as δ values with tetramethylsilane or the $CHCl_3$ proton at 7.27 as the internal standard. Mass spectra were recorded on a Kratos MS-50 mass spectrometer.

4.2. General procedure for the synthesis of symmetrically substituted *N*,*N*-diarylaminostyrenes

An oven dried Schlenk tube equipped with a magnetic stirring bar was charged with Pd_2dba_3 (2 mol%) and NaO*t*Bu (1.75 mmol). The tube was capped with a rubber septum, evacuated and then flushed with argon three times. Ligand **1** (4 mol%), 4-aminostyrene (0.5 mmol), arylhalide **3** (1 mmol) and toluene (10 mL) were successively added

via syringe. The tube was heated at the temperature and for the time specified in Table 1, all the starting material was converted in to the corresponding *N*,*N*-dirylaminostyrenes as judged by TLC. To this reaction mixture, aryl halide **4** (0.6 mmol) was added and the temperature was raised to 110 °C. After heating for another 16 h, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a short column of silica gel to remove the solid impurities and the filtrate was concentrated in vacuo. The crude products were purified by column chromatography using 0.5–2% EtOAc/hexane mixtures as eluants to afford the coupled products.

4.2.1. *N*,*N*-Diphenyl-4-[2-(4-methylphenyl)ethenyl]benzenamine. See Table 1, entry 1.[15]

4.2.2. *N*,*N*-Bis(4-methoxyphenyl)-4-[2-phenylethenyl] benzenamine. See Table 1, entry 2.[15]

4.2.3. *N*,*N*-Bis(3-methylphenyl)-4-[2-phenylethenyl]benzenamine. See Table 1, entry 3.[15]

4.2.4. *N*,*N*-Bis(4-methylphenyl)-4-[2-phenylethenyl]benzenamine. See Table 1, entries 4 and 8.[15]

4.2.5. *N*,*N*-Bis(3-methoxyphenyl)-4-[2-phenylethenyl] benzenamine. See Table 1, entry 5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 6H), 6.59–6.72 (m, 6H), 7.04–7.27 (m, 7H), 7.34–7.42 (m, 4H), 7.50 (d, J=7.32 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.48, 108.72, 110.42, 117.16, 124.24, 126.49, 127.32, 127.49, 128.31, 128.84, 130.03, 131.92, 137.75, 147.23, 148.81, 160.60. HRMS: calcd for $C_{28}H_{25}NO_2$ (M^+) 407.18853, found: 407.18903.

4.2.6. *N*,*N*-Bis(4-methoxyphenyl)-4-[2-(4-methylphenyl) ethenyl]benzenamine. See Table 1, entry 6.[15]

4.2.7. *N*,*N*-Bis(4-methoxyphenyl)-4-[2-(3-methylphenyl) ethenyl]benzenamine. See Table 1, entry 7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.81 (s, 6H), 6.84–6.96 (m, 7H), 7.02–7.10 (m, 6H), 7.24–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.68, 55.67, 114.84, 120.64, 123.54, 126.26, 126.76, 127.04, 127.33, 128.06, 128.28, 128.68, 129.78, 137.88, 138.28, 140.89, 148.39, 156.03. HRMS: calcd for $C_{29}H_{27}NO_2$ (M^+) 421.20418, found:421.20489.

4.2.8. *N*-(4-Methylphenyl)-*N*-(phenyl)-4-[2-phenylethenyl]benzenamine. See Table 2, entries 1, 3, 5, and 7.[16]

4.2.9. *N*-(4-Methoxyphenyl)-*N*-(phenyl)-4-[2-phenylethenyl]benzenamine. See Table 2, entries 2 and 8.[9]

4.2.10. *N*-(4-Methoxyphenyl)-*N*-(4-methylphenyl)-4-[2-(4-methylphenyl)ethenyl]benzenamine. See Table 2, entry 4.[16]

4.2.11. *N*-(4-*tert*-Butyl-phenyl)-*N*-(phenyl)-4-[2-phenylethenyl]benzenamine. See Table 2, entry 6. Pd_2dba_3 (9.2 mg, 2.0 mol%), NaO*t*Bu (168 mg, 1.75 mmol), ligand **1** (6.8 mg, 4.0 mol%), 4-aminostyrene (59.5 mg, 0.499 mmol), 1-bromo-4-*tert*-butyl benzene (106.5 mg, 0.4997 mmol), and 10 mL of dry toluene was heated at 85 °C for 3 h and to the same reaction mixture iodobenzene (224.4 mg, 1.099 mmol) was added and heated at 110 °C for 16 h afforded the coupled product **6f** (143 mg, 71%) as a yellow solid after chromatography with 1% EtOAc/hexane mixtures as eluant.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 9H), 6.90–7.02 (m, 9H), 7.12–7.28 (m, 9H), 7.37 (d, J=7.52 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.66, 34.54, 122.90, 123.41, 124.40, 124.47, 126.31, 126.46, 126.99, 127.39, 127.47, 128.43, 128.82, 129.37, 131.30, 137.85, 144.88, 146.29, 147.69, 147.83. HRMS: calcd for $C_{30}H_{29}N$ (M^+) 403.23000, found: 403.23052.

4.2.12. *N*-(3-Methoxyphenyl)-*N*-(phenyl)-4-[2-phenylethenyl]benzenamine. See Table 2, entry 9.[15]

4.2.13. *N*-(3-Pyridyl)-*N*-(phenyl)-4-[2-phenylethenyl] benzenamine. See Table 2, entry 10. Chromatography with 20–50% EtOAc/hexane mixture as eluants. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94–7.03 (m, 8H), 7.18–7.33 (m, 8H), 7.39 (d, J=7.56 Hz, 2H), 8.13–8.14 (m, 1H), 8.31 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.12, 124.80, 126.51, 127.77, 128.82, 129.78, 132.72, 137.53, 143.34, 144.22, 145.44, 146.38, 146.71. HRMS: calcd for $C_{25}H_{20}N_2$ (M^+) 348.16265, found: 348.16317.

4.3. General procedure for the synthesis of unsymmetrically substituted *trans*-4-*N*,*N*-diarylaminostilbenes (different aryl groups on nitrogen)

An oven dried Schlenk tube equipped with a magnetic stirring bar was charged with Pd_2dba_3 (2 mol%) and NaO*t*Bu (1.75 mmol). The tube was capped with a rubber septum, evacuated and then flushed with argon three times. Ligand **1** (4 mol%), 4-aminostyrene (0.5 mmol), arylhalide **3** (1.1 mmol) and toluene (10 mL) were successively added via syringe. The tube was heated at the temperature and for the time specified in Table 1, the reaction mixture was cooled to room temperature. The reaction mixture was filtered through a short column of silica gel to remove the solid impurities and the filtrate was concentrated in vacuo. The crude products were purified by column chromatography using 0.5–2% EtOAc/hexane mixtures as eluant to afford the coupled products.

4.3.1. 4-Ethenyl-*N*,*N*-diphenylbenzenamine. See Table 3, entry 1.[17b]

4.3.2. 4-Ethenyl-*N*,*N*-bis(4-methylphenyl)benzenamine. See Table 3, entries 2 and 8.[17b]

4.3.3. 4-Ethenyl-*N*,*N*-bis(3-methylphenyl)benzenamine. See Table 3, entry 3.[19]

4.3.4. 4-Ethenyl-*N*,*N*-bis(3,5-dimethylphenyl)benzenamine. See Table 3, entry 4.[13]

4.3.5. 4-Ethenyl-*N*,*N*-bis(4-*tert*-butylphenyl)benzenamine. See Table 3, entry 5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 18H), 5.10 (d, J=10.89 Hz, 1H), 5.58 (d, J=17.58 Hz, 1H), 6.60 (dd, J_1=10.86 Hz, J_2=17.58 Hz, 1H), 6.99–7.03 (m, 6H), 7.24–7.27 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.66, 34.50, 111.81, 122.96, 124.19, 126.22,

127.10, 131.27, 136.55, 145.10, 145.92, 148.04. HRMS: calcd for $C_{28}H_{33}N$ (M^+) 383.26130, found: 383.26190.

4.3.6. 4-Ethenyl-*N*,*N*-bis(4-chlorophenyl)benzenamine. See Table 3, entry 6. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.15 (d, $J=10.86$ Hz, 1H), 5.61 (d, $J=17.58$ Hz, 1H), 6.59 (dd, $J_1=10.86$ Hz, $J_2=17.58$ Hz, 1H), 6.96–6.99 (m, 6H), 7.15–7.17 (m, 4H), 7.19–7.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.04, 124.16, 125.42, 127.49, 128.30, 129.64, 133.01, 136.18, 146.07, 146.81. HRMS: calcd for $C_{20}H_{15}NCl_2$ (M^+) 339.05816, found: 339.05855.

4.3.7. 4-Ethenyl-*N*,*N*-bis(1-naphthyl)benzenamine. See Table 3, entry 7.[19]

4.4. General procedure for the synthesis of unsymmetrically substituted *N*,*N*-diarylaminostyrenes

An oven dried Schlenk tube equipped with a magnetic stirring bar was charged with Pd_2dba_3 (2 mol%) and NaO*t*Bu (1.75 mmol). The tube was capped with a rubber septum, evacuated and then flushed with argon three times. Ligand **1** (4 mol%), 4-aminostyrene (0.5 mmol), arylbromide (0.5 mmol), aryl chloride (0.6 mmol) and toluene (10 mL) were successively added via syringe. The tube was heated at 85 °C for 2 h and then the temperature was raised to 110 °C for an additional 16 h. The reaction mixture was cooled to room temperature and filtered through a short column of silica gel to remove the solid impurities and the filtrate was concentrated in vacuo. The crude products were purified by column chromatography using hexane—1% EtOAc/hexane mixtures as eluant to afford the coupled products.

4.4.1. 4-Ethenyl-*N*-(4-methylphenyl)-*N*-(4-*tert*-butylphenyl)benzenamine. See Table 4, entry 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 9H), 2.31 (s, 3H), 5.10 (d, $J=10.98$ Hz, 1H), 5.58 (d, $J=17.58$ Hz, 1H), 6.60 (dd, $J_1=11.01$ Hz, $J_2=17.58$ Hz, 1H), 6.98–7.05 (m, 8H), 7.22–7.27 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.07, 31.66, 34.50, 111.80, 122.76, 123.89, 124.17, 125.07, 126.19, 127.08, 130.06, 131.19, 132.87, 136.50, 145.10, 145.28, 145.79, 148.04. HRMS: calcd for $C_{25}H_{27}N$ (M^+) 341.21435, found: 341.21500.

4.4.2. 4-Ethenyl-*N*-(4-methylphenyl)-*N*-(3-methylphenyl)benzenamine. See Table 4, entry 2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.34 (s, 3H), 5.13 (d, $J=10.98$ Hz, 1H), 5.61 (d, $J=17.70$ Hz, 1H), 6.62 (dd, $J_1=10.89$ Hz, $J_2=17.58$ Hz, 1H), 6.82–6.92 (m, 3H), 6.99–7.16 (m, 7H), 7.27–7.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.06, 21.62, 111.98, 121.47, 123.16, 123.74, 124.89, 125.19, 127.14, 129.18, 130.11, 131.45, 133.00, 136.49, 139.22, 145.28, 147.89, 148.00. HRMS: calcd for $C_{22}H_{21}N$ (M^+) 299.16740, found: 299.16778.

4.4.3. 4-Ethenyl-*N*-(4-methylphenyl)-*N*-(2,5-dimethylphenyl)benzenamine. See Table 4, entries 3 and 5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 2.28 (s, 3H), 2.32 (s, 3H), 5.10 (d, $J=10.86$ Hz, 1H), 5.58 (d, $J=17.58$ Hz, 1H), 6.61 (dd, $J_1=10.86$ Hz, $J_2=17.58$ Hz, 1H), 6.85–7.07 (m, 8H), 7.12–7.15 (m, 1H), 7.24–7.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.33, 20.96, 21.06, 111.27, 120.36, 122.72, 127.05, 127.09, 129.87, 130.12, 130.15, 131.65, 133.36, 136.57, 137.23, 144.83, 145.18, 147.74. HRMS: calcd for $C_{23}H_{23}N$ (M^+) 313.18305, found: 313.18347.

4.4.4. 4-Ethenyl-*N*-(4-*tert*-butylphenyl)-*N*-(2-methylphenyl)benzenamine. See Table 4, entry 4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 9H), 2.05 (s, 3H), 5.09 (d, $J=10.89$ Hz, 1H), 5.57 (d, $J=17.61$ Hz, 1H), 6.60 (dd, $J_1=10.89$ Hz, $J_2=17.58$ Hz, 1H), 6.87–6.97 (m, 4H), 7.13–7.27 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.80, 31.65, 34.41, 111.36, 120.48, 122.04, 126.06, 126.22, 127.09, 127.54, 129.79, 130.29, 131.87, 136.55, 136.73, 144.59, 144.96, 145.42, 147.56. HRMS: calcd for $C_{25}H_{27}N$ (M^+) 341.21435, found: 341.21499.

4.4.5. 4-Ethenyl-*N*-(4-methylphenyl)-*N*-(4-methoxyphenyl)benzenamine. See Table 4, entry 6. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 3.69 (s, 3H), 5.00 (d, $J=8.10$ Hz, 1H), 5.48 (d, $J=13.17$ Hz, 1H), 6.50 (dd, $J_1=8.16$ Hz, $J_2=13.00$ Hz, 1H), 6.72–6.74 (m, 2H), 6.83–6.97 (m, 8H), 7.13–7.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.00, 55.65, 111.54, 114.86, 121.67, 124.22, 127.05, 127.16, 129.99, 130.64, 132.38, 136.46, 140.86, 145.43, 148.26, 156.18. HRMS: calcd for $C_{22}H_{21}NO$ (M^+) 315.16231, found: 315.16277.

4.4.6. 5,6-Dihydro-7*H*-dibenz[*b*,*d*]azepine (11). An oven dried Schlenk tube equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (4.48 mg, 3.99 mol%), Cs_2CO_3 (652 mg, 2.00 mmol) and 2-bromophenylboronic acid (100 mg, 0.497 mmol). The tube was capped with a rubber septum, evacuated and then flushed with argon three times. Ligand **1** (13.68 mg, 7.988 mol%), 2-bromophenethylamine (100 mg, 0.499 mmol) and toluene (10 mL) were successively added via syringe. The tube was heated at 110 °C for 24 h. Then the reaction mixture was cooled to room temperature and filtered through a short column of silica gel to remove the solid impurities and then the filtrate was concentrated in vacuo. The crude product was purified by column chromatography using hexanes as eluant to afford the **11** (51 mg, 53%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (t, $J=8.4$ Hz, 2H), 3.95 (t, $J=8.4$ Hz, 2H), 6.75 (t, $J=7.32$ Hz, 1H), 6.96–7.00 (m, 1H), 7.09–7.11 (m, 1H), 7.16 (t, $J=8.6$ Hz, 2H), 7.24–7.27 (m, 2H), 7.34–7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.37, 52.27, 108.27, 117.80, 118.98, 121.06, 125.20, 127.22, 129.31, 131.42, 144.28. HRMS: calcd for $C_{14}H_{13}N$ (M^+) 195.10480, found: 195.10506.

Acknowledgements

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Palladium–benzimidazolium salt catalyst systems for Suzuki coupling: development of a practical and highly active palladium catalyst system for coupling of aromatic halides with arylboronic acids

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Abstract—Palladium–benzimidazolium salt catalyst systems have been studied for the Suzuki coupling. A different substitutent effect has been uncovered with respect to nitrogen substituents in the benzimidazolium salts from the palladium–imidazolium salt analogs. A practical and highly active palladium catalyst system, $PdCl_2$/*N*,*N*′-dibenzylbenzimidazolium chloride **2**, has been identified for the Suzuki coupling of aromatic halides with arylboronic acids. The coupling of a wide array of aromatic halides with arylboronic acids with the $PdCl_2$–**2** catalyst system gave good to excellent yields. The effective palladium loading could be as low as 0.0001 mol% and 0.01–0.1 mol% for iodide and bromide substrates, respectively. The coupling of unactivated aromatic chlorides with arylboronic acids also gave good results using Cs_2CO_3 as base with a 2 mol% palladium loading. The electronic factors from aromatic halides exert a significant influence on the Suzuki coupling catalyzed by the $PdCl_2$–**2** system while the electronic effect from the arylboronic counterparts is negligible. The aromatic halides with modest steric hindrance could also couple smoothly with phenylboronic acids using the $PdCl_2$–**2** catalyst system.

1. Introduction

The imidazolium-based nucleophilic *N*-heterocyclic carbenes (NHC), imidazolylidenes, have recently emerged as a versatile class of ligands in transition metal chemistry.[1] With their stronger donor electronic property, thus high dissociation energies of the corresponding metal–carbon bonds,[2] the transition metal complexes of imidazolylidenes appeared to be extraordinarily stable toward heat, air and moisture, showing potential in practical organic synthesis. These advantages of imidazolylidene ligands make them ideal alternatives to tertiary phosphines used in a variety of transition-metal based homogeneous catalysts. Through formation of catalytic species in situ, use of a combination of imidazolium salts with metal precursors has proven to be not only practical but also more efficient in some cases than the isolated NHC–metal complexes of imidazolylidenes.[3] A variety of highly active catalyst systems have recently been developed by combination of proper imidazolium salts with palladium precursors.[3,4] However, possibly due to the lower stability of free benzimidazolylidenes than imidazolylidenes few attention has been paid to the nucleophilic *N*-heterocyclic carbenes derived from benzimidazole[5] although fundamental thermodynamic studies have shown that benzimidazolylidenes behave intermediately between imidazolylidenes and their saturated analogs, imidazolinylidenes.[6] The first NHC, derived from benzimidazole, *N*,*N*′-bis(2,2-dimethylpropyl)benzimidazolylidene, was isolated in 1998 by reduction of thione.[7] Direct deprotonation of *N*,*N*′-bis-alkylsubstituted benzimidazolium salts with a less sterically demanding substituent yields an enetetramine instead of a free carbene.[8] However, it has recently been shown that NHC-transition metal complexes containing benzimidazolylidene ligands could be generated from the corresponding benzimidazolium salts as well as enetetramines under mild conditions.[9] That means, similar to imidazolium salts, a combination of benzimidazolium salts with metal precursors would finally lead to the corresponding NHC–metal complexes under proper conditions.

The Suzuki coupling, where organoboronic acids are employed as neuclophilic partners to couple with electrophiles such as arylhalides, is one of the most important protocols in organic synthesis, permitting the construction of a wide variety of organic compounds ranging from

Keywords: Palladium; Suzuki coupling; Benzimidazolium; Arylboronic acid; Aromatic halide.
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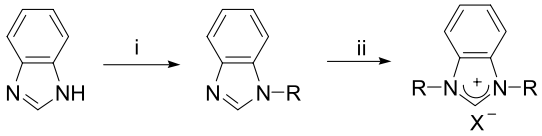
artificial materials to natural products.[10] Compared with the other nucleophilic partners in the cross-coupling with organic halides, such as organomagnesium, organotin, and organozinc, organoboron compounds possess many attractive features, such as air- and water-stability, non-toxicity and excellent compatibility with a variety of functional groups. The palladium–imidazolium salt systems have proved to be one of the most successful catalysts for the Suzuki coupling. Substituents on nitrogen atoms of imidazolium significantly influence the catalytic activities of the corresponding palladium–imidazolium salt systems in the Suzuki coupling. As mentioned above, little is known about the catalyst systems based on benzimidazolium salts in the Suzuki coupling. We report here the development of a highly active palladium–benzimidazolium catalyst system employing the simplest palladium source $PdCl_2$ and the readily accessible *N*,*N*′-dibenzylbenzimidazolium chloride for Suzuki coupling of aromatic halides, including chlorides.

2. Results and discussion

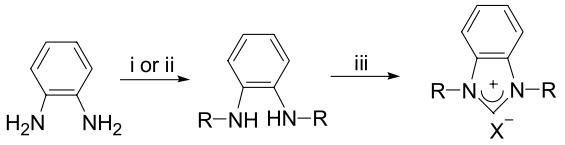
2.1. Synthesis of benzimidazolium salts

N,*N*′-Dialkylbenzimidazolium salts with primary alkyl groups could be readily prepared from benzimidazoles by consecutive alkylations with alkylhalides. *N*,*N*′-Dibutylbenzimidazolium bromide **1**, *N*,*N*′-dibenzylbenzimidazolium chloride **2** and *N*,*N*′-bis-ethoxycarbonylmethylbenzimidazolium bromide **3** were obtained following this procedure in good yields (Scheme 1).



Scheme 1. Reagents and conditions: (i) 1.2 equiv RX, 30% NaOH(aq), $Bu_4N^+Br^-$ (1.5% equiv), 55 °C. (ii) 2.0 equiv RX, toluene, reflux.

According to the systematic work from Nolan group that aryl or bulky alkyl substituents on nitrogen atoms were crucial to the high performance of the corresponding palladium–imidazolium salt systems.[4] Thus, we wonder if the palladium–benzimidazolium systems show a similar trend. However, synthesis of *N*,*N*′-dibenzhydrylbenzimidazolium chloride **4** with the same procedure suffered from poor yields under various conditions although the first alkylation of benzimidazole with benzhydryl chloride proceeded smoothly. Benzimidazolium salts with aromatic substituents on *N* atoms are not accessible with a simple alkylation procedure from benzimidazole. Thus, alternative procedures were used to obtain **4** and *N*,*N*′-diphenylbenzimidazolium chloride **5** (Scheme 2). Benzimidazolium **4** was prepared by alkylation of 1,2-diaminobenzene with benzhydryl chloride followed by cyclization of the resulting *N*,*N*′-dibenzhydryl 1,2-diaminobenzene with orthoformate in the presence of HCl (aq). Introduction of phenyl group to the amino groups of 1,2-diaminobenzene was first tried using palladium-catalyzed procedures with iodobenzene[11] and copper-promoted arylation[12] with phenylboronic acid. Unfortunately, both resulted in complicated mixtures, from which only trace amount of the desired product, *N*,*N*′-diphenyl-1,2-diaminobenzene, was isolated. The preparation of *N*,*N*′-diphenyl-1,2-diaminobenzene was finally achieved by a slightly modified amino acid-promoted Ullmann coupling in 30% yield.[13] A similar cyclization to that for **4** with orthoformate in the presence of HCl(con.) provided *N*,*N*′-diphenylbenzimidazolium chloride **5** in 90% yield.

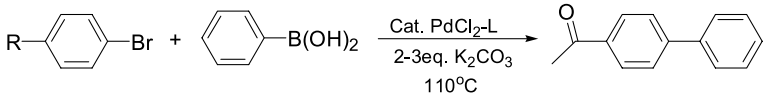


Scheme 2. Reagents and conditions: (i) 2.5 equiv Ph_2CHCl, 30% NaOH (aq), $Bu_4N^+Br^-$ (1.5% equiv), 55 °C. (ii) iodobenzene (5.0 equiv) CuI (0.20 equiv), L-proline (0.40 equiv), K_2CO_3 (4.1 equiv), DMSO, N_2, 80 °C, 18 h. (iii) $HC(OEt)_3$, HCl (con. aq), HCO_2H, N_2, 80 °C, 2 h.

2.2. Suzuki coupling of arylboronic acids with aromatic halides

2.2.1. Establishing catalyst system. With these benzimidazolium derivatives in hand, we started to investigate the performance of the palladium–benzimidazolium catalyst systems in the Suzuki coupling. Cross-coupling of 4-bromoacetophone with phenylboronic acid was selected as the model reaction considering the ease of monitoring the reaction progress. Although there are a couple of parameters, such as base, temperature and solvent to be scanned to optimize the reaction conditions, thanks to the extensive research on NHC–palladium catalysts in recent years, we have readily set the starting point: 0.01%Pd loading, 2–3 equiv K_2CO_3 in DMF–H_2O at 110 °C. Although palladium sources have showed effects on the performance of the corresponding palladium catalyst systems,[3] it is possibly the most practical and economical to use palladium chloride. Thus palladium chloride $PdCl_2$ was chosen as the palladium source in our palladium–benzimidazolium catalyst systems. The reaction 4-bromoacetophone with phenylboronic acid catalyzed by the palladium–benzimidazolium **1**–**5** catalyst systems gave the cross-coupling product in good to excellent yields while no reaction occurred in the absence of a benzimidazolium salt under the otherwise identical conditions (Table 1, entries 1–6). On the effects of *N*,*N*′-substituents of benzimidazolium on the performance of the catalyst systems, benzimidazolium salts displayed a trend in contrast to the reported imidazolium analogs. Aromatic or bulky substituents on the N atoms of imidazolium normally increase the catalytic activity of the corresponding systems.[4d] However, the palladium–benzimidazolium catalyst system based on **5**, the *N*,*N*′-diphenylbenzimidazolium salt, displayed lower catalytic activity in the model reaction than those based on alkyl substituted ones, such as butyl **1**, benzyl **2** and benzhydryl **4**. Bis-ethoxycarbonylmethyl imidazolium **3** also showed a lower activity although the imidazolium with coordinative side arms was reported to display higher activities than the corresponding simple alkyl analogs in palladium-catalyzed C–C bond forming reactions.[14] The systems of dibenzylbenzimidazolium **2** and dibenzhydryl imidazolium **4** displayed higher activities than that of **1** and

Table 1. Cross-coupling of 4-bromoacetophone with phenylboronic acid catalyzed by palladium–benzimidazolium catalyst systems



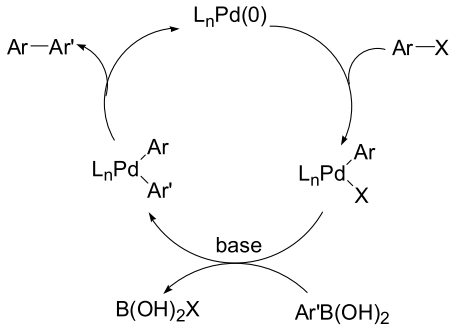
Entry	Ligand	R	Pd loading (%)	Pd/L	Solvent (vol%)	Time (h)	Yield (%)[a]
1	/	CH_3CO	0.01	/	DMF–5%H_2O	3	Trace
2	**1**	CH_3CO	0.01	1/2	DMF–5%H_2O	3	91
3	**2**	CH_3CO	0.01	1/2	DMF–5%H_2O	1	94
4	**3**	CH_3CO	0.01	1/2	DMF–5%H_2O	12	85
5	**4**	CH_3CO	0.01	1/2	DMF–5%H_2O	1	96
6	**5**	CH_3CO	0.01	1/2	DMF–5%H_2O	3	94
7	**2**	CH_3CO	0.001	1/2	DMF–5%H_2O	12	12[b,c]
8	**2**	CH_3	0.01	1/2	DMF–5%H_2O	12	20[b,c]
9	**1**	CH_3	0.1	1/2	DMF–5%H_2O	3	86
10	**2**	CH_3	0.1	1/2	DMF–5%H_2O	2	87
11	**3**	CH_3	0.1	1/2	DMF–5%H_2O	12	73
12	**4**	CH_3	0.1	1/2	DMF–5%H_2O	4	83
13	**5**	CH_3	0.1	1/2	DMF–5%H_2O	6	71[c]
14	**2**	CH_3CO	0.01	1/1	DMF–5%H_2O	5	93
15	**2**	CH_3CO	0.01	1/5	DMF–5%H_2O	1	90
16	**2**	CH_3CO	0.01	1/2	DMF–25%H_2O	8	82
17	**2**	CH_3CO	0.01	1/2	DMF	3	12[b,c]
18	**2**	CH_3CO	0.01	1/2	Dioxane–5%H_2O	3	20[b,c]
19	**2**	CH_3CO	0.01	1/2	Tol–10%H_2O	3	25[b,c]

[a] Isolated yield.
[b] Conversion determined by GC.
[c] Aromatic halides recovered.

3 with butyl and ethoxycarbonylmethyl groups, respectively. These results clearly indicated a sharp difference between the imidazolium and benzimidazolium catalyst systems. The trend displayed in the model reaction was unmistakably confirmed by the coupling of 4-bromotoluene with phenylboronic acid although the reaction required a higher loading of palladium (Table 1, entries 8–13). Indeed, the loading of palladium showed a significant effect on the performance of the catalyst systems. When the loading of $PdCl_2$ was decreased to 0.001 mol% from 0.01 mol%, the coupling of 4-bromoacetophone with phenylboronic acid became rather sluggish (Table 1, entry 7). *N*,*N*′-Dibenzylbenzimidazolium salt **2** was chosen for further optimization of the reaction conditions considering its easy accessibility. The palladium–ligand ratio did not show significant impact on the model reaction (Table 1, entries 3, 14 and 15). The 2:1 ratio of benzimidazolium salt to palladium gave slightly better results than 1:1 ones. But an excess amount of benzimidazolium salt looked like not necessary for the stabilization of the active catalytic species. DMF proved to be the choice of solvent (Table 1, entries 3, 18 and 19). The presence of some amount (5–10% v/v) of water as co-solvent was crucial to the success of the coupling albeit larger amount of water depressed the reaction (Table 1, entries 2, 16 and 17).

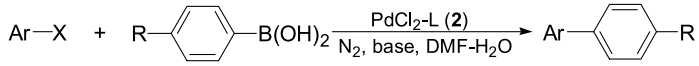
The generally accepted catalytic cycle for the Suzuki coupling reaction involves an oxidative-addition of the arylhalide to a coordinatively unsaturated palladium $L_nPd(0)$, transmetalation between organoboronic acid and the palladium intermediate $L_nPd(Ar)(X)$ assisted by base and a reductive-elimination producing the coupling product and regeneration of $L_nPd(0)$ (Scheme 3).[10]

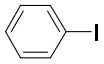
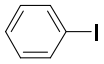
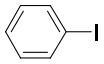
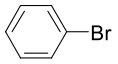
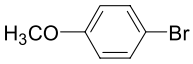
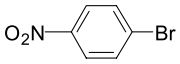
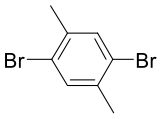
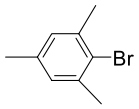
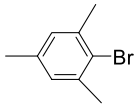
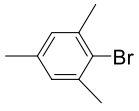
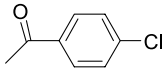
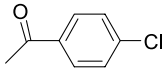
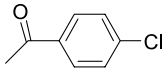
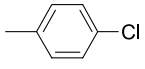
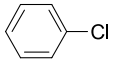
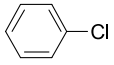
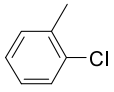
In the model reactions with 4-bromoacetophone or 4-bromotoluene, the behavior of these catalyst systems employing **1**–**5** as supporting ligands looked like to abide by a general rule for phosphine–palladium systems, that is electronic-rich ligands perform better for substrates resistant to oxidative-addition, for example, chlorides, while sterically demanding ligands would show higher activities in coupling reactions if the reductive-elimination is the rate-determining step.[15] For example, the comparative electronic-rich *N*,*N*′-dialkylbenzimidazolium salts **1**, **2** and **4** displayed better performances than **3** and **5** with ethoxycarbonylmethyl and phenyl groups, respectively (Table 1, entries 2–6 and 9–13). Within the sub-sort of *N*,*N*′-dialkylbenzimidazolium salts **1**, **2** and **4**, the catalytic activities to the activated substrate, 4-bromoacetophone, slightly increased with the increase of the bulk of alkyl groups, implying that the reductive-elimination could be a slow step. However, these are in contrast to those reported for the imidazolium catalyst systems, in which electronic-rich *N*,*N*′-dialkylimidazoliums showed lower activities, especially for the substrates resistant to oxidative addition, than the comparative electronic-poor *N*-aryl analogs in Suzuki coupling.[4d] Obviously, further investigations employing benzimidazoliums with various electron properties are needed to shed light on the issue.



Scheme 3. A general catalytic cycle for Suzuki coupling.

Table 2. Suzuki coupling of arylboronic acids with aromatic halides catalyzed by the palladium–benzimidazolium catalyst system



Entry	Ar–X	R	Pd loading (%)	Base	T (°C)	Time (h)	Yield (%)[a]
1		H	0.01	3 equiv K_2CO_3	110	1	93 (100)[b]
2		H	0.0001	3 equiv K_2CO_3	110	1	/ (91)[b]
3		H	0.0001	3 equiv K_2CO_3	110	2	94 (100)[b]
4		H	0.1	3 equiv K_2CO_3	110	2	93 (100)[b]
5		H	0.1	3 equiv K_2CO_3	110	12	76
6		H	0.1	3 equiv K_2CO_3	110	2	92
7[c]		H	0.1	3 equiv K_2CO_3	110	8	90
8		H	0.1	3 equiv K_2CO_3	110	12	16
9		H	0.5	3 equiv K_2CO_3	110	12	44
10[d]		H	3	3 equiv K_2CO_3	110	6	94
11		H	0.5	3 equiv $Ba(OH)_2$	140	12	70
12		H	2	3 equiv $Ba(OH)_2$	140	6	82
13		H	2	3 equiv Cs_2CO_3	140	6	88 (100)[b]
14[d]		H	2	3 equiv Cs_2CO_3	140	12	64
15[d]		*p*-CH_3CO	2	3 equiv Cs_2CO_3	140	12	70
16[d]		*p*-CH_3O	2	3 equiv Cs_2CO_3	140	12	77
17[d]		H	2	3 equiv Cs_2CO_3	140	12	69

[a] Isolated yield and the products were identified by comparison data with those reported in literature, see Section 4 for details.
[b] Conversion determined by GC.
[c] 2.5 equiv phenylboronic acid was used and diarylation product was isolated.
[d] Xylenes (2 mL) were added to maintain a reflux and prevent the chlorides from evaporating.

2.3. Coupling of arylboronic acids with aromatic halides

The Suzuki coupling catalyzed by the $PdCl_2$–**2**–K_2CO_3 system was explored in details (Table 2). At the loading of $PdCl_2$ as low as 0.0001 mol%, the coupling of iodobenzene with phenylboronic acid still proceeded smoothly, indicating the system are highly active for aromatic iodides. The conversion of iodobenzene reached to 91% in 1 h determined by GC, showing TOF up to 9.1×10^5 mol/mol h. We next focused on the Suzuki reactions of usually less reactive electrophiles, aromatic bromides and chlorides using the $PdCl_2$–**2**–K_2CO_3 catalyst system. However, at the low loading of palladium (0.001 mol%) for iodobenzene, bromobenzene remained almost untouched under the otherwise identical conditions. When 0.1 mol% palladium loading was used bromobenzene could be smoothly converted and gave biphenyl in 93% isolated yield. The electronic factor from aromatic halides exerted a significant influence on the coupling. The reactions of unactivated (electron-neutral) arylbromides employing the $PdCl_2$–**2**–K_2CO_3 catalyst system proceeded in good yields while deactivated (electron-rich) arylbromides with electron-donating groups, such as MeO, reacted slowly and the yield decreased to 76% (Table 2, entry 5). In contrast, activated (electron-poor) arylbromides with electron-withdrawing groups, such as CH_3CO and NO_2, reacted fast and provided cross-coupling product in high yields (Table 1, entry 3 and Table 2, entry 6). For an aromatic bromide with modest steric hindrance, 2,5-dibromoxylene, the coupling still went well, giving diarylation product, in 90% yield (Table 2, entry 7). Even, the sterically demanding di-*ortho*-substituted-2-bromomesitylene also reacted well providing the cross-coupling product in 94% yield with an increased loading of palladium (3 mol%) (Table 2, entry 10).

The usually unreactive aromatic chlorides were further explored as the coupling partner using the $PdCl_2$–**2**–K_2CO_3 catalyst system. The low reactivity of aromatic chlorides has been attributed to their resistance to the oxidative addition to Pd(0) species because of a large C_{sp^2}–Cl bond dissociation energy.[16] Due to the low cost of aromatic chlorides and the challenge to activate the C_{sp^2}–Cl bond, it has attracted much attention from both the industry and academic communities to couple aromatic chlorides with arylboronic acids.[15,16] Electron-rich phosphine ligands, such as tri(*tert*-butylphosphine), and *N*,*N*′-diarylsubstituted imidazolium–palladium systems have been reported to be suitable for the Suzuki coupling of aromatic chlorides. Using the $PdCl_2$–**2**–K_2CO_3 catalyst system, which worked well for the coupling of aromatic bromides, only trace amount of the activated chloride, 4-chloroacetophone, was converted. A stronger base $Ba(OH)_2$, a higher loading of palladium (0.5 mol%) and higher reaction temperature (130–140 °C) were required for the reaction to proceed to completion (Table 2, entries 11 and 12). The yields of the cross-coupling increased from 70 to 82% with the increase of the loading of $PdCl_2$ from 0.5 to 2 mol%. However, palladium black was observed on the wall of the reaction vessel with 2 mol% palladium loading, indicating the true catalytic species should be less than 2 mol% and ratio of palladium to benzimidazolium should be lower than 1:2. Further increasing the loading of palladium did not increase the yield of the cross-coupling. When Cs_2CO_3 was used instead of $Ba(OH)_2$, the yield of cross-coupling product reached 88% under the otherwise identical conditions (Table 2, entry 13). Using the $PdCl_2$–**2**–Cs_2CO_3 catalyst system, the cross-coupling of unactivated aromatic chlorides, such as chlorobenzene and 4-chlorotoluene, with arylboronic acids also gave the biaryl products in good yields (Table 2, entries 14–16). In contrast to the electronic effect from aromatic halides, the electronic factor from arylboronic acids showed a negligible influence on the coupling. Sterically hindered 2-chlorotoluene was equally reactive producing the cross-coupling product in 70% yield (Table 2, entry 17).

3. Conclusion

In summary, five representative benzimidazolium salts have been studied in constructing palladium catalyst systems for the Suzuki coupling, from which a practical and highly active palladium catalyst system has been developed from the simplest palladium source $PdCl_2$ and readily available *N*,*N*′-dibenzylbenzimidazolium chloride **2** for the Suzuki coupling of aromatic halides with arylboronic acids. A different substitutent effect has been uncovered with respect to nitrogen substituents of benzimidazolium salts from the imidazolium salt analogs. The $PdCl_2$–**2** catalyst system has proven to be highly efficient for the coupling of a wide array of aromatic halides including chlorides with arylboronic acids. The effective palladium loading could be as low as 0.0001 mol% and 0.01–0.1 mol% for iodide and bromide substrates, respectively. The coupling of aromatic chlorides with arylboronic acids also gave good results using the $PdCl_2$–**2** catalyst system with 2 mol% palladium loading and Cs_2CO_3 as the base. Electron-deficient aromatic halides reacted faster and gave higher yields than the electron-rich ones, indicating electronic factor from aromatic halides exerted a significant influence on the Suzuki coupling catalyzed by the palladium–benzimidazolium system while the electronic effect from the arylboronic counterparts is almost negligible. The obvious advantages of the $PdCl_2$–**2** system lie in its ready availability and yet high catalytic activity. These results suggest that the *N*-heterocyclic carbenes from benzimidazolium salts are promising ligands for the homogenous transition metal catalysts. Further modification of the benzimidazolium salts and applications in transition metal catalyzed organic transformations are in progress in our laboratory.

4. Experimental

4.1. General

All reactions and manipulations were performed in air unless otherwise indicated. All the commercially available chemicals, reagents and solvents, were used as received with an exception of iodobenzene that was distilled prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 spectrometer using the residue of deuterated solvents as the internal standard. GC and Mass analyses were performed using a Hewlett Packard Model HP 6890 Series with HP-5 column. Elemental analysis was performed at the Center of Analysis and Structure Determination of ECNU.

4.2. Synthesis of benzimidazolium salts

4.2.1. *N,N′*-Dibutylbenzimidazolium bromide 1. To a 50 mL flask charged with benzimidazole (1.18 g, 10 mmol) was added 10 mL 30% NaOH(aq) and 1.5% equiv $Bu_4N^+Br^-$ (TBAB) (50 mg, 0.15 mmol) followed by 1.2 equiv 1-bromobutane (1.3 mL, 12 mmol) at room temperature. The mixture was stirred at 55 °C for 3 h before being poured into 50 mL water and extracted with toluene (20 mL×3). The toluene extracts was dried with Na_2SO_4, filtrated and added to a solution of 1-bromobutane (2.3 mL, 20 mmol) in a 100 mL flask. The mixture was refluxed for 6 h and slowly cooled to room temperature giving *N,N′*-dibutylbenzimidazolium bromide **1** as a white powder, which was further purified by recrystallization from CH_2Cl_2 to give **1** as colorless crystals 1.9 g (61%, two steps), mp: 140–142 °C. ^{1}H NMR ($CDCl_3$, 25 °C), δ, ppm: 11.33 (1H, s, H2), 7.77–7.80 (2H, m, H4, H7), 7.67–7.70 (m, 2H, H5, H6), 4.67 (4H, t, J=7.0 Hz, CH_2), 2.24 (2H, s, H_2O), 2.05–2.10 (4H, m, CH_2), 1.45–1.52 (4H, m, CH_2), 0.98–1.01 (6H, t, J=7 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C), δ, ppm: 142.5, 131.3, 127.2, 113.2, 47.5, 31.4, 19.8, 13.6. Anal. Calcd for $C_{15}H_{25}N_2OBr$ (**1**·H_2O): C, 54.71; H, 7.65; N, 8.51. Found: C, 54.86; H, 7.55; N, 8.28.

4.2.2. *N,N′*-Dibenzylbenzimidazolium chloride 2. A similar procedure to that for the preparation of **1** was adopted employing benzimidazole (5.9 g, 50 mmol) to provide **2** as colorless microcrystals 10.2 g (61%), mp: 210–212 °C. ^{1}H NMR (DMSO, 25 °C), δ, ppm: 10.36 (1H, s, H2), 7.98–8.01 (2H, m, H4, H7), 7.63–7.65 (m, 2H, H5, H6), 7.56 (4H, d, J=7.2 Hz, Ph), 7.35–7.45 (6H, m, Ph), 5.84 (4H, s, CH_2Ph). ^{13}C NMR (DMSO, 25 °C), δ, ppm: 142.8, 133.9, 130.9, 128.8, 128.5, 128.2, 126.6, 113.9, 49.8. Anal. Calcd for $C_{21}H_{21}N_2OCl$ (**2**·H_2O): C, 71.48; H, 6.00; N, 7.94. Found: C, 71.24; H, 5.87; N, 7.68.

4.2.3. *N,N′*-Bis-ethoxycarbonylmethyl benzimidazolium bromide 3. A similar procedure to that for the preparation of **1** was adopted employing benzimidazole (1.18 g, 10 mmol) to provide **3** as colorless microcrystals 3.2 g (86%), mp: 157–159 °C. ^{1}H NMR (DMSO, 25 °C), δ, ppm: 9.80 (1H, s, H2), 8.08–8.10 (2H, m, H4, H7), 7.71–7.73 (2H, m, H5, H6), 5.70 (4H, s, CH_2CO_2Et), 4.23 (4H, q, J=7.2 Hz, CH_2), 1.26 (6H, t, J=7.2 Hz, CH_3). ^{13}C NMR (DMSO, 25 °C), δ, ppm: 166.4, 144.3, 131.0, 126.9, 113.9, 62.0, 47.7, 13.9. Anal. Calcd for $C_{21}H_{21}N_2OCl$ (**3**·H_2O): C, 46.29; H, 5.44; N, 7.20. Found: C, 46.08; H, 5.23; N, 6.88.

4.2.4. *N,N′*-Dibenzhydrylbenzimidazolium chloride 4. To a 100 mL flask charged with 1,2-diaminobenzene (1.08 g, 10 mmol) was added 20 mL 30% NaOH(aq) and 1.5% equiv $Bu_4N^+Br^-$ (TBAB) (50 mg, 0.15 mmol) followed by 2.5 equiv benzhydryl chloride (5.0 g, 25 mmol) at room temperature. The mixture was stirred at 55 °C for 8 h before being poured into 50 mL water and extracted with ether (20 mL×3). The ether extracts were dried over Na_2SO_4 and concentrated. The resulting residue was purified by flash chromatography through a short pad of silica gel (eluent: ethyl acetate/petroleum ether=1:50 v/v). Spectroscopically pure *N,N′*-dibenzhydryl-1,2-diaminobenzene was obtained as a yellow powder (2.5 g, 57%). To the yellow powder in 100 mL flask was added 50 mL $HC(OEt)_3$, 0.50 mL HCl(con. aq) and two drops of HCO_2H. The resulting mixture was stirred under nitrogen at 80 °C for 2 h. A white fine powder formed was collected by filtration. Recrystallization of the residue from EtOH gave *N,N′*-dibenzhydrylbenzimidazolium chloride **4**, 2.39 g (86%), mp: 245–247 °C. ^{1}H NMR (DMSO, 25 °C), δ, ppm: 9.15 (1H, s, H2), 7.56–7.60 (6H, m, overlapping), 7.41–7.50 (20H, m, overlapping). ^{13}C NMR (CD_3OD, 25 °C), δ, ppm: 142.1, 136.9, 133.7, 130.7, 130.7, 129.5, 128.6, 116.3, 67.6. Anal. Calcd for $C_{33}H_{27}N_2Cl$: C, 81.38; H, 5.59; N, 5.75. Found: C, 80.88; H, 5.63; N, 5.58.

4.2.5. *N,N′*-Diphenylbenzimidazolium chloride 5. To a 100 mL flask charged with 1,2-diaminobenzene (1.08 g, 10 mmol) in 30 mL DMSO was added 0.2 equiv CuI (0.39 g, 2.0 mmol), 0.4 equiv L-proline (0.46 g, 4.0 mmol), 5 equiv iodobenzene (5.6 mL, 50 mmol) and 4.1 equiv K_2CO_3 (5.7 g, 41 mmol) under nitrogen at room temperature. The mixture was stirred at 80 °C for 18 h before being cooled and poured into 50 mL water and extracted with ethyl acetate (30 mL×3). The extracts were dried with Na_2SO_4 and solvents were removed under reduced pressure. The residue was purified by flash chromatography through a short pad of silica gel (eluent: ethyl acetate/petroleum ether=1:50 v/v). *N,N′*-Diphenyl-1,2-diaminobenzene was obtained as a slight yellow powder containing about 2–3% isomers (0.78 g, 30%). To the powder in 50 mL flask was added 20 mL $HC(OEt)_3$, 0.30 mL HCl(con.) and two drops of HCO_2H. The resulting mixture was stirred under nitrogen at 80 °C for 2 h. After removal of solvents, the slight yellow residue was purified by recrystallization from EtOH to provide slight yellow microcrystals 0.83 g (90%), mp: 241–243 °C (dehydrolyze 127–131 °C). ^{1}H NMR ($CDCl_3$, 25 °C), δ, ppm: 11.19 (1H, s, H2), 8.10 (4H, d, J=7.0 Hz, Ph), 7.79–7.81 (2H, m, H4, H7), 7.62–7.72 (6H, m, Ph), 7.29–7.35 (2, m, H5, H6). ^{13}C NMR ($CDCl_3$), δ, ppm: 141.9, 132.8, 131.6, 131.1, 130.7, 128.3, 125.5, 114.1. Anal. Calcd for $C_{19}H_{17}N_2ClO$ (**5**·H_2O): C, 70.26; H, 5.28; N, 8.62. Found: C, 69.80; H, 5.05; N, 8.46.

4.3. General procedure for Suzuki coupling of aromatic halides with arylboronic acids

Under an atmosphere of nitrogen to a 25 mL Schlenk flask charged with 1.0 mmol arylhalide, 1.1–1.2 mmol arylboronic acid and a base (3 equiv) in DMF (10 mL)–H_2O (0.5 mL) were added stock solutions of $PdCl_2$ and benzimidazolium salts in DMF, respectively. The flask was placed and stirred in an oil bath at the temperature as required. The progress of the reactions was monitored by TLC or GC. After be cooled to room temperature, the mixture was poured into water and extracted with ether. Removal of solvents gave the crude products, which were purified either by flash chromatography or by recrystallization.

4.4. Data for biaryls

4.4.1. 4-Acetylbiphenyl. Mp: 121–123 °C (lit.[17] 120–121 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 8.00 (2H, d, J=8.3 Hz), 7.69 (2H, d, J=8.3 Hz), 7.63 (2H, dd, J_1=7.2 Hz, J_2=1.1 Hz), 7.46 (2H, t, J=7.5 Hz), 7.39 (1H,

t, 7.3 Hz), 2.62 (s, 3H, $COCH_3$. EI-MS: *m/z* (relative intensity) 196 (99%, M^+), 181 (100%).

4.4.2. 4-Methylbiphenyl. Mp: 48–50 °C (lit.[18] 44–46 °C, 49–50 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 7.58 (2H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 7.50 (2H, d, $J=$ 7.5 Hz), 7.38–7.44 (2H, m), 7.29–7.33 (1H, m), 7.24 (2H, d, $J=8.0$ Hz), 2.38 (s, 3H, CH_3). EI-MS: *m/z* (relative intensity) 168 (100%, M^+).

4.4.3. Biphenyl. Mp: 69–70 °C (lit.[18b] 69–72 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 7.60 (4H, dd, $J_1=$ 7.5 Hz, $J_2=1.0$ Hz), 7.42–7.46 (4H, m), 7.32–7.36 (2H, m). EI-MS: *m/z* (relative intensity) 154 (100%, M^+).

4.4.4. 4-Nitrobiphenyl. Mp: 112–113 °C (lit.[17,19] 102–103 °C, 114–114.5 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 8.29 (2H, d, $J=8.5$ Hz), 7.93 (2H, d, $J=8.5$ Hz), 7.62 (2H, d, $J=7.5$ Hz), 7.49 (2H, t, $J=7.5$ Hz), 7.44 (1H, t, $J=7.5$ Hz). EI-MS: *m/z* (relative intensity) 199 (99%, M^+), 169 (59%), 152 (100%).

4.4.5. 1,4-Diphenyl-2,5-dimethylbenzene. Mp: 180–182 °C (lit.[20] 180 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 7.38–7.44 (4H, m), 7.31–7.36 (6H, m), 7.15 (2H, s), 2.27 (6H, s, CH_3). EI-MS: *m/z* (relative intensity) 258 (100%, M^+).

4.4.6. 1-Phenyl-2,4,6-trimethylbenzene.[21] Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 7.35–7.50 (2H, m), 7.30–7.35 (1H, m), 7.15 (2H, d, $J=7.5$ Hz), 6.95 (2H, s), 2.33 (3H, s), 2.00 (6H, s). EI-MS: *m/z* (relative intensity): 196 (98%, M^+), 181 (100%).

4.4.7. 2-Methylbiphenyl.[22] Slight yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 7.35–7.40 (2H, m), 7.26–7.33 (3H, m), 7.20–7.25 (4H, m), 2.25 (3H, s, CH_3). EI-MS: *m/z* (relative intensity) 168 (100%, M^+).

4.4.8. 4-Methoxybiphenyl. Mp: 87–88 °C (lit.[18a,23] 83–84 °C, 87 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C), δ, ppm: 7.52–7.56 (4H, m), 7.35–7.50 (2H, m), 7.30 (1H, t, $J=$ 7.5 Hz), 7.00 (2H, d, $J=8.5$ Hz), 3.85 (3H, s, CH_3O). EI-MS: *m/z* (relative intensity) 184 (84%, M^+), 169 (53%), 141 (88%), 115 (100%).

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Use of tetrahydropyrimidinium salts for highly efficient palladium-catalyzed cross-coupling reactions of aryl bromides and chlorides

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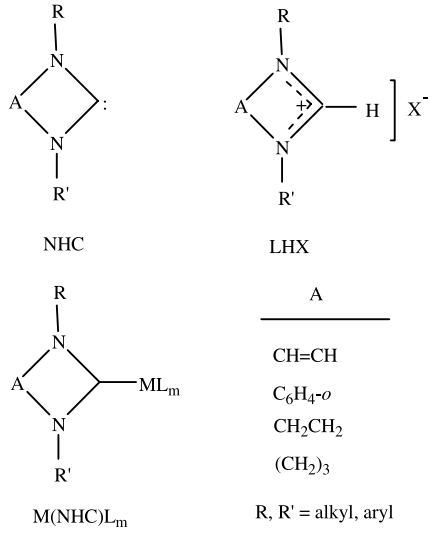
Abstract—New, sterically demanding 1,3-dialkyl-3,4,5,6-tetrahydropyrimidinium salts (**2**) as NHC precursors have been synthesized and characterized. These salts, in combination with palladium acetate, provided active catalysts for the cross-coupling of aryl chlorides and bromides under mild conditions. The catalytic system was applied to the Heck, Suzuki and benzaldehyde (Kumada) coupling reactions. Catalyst activity was found to be influenced by the presence of a methoxy group on the ring of the *p*-position of benzyl substituent of the ligand precursor.

1. Introduction

Transition metal complexes incorporating 1,3-diorganyl *N*-heterocyclic carbene (NHC) ligands, such as imidazol-2-ylidene (A=CH=CH), imidazolidin-2-ylidene (A=CH_2CH_2) and benzimidazol-2-ylidene (A=C_6H_4-*o*) have attracted a great interest in recent years.[1–6] They are often synthesized by reaction of an azolinium salt (LHX) with a basic salt such as $Pd(OAc)_2$, to give M(NHC)Lm.



Research in this area was principally driven by the employment of these complexes as potential catalysts. Many catalytic applications of NHC complexes have been described.[7–9] Palladium-catalyzed cross-coupling reactions are particularly attractive because of their versatility in the formation of C–C and C–X bonds (X=O, S, N etc.).[10–13] The main advantages of these coupling processes stems from the readily availability of starting materials and the broad tolerance of palladium catalysts to various functional groups. Pd-catalyzed cross-coupling reactions are generally thought to proceed through three distinctive steps:[14] (i) an aryl halide reacts with Pd(0) through oxidative addition to give an electrophilic Pd(II) species. (ii) A transmetallation reaction then occurs with an appropriate nucleophile to yield a Pd(II) complex, containing the two moieties to be coupled. (iii) Reductive elimination of the product, which regenerates the active Pd(0) species.

The ancillary ligand (NHC) coordinated to the metal center has a number of important roles in homogeneous catalysis such as providing a stabilizing effect and governing the activity and selectivity through alteration of the steric and electronic parameters. The number, nature and position of the substituents on the nitrogen atom(s) and/or NHC ring have been found to play a crucial role in tuning the catalytic activity. Whilst modifications to the five-membered ring of the ligand aryl substituent have been described, relatively little attention has been paid to the effect of the ring size.[15] For the present study, we selected 3,4,5,6-tetrahydopyrimidin-2-ylidene precursors (**2**). This choice was guided by several considerations. An important characteristic of the carbene ligands in active complexes is their strong-electron

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donating effect, primarily a σ-effect. We have previously reported the use of a in situ formed imidazolidin-2-ylidenepalladium(II) system, which exhibits high activity in various coupling reactions of aryl bromides and aryl chlorides.[16] In order to obtain a more stable, efficient and active system, we have also investigated benzo-annelated derivatives.[17] Due to their six-membered ring geometry, tetrahydopyrimidine-2-ylidenes are stronger σ-donating ligands in comparison to their five-membered relatives.[15]

2. Results and discussion

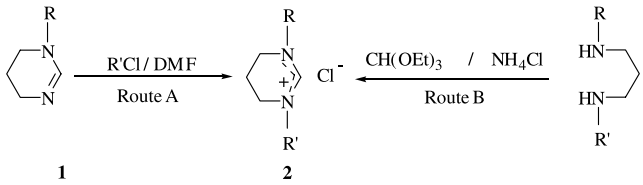
2.1. Synthesis and characterization of the salts, 2

The synthesis of the tetrahydropyrimidinium chlorides was achieved via two synthetic routes (Scheme 1). The alkylation of 1-alkyltetrahydropyrimidine derivatives[18] with alkyl chlorides produced symmetrical or unsymmetrical 1,3-dialkylpyrimidinium salts (Route A). On the other hand, reaction of *N*,*N*′-dialkylpropan-1,3-diamine with triethyl orthoformate and ammonium chloride yielded the symmetrical tetrahydropyrimidinium salt (Route B) (Scheme 1).

Elemental analysis and ^{1}H and ^{13}C NMR spectra confirmed the formation of **2** (see Section 4). An important feature of the ligand precursors (**2**) is their facile preparation. While these studies were in progress, other workers have addressed the synthesis and catalytic properties of 1,3-dimesityltetrahydropyrimidine-2-ylidene complexes of palladium.[19,20] Contrary to the claims made by Buchmeister and co-workers,[19a] and unlike other silver NHC complexes, it has been reported that the chlorodimesityltetrahydrpyrimidin-2-ylidenesilver does not transfer the carbene ligand to $Pd(NCCH_3)_2Cl_2$ to afford $Pd(NHC)_2Cl_2$.[20]

2.2. The Heck reaction

The Heck alkenylation reaction[21] is useful approach to the preparation of disubstituted olefins. The rate of coupling is dependent on a variety of parameters such as temperature, solvent, base and catalyst loading. Generally, Heck reactions conducted with tertiary phosphine[22] or NHC[9,23] complexes require high temperatures (higher than 120 °C) and polar solvents. For the choice of base, we chose to use Cs_2CO_3, K_2CO_3, and K_3PO_4. Finally, use of 1.5% mol $Pd(OAc)_2$, 3% mol **2**, 2 equiv Cs_2CO_3 in DMF/H_2O (1:1) at 50 °C led to the best conversion within 5 h. We initially evaluated the catalytic activity of $Pd(OAc)_2$/**2a** for the coupling of bromobenzene with styrene (Table 1, entry 1).



2a R = R′ = $CH_2C_6H_2(CH_3)_3$-2,4,6

2b R = R′ = $CH_2C_6H_2(OCH_3)_3$-2,4,6

2c R = R′ = $CH_2C_6H_2(OCH_3)_3$-3,4,5

2d R = C_6H_{11}; R′ = $CH_2C_6H_2(CH_3)_3$-2,4,6

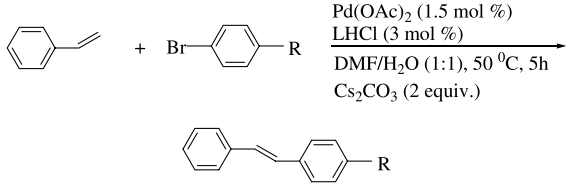
2e R = $CH_2CH_2OCH_3$; R′ = $CH_2C_6H_2(CH_3)_3$-2,4,6

Scheme 1. Synthesis of ligand precursors.

Control experiments indicate that the coupling reaction did not occur in the absence of **2a**. Under these reaction conditions a wide range of aryl bromides bearing electron-donating or electron-withdrawing groups react with styrene affording the coupled products in excellent yields. As expected, electron-deficient bromides coupled well under the conditions. Enhancement in activity, although less significant, is further observed employing 4-bromobenzaldehyde instead of 4-bromoacetophenone (entries 16–20 and 21–25, respectively).

A systematic study on the substituent effect in the tetrahydropyrimidinium salts **2** indicated that the introduction of a methoxy group to the *p*-position of the benzyl substituent on the *N*-atoms notably increased the reaction rate and the yield of the coupled product. The catalytic activity of the salts used fall in the order of **c**>**b**>**d**>**a**>**e**. The ether functionality in **2e** does not contribute with any great effect as seen with the arylation of benzaldehyde derivatives (see Section 2.4). These results indicated that the catalytic system generated in situ from tetrahydropyrimidinium salts and $Pd(OAc)_2$ have an activity, which is superior

Table 1. Pd-catalyzed Heck coupling



Entry	LHCl	R	Yield (%)[a–c]
1	**2a**	H	80
2	**2b**	H	88
3	**2c**	H	89
4	**2d**	H	85
5	**2e**	H	78
6	**2a**	OCH_3	88
7	**2b**	OCH_3	87
8	**2c**	OCH_3	88
9	**2d**	OCH_3	90
10	**2e**	OCH_3	80
11	**2a**	CH_3	84
12	**2b**	CH_3	90
13	**2c**	CH_3	92
14	**2d**	CH_3	83
15	**2e**	CH_3	80
16	**2a**	$COCH_3$	90
17	**2b**	$COCH_3$	88
18	**2c**	$COCH_3$	92
19	**2d**	$COCH_3$	85
20	**2e**	$COCH_3$	84
21	**2a**	CHO	91
22	**2b**	CHO	94
23	**2c**	CHO	96
24	**2d**	CHO	87
25	**2e**	CHO	85

[a] Reaction conditions: 1.0 mmol of R-C_6H_4X-*p*, 1.5 mmol of styrene, 2 mmol Cs_2CO_3, 1.50 mmol% $Pd(OAc)_2$, 3.0 mmol% **2**, water (3 mL)-DMF (3 mL).

[b] The purity of the products were confirmed by NMR and yields are based on aryl bromide.

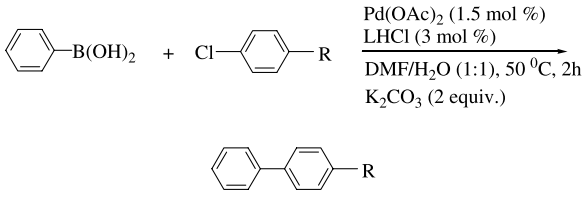
[c] 50 °C, 5 h.

or comparable to the imidazolinium/$Pd(OAc)_2$ system.[16] However, chloroarenes do not react under standard conditions; yields of <5% were recorded.

2.3. The Suzuki coupling

Suzuki cross-coupling represents a powerful method for carbon–carbon bond formation.[24] Recently, the reaction of aryl chlorides catalyzed by palladium/tertiary phosphine[22] and palladium/NHC[25–28] systems have been extensively studied due to the economically attractive nature of the starting materials and the production of the less toxic salt by-products, for example, NaCl as opposed to NaBr. Here, various tetrahydropyrimidinium salts (**2a–e**) were compared as ligand precursors under the same reaction conditions. To survey the parameters for Suzuki coupling, we chose to examine Cs_2CO_3, K_2CO_3, and K_3PO_4 as base and DMF/H_2O (1:1) and dioxane as the solvent mixture. We found that the reactions performed in DMF/H_2O (1:1) with Cs_2CO_3 or K_2CO_3 at 50 °C appeared to be best. We initiated our investigation with coupling of chlorobenzene and phenylboronic acid, in the presence of $Pd(OAc)_2$/**2**. Table 2 summarizes the results obtained in the presence of **2a–e** (Table 2, entries 1–5).

Table 2. Pd-catalyzed Suzuki coupling



Entry	LHCl	R	Yield (%)[a–d]
1	**2a**	H	93
2	**2b**	H	89
3	**2c**	H	93
4	**2d**	H	85
5	**2e**	H	81
6	**2a**	OCH_3	88
7	**2b**	OCH_3	90
8	**2c**	OCH_3	92
9	**2d**	OCH_3	87
10	**2e**	OCH_3	72
11	**2a**	CH_3	87
12	**2b**	CH_3	91
13	**2c**	CH_3	94
14	**2d**	CH_3	85
15	**2e**	CH_3	83
16	**2a**	$COCH_3$	96
17	**2b**	$COCH_3$	96
18	**2c**	$COCH_3$	98
19	**2d**	$COCH_3$	94
20	**2e**	$COCH_3$	91
21	**2a**	CHO	94
22	**2b**	CHO	94
23	**2c**	CHO	95
24	**2d**	CHO	90
25	**2e**	CHO	84

[a] Reactions conditions: 1.0 mmol of R-C_6H_4Cl-*p*, 1.2 mmol of phenylboronic acid, 2 mmol K_2CO_3, 1.5 mmol% $Pd(OAc)_2$, 3 mmol% **2**, water (3 mL)–DMF (3 mL).
[b] The purity of the products was confirmed by NMR and yields are based on aryl chloride.
[c] All reactions were monitored by GC.
[d] 50 °C, 2 h.

The scope of the reaction with respect to the aryl chloride component was also investigated. It can be seen that **2c** is an effective ligand precursor for the coupling of unactivated, activated and deactivated chlorides (entries 1–25). With chlorobenzene, 4-chloroanisole, 4-chloroacetophenone and 4-chlorobenzaldehyde, a similar activity sequence was observed: **c** > **b** > **d** > **a** > **e**.

In summary, we have demonstrated that in situ generated tetrahydropyrimidin-2-ylidene complexes of palladium are effective catalyst systems for Suzuki cross-coupling, surpassing the catalytic activity observed with the corresponding imidazolidin-2-ylidene palladium complexes.

2.4. Arylation of benzaldehyde derivatives

Another interesting cross-coupling process (Miura reaction) is palladium-catalyzed *o*-arylation(s) of benzaldehyde derivatives with aryl halides providing 2- or 2,6-diarylbenzaldehydes.[29] Using similar reaction conditions, we investigated the arylation of benzaldehyde derivatives using in situ generated palladium complexes of tetrahydropyrimidine-2-ylidene derived from **2**. The results are summarized in Table 3.

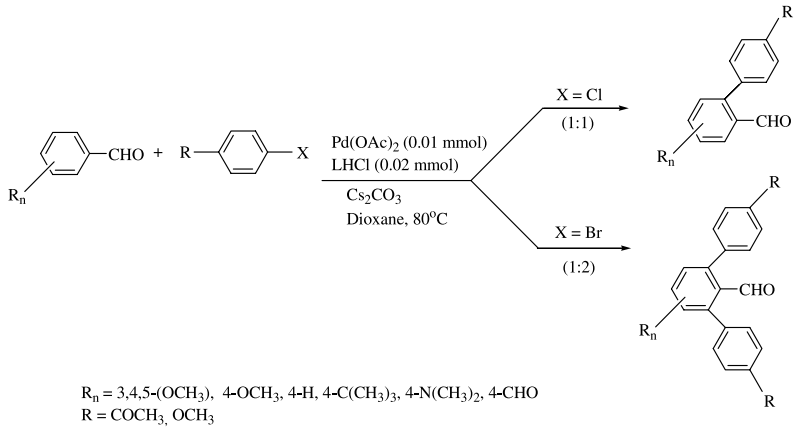
Here, **2e** is one of the best ligand precursors for the reaction of aryl chlorides. The use of cesium carbonate as the base in dioxane produced good to excellent yields of the corresponding products. The selectivity for mono- or di-arylation can be shifted to some extent by judicious choice of halide X, that is, for X=Cl, only the monoarylated product is seen; whereas for X=Br; the 2,6-diarylated product is formed predominantly when the aldehyde/aryl bromide ratio is 1:2.

3. Conclusions

We have shown that amongst the various saturated NHC precursors, tetrahydopyrimidinium salts (**2**) are excellent ligand precursors for the direct functionalization of aryl halides, in particular, aryl chlorides. The Heck, Suzuki and a variant of the Miura reaction of aryl bromides and chlorides have been investigated in the presence of a $Pd(OAc)_2$/**2** catalyst system. The cross-coupling results obtained using the $Pd(OAc)_2$/**2** mixture do not necessarily indicate a palladium carbene complex as the active catalyst species. Good to excellent yields of the desired products were obtained for the benchmark reactions in this study. In general, the **2c** catalyst system appears to be more efficient for the Heck reactions of aryl bromides; the activity is lower for the coupling of aryl chlorides. On the other hand, the catalyst **2e** work well in a version of Miura coupling of aryl chlorides.

Clearly, 1,3-dialkyltetrahydropyrimidin-2-ylidene palladium complexes are superior when compared to the corresponding 1,3-dialkylimidazolidin-2-ylidene palladium complexes. Once again, we observed that the in situ formed Pd–NHC catalysts, which consist of mixtures of palladium and ligands, gave better yields in the coupling reactions compared to the isolated carbene palladium(II) complexes.

Table 3. Arylation of benzaldehyde derivatives



R_n = 3,4,5-(OCH_3), 4-OCH_3, 4-H, 4-$C(CH_3)_3$, 4-$N(CH_3)_2$, 4-CHO
R = $COCH_3$, OCH_3

Entry	Ar–X	Aldehyde	Product	LHCl	Time (h)	Yield[a–d] (%)
1	4-(CH_3CO)–C_6H_4–	3,4,5-Trimethoxy benzaldehyde	2-(*p*-Acetylphenyl)-3,4,5-(trimethoxy)benzaldehyde	**2a**	5	89
2	4-(CH_3CO)–C_6H_4–			**2b**	5	92
3	4-(CH_3CO)–C_6H_4–			**2c**	5	86
4	4-(CH_3CO)–C_6H_4–			**2d**	5	96
5	4-(CH_3CO)–C_6H_4–			**2e**	5	93
6	4-(CH_3O)–C_6H_4–	3,4,5-Trimethoxy benzaldehyde	2-(*p*-Methoxyphenyl)-3,4,5-(trimethoxy)benzaldehyde	**2a**	5	90
7	4-(CH_3O)–C_6H_4–			**2b**	24	87
8	4-(CH_3O)–C_6H_4–			**2c**	20	93
9	4-(CH_3O)–C_6H_4–			**2d**	24	84
10	4-(CH_3O)–C_6H_4–			**2e**	24	89
11	4-(CH_3O)–C_6H_4–	*p*-Methoxy benzaldehyde	2-(*p*-Methoxyphenyl)-4-methoxybenzaldehyde	**2a**	20	95
12	4-(CH_3O)–C_6H_4–			**2b**	24	87
13	4-(CH_3O)–C_6H_4–			**2c**	24	91
14	4-(CH_3O)–C_6H_4–			**2d**	24	93
15	4-(CH_3O)–C_6H_4–			**2e**	24	97
16	4-(CH_3CO)–C_6H_4–	*p*-Methoxy benzaldehyde	2-(*p*-Acetylphenyl)-4-methoxybenzaldehyde	**2a**	10	90
17	4-(CH_3CO)–C_6H_4–			**2b**	10	92
18	4-(CH_3CO)–C_6H_4–			**2c**	10	89
19	4-(CH_3CO)–C_6H_4–			**2d**	10	95
20	4-(CH_3CO)–C_6H_4–			**2e**	10	97
21	4-(CH_3O)–C_6H_4–	Benzaldehyde	2-(*p*-Methoxyphenyl) benzaldehyde	**2a**	24	76
22	4-(CH_3O)–C_6H_4–			**2b**	24	79
23	4-(CH_3O)–C_6H_4–			**2c**	24	83
24	4-(CH_3O)–C_6H_4–			**2d**	24	78
25	4-(CH_3O)–C_6H_4–			**2e**	24	84
26	4-(CH_3CO)–C_6H_4–	*p*-(*tert*-Butyl) benzaldehyde	2-(*p*-Acetylphenyl)-4-*tert*-butylbenzaldehyde	**2a**	10	83
27	4-(CH_3CO)–C_6H_4–			**2b**	10	77
28	4-(CH_3CO)–C_6H_4–			**2c**	10	82
29	4-(CH_3CO)–C_6H_4–			**2d**	10	86
30	4-(CH_3CO)–C_6H_4–			**2e**	10	85
31	4-(CH_3O)–C_6H_4–	*p*-(*tert*-Butyl) benzaldehyde	2-(*p*-Methoxyphenyl)-4-*tert*-butylbenzaldehyde	**2a**	15	90
32	4-(CH_3O)–C_6H_4–			**2b**	24	89
33	4-(CH_3O)–C_6H_4–			**2c**	24	82
34	4-(CH_3O)–C_6H_4–			**2d**	24	86
35	4-(CH_3O)–C_6H_4–			**2e**	15	92
36	4-(CH_3CO)–C_6H_4–	*p*-Dimethylaminobenzaldehyde	2-(*p*-Acetylphenyl)-4-dimethylamino benzaldehyde	**2a**	5	88
37	4-(CH_3CO)–C_6H_4–			**2b**	5	88
38	4-(CH_3CO)–C_6H_4–			**2c**	5	91
39	4-(CH_3CO)–C_6H_4–			**2d**	5	95
40	4-(CH_3CO)–C_6H_4–			**2e**	5	98
41	4-(CH_3O)–C_6H_4–	*p*-Dimethylaminobenzaldehyde	2-(*p*-Methoxyphenyl)-4-dimethylamino benzaldehyde	**2a**	28	79
42	4-(CH_3O)–C_6H_4–			**2b**	28	70
43	4-(CH_3O)–C_6H_4–			**2c**	28	74
44	4-(CH_3O)–C_6H_4–			**2d**	36	74
45	4-(CH_3O)–C_6H_4–			**2e**	36	81
46	4-(CH_3O)–C_6H_4–	*p*-Methoxy benzaldehyde	2,6-Bis(*p*-methoxyphenyl)-4-methoxybenzaldehyde	**2a**	12	90
47	4-(CH_3O)–C_6H_4–			**2b**	12	85
48	4-(CH_3O)–C_6H_4–			**2c**	12	80
49	4-(CH_3O)–C_6H_4–			**2d**	12	83
50	4-(CH_3O)–C_6H_4–			**2e**	12	92

Table 3 (*continued*)

Entry	Ar–X	Aldehyde	Product	LHCl	Time (h)	Yield[a–d] (%)
51	4-(CH_3O)–C_6H_4–			**2a**	12	86
52	4-(CH_3O)–C_6H_4–		2,6-Bis(*p*-methoxyphe-	**2b**	12	80
53	4-(CH_3O)–C_6H_4–	*p*-Dimethylami-nobenzaldehyde	nyl)-4-dimethylamino	**2c**	12	89
54	4-(CH_3O)–C_6H_4–		benzaldehyde	**2d**	12	85
55	4-(CH_3O)–C_6H_4–			**2e**	12	91
56	4-(CH_3O)–C_6H_4–			**2a**	12	83
57	4-(CH_3O)–C_6H_4–		2,6-Bis(*p*-methoxyphe-	**2b**	12	85
58	4-(CH_3O)–C_6H_4–	*p*-(*tert*-Butyl) benzaldehyde	nyl)-4-*tert*-butylbenzalde-	**2c**	12	87
59	4-(CH_3O)–C_6H_4–		hyde	**2d**	12	82
60	4-(CH_3O)–C_6H_4–			**2e**	12	88
61	4-(CH_3O)–C_6H_4–	Terephtalaldehyde	2,5-Bis(*p*-methoxyphe- nyl) terephtalaldehyde	**2e**	12	91

[a] For entries 46–61, aryl bromides (2 equiv) were used as aryl halide. In all other cases aryl chlorides were used.
[b] Reactions conditions: 1.0 mmol of R–C_6H_4Cl-*p*, 1.0 mmol of aldehyde, 2 mmol Cs_2CO_3, 1.0 mmol% $Pd(OAc)_2$, 2 mmol% 1,3-dialkyl pyrimidinium salt **2**, dioxane (3 mL), 80 °C.
[c] The purity of the products was confirmed by NMR and yields are based on aldehyde.
[d] All reactions were monitored by TLC.

4. Experimental

4.1. General

All reactions for the preparation of 1,3-dialkylpyrimidinium salts were carried out under argon using standard Schlenk flasks. Test reactions for the catalytic activity of palladium catalysts in the Suzuki and Heck cross-coupling reactions were carried out in the presence of air. All reagents were purchased from Aldrich Chemical Co. The solvents, Et_2O over Na, DMF over BaO, EtOH over Mg were distilled prior to use. All ^1H and ^{13}C NMR spectra were performed in $CDCl_3$. ^1H and ^{13}C NMR spectra were recorded using a Bruker AC300P FT spectrometer operating at 300.13 MHz (^1H), 75.47 MHz (^{13}C). Chemical shifts (δ) are given in ppm relative to TMS; coupling constants (J) in Hz. FT-IR spectra were recorded on a Mattson 1000 spectrophotometer, wave numbers in cm^{-1}. Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus and uncorrected. Elemental analyses were performed by TUBITAK (Ankara, Turkey) Microlab.

4.1.1. Preparation of 1,3-bis(2,4,6-trimethylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride (2a). A mixture of *N*,*N*′-bis(2,4,6-trimethylbenzyl)propane (3.38 g, 10.0 mmol), NH_4Cl (0.53 g, 10.0 mmol) in triethyl orthoformate (50 mL) was heated in a distillation apparatus until the distillation of ethanol ceased. The temperature of the reaction mixture reached 110 °C. Upon cooling to rt, a colorless solid precipitated, which was collected by filtration, and dried in vacuum. The crude product was recrystallized from absolute ethanol to give colorless needles, and the solid was washed with diethyl ether (2×10 mL), dried under vacuum, and the yield was 3.77 g (98%). Mp 288–289 °C, $\nu_{(CN)}$= 1688 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ 8.56 (s, 1H, NC*H*N), 6.73 (s, 4H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 4.74 (s, 4H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 3.36 (t, J=5.7 Hz, 4H, $NCH_2CH_2CH_2N$), 2.16 and 2.20 (s, 18H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 2.01 (quint, J=5.3 Hz, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 151.9 (N*C*HN), 125.3, 130.0, 137.9 and 138.9 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 52.1 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 42.6 ($NCH_2CH_2CH_2N$), 19.8 and 20.9 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 19.1 ($NCH_2CH_2CH_2N$). Anal. Calcd for $C_{24}H_{33}N_2Cl$: C, 74.87; H, 8.64; N, 7.27. Found: C, 74.83; H, 8.66; N, 7.30.

4.1.2. Preparation of 1,3-bis(2,4,6-trimethoxybenzyl)-3,4,5,6-tetrahydropyrimidinium chloride (2b). Compound **2b** was prepared in the same way as **2a** from *N*,*N*′-bis(2,4,6-trimethoxybenzyl)propane (4.34 g, 10 mmol), NH_4Cl (0.53 g, 10 mmol) in triethyl orthoformate (50 mL) to give white crystals of **2b** 4.27 g (89%). Mp 233–234 °C, $\nu_{(CN)}$= 1682 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ 7.82 (s, 1H, NC*H*N), 6.03 (s, 4H, $CH_2C_6H_2(OCH_3)_3$-2,4,6), 4.46 (s, 4H, $CH_2C_6H_2(OCH_3)_3$-2,4,6), 3.69 and 3.75 (s, 18H, $CH_2C_6H_2(OCH_3)_3$-2,4,6), 3.32 (t, J=5.6 Hz, 4H, $NCH_2CH_2CH_2N$), 1.96 (quint, J=5.2 Hz, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 162.7 (N*C*HN), 90.8, 101.7, 151.8 and 159.9 ($CH_2C_6H_2(OCH_3)_3$-2,4,6), 58.1 ($CH_2C_6H_2(OCH_3)_3$-2,4,6), 55.7 and 56.1 ($CH_2C_6H_2(OCH_3)_3$-2,4,6), 43.3 ($NCH_2CH_2CH_2N$), 19.4 ($NCH_2CH_2CH_2N$). Anal. Calcd for $C_{24}H_{33}N_2O_6Cl$: C, 59.93; H, 6.91; N, 5.82. Found: C, 59.89; H, 6.94; N, 5.80.

4.1.3. Preparation of 1,3-bis(3,4,5-trimethoxybenzyl)-3,4,5,6-tetrahydropyrimidinium chloride (2c). Compound **2c** was prepared in the same way as **2a** from *N*,*N*′-bis(3,4,5-trimethoxybenzyl)propane (4.34 g, 10 mmol), NH_4Cl (0.53 g, 10 mmol) in triethyl orthoformate (50 mL) to give white crystals of **2c** 4.51 g (94%). Mp 266–267 °C, $\nu_{(CN)}$= 1701 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ 10.43 (s, 1H, NC*H*N), 6.72 (s, 4H, $CH_2C_6H_2(OCH_3)_3$-3,4,5), 4.75 (s, 4H, $CH_2C_6H_2(OCH_3)_3$-3,4,5), 3.76 and 3.81 (s, 18H, $CH_2C_6H_2(OCH_3)_3$-3,4,5), 3.21 (t, J=5.2 Hz, 4H, $NCH_2CH_2CH_2N$), 1.93 (quint, J=5.2 Hz, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 154.7 (N*C*HN), 106.6, 129.0, 138.7 and 153.9 ($CH_2C_6H_2(OCH_3)_3$-3,4,5), 61.0 ($CH_2C_6H_2(OCH_3)_3$-3,4,5), 56.8 and 59.0 ($CH_2C_6H_2(OCH_3)_3$-3,4,5), 42.0 ($NCH_2CH_2CH_2N$), 19.3 ($NCH_2CH_2CH_2N$). Anal. Calcd for $C_{24}H_{33}N_2O_6Cl$: C, 59.93; H, 6.91; N, 5.82. Found: C, 59.95; H, 6.90; N, 5.84.

4.1.4. Preparation of 1-(2,4,6-trimethylbenzyl)-3-cyclohexyl-(3,4,5,6-tetrahydropyrimidinium chloride (2d). To a solution of 1-cyclohexyl(3,4,5,6-tetrahydropyrimidine) (1.66 g, 10 mmol) in DMF (10 mL) was added slowly 2,4,6-trimethylbenzyl chloride (1.68 g, 10.1 mmol) at 25 °C

and the resulting mixture was stirred at rt for 5 h. Diethyl ether (15 mL) was added to obtain a white crystalline solid, which was filtered off. The solid was washed with diethyl ether (3×15 mL), dried under vacuum, and the yield was 3.07 g (92%). Mp 210–211 °C. $\nu_{(CN)}=1682\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.50 (s, 1H, NC*H*N), 6.60 (s, 4H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 4.81 (s, 4H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 3.50 (quint, $J=8.2$ Hz, 1H, NC*H*$(CH_2)_4CH_2$), 3.19 and 2.87 (t, $J=5.6$ Hz, 4H, $NCH_2CH_2CH_2N$), 2.01 and 2.07 (s, 9H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 1.39 (m, 10H, $NCH(CH_2)_4CH_2$), 1.79 (quint, $J=5.3$ Hz, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 153.0 (N*C*HN), 125.6, 129.7, 137.9 and 138.5 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 64.0 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 51.9 ($NCH(CH_2)_4CH_2$), 40.2 and 41.2 ($NCH_2CH_2CH_2N$), 24.5, 24.9 and 30.8 ($NCH(CH_2)_4CH_2$), 20.2 and 20.8 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 19.2 ($NCH_2CH_2CH_2N$). Anal. Calcd for $C_{20}H_{31}N_2Cl$: C, 71.72; H, 9.33; N, 8.36. Found: C, 71.71; H, 9.35; N, 8.40.

4.1.5. Preparation of 1-methoxyethyl-3-(2,4,6-trimethylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride (2e). Compound **2e** was prepared in the same way as **2d** from 1-methoxyethyl(3,4,5,6-tetrahydropyrimidine) (1.42 g, 10 mmol) and 2,4,6-trimethylbenzyl chloride (1.68 g, 10.1 mmol) to give white crystals of **2e** 2.69 g (87%). Mp 118–119 °C, $\nu_{(CN)}=1688\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.26 (s, 1H, NC*H*N), 6.80 (s, 4H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 4.84 (s, 4H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 3.26 (s, 3H, $CH_2CH_2OCH_3$), 3.77 (t, $J=4.5$ Hz, 2H, $CH_2CH_2OCH_3$), 3.49 (t, $J=4.7$ Hz, 2H, $CH_2CH_2OCH_3$), 3.12 and 3.36 (t, $J=5.7$ Hz, 4H, $NCH_2CH_2CH_2N$), 2.19 and 2.25 (s, 9H, $CH_2C_6H_2(CH_3)_3$-2,4,6), 2.00 (quint, $J=5.6$ Hz, 2H, $NCH_2CH_2CH_2N$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 153.9 (N*C*HN), 125.2, 129.7, 138.0 and 138.9 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 69.1 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 58.8 ($CH_2CH_2OCH_3$), 54.2 ($CH_2CH_2OCH_3$), 52.2 ($CH_2CH_2OCH_3$), 43.9 and 41.3 ($NCH_2CH_2CH_2N$), 19.8 and 20.8 ($CH_2C_6H_2(CH_3)_3$-2,4,6), 19.0 ($NCH_2CH_2CH_2N$). Anal. Calcd for $C_{17}H_{27}N_2OCl$: C, 65.68; H, 8.75; N, 9.01. Found: C, 65.65; H, 8.73; N, 9.00.

4.2. General procedure for the Heck coupling reaction

$Pd(OAc)_2$ (1.0 mmol%), 1,3-dialkyl(3,4,5,6-tetrahydropyrimidinium) chloride, **2** (2 mmol%), aryl chloride (1.0 mmol), styrene (1.5 mmol), C_2CO_3 (2 mmol) and water (3 mL)/DMF (3 mL) were added to a small Schlenk tube and the mixture heated to 50 °C for 5 h. At the conclusion of the reaction, the mixture was cooled, extracted with ethyl acetate/hexane (1:5), filtered through a pad of silica gel with copious washings ether, the filtrate concentrated in vacuo to afford a solid, which was purified by flash chromatography on silica gel. The purity of the compounds was confirmed by NMR spectroscopy and yields are based on the aryl halide.

4.3. General procedure for Suzuki coupling

$Pd(OAc)_2$ (1.5 mmol%), 1,3-dialkyl(3,4,5,6-tetrahydropyrimidinium) chloride, **2** (3 mmol%), aryl chloride (1.0 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2 mmol) and water (3 mL)/DMF (3 mL) were added to a small Schlenk tube and the mixture heated to 50 °C for 2 h. At the conclusion of the reaction, the mixture was cooled, extracted with Et_2O, filtered through a pad of silica gel with copious washings ether, then concentrated in vacuo and purified by flash chromatography on silica gel. The purity of the compounds was confirmed by NMR spectroscopy and yields are based the on aryl halide.

4.4. General procedure for the arylation of benzaldehyde reaction

A dried Schlenk flask equipped with a magnetic stirring bar was charged with the aldehyde (1.0 mmol), aryl chloride (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), 1,3-dialkyl(3,4,5,6-tetrahydropyrimidinium)chloride, **2** (0.02 mmol), Cs_2CO_3 (2.0 mmol) and dioxane (3 mL). After stirring at 80 °C for 5–24 h, the mixture was cooled to rt and then quenched by addition of aqueous 1 N HCl and extracted with diethyl ether. The organic layer was dried over $MgSO_4$, filtered, then concentrated in vacuo and purified by column chromatography on silica gel eluting with ethyl acetate/hexane (1:5). Analysis of the reaction product was carried out by NMR spectroscopy and GC–MS.

4.4.1. 2-(*p*-Acetylphenyl)-3,4,5-(trimethoxy)benzaldehyde. Colourless oil, $\nu_{(C=O)}=1708\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.80 (s, 1H, 2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5C*H*O), 7.85 and 7.48 (d, $J=2.5$ Hz, 4H, 2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO), 7.06 (s, 1H, 2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO), 3.89 and 3.88 (s, 9H, 2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO), 2.54 (s, 3H, 2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 188.9 (2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5*C*HO), 108.2, 121.4, 126.7, 127.2, 127.9, 128.7, 130.1, 132.3, 136.7 and 154.5 (2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO), 194.2 (2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO), 54.1 and 54.6 (2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO), 24.8 (2-C_6H_4(*p*-$COCH_3$)$C_6H(OCH_3)_3$-3,4,5CHO). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.75; H, 5.80.

4.4.2. 2-(*p*-Methoxyphenyl)-3,4,5-(trimethoxy)benzaldehyde. Colourless crystals. Mp 65–66 °C, $\nu_{(C=O)}=1716\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.85 (s, 1H, 2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5C*H*O), 7.21 and 6.79 (d, $J=4.7$ Hz, 4H, 2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO), 7.11 (s, 1H, 2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO), 3.91 and 3.92 (s, 9H, 2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO), 3.76 (s, 3H, 2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 189.2 (2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5*C*HO), 113.7, 123.8, 124.5, 125.1, 127.6, 128.2, 129.0, 130.3, 132.7 and 156.8 (2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO), 54.3 and 54.8 (2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO), 53.7 (2-C_6H_4(*p*-OCH_3)$C_6H(OCH_3)_3$-3,4,5CHO). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.51; H, 6.04.

4.4.3. 2-(*p*-Methoxyphenyl)-4-methoxybenzaldehyde. Colourless oil, $\nu_{(C=O)}=1708\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.88 (s, 1H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)C*H*O), 7.66 and 7.38 (d, $J=4.9$ Hz, 4H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)CHO), 6.81 (m, 3H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)CHO), 3.88 (s, 3H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)CHO), 3.77 (s, 3H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)$_3$CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 188.7 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)*C*HO), 110.8, 111.2, 112.9, 113.8, 124.1,

126.2, 130.0, 131.1, 153.1 and 157.2 (2-C_6H_4(*p*-OCH_3) C_6H_3(*p*-OCH_3)CHO), 54.2 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)CHO), 53.8 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-OCH_3)CHO). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.40; H, 5.80.

4.4.4. 2-(*p*-Acetylphenyl)-4-methoxybenzaldehyde. Colourless needles. Mp 53–54 °C, $\nu_{(C=O)}=1689\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.78 (s, 1H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-OCH_3)C*H*O), 7.87 and 7.62 (d, $J=2.5$ Hz, 4H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-OCH_3)CHO), 7.82 (m, 3H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-OCH_3)CHO), 3.85 (s, 3H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-OCH_3)CHO), 2.55 (s, 3H, 2-C_6H_4(*p*-$COCH_3$) C_6H_3(*p*-OCH_3)$_3$CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 188.7 (2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-OCH_3)*C*HO), 110.1, 123.8, 126.8, 127.4, 128.5, 130.1, 134.8, 138.1 and 155.0 (2-*C*$_6H_4$(*p*-$COCH_3$) *C*$_6H_3$(*p*-OCH_3)CHO), 194.3 (2-C_6H_4(*p*-*C*OCH_3)C_6H_3(*p*-OCH_3) CHO), 54.4 (2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-O*C*H$_3$)CHO), 24.9 (2-C_6H_4(*p*-CO*C*H$_3$)C_6H_3(*p*-OCH_3)CHO). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.60; H, 5.58.

4.4.5. 2-(*p*-Methoxyphenyl)benzaldehyde. Colourless oil, $\nu_{(C=O)}=1688\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 10.03 (s, 1H, 2-C_6H_4(*p*-OCH_3)C_6H_4C*H*O), 7.24 and 6.83 (d, $J=4.8$ Hz, 4H, 2-C_6H_4(*p*-OCH_3)C_6H_4CHO), 7.55 (m, 4H, 2-C_6H_4(*p*-OCH_3)C_6H_4CHO), 3.78 (s, 3H, 2-C_6H_4(*p*-O*C*H$_3$) C_6H_4CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 192.5 (2-C_6H_4(*p*-OCH_3)C_6H_4*C*HO), 114.8, 125.2, 125.9, 126.0, 127.8, 128.3, 129.7, 130.1, 134.2 and 156.8 (2-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_4$CHO), 53.4 (2-C_6H_4(*p*-O*C*H$_3$)C_6H_4CHO). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.25; H, 5.68.

4.4.6. 2-(*p*-Acetylphenyl)-4-*tert*-butylbenzaldehyde. Colourless oil, $\nu_{(C=O)}=1708\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.88 (s, 1H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-C(CH_3)$_3$) C*H*O), 7.74 and 7.46 (d, $J=2.4$ Hz, 4H, 2-*C*$_6H_4$(*p*-$COCH_3$) C_6H_3(*p*-C(CH_3)$_3$)CHO), 7.29 (m, 3H, 2-C_6H_4(*p*-$COCH_3$) *C*$_6H_3$(*p*-C(CH_3)$_3$)CHO), 2.48 (s, 3H, 2-C_6H_4(*p*-CO*C*H$_3$) C_6H_3(*p*-C(CH_3)$_3$)CHO), 1.21 (s, 9H, 2-C_6H_4(*p*-$COCH_3$) C_6H_3(*p*-C(*C*H$_3$)$_3$)CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 190.3 (2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-C(CH_3)$_3$)*C*HO), 108.7, 123.5, 126.9, 127.4, 128.2, 129.4, 131.7, 133.8, 137.2 and 154.7 (2-*C*$_6H_4$(*p*-$COCH_3$)*C*$_6H_3$(*p*-C(CH_3)$_3$)CHO), 193.7 (2-C_6H_4(*p*-*C*OCH_3)C_6H_3(*p*-C(CH_3)$_3$)CHO), 33.7 (2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-*C*(CH_3)$_3$)CHO), 30.8 (2-C_6H_4(*p*-$COCH_3$) C_6H_3(*p*-C(*C*H$_3$)$_3$)CHO), 24.8 (2-C_6H_4(*p*-CO*C*H$_3$)C_6H_3(*p*-C(CH_3)$_3$)CHO). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.36; H, 7.20.

4.4.7. 2-(*p*-Methoxyphenyl)-4-*tert*-butylbenzaldehyde. Pale yellow needles. Mp 74–75 °C, $\nu_{(C=O)}=1722\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.98 (s, 1H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-C(CH_3)$_3$)C*H*O), 7.82 and 7.55 (d, $J=$ 8.8 Hz, 4H, 2-*C*$_6H_4$(*p*-OCH_3)C_6H_3(*p*-C(CH_3)$_3$)CHO), 7.11 (m, 3H, 2-C_6H_4(*p*-OCH_3)*C*$_6H_3$(*p*-C(CH_3)$_3$)CHO), 3.77 (s, 3H, 2-C_6H_4(*p*-O*C*H$_3$)C_6H_3(*p*-C(CH_3)$_3$)CHO), 1.36 (s, 9H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-C(*C*H$_3$)$_3$)CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 191.0 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-C(CH_3)$_3$)*C*HO), 114.2, 124.4, 124.9, 125.5, 128.3, 128.7, 129.1, 130.4, 133.1 and 157.4 (2-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_3$(*p*-C(CH_3)$_3$)CHO), 34.3 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-*C*(CH_3)$_3$) CHO), 30.1 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-C(*C*H$_3$)$_3$)CHO), 54.4 (2-C_6H_4(*p*-O*C*H$_3$)C_6H_3(*p*-C(CH_3)$_3$)CHO). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.53; H, 7.55.

4.4.8. 2-(*p*-Acetylphenyl)-4-dimethylaminobenzaldehyde. Yellow crystals. Mp 59–60 °C, $\nu_{(C=O)}=1689\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.69 (s, 1H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-$(CH_3)_2N$)C*H*O), 7.84 and 7.68 (d, $J=$ 2.4 Hz, 4H, 2-*C*$_6H_4$(*p*-$COCH_3$)C_6H_3(*p*-$(CH_3)_2N$)CHO), 6.89 (m, 3H, 2-C_6H_4(*p*-$COCH_3$)*C*$_6H_3$(*p*-$(CH_3)_2N$)CHO), 2.54 (s, 3H, 2-C_6H_4(*p*-CO*C*H$_3$)C_6H_3(*p*-$(CH_3)_2N$)CHO), 3.02 (s, 6H, 2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-$(CH_3)_2N$)CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 189.2 (2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-$(CH_3)_2N$)*C*HO), 109.9, 124.1, 127.8, 127.9, 128.6, 129.8, 130.8, 134.4, 138.5 and 153.3 (2-*C*$_6H_4$(*p*-$COCH_3$)*C*$_6H_3$(*p*-$(CH_3)_2N$)CHO), 195.7 (2-C_6H_4(*p*-*C*OCH_3) C_6H_3(*p*-$(CH_3)_2N$)CHO), 38.9 (2-C_6H_4(*p*-$COCH_3$)C_6H_3(*p*-(*C*H$_3$)$_2N$)CHO), 25.4 (2-C_6H_4(*p*-CO*C*H$_3$)C_6H_3(*p*-$(CH_3)_2N$) CHO). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.40; H, 6.44; N, 5.20.

4.4.9. 2-(*p*-Methoxyphenyl)-4-dimethylaminobenzaldehyde. Colourless needles. Mp 67–68 °C, $\nu_{(C=O)}=$ 1716 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.72 (s, 1H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-$(CH_3)_2N$)C*H*O), 7.71 and 7.34 (d, $J=4.8$ Hz, 4H, 2-*C*$_6H_4$(*p*-OCH_3)C_6H_3(*p*-$(CH_3)_2N$)CHO), 6.74 (m, 3H, 2-C_6H_4(*p*-OCH_3)*C*$_6H_3$(*p*-$(CH_3)_2N$)CHO), 3.74 (s, 3H, 2-C_6H_4(*p*-O*C*H$_3$)C_6H_3(*p*-$(CH_3)_2N$)CHO), 3.04 (s, 6H, 2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-$(CH_3)_2N$)CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 189.2 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-$(CH_3)_2N$)*C*HO), 110.3, 111.7, 113.6, 114.7, 124.4, 126.6, 130.9, 131.2, 153.2 and 157.6 (2-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_3$(*p*-$(CH_3)_2N$)CHO), 39.1 (2-C_6H_4(*p*-OCH_3)C_6H_3(*p*-(*C*H$_3$)$_2N$) CHO), 54.4 (2-C_6H_4(*p*-O*C*H$_3$)C_6H_3(*p*-$(CH_3)_2N$)CHO). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.25; H, 6.68; N, 5.50.

4.4.10. 2,6-Bis(*p*-methoxyphenyl)-4-methoxybenzaldehyde. Colourless solid. Mp 91–92 °C, $\nu_{(C=O)}=1697\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.87 (s, 1H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-OCH_3)C*H*O), 7.34 and 6.75 (d, $J=2.4$ Hz, 8H, 2,6-*C*$_6H_4$(*p*-OCH_3)C_6H_2(*p*-OCH_3)CHO), 7.83 (s, 2H, 2,6-C_6H_4(*p*-OCH_3)*C*$_6H_2$(*p*-OCH_3)CHO), 3.75 (s, 3H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-O*C*H$_3$)CHO), 3.86 (s, 6H, 2,6-C_6H_4(*p*-O*C*H$_3$)C_6H_2(*p*-OCH_3)$_3$CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 189.7 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-OCH_3)*C*HO), 113.3, 114.7, 126.6, 128.9, 130.9, 131.2, 157.7 and 163.6 (2,6-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_2$(*p*-OCH_3)CHO), 54.3 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-O*C*H$_3$)CHO), 54.5 (2,6-C_6H_4(*p*-O*C*H$_3$) C_6H_2(*p*-OCH_3)CHO). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.86; H, 5.82.

4.4.11. 2,6-Bis(*p*-methoxyphenyl)-4-dimethylaminobenzaldehyde. Pale yellow solid. Mp 108–109 °C, $\nu_{(C=O)}=$ 1708 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.75 (s, 1H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-$(CH_3)_2N$)C*H*O), 7.37 and 6.76 (d, $J=2.4$ Hz, 8H, 2,6-*C*$_6H_4$(*p*-OCH_3)C_6H_2(*p*-$(CH_3)_2N$) CHO), 7.63 (s, 2H, 2,6-C_6H_4(*p*-OCH_3)*C*$_6H_2$(*p*-$(CH_3)_2N$) CHO), 3.77 (s, 6H, 2,6-C_6H_4(*p*-O*C*H$_3$)C_6H_2(*p*-$(CH_3)_2N$) CHO), 3.08 (s, 6H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-(*C*H$_3$)$_2N$) CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 190.2 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-$(CH_3)_2N$)*C*HO), 112.7, 114.8, 125.9, 126.4, 128.7, 130.9, 132.5 and 157.6 (2,6-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_2$

(*p*-(CH_3)$_2$N)CHO), 39.3 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-(*C*H_3)$_2$N)CHO), 54.7 (2,6-C_6H_4(*p*-O*C*H_3)C_6H_2(*p*-(CH_3)$_2$N)CHO). Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.45; H, 6.43; N, 3.84.

4.4.12. 2,6-Bis(*p*-methoxyphenyl)-4-*tert*-butylbenzaldehyde. Colourless solid. Mp 86–87 °C, $\nu_{(C=O)}=1702\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.98 (s, 1H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(CH_3)$_3$)C*H*O), 7.38 and 6.77 (d, J= 2.4 Hz, 8H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(CH_3)$_3$)CHO), 7.54 (s, 2H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(CH_3)$_3$)CHO), 3.84 (s, 6H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(CH_3)$_3$)CHO), 1.36 (s, 9H, 2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(CH_3)$_3$)CHO). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 192.3 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(CH_3)$_3$)*C*HO), 113.1, 115.9, 125.7, 126.2, 129.9, 130.3, 132.4 and 158.9 (2,6-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_2$(*p*-C(CH_3)$_3$)CHO), 35.5 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-*C*(CH_3)$_3$)CHO), 31.3 (2,6-C_6H_4(*p*-OCH_3)C_6H_2(*p*-C(*C*H_3)$_3$)CHO), 55.6 (2,6-C_6H_4(*p*-O*C*H_3)C_6H_2(*p*-C(CH_3)$_3$)CHO). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.20; H, 6.97.

4.4.13. 2,5-Bis(*p*-methoxyphenyl)terephtalaldehyde. Colourless solid. Mp 121–122 °C, $\nu_{(C=O)}=1716\ cm^{-1}$. ^1H NMR (300.13 MHz, $CDCl_3$) δ 10.12 (s, 2H, 2,5-C_6H_4(*p*-OCH_3)C_6H_2(C*H*O)$_2$), 7.42 and 6.90 (d, J=8 Hz, 4H, 2,5-C_6H_4(*p*-OCH_3)C_6H_2(CHO)$_2$), 7.35 and 6.75 (d, J=1.2 Hz, 4H, 2,5-C_6H_4(*p*-OCH_3)C_6H_2(CHO)$_2$), 7.98 (s, 2H, 2,5-C_6H_4(*p*-OCH_3)C_6H_2(CHO)$_2$), 3.79 (s, 6H, 2,5-C_6H_4(*p*-OCH_3)C_6H_2(CHO)$_2$). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 189.5 (2,5-C_6H_4(*p*-OCH_3)C_6H_2(*C*HO)$_2$), 95.1, 113.0, 114.6, 126.6, 128.9, 131.1 and 157.6 (2,5-*C*$_6H_4$(*p*-OCH_3)*C*$_6H_2$(CHO)$_2$), 54.1 (2,5-C_6H_4(*p*-O*C*H_3)C_6H_2(CHO)$_2$). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.32; H, 5.26.

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Asymmetric styrene dimerisation using mixed palladium–indium catalysts

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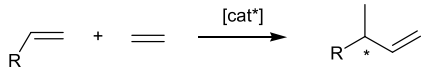
Abstract—Catalysts formed in situ from mixtures of palladium acetate, indium(III) triflate and a chiral non-chelating bis(phosphite) ligand give good to excellent conversions and reasonable enantioselectivity in the asymmetric dimerisation of styrenes.

1. Introduction

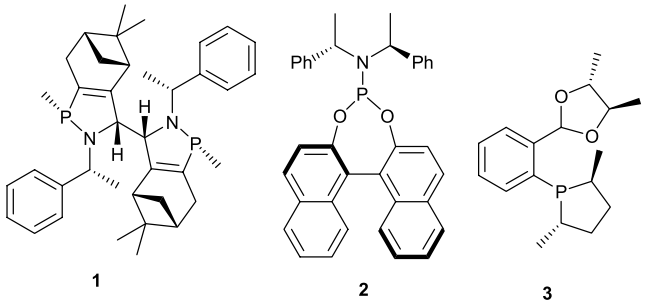
The asymmetric hetero-dimerisation of α-olefins with ethene (Eq. 1)—the asymmetric hydrovinylation reaction—is a well studied and topical area of research.[1,2] It provides access to chiral building-blocks from simple, cheap precursors with 100% atom economy; that is to say that all the atoms of all the starting material are incorporated into the product.



(1)

Typically, the most active and selective catalysts for this class of reaction are nickel based with appropriate chiral ligands.[1] Ligands **1**–**3** are amongst the best ligands yet reported, giving high activities and good to excellent enantioselectivities. The original benchmark was set by Wilke and co-workers who introduced the bis(azaphospholene) ligand **1**, which shows excellent activity and stereoselectivity.[3] Not only does this ligand perform well in classical media, but Leitner and co-workers demonstrated that catalysts containing **1** can be used in super-critical CO_2.[4] Leitner's group has also shown that phosphoramidite ligands such as ligand **2**, introduced by Ferringa and co-workers,[5] are remarkably active and selective.[6] Rajan-Babu and co-workers have extensively investigated the use of a range of chiral monodentate phosphines with secondary hemi-labile functions.[2e] One such ligand—ligand **3**—proves to be particularly effective in the asymmetric hydrovinylation of challenging substrates such as 4-isobutylstyrene.[2b,c]

Chiral palladium catalysts can also be exploited, however, their use is sometimes hampered by the deleterious isomerisation of the desired chiral products to non-chiral internal alkenes.[2a,7]



In contrast with hydrovinylation, the related asymmetric homo-dimerisation of alkenes has been somewhat under-investigated. One example of this class of reaction, which has been explored to a limited extent is the intramolecular cycloisomerisation of 1,6-dienes.[8] Recently, Leitner and co-workers demonstrated that nickel catalysts with appropriate chiral phosphoramidite or azaphospholene ligands could give the *exo*-methylene carbocycle **4** in high regioselectivity and good enantioselectivity from diethyl diallylmalonate (Eq. 2).[9]

Keywords: Palladium; Indium; Catalysis; Styrene; Dimerisation; Hydrovinylation.
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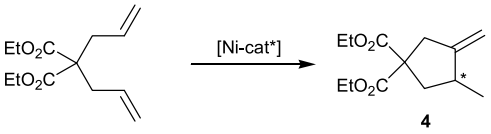
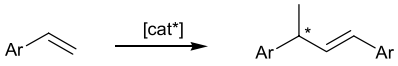


4 (2)

Intermolecular asymmetric alkene dimerisation reactions remain rare. One example of a non-selective reaction that is potentially amenable to the development of an enantioselective version is the dimerisation of styrenes (Eq. 3). RajanBabu and co-workers found that when a typical nickel catalyst system is used—[{NiBr(η^3-allyl)}$_2$]/PPh_3/AgOTf—poor conversion to the dimer is obtained, along with substantial formation of polystyrene.[2e] In contrast, palladium catalysts appear far more attractive; Shirakawa and co-workers demonstrated that a catalyst formed in situ from palladium acetate, triphenylphosphine and indium triflate is particularly effective.[10] We were interested to see whether an asymmetric version of this reaction could be realised, and we now report that mixed palladium–indium systems containing non-chelating chiral bis(phosphites) show considerable promise.

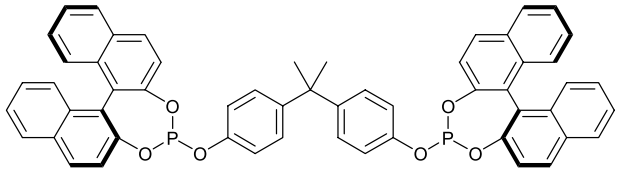


(3)

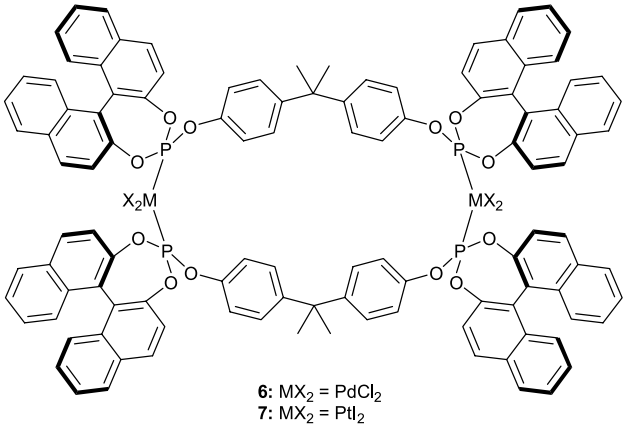
2. Results and discussion

2.1. Synthesis of ligands

The chiral non-chelating bis(phosphite) ligand **5** was shown by Faraone and co-workers to furnish the dimetallamacrocycles **6** and **7**.[11] We reasoned that any bimetallic asymmetric activation of styrene may be best served by such structural types and therefore, synthesized the analogous ligands **8** and **9**.



5



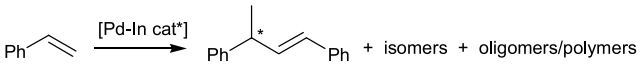
6: $MX_2 = PdCl_2$
7: $MX_2 = PtI_2$

These ligands were prepared by the reaction of the phosphine chloride **10**, derived from (*S*)-BINOL, with the bis-phenols **11a** and **b**, respectively, in the presence of triethylamine (Scheme 1). Ligand **9** could also be prepared by the reaction of the bis(chlorophosphite) **12a** with (*S*)-BINOL in the presence of triethylamine. The analogous reaction with the bulkier analogue **12b** proved unsuccessful. The compounds **12** were synthesised from the appropriate diols **11b** and **c** and PCl_3 in the presence of triethylamine.

The ^{31}P NMR spectrum for the ligand **8** shows a singlet at δ 145.6 ppm, very close to that reported for ligand **5** (δ 144.8 ppm, C_6D_6).[11] The ^{1}H NMR spectrum shows distinctive signals for the cyclohexyl ring in addition to resonances for the aromatic protons. The ^{31}P NMR spectrum of ligand **9** shows a singlet at δ 149.3 ppm, a little down-field of those for **8** and **5**, presumably due to the presence of the *ortho*-methyl groups. As well as aromatic signals, the ^{1}H NMR spectrum of ligand **8** shows two methyl signals at 1.44 and 2.28 corresponding to the xylyl and bridgehead methyl groups, respectively.

2.2. Catalysis

The reaction chosen for the optimisation studies was the dimerisation of unsubstituted styrene (Eq. 4).



13a (4)

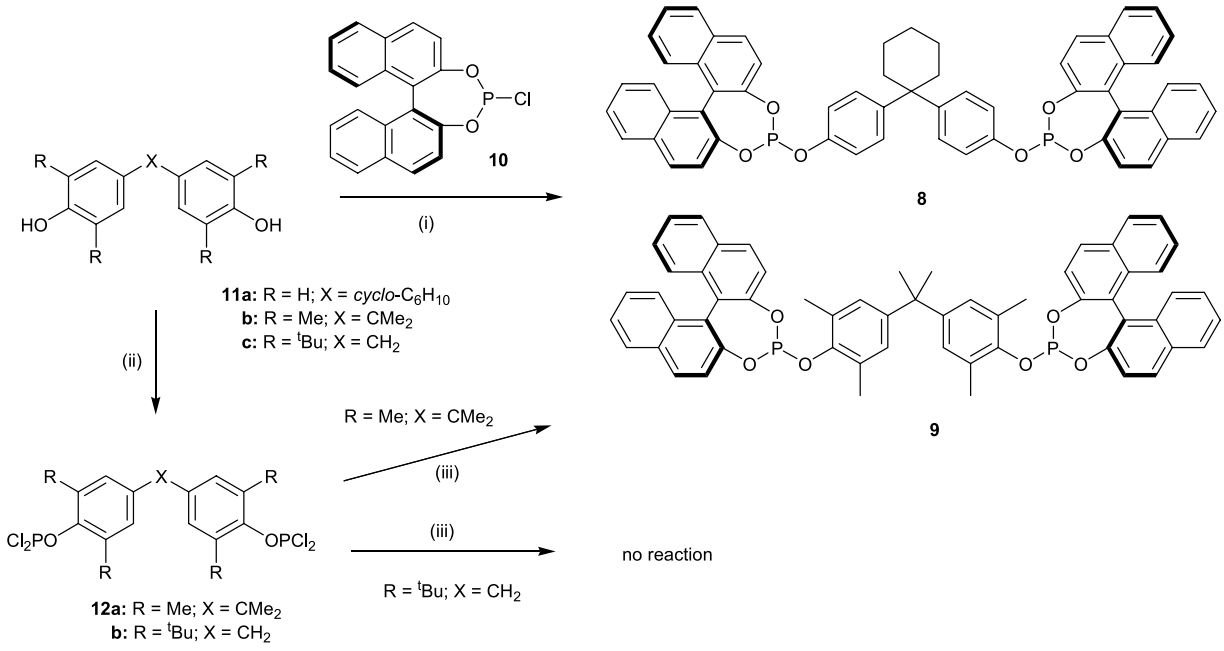
We initially performed a brief solvent optimisation study using ligand **9**, the results of which are summarised in Table 1. The use of 1,4-dioxane gives excellent yield and selectivity for the desired product dimer *E*-**13a** as well as moderate enantioselectivity. Dichloromethane, DME and THF give lower conversions and poorer selectivity for the desired product versus isomerisation and/or oligomerisation products. No reaction was observed in the absence of solvent. Having established that the best results are obtained in the dimerisation with dioxane as solvent, this was then used for the rest of the studies.

The effect of varying the ratios of palladium, indium and ligand **9** was examined next and the results are summarised in Table 2. At 1 mol% loading of palladium and ligand **9**, in the absence of indium triflate, no activity is observed (Table 2, entry 1), implying either that the active catalyst is a heterobimetallic species or that the indium triflate is

Table 1. Solvent optimisation

Entry	Solvent	Conversion, %[a]	Yield of **13a**, %[b]	ee %[c]
1	1,4-Dioxane	>99	99	30
2	Dichloromethane[d]	90	68	23
3	DME	82	57	22
4	THF	70	45.5	18
5	No solvent[e]	0	0	–

Conditions: $Pd(OAc)_2$ (1.0 mol%), $In(OTf)_3$ (5 mol%), ligand **9** (1.0 mol%), styrene (4.36 mmol), solvent (5 ml), rt, 18 h.
[a] Conversion of styrene determined by GC (hexadecane internal standard).
[b] Determined by GC (hexadecane internal standard).
[c] Determined by HPLC.
[d] Ligand **9** (0.5 mol%), 2.5 mol% $In(OTf)_3$.
[e] Ligand **9** (0.5 mol%).



Scheme 1. Conditions: (i) Et_3N, toluene, −40–90 °C, 18 h; (ii) PCl_3, Et_3N, toluene, −40 °C–rt, 18 h; (iii) (*S*)-BINOL, Et_3N, toluene, −40 °C–rt, 18 h.

required as a catalyst activator. By 0.5 mol% indium loading, good activity is seen (entry 3). Holding the loadings of palladium and ligand **9** at 1 mol% and increasing the amount of indium triflate leads to an increase in stereoselectivity to a maximum of 37% at 2.5 mol% loading (entry 5). Further, increasing the amount of indium leads to an increase in activity (entries 6–8) but this is sometimes offset by concomitant erosion in enantioselectivity. It may be imagined that this is due to a competing dimerisation mediated by the indium triflate. Indeed, when the reaction is repeated in the absence of palladium acetate (entry 9), small amounts of dimer **13a** are produced as a racemic mixture. By contrast, in the absence of the ligand **9**, indium triflate does not give any dimer **13a** (entry 10). Some conversion to the dimer **13a** is seen using a palladium–indium mixture in the absence of the phosphite ligand (entry 11).

The data obtained are consistent with a heterobimetallic active catalyst, but do such species form in the presence of ligand **9**? A ^{31}P NMR spectrum of a 2.3:1 mixture of ligand **9** and indium triflate in 1,4-dioxane/$CDCl_3$ (3:1) shows a very broad peak centred around δ 2 ppm demonstrating that the phosphite donor is perfectly capable of coordinating to the indium centre. The broadening of the peak is due to the quadrupolar nature of indium (96% $I=9/2$). This is very similar to the ^{31}P spectroscopic data reported for $[In(OTf)_3\{P(O^iPr\}_3]$, which shows a broad peak at 6.6 ppm.[12] In addition a sharp peak is seen at δ −1.5 ppm (as well as minor peaks at 21.88, 41.66 and 56.30 ppm) possibly corresponding to a hydrolysed species.

The spectrum of a 1:1 mixture of palladium acetate and ligand **9** in dioxane/$CDCl_3$ (3:1) shows two major peaks at δ 98.71 and 99.05 as well as smaller peaks at 164.43, 102.03 and −2.23 ppm. The peaks between 98 and 103 ppm are consistent with the formation of simple phosphite adducts of Pd(II). The smaller, downfield shift we very tentatively assign as a palladacycle resulting from C–H activation of one of the *ortho*-methyl groups of the ligand by the palladium acetate,[13] whilst the high field resonance is presumably due to hydrolysis of the ligand. Mixing palladium acetate, indium triflate and ligand **9** in a 1:2.3:1

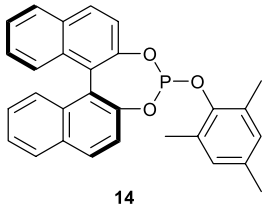
Table 2. Effect of varying relative ratios of Pd/In/ligand

Entry	Pd mol%	$In(OTf)_3$ mol%	Ligand **9** mol%	Conversion, %[a]	Yield of **13a**, %[b]	ee %[c]
1	1	0	1	<1	<1	nd
2	1	0.1	1	9	9	14 (*R*)
3	1	0.5	1	87	81	28 (*R*)
4	1	1	1	80	80	32 (*R*)
5	1	2.5	1	75	75	37 (*R*)
6	1	3	1	87	87	31 (*R*)
7	1	5	1	>99	>99	30 (*R*)
8	1	10	1	75	43	35 (*R*)
9	0	2.5	1	24	8	0
10	0	5	0	55	0	—
11	1	2.5	0	55	15	—

Conditions: styrene (4.36 mmol), dioxane (5 ml), rt, 18 h.
[a] Conversion of styrene determined by GC (hexadecane internal standard).
[b] Determined by GC (hexadecane internal standard).
[c] Determined by HPLC.

ratio in dioxane/$CDCl_3$ (3:1) led to immediate and substantial precipitation. A ^{31}P NMR spectrum of this mixture at a reaction time of 1.5 h shows a broad peak centred around δ 164 ppm, a smaller broad peak at 126 ppm and a third at around -3 ppm (major species). The high-field shift is again probably due to hydrolysis of the ligand but we are not able to completely rule out the possibility that it may be an indium–phosphite species, due to the broad nature of the peak. When the reaction is left longer (hours) the precipitate dissolves and the ^{31}P NMR shows only one sharp peak at -2.0 ppm. When the reaction is performed in $CDCl_3$, the precipitate is not observed and the ^{31}P NMR spectrum recorded within 45 min shows only the broad peak at 165 ppm and a sharp peak at -1.99 ppm (major species). Again, over the course of several hours, the ^{31}P spectrum reveals complete hydrolysis.

Taken together, the spectroscopic data show that palladium competes effectively with indium triflate for the ligand **9** with little or no evidence for the formation of indium–phosphite complexes in the presence of palladium. It is also apparent that the hydrolysis of the ligand **9** is relatively facile in the presence of either indium triflate or palladium acetate. The reaction of the model ligand **14** with palladium acetate (1:1, toluene, rt) again leads to the formation of a small amount of a compound tentatively assigned as a palladacycle formed by C–H activation of an *ortho*-methyl group as well as substantial amounts (major compound) of hydrolysis product.



14

If the indium triflate, either free or complexed with ligand **9**, plays a role in enantiodiscrimination then it may be imagined that the use of a chiral indium analogue would have an influence on the enantioselectivity of the reaction. This could be either positive or deleterious, depending on diastereomeric matching or mis-matching. BINOL-modified indium species, formed in situ from (*S*)-BINOL and $InCl_3$ give good to excellent enantioselectivity in allylation of aldehydes with allyl tin reagents.[14] Therefore, $In(OTf)_3$ was pre-treated with (*S*)-BINOL in 1,4-dioxane and the resultant mixture was used in the dimerisation of styrene with palladium acetate and ligand **9**. Surprisingly the results from this experiment (Table 3, entry 2) do not show particularly significant deviation from those obtained in a control experiment performed in the absence of the BINOL (entry 1). It is possible that the triflic acid produced in the reaction of BINOL with indium triflate provides an alternative activation pathway that coincidently gives similar performance/activity to the non-BINOL modified catalyst system. In order to test this, anhydrous triflic acid was used in place of indium triflate in the standard reaction (entry 3). Conversion remains high but selectivity for the desired dimer is substantially reduced, as is enantioselectivity. Interestingly, when triflic anhydride is used in place of triflic acid (entry 4) then the opposite enantiomer of **13a** predominates.

Table 3. Effect of varying Lewis acid co-catalyst

Entry	Lewis acid	Conversion, %[a]	Yield of **13a**, %[b]	ee %[c]
1	$In(OTf)_3$	94	94	31 (*R*)
2	$In(OTf)_3+2.7$ (*S*)-BINOL	96	96	33 (*R*)
3	HOTf	77	45	23 (*R*)
4	Tf_2O	47	43	22 (*S*)
5	$Yb(OTf)_3$	10	2	27.5 (*R*)
6	AgOTf	17	13	21.5 (*R*)
7	$Sc(OTf)_3$	100	67	21 (*R*)
8	$Sn(OTf)_2$	8	8	20 (*R*)
9	$La(OTf)_3$	17	<1	nd
10	$Zn(OTf)_2$	<1	<1	nd
11	$InCl_3$	4	<1	nd
12	$SmCl_3$	<1	<1	nd

Conditions: $Pd(OAc)_2$ (1.0 mol%), additive (2.5 mol%), ligand **9** (1.0 mol%), styrene (4.36 mmol), 1,4-dioxane (5 ml), rt, 18 h.
[a] Conversion of styrene determined by GC (hexadecane internal standard).
[b] Determined by GC (hexadecane internal standard).
[c] Determined by HPLC.

A range of alternative Lewis acid co-catalysts was examined and in all cases, where discernable, the same enantiomer (*R*) of product dimer **13a** predominates (Table 3, entries 5–12). Of the other triflate salts tested, only scandium triflate shows good conversion (entry 7), however, the selectivity to the desired product is substantially lower than with indium triflate. Both indium chloride and samarium chloride prove ineffective.

The effect on activity of changing the chiral ligand was examined next and the results are presented in Table 4. Small changes in the non-coordinating bis(phosphite) ligand's structure appear to have a substantial impact on both activity and enantioselectivity (entry 1). One significant structural difference between the ligands **9** and **8** is the absence in the latter of *ortho*-methyl functions on the bridging bis-phenol group, indicating that steric bulk in these positions is a prerequisite for decent performance. However, as outlined above, attempts to produce analogues of these ligands with *ortho-tert*-butyl groups have so far proved unsuccessful.

The ligand **14** can be envisaged as half of the non-chelating bis(phosphite), **9**. As can be seen whilst activity remains high using **14**, selectivity for the dimeric product **13a** is vastly reduced (entry 2). Interestingly, the enantioselectivity obtained, while reduced, is substantially higher than that obtained with ligand **8**, again supporting the idea that the *ortho*-methyl groups are an important structural motif. Replacing one of the two *ortho*-methyl groups with a proton and the other with a *tert*-butyl leads to an erosion in both activity and enatioselectivity (ligand **15**; entry 3). The incorporation of a 2-phenyl group leads to increased selectivity for **13a** but at the expense of enantioselectivity (ligands **16** and **17**; entries 4 and 5). Whilst two phenyl groups in the 2- and 6-positions give substantially improved selectivity for the dimer **13a** compared with methyl groups (compare entries 6 and 2) this is again is at the detriment of enantioselectivity. It is interesting to note that, in this case,

Table 4. Effect of varying chiral ligands

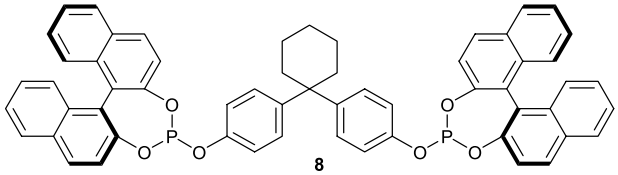
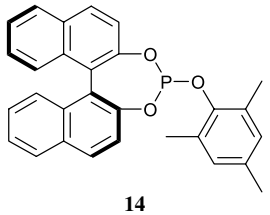
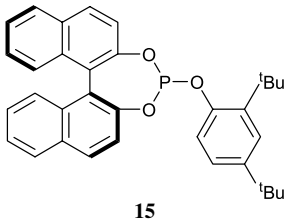
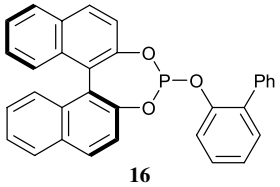
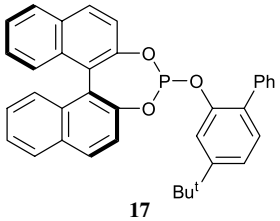
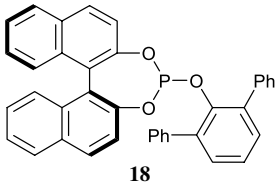
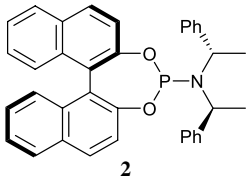
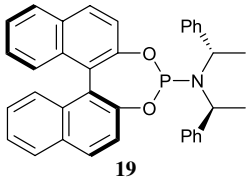
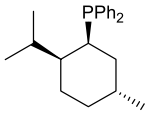
Entry	Ligand (or preformed palladium complex)	Ratio Pd:In:ligand (mol%)	Conversion, %[a]	Yield of **13a**, %[b]	ee %[c]
1	 **8**	1:2.5:1	52	33	5.5 (*R*)
2	 **14**	1:2.5:2	93	11	29 (*R*)
3	 **15**	1:2.5:2	60	10	12 (*R*)
4	 **16**	1:5:2	75	64	1.5 (*S*)
5	 **17**	1:5:2	84	63	1.5 (*R*)
6	 **18**	1:5:2	>99	69	9 (*S*)
7	 **2**	1:2.5:2	<1	<1	nd
8	 **19**	1:2.5:2	<1	<1	nd
9		1:2.5:2	62	9	7 (*S*)

Table 4 (*continued*)

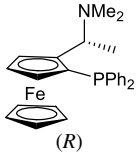
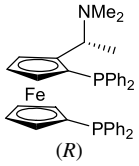
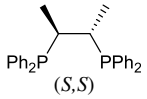
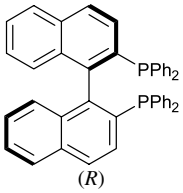
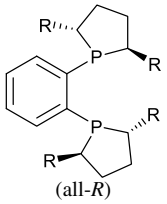
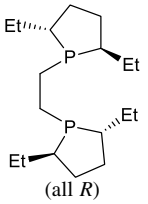
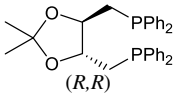
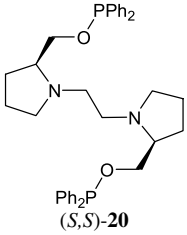
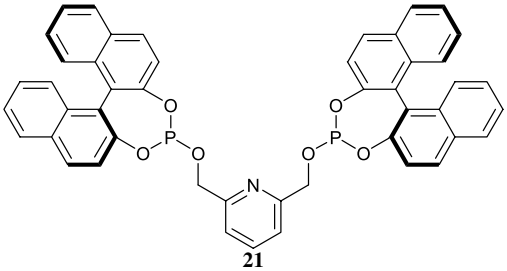
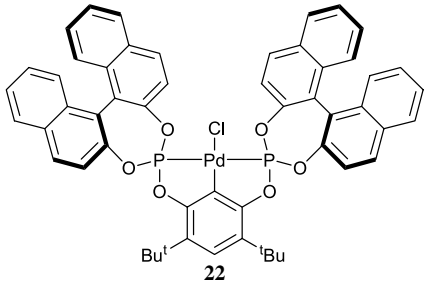
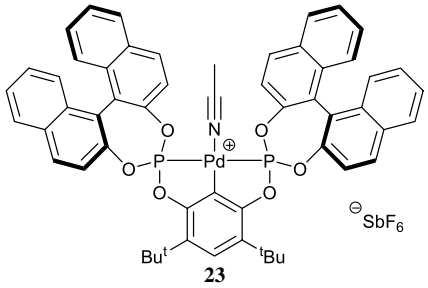
Entry	Ligand (or preformed palladium complex)	Ratio Pd:In:ligand (mol%)	Conversion, %[a]	Yield of **13a**, %[b]	ee %[c]
10	 (*R*)	1:2.5:2	<1	<1	20.5 (*R*)
11	 (*R*)	1:2.5:1	10	4	2.5 (*S*)
12	 (*S,S*)	1:2.5:1	27	<1	n.d
13	 (*R*)	1:2.5:1	5	3	3.5 (*R*)
14	 (all-*R*)	1:2.5:1	R=Et<1	0	nd
15			R=^{i}Pr<1	0	nd
16	 (all *R*)	1:2.5:2	4	2	9.5 (*S*)
17	 (*R,R*)	1:2.5:1	51	51	12.5 (*S*)
18	 (*S,S*)-**20**	1:2.5:1	89	49	0.5 (*S*)
19	 **21**	1:2.5:1	97	73	0.5 (*S*)

Table 4 (*continued*)

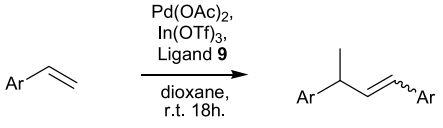
Entry	Ligand (or preformed palladium complex)	Ratio Pd:In:ligand (mol%)	Conversion, %[a]	Yield of **13a**, %[b]	ee %[c]
20	 **22**	Pd:In = 1:2.5	62	0	—
21	 **23**	Pd:In = 1:2.5	70	2	nd

Conditions: $Pd(OAc)_2$ (1.0 mol%), additive (2.5 mol%), ligand **9** (1.0 mol%), styrene (4.36 mmol), 1,4-dioxane (5 ml), rt, 18 h.
[a] Conversion of styrene determined by GC (hexadecane internal standard).
[b] Determined by GC (hexadecane internal standard).
[c] Determined by HPLC.

the opposite enantiomer of **13a** is obtained compared with using ligands **8**, **9**,**14** and **15**, despite the fact that they are all derived from (*S*)-BINOL. This may be due to the fact that the 2,6-diphenyl groups of ligand **18** show a pronounced tendency to undergo π-interactions with a metal centre.[15] This may well lead to the adoption of an alternative catalytic manifold.

Interestingly, in contrast with the monodentate ligands **14**–**18**, the diastereomeric phosphoramidite ligands **2** and **19** show essentially no activity (entries 7 and 8). This is despite the fact that these ligands are amongst the most effective tested in asymmetric hydrovinylation reactions with nickel catalysts.[9,6] The other monodentate ligands tested also proved to be poor (entries 9 and 10) as did the chelating bisphosphines BPPFA, chiraphos, BINAP, Et-Duphos, ^{i}Pr-Duphos and Et-BPE (entries 11–16, respectively). This is perhaps not surprising since RajanBabu and co-workers found that the chelating bisphosphines BINAP and Me-Duphos show no activity in asymmetric hydrovinylation reactions.[2e] By contrast (−)-diop (entry 17) shows moderate conversion with high regioselectivity and some enantioselectivity. This may be due to increased size and flexibility of the chelate ring. Indeed the more flexible bidentate ligands **20**[16] and **21** (entries 18 and 19) both show good activity and reasonable selectivity but give the desired product as essentially racemic mixtures. Both of the preformed 'PCP'-pincer complexes **22** and **23** do not yield the desired dimerisation product (entries 20 and 21).

Having established that the initial catalyst system tested—that formed in situ from palladium acetate, indium triflate and ligand **9**—shows the best performance and enantioselectivity. We briefly screened this against selected substrates. Both 4-fluorostyrene and 2-methylstyrene are converted to the desired dimers in reasonable yields at rt (Scheme 2). The enantioselectivity observed in the dimerisation of 4-fluorostyrene is somewhat lower than that with styrene and in contrast with the unsubstituted substrate, the product **13b** is formed exclusively as the *Z*-isomer. The dimerisation of 2-methylstyrene yields the *E*-isomer in an encouraging 56% ee.



13b: Ar = 4-FC_6H_4: 77%; *Z*-isomer; 20% e.e. [a]
c: Ar = 2-MeC_6H_4: 79%; *E*-isomer; 56% e.e.[b]

Scheme 2. [a] Isolated yield, ee determined by HPLC. [b] Spectroscopic yield determined by ^{1}H NMR, isolated yield = 20%, ee determined by HPLC.

The electron rich substrate 4-methoxystyrene does not give any of the desired dimerisation product under the standard conditions, but rather yields polymeric material. It appears that the polymerisation is catalysed by an indium species; control reactions with indium triflate with or without ligand **9** also give essentially quantitative conversion to polymeric materials, whereas a reaction containing palladium acetate and ligand **9** in the absence of indium leads only to recovered starting material.

3. Conclusions

In summary, we have realised the asymmetric dimerisation of styrenes using mixed palladium–indium catalysts

supported by chiral non-chelating bis(phosphite) ligands. While the enantioselectivities obtained with the current catalyst systems are modest, the performances observed are considerably better than those using some of the best ligand systems reported for the related asymmetric hydrovinylation reaction. In addition, the more successful catalyst systems identified are amenable to simple modification, which holds promise for future optimisation of both activity and selectivity. These studies are ongoing in our group and the results will be reported at a later date.

4. Experimental

4.1. General

All reactions and manipulations of air-sensitive materials were performed under nitrogen, either in a glove-box or using standard Schlenk techniques. Solvents were distilled from appropriate drying reagents prior to use. Ligands **14–18** were prepared by modification of a procedure reported for a closely related phosphite.[17] Ligand **21** and complexes **22** and **23** were prepared according to literature methods.[18,19] All other materials, except where noted, were obtained commercially and used as received. GC analysis was performed on a Varian 3800 GC fitted with a 25 m CP Sil 5CB column and data were recorded on a Star workstation. Enantioselectivity was determined by HPLC on a Varian Prostar 210 fitted with a Chiralcel OD or OB column.

4.1.1. Synthesis of ligand 8. A mixture of bisphenol, **11a**, (1.53 g, 5.70 mmol) and the chlorophosphite **10** (2.00 g, 5.70 mmol) in toluene (60 ml) was cooled to −40 °C and then treated drop-wise with a solution of Et_3N (3.0 ml, 21.4 mmol) in toluene (20 ml). The reaction was stirred and allowed to warm to rt overnight. The mixture was filtered through a pad of Celite, which was then washed with toluene (2×20 ml) and the solvent removed from the combined solutions in vacuo and the resultant solid was recrystallised from dichloromethane/hexane to give compound **8** as a white solid. Yield 3.48 g, 70%, $C_{58}H_{42}O_6P_2$ requires C, 77.7; H, 4.7%; Found: C, 74.60; H, 5.47. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36–1.51 (8H, br s, CyH), 2.07–2.19 (2H, br s, CyH), 6.97–7.23 (16H, m, ArH), 7.25–7.51 (8H, m, ArH), 7.75–7.96 (8H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.43, 25.25, 36.24 (CH_2), 44.05 (*C*-(CH_2)$_2$), 114.00, 118.78, 118.88, 121.80 (ArH), 123.37 (ArC), 123.97, 124.19, 125.34, 125.68, 125.99, 126.52, 126.84, 126.89, 128.06, 128.83 (ArH), 130.19, 130.60, 131.49, 131.76, 143.45, 146.47, 146.52, 148.21, 148.32 (ArC); ^{31}P NMR (121 MHz, $CDCl_3$): δ 145.63.

4.1.2. Synthesis of ligand 9. *Method A*. This was prepared by an analogous method to that outlined above. Yield 87%. $C_{59}H_{46}O_6P_2$ requires C, 77.6; H, 5.1%; Found: C, 75.5; H, 5.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (6H, s, CH_3), 2.28 (12H, s, CH_3), 6.83 (4H, s, ArH), 7.14–7.24 (4H, m, ArH), 7.28–7.40 (8H, m, ArH), 7.41 (4H, d, $^1J_{HH}$=8 Hz, ArH), 7.81–7.94 (8H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.81, 31.58 (CH_3), 42.44 (*C*(CH_3)$_2$), 122.31, 122.49 (ArH), 123.40 (ArC), 125.70, 125.85, 126.72, 126.89, 127.52, 127.59, 127.84, 128.78, 128.87 (ArH), 130.32 (ArC), 130.97, 131.69 (ArH), 132.15, 133.11, 133.36, 133.38, 147.30, 147.54, 147.65, 148.40 (ArC); ^{31}P NMR (121 MHz, $CDCl_3$) δ 149.33.

Method B. A mixture of the appropriate bisphenol **11a** (4.0 g, 16.1 mmol) and freshly distilled PCl_3 (10 ml, 115 mmol) in toluene (80 ml) was cooled to −40 °C and treated drop-wise with Et_3N (8 ml, 58 mmol) in toluene (20 ml). The reaction was allowed to warm to rt overnight. The mixture was filtered through a pad of Celite, which was then washed with toluene (2×20 ml) and the solvent removed from the combined solutions in vacuo to give the intermediate **12a** as a white solid. This was held under vacuum until all of the PCl_3 had been removed as determined by ^{31}P NMR. Yield 6.67 g; 86%. ^{31}P NMR ($CDCl_3$): δ 200.8 ppm. This was used in the subsequent step without further purification.

A mixture of Et_3N (8.0 ml, 57.1 mmol) and **12a** (3.29 g, 6.76 mmol) in toluene (60 ml) was cooled to −40 °C and treated drop-wise with a solution of (*S*)-binaphthol (3.90 g, 13.62 mmol) in toluene (20 ml). The reaction was allowed to warm to rt overnight. The mixture was filtered through a pad of Celite, which was then washed with toluene (2× 20 ml), the solvent removed from the combined solutions in vacuo and the resultant solid was recrystallised (dichloromethane/hexane) to give ligand **9** as a white solid (5.12 g, 83%). Spectroscopic data as above.

4.2. Typical method for catalysis

Ligand **9** (0.041 g, 0.044 mmol) was added to a solution of palladium acetate in 1,4-dioxane (0.022 M, 2.00 ml), the solution was diluted with dioxane (2 ml) and stirred at rt for 5 min. The appropriate stryrene (4.36 mmol) was added followed by indium triflate (0.061 g, 0.1085 mmol) in one portion. More dioxane (1 ml) was used to wash down any indium triflate stuck to the side of the reaction flask and the reaction mixture was then stirred at rt for 18 h. The reaction was quenched with water (25 ml), the resultant mixture extracted with dichloromethane (3×25 ml), the organic phase dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was dissolved in toluene (10 ml) and hexadecane (internal standard, 0.068 M in toluene, 5.00 ml) was added. The conversion and yield were determined by GC analysis.

4.2.1. Compound 13a. Isolated by column chromatography (silica, chloroform) as a yellow oil, 0.431 g, 48%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, d, $^3J_{HH}$=7 Hz, CH_3), 3.42–3.50 (1H, dq, $^3J_{HH}$=5, 7 Hz, R_3CH), 6.24 (1H, d, $^3J_{HH}$= 5 Hz, =CH), 6.25 (1H, s, =CH), 6.98–7.20 (10H, m, ArH). The ee was determined by HPLC, Chiralcel OD, heptane/isopropanol 99.8:0.2, flow rate 0.9 ml/min, λ 215 cm^{-1}, R_f *S*-isomer=11.24 min, *R*-isomer=11.87 min, absolute configuration determined by order of R_f in comparison with literature data.[20]

4.2.2. Compound 13b. Isolated by column chromatography (silica, hexane then 5% dichloromethane in hexane), as a yellow oil, 0.041 g, 77%. HRMS *m*/*z*=244.1074; $C_{16}H_{14}F_2$ requires 244.1064. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, d, $^3J_{HH}$=7 Hz, CH_3), 3.52 (1H, m, R_3CH), 6.10–6.20 (1H,

dd, $^3J_{HH}=7$, 16 Hz, =CH), 6.26 (1H, d, $^3J_{HH}=16$ Hz,=CH), 6.85–6.89 (2H, d, $^3J_{HH}=9$ Hz, ArH), 6.91–6.94 (2H, d, $^3J_{HH}=9$ Hz, ArH), 7.09–7.15 (2H, q, $^3J_{HF}=5$, 9 Hz, ArH). The ee was determined by HPLC, Chiralcel OD, heptane/isopropanol 99.8:0.2, flow rate 0.9 ml/min, λ 215 cm^{-1}, R_f major isomer=9.39 min, minor isomer=10.26 min, absolute configuration not determined.

4.2.3. Compound 13c. Isolated by column chromatography (silica, chloroform), as a yellow oil, 0.01 g, 19%. HRMS *m/z*=236.1558; $C_{18}H_{20}$ requires 236.1565. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36–1.39 (3H, d, $^3J_{HH}=7$ Hz, CH_3), 2.23 (3H, s, $ArCH_3$), 2.33 (3H, s, $ArCH_3$), 3.75–3.84 (1H, dq, $^3J_{HH}=7$, 7 Hz, R_3CH), 6.10–6.17 (1H, dd, $^3J_{HH}=7$, 16 Hz, =CH), 6.46–6.52 (1H, d, $^3J_{HH}=16$ Hz, =CH), 7.03–7.11 (6H, m, ArH), 7.14–7.20 (1H, d, $^3J_{HH}=7$ Hz, ArH). The ee was determined by HPLC, Chiralcel OB, heptane/isopropanol 98.0:2.0, flow rate 0.5 ml/min, λ 254 cm^{-1}, R_f major isomer=11.24 min, minor isomer=14.36 min, absolute configuration not determined.

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The preparation and resolution of 2-(2-pyridyl)- and 2-(2-pyrazinyl)-Quinazolinap and their application in palladium-catalysed allylic substitution

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Abstract—The preparation and resolution of two new axially chiral quinazoline-containing phosphinamine ligands, 2-(2-pyridyl)-Quinazolinap and 2-(2-pyrazinyl)-Quinazolinap, is described. The ligands were synthesised in good yield over eight steps and included two Pd-catalysed reactions, a Suzuki coupling to form the biaryl linkage and the introduction of the diphenylphosphino group, as the key transformations. The racemic ligands were resolved via the fractional crystallisation of diastereomeric palladacycles derived from (+)-di-μ-chlorobis{(*R*)-dimethyl[1-(1-naphthyl)ethyl]aminato-C_2,N}dipalladium (II) X-ray crystal structures of the (*S*,*R*)-2-pyridyl- and (*S*,*R*)-2-pyrazinyl-palladacycles are included. Displacement of the resolving agent by reaction with 1,2-bis(diphenylphosphino)ethane gave enantiopure 2-(2-pyridyl)-Quinazolinap and 2-(2-pyrazinyl)-Quinazolinap, new atropisomeric phosphinamine ligands for asymmetric catalysis. These ligands were applied in the palladium-catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate resulting in moderate conversions and enantioselectivities of up to 81%.

1. Introduction

To date, atropisomeric ligands have been applied in a wide range of transition metal catalysed asymmetric transformations.[1] One of the most successful and widely applicable of these ligands is Noyori's diphosphine BINAP.[2] The principle of inducing enantioselectivity through the influence of electronic as well as steric factors led to the design of axially chiral heterobidentate ligands such as Brown's Quinap (**1**), the first example of this class successfully applied in asymmetric catalysis.[3] During solid state and solution ^{1}H NMR investigations into the mechanism of allylic substitution catalysed by Pd–Quinap complexes, it had been determined that the 3H of the isoquinoline unit occupies a position of crucial steric influence over ligand–reactant interactions and hence over the stereochemical outcome of the reaction.[4] This led to the preparation of the vaulted analogue Phenap, also developed by Brown, which was applied in the rhodium-catalysed hydroboration of olefins and palladium-catalysed allylic alkylation resulting in enantioselectivities of up to 84 and 95%, respectively.[5,6]

Within our research group, attention has focused on the development of a new class of atropisomeric ligands with a quinazoline unit incorporated into the biaryl framework. We call this ligand series 'Quinazolinaps' and their preparation involves a synthetic route similar to that of Quinap and Phenap. The first of these synthesised and resolved was 2-phenyl-Quinazolinap (**2a**), which was successfully applied in Pd-catalysed allylic substitution providing good conversions but moderate enantioselectivities.[7,8] Following on from the aforementioned mechanistic insight into allylic substitution provided by Brown's study, we were prompted to vary the size of the substituent at the corresponding 2-position of the quinazoline moiety and hence the series of ligands **2b–f** were prepared and resolved.[9] Improved conversions and enantioselectivities up to 91% were obtained in the Pd-catalysed allylic alkylation of 1,3-diphenyl-propenyl acetate[10] and dimethyl malonate and up to 99% in the Rh-catalysed hydroboration of vinylarenes.[9]

Due to the success of this ligand series we wished to examine the effect of altering the electronic nature of the 2-substituent. Herein we report the extension of the Quinazolinap ligand class to include the 2-(2-pyridyl)- and 2-(2-pyrazinyl)-variants (**3a–b**). It was intended that the presence of the nitrogen atom(s) of the pyridyl and

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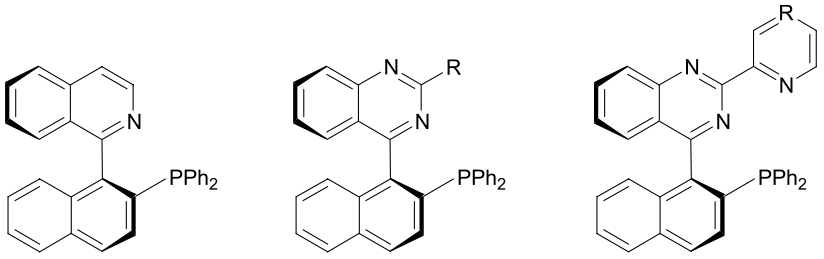
pyrazinyl rings would alter the basicity of the donor nitrogen of the quinazoline unit. There is also the added possibility of hemi-labile coordination of the extra nitrogen atom (**3** vs **2**) with potentially beneficial effects in transition metal catalysed asymmetric transformations.



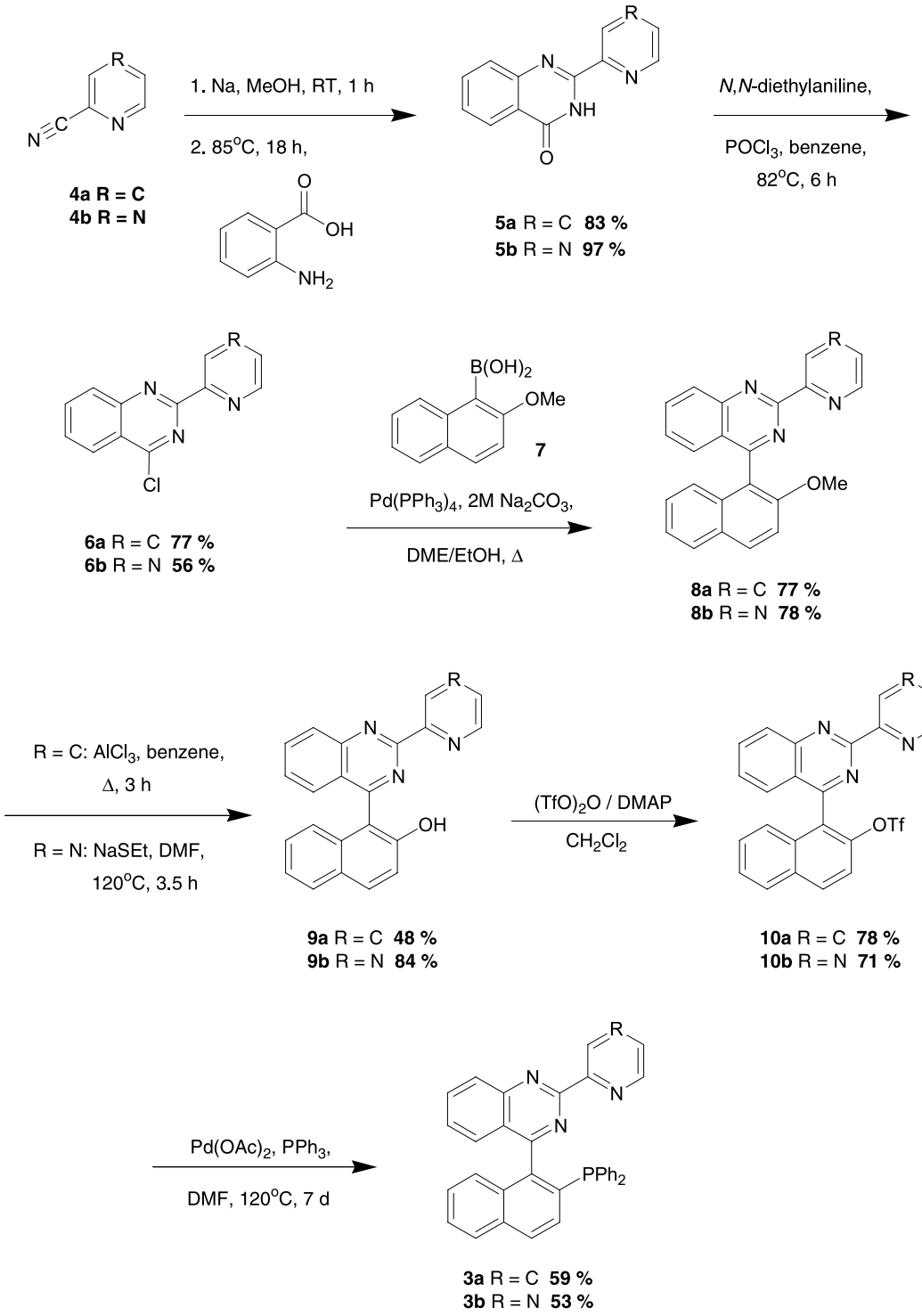
1 **2a,** R = Ph; **2b**, R = Me; **2c**, R = ^{i}Pr; **2d**, R = ^{t}Bu; **2e**, R = H; **2f**, R = Bn. **3a,** R = C **3b,** R = N

2. Ligand preparation

The synthetic approach chosen to prepare ligands **3a–b** is analogous to that used to obtain Quinazolinaps **2a–f**. The two key steps in the synthesis are the Pd-catalysed reactions to effect the biaryl coupling, and the formation of the naphthyl–phosphorus bond. The introduction of the phosphine in the final step is preferred as it allows facile handling of the intermediate compounds. The coupling partners of the palladium catalysed Suzuki reaction were the appropriate 4-chloroquinazoline (**6a–b**) and 2-methoxy-1-naphthylboronic acid (**7**), Scheme 1. The boronic acid was easily prepared from 1-bromo-2-methoxynaphthalene via a Grignard reaction, while the 4-chloroquinazolines were derived from the corresponding 2-substituted 4(3*H*)-quinazolinones (**5a–b**). These quinazolinones were readily obtained in yields of 83 and 97%, respectively, using a highly versatile methodology developed within our research group involving a sodium methoxide-mediated cyclisation between anthranilic acid and the appropriately substituted nitrile (**4a–b**).[11] The Suzuki coupling was catalysed by 3 mol% of tetrakis(triphenylphosphine)palladium (0) in dimethoxyethane at reflux in the presence of 2 M aqueous sodium carbonate and gave the methyl ethers (**8a–b**) as white solids in good yield (77 and 78%) after column chromatography. In order to introduce the diphenylphosphino group, it is first necessary to convert the methoxy group to a trifluoromethanesulfonate. For the earlier ligands of the Quinazolinap series, treatment with boron tribromide in dichloromethane provided the desired naphthol in all cases in high yields. However, the presence of the extra nitrogen atom(s) of the 2-pyridyl and 2-pyrazinyl analogues altered the process sufficiently that none of the required naphthol was obtained when boron tribromide was employed. The problem was solved through the use of aluminium chloride for the demethylation of 2-(2-pyridyl)-4-(2-methoxynaphthalen-1-yl)-quinazoline,[12] whereas heating at 120 °C with sodium ethanethiolate in dimethyl formamide removed the methyl group of the pyrazinyl analogue.[13] Both naphthols (**9a–b**) were then converted to their trifluoromethanesulfonate analogues (**10a–b**) by reaction with trifluoromethanesulfonic anhydride in the presence of 4-dimethylaminopyridine. The trifluoromethanesulfonates were formed in good yield (71–78%) although a longer reaction time of 48 h was necessary in the case of the 2-pyrazinyl variant. The Ni-catalysed process developed by Cai et al. had been successfully employed for the incorporation of the diphenylphosphino group into Quinazolinaps (**2a–f**) but it proved unsuitable for the transformation of the 2-pyridyl and 2-pyrazinyl triflates with a substantial amount of unreacted triflate remaining after 6 days at reflux.[14] Conversion of **10a** to the aryldiphenylphosphine oxide followed by subsequent reduction using trichlorosilane and triethylamine also resulted in low yields.[15] Direct formation of the desired products was achieved through the use of palladium acetate as catalyst and triphenylphosphine as the phosphinylating agent in dimethyl formamide, as reported by Chan and co-workers.[16] Thus 2-(2-pyridyl)-Quinazolinap (**3a**) and 2-(2-pyrazinyl)-Quinazolinap (**3b**) were obtained in racemic form over eight steps in good yields.

3. Ligand resolution

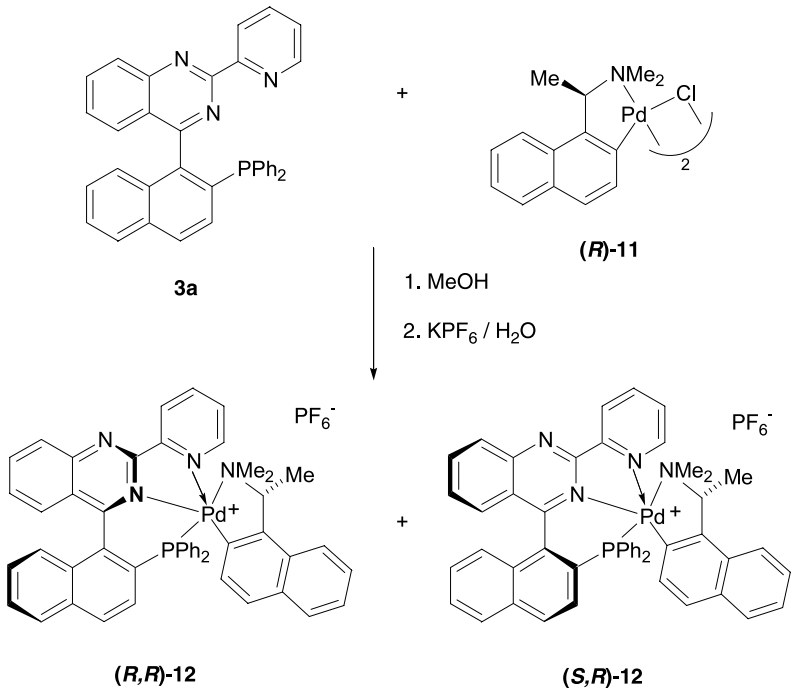
The resolution of many racemic phosphorus-containing ligand systems has been accomplished by the formation of diastereomeric complexes with enantiopure palladium amine complexes, followed by fractional crystallisation to obtain diastereomerically pure material.[17] As the *ortho*-palladated derivative of (*R*)-dimethyl[1-(1-naphthyl)ethyl] amine (**11**) had been successfully employed as the resolving agent for the resolution of Quinap and the earlier members of the Quinazolinap series, it was also applied in the attempts to resolve 2-(2-pyridyl)- and 2-(2-pyrazinyl)-Quinazolinap. Therefore, 2-(2-pyridyl)-Quinazolinap (**3a**) and (+)-di-μ-chlorobis{(*R*)-dimethyl[1-(1-naphthyl)ethyl] aminato-C_2,N}dipalladium (II) (**11**) were stirred in a 2:1 ratio in methanol for 18 h at room temperature, Scheme 2. An aqueous solution of KPF_6 was added to precipitate a yellow solid, which was shown by ^{1}H NMR to consist of a 2:1 mixture of diastereomers. The benzylic methines appeared as quintets, at 4.10 ppm for the major diastereomer and at 4.46 ppm for the minor. In the ^{31}P NMR spectrum the resonances associated with the two species appear at 27.61 and 22.16 ppm, respectively. A range of solvent systems was investigated to separate the diastereomeric pair before a mixture of hot butanone and diethyl ether proved successful. The precipitate that had formed was found to be a mixture of the two diastereomers but the mother liquor was proven to contain only the major one with a single peak in the ^{31}P



Scheme 1.

NMR at 27.61 ppm. A sample of this diastereomer was recrystallised from a dichloromethane–diethyl ether mixture to obtain crystals suitable for X-ray analysis. The crystal structure indicated that the (*S*,*R*)-diastereomer had been isolated, Figure 1. It also shows that, interestingly, the Pd atom adopts an almost ideal trigonal-bipyramidal coordination geometry in which the equatorial ligand and the metal are almost coplanar (rms deviation 0.04 Å).

Resolution of 2-(2-pyrazinyl)-Quinazolinap (**3b**) followed a similar approach, Scheme 3, although the mixture containing the ligand and resolving agent had to be stirred at 60 °C for 18 h to ensure complete complexation. By this time a pale yellow precipitate had formed and was removed by filtration. ^{1}H NMR spectroscopy confirmed the presence of a single diastereomer with the benzylic methine quintet at 4.11 ppm and only one peak appeared in the ^{31}P NMR at 39.50 ppm. The filtrate was found to contain both diastereomers but attempts to separate the two failed and so the residue was re-dissolved in methanol and the counter-ion



Scheme 2.

changed to PF_6^-. Both diastereomers were apparent in the ^1H NMR spectrum, this time in a 1:1 ratio with the benzylic methine quintets appearing at 4.37 and 4.12 ppm and the phosphorus resonances at 28.97 and 24.50 ppm. Again, isolation of diastereomerically pure material was effected by fractional crystallisation from hot butanone–diethyl ether and crystals for X-ray analysis were obtained through recystallisation from chloroform–diethyl ether. The X-ray structure showed this to be the (*S*,*R*)-2-(2-pyrazinyl) diastereomer, which adopts a similar trigonal–bipyramidal geometry as had been found for the (*S*,*R*)-2-(2-pyridyl) diastereomer, Figure 2. The geometries of the two palladium cations in both crystal structures are markedly similar in spite of their different crystal environments. The most significant difference between the two structures is a shortening of the Pd–N3 bond by 0.062(4) Å and an

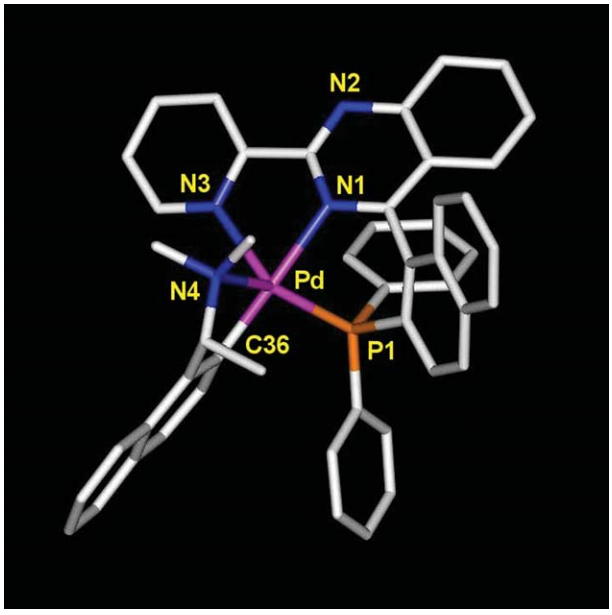


Figure 1. Structure of the cation in (*S*,*R*)-**12**·1.5(CH_2Cl_2), showing the approximate trigonal–bipyramidal coordination geometry of the Pd atom. Selected distances (Å) and angles (°): Pd–P1 2.223(1), Pd–N1 2.182(3), Pd–N3 2.408(3), Pd–N4 2.216(3), Pd–C36 1.982(3), P1–Pd–N1 83.7(1), P1–Pd–N3 120.7(1), P1–Pd–N4 145.8(1), P1–Pd–C36 96.2(1), N1–Pd–N3 72.9(1), N1–Pd–N4 102.5(1), N1–Pd–C36 176.2(1), N3–Pd–N4 93.0(1), N3–Pd–C36 104.1(1), N4–Pd–C36 79.8(1).

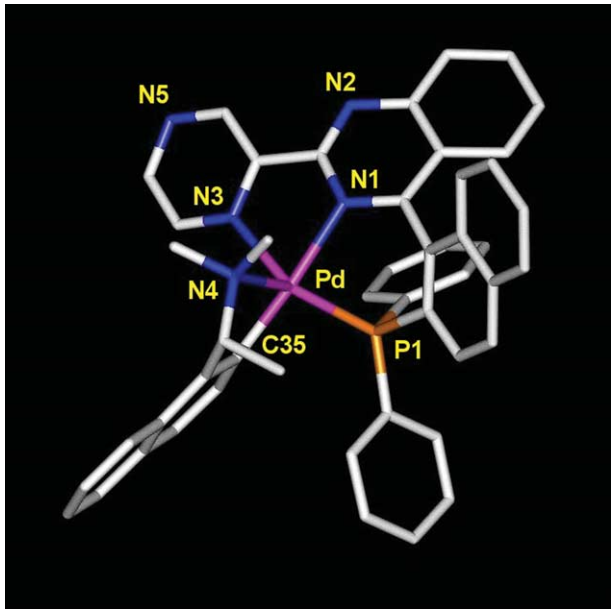
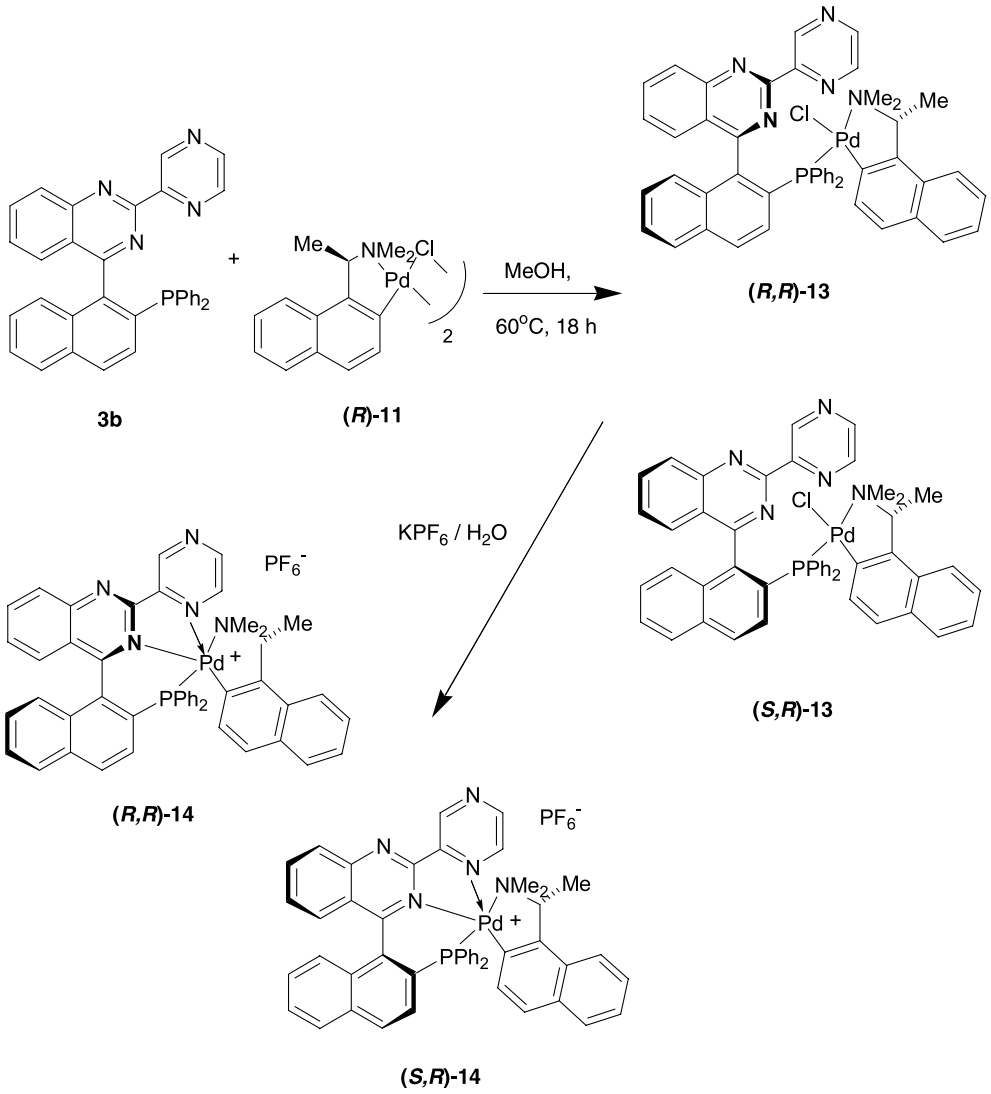


Figure 2. Structure of the cation in (*S*,*R*)-**14**·$C_4H_{10}O$, with the (*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato ligand in the same orientation as for Figure 1. Selected distances (Å) angles (°): Pd–P1 2.2211(4), Pd–N1 2.185(1), Pd–N3 2.346(2), Pd–N4 2.245(2), Pd–C35 1.981(2), P1–Pd–N1 85.06(4), P1–Pd–N3 124.49(4), P1–Pd–N4 139.66(4), P1–Pd–C35 97.5(1), N1–Pd–N3 74.3(1), N1–Pd–N4 102.7(1), N1–Pd–C35 173.3(1), N3–Pd–N4 95.5(1), N3–Pd–C35 99.2(1), N4–Pd–C35 79.4(1).



Scheme 3.

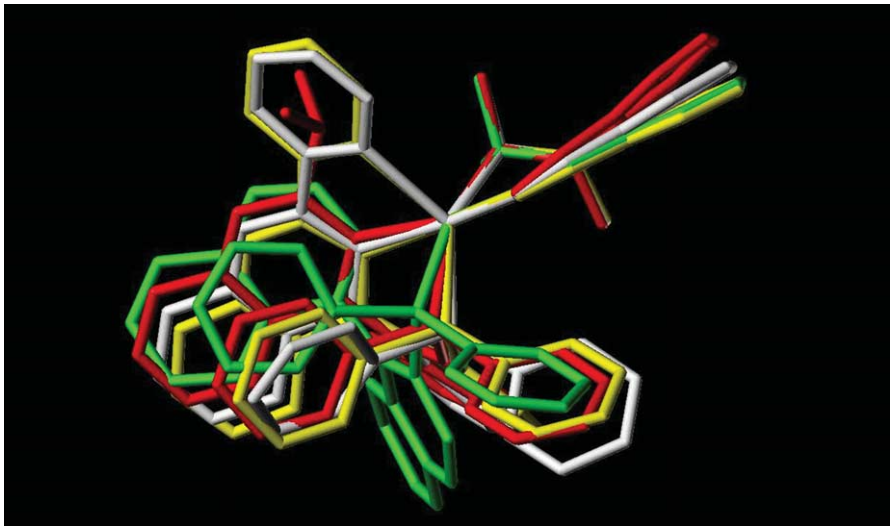


Figure 3. Structures of the palladium cations of variously substituted 2-Quinazolinaps (H=green; isopropyl=red; pyridyl=yellow; pyrazinyl=white) with the (*R*)-dimethyl[1-(1-naphthyl)ethyl]aminato ligand in the same orientation as for Figures 1 and 2.

Table 1. A comparison of the geometries of cationic substituted (*S*,*R*)-Quinazolinap Pd complexes

Quinazolinap ligand								
Ligand	R	P1–Pd–N1 angle (deg)	N1–Pd–N3 angle (deg)	Plane (naphthyl)/ plane (quinazolinyl) dihedral angle (deg)	Plane (quinazolinyl)/ plane (pyr/pyraz) dihedral angle (deg)	Pd–P1 distance (Å)	Pd–N1 distance (Å)	Pd–N3 distance (Å)
2a[a]	H	84.7(1)	—	112(2)	—	2.256(2)	2.189(5)	—
2b[a]	Me	82.34(6)	—	119(1)	—	2.2423(5)	2.187(2)	—
2e[a]	^{i}Pr	84.6(2)	—	113(2)	—	2.238(2)	2.192(5)	—
3a[b]	Pyr	83.7(1)	72.9(1)	115(1)	159(1)	2.223(1)	2.182(3)	2.408(3)
3b[b]	Pyraz	85.06(4)	74.3(1)	118(1)	154(1)	2.2211(4)	2.185(1)	2.346(2)

Aminato ligand				Inter-ligand geometry		
C[c]–Pd–N4 angle (deg)	Pd–N3[a]/N4[b] distance (Å)	Pd–C[c] distance (Å)	Trans-N1-Pd-C[c] angle (deg)	N3[b]–Pd–N4[b] angle (deg)	P1–Pd–N3[a]/N4[b] angle (deg)	Plane(P1,Pd,N1)/plane (N3[a]/N4[b],Pd,C[c]) dihedral angle (deg)
80.4(2)	2.132(5)	2.002(6)	171.2(2)	—	165.9(2)	17(2)
80.2(1)	2.147(2)	1.978(3)	171.0(1)	—	155.3(1)	28(1)
80.9(2)	2.164(6)	1.993(6)	166.7(2)	—	152.9(2)	32(2)
79.8(1)	2.216(3)	1.982(3)	176.2(1)	93.0(1)	145.8(1)	35(1)
79.4(1)	2.245(2)	1.981(2)	173.3(1)	95.5(1)	139.7(1)	42(1)

[a] Ref. 9.
[b] This publication.
[c] Carbon atom attached to Pd.

associated increase in the N3–Pd–N4 angle of 2.5(2)° on substitution of the 2-pyridyl group by the 2-pyrazinyl group on the Quinazolinap ligand. Since both the pyridyl and pyrazinyl groups are sterically similar, the difference is presumably due to the increased electron donor ability of the pyrazinyl substituent compared with the pyridyl group.

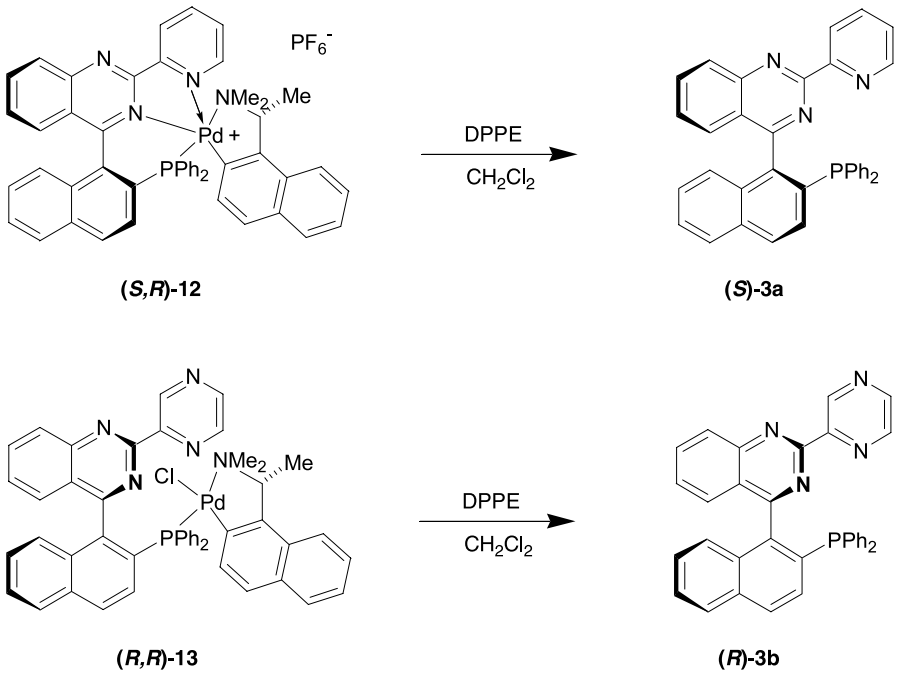
If one compares the structures of various 2-substituted Quinazolinap Pd cations containing the same (*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato ligand, there is a clear rearrangement of the ligands with respect to one another depending on the nature of the 2-substituent, Figure 3. Thus, in going from H→Me→isopropyl→2-pyridyl→2-pyrazinyl, the P1–Pd–N angle between the P atom of the Quinazolinap ligand and the N atom of the amidato ligand decreases steadily from 166 to 140° whereas the dihedral angle between the planes defined by P1, Pd and N1 of the Quinazolinap ligand and N, Pd and C of the amidato ligand increases by 25° (Table 1). Although the most significant change takes place in the equatorial plane of the metal, increase in steric bulk of the ligand along the series is likely to be the most dominant cause, though donor ability of the substituent must be a contributing factor since steric bulk alone does not explain the difference resulting from substitution of the 2-pyridyl substituent by the more electron-donating 2-pyrazinyl group.

Enantiomerically pure 2-(2-pyridyl)- and 2-(2-pyrazinyl)-Quinazolinap derived from the resolved diastereomers were readily obtained following decomplexation by stirring in dichloromethane in the presence of 1,2-bis(diphenylphosphino)ethane and purification by column chromatography, Scheme 4.

4. Pd-catalysed allylic alkylation

The formation of asymmetric carbon–carbon linkages catalysed by palladium complexes of chiral ligands is a useful way of assessing the ability of the ligand to induce enantioselectivity.[18] One of the most typically used systems involves nucleophilic attack of the dimethyl malonate anion on 1,3-diphenylprop-2-enyl acetate. Palladium complexes of homobidentate ligands have proven to be successful in this transformation by creating a chiral environment, which influences the orientation of the reactants sufficiently to cause one enantiomer of product to predominate.[19] Heterobidentate ligands such as the phosphinamines developed by Pfaltz,[20] Williams,[21] Helmchen[22] and Brown[3] affect the stereochemical outcome of the bond-forming process by the desymmetrisation of the substrate allyl through electronic effects. The incoming nucleophile then reacts preferentially at the more electrophilic end of the substrate, giving rise to the enantioselectivity observed. This is referred to as the trans effect as nucleophilic attack tends to occur trans to the phosphorus atom of the ligand–Pd complex.[23] The two standard methods employed for the reaction between dimethyl malonate and 1,3-diphenylprop-2-enyl acetate are the malonate procedure (method A), in which the nucleophile is preformed as its sodium salt, and the BSA procedure (method B), in which it is generated in situ upon addition of a base (typically a bis(trimethylsilyl)acetamide–KOAc mixture). Both methods were applied in the alkylation of 1,3-diphenylprop-2-enyl acetate catalysed by palladium complexes of Quinazolinaps **3a** and **3b**. In some cases, 15-crown-5 was added to aid the dissolution of the preformed sodium malonate.

The application of the palladium complex derived from (*S*)-(2-pyridyl)-Quinazolinap resulted in good conversions to product **15** when dichloromethane was used as solvent, reaching an optimum of 92% when the BSA method was employed (Table 2, entry 3). However, the enantioselectivities were low in all cases (13–19% (*S*)). When acetonitrile was used, conversions were poor for both the malonate and BSA procedures but showed a substantial improvement when 15-crown-5 was added (entry 5 vs entry 4). Again, the enantioselectivities were quite poor with the

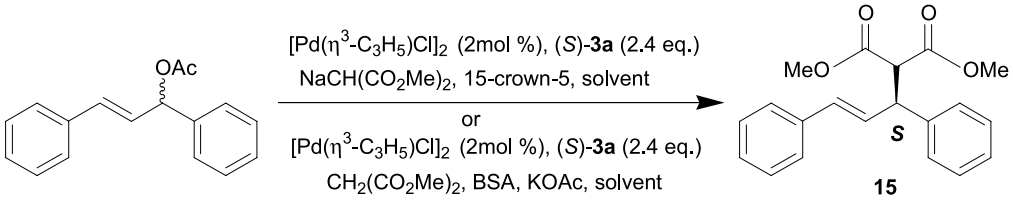


Scheme 4.

(*R*)-product predominating when the conversions were low (entries 4 and 6). When the reactions were carried out in THF, the malonate procedure resulted in a yield of 59% and an ee of 12% (entry 7). The conversion showed an increase to 84% when 15-crown-5 was added but the opposite enantiomer of product was obtained (entry 8). When the BSA method was applied the reaction proceeded much more slowly, with only an 11% conversion being recorded (entry 9). Poor, if any, enantio-differentiation was also achieved in DMF (entries 10–12). Again, the conversion was lowest for the BSA method (11%) but contrary to the results obtained when dichloromethane, acetonitrile and THF were used, the addition of 15-crown-5 actually lead to a decrease in the conversion from 63 to 20% (entries 10 vs 11).

Improved enantioselectivities were obtained when (*R*)-2-(2-pyrazinyl)-Quinazolinap was applied, Table 3. When dichloromethane was employed an increase in conversion from 15 to 38% was apparent with the addition of 15-crown-5 (entry 1 vs 2). The conversion was further improved to 72% with the BSA method (entry 3). When acetonitrile or dimethylformamide were used as solvent, the inclusion of the additive to increase the solubility of the malonate nucleophile had a slightly detrimental effect on the yield and

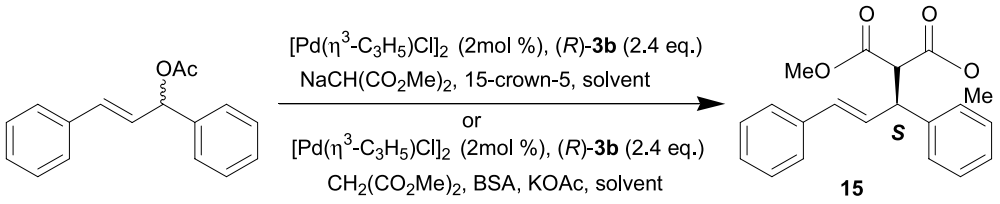
Table 2. Palladium-catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with 2-(2-pyridyl)-Quinazolinap **3a**



Entry	Method[a]	Solvent	Conv. (%)[b]	Ee (%)[c]
1	A	CH_2Cl_2	79	16 (*S*)
2	A[d]	CH_2Cl_2	89	19 (*S*)
3	B	CH_2Cl_2	92	13 (*S*)
4	A	MeCN	27	6 (*R*)
5	A[d]	MeCN	82	12 (*S*)
6	B	MeCN	25	8 (*R*)
7	A	THF	59	12 (*S*)
8	A[d]	THF	84	23 (*R*)
9	B	THF	11	3 (*R*)
10	A	DMF	63	10 (*S*)
11	A[d]	DMF	20	5 (*S*)
12	B	DMF	11	Racemic

[a] Reactions performed at room temperature for 3 days.
[b] Conversions detemined by ^{1}H NMR.
[c] Enantiomeric excesses of **15** determined by chiral HPLC.
[d] 15-crown-5 added.

Table 3. Palladium-catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with 2-(2-pyrazinyl)-Quinazolinap **3b**



Entry	Method[a]	Solvent	Conv. (%)[b]	Ee (%)[c]
1	A	CH_2Cl_2	15	14 (*S*)
2	A[d]	CH_2Cl_2	38	24 (*S*)
3	B	CH_2Cl_2	72	26 (*S*)
4	A	MeCN	25	60 (*S*)
5	A[d]	MeCN	13	19 (*S*)
6	B	MeCN	52	45 (*S*)
7	A	THF	20	22 (*S*)
8	A[d]	THF	22	20 (*S*)
9	B	THF	8	6 (*S*)
10	A	DMF	18	68 (*S*)
11	A[d]	DMF	15	6 (*S*)
12	B	DMF	79	38 (*S*)

[a] Reactions performed at room temperature for 3 days.
[b] Conversions determined by ^{1}H NMR.
[c] Enantiomeric excesses of **15** determined by chiral HPLC.
[d] 15-crown-5 added.

also led to a dramatic decrease in the enantioselectivity from 60 to 19% in the case of acetonitrile (entries 4 and 5), and from 68 to 6% for DMF (entries 10 and 11). On changing to the BSA method, the conversions obtained in both these solvents increased, however, the enantioselectivities were lower with respect to those seen for the malonate procedure (entries 6 vs 4 and 12 vs 10). The reaction was also carried out in THF but in all instances the conversions and enantioselectivities were poor (entries 7–9).

When the reaction temperature was lowered to 0 °C the yields decreased sharply, although enhanced ees were achieved with an optimum result for (*R*)-2-(2-pyrazinyl)-Quinazolinap of 81% being obtained in acetonitrile (Table 4, entry 2). Improvements were also seen for the reaction in DMF, wherein the enantioselectivity rose from 38 to 61% (Table 3, entry 12 vs Table 4, entry 5). In an effort to increase the conversion, reactions were then carried out at 40 °C (entries 6–8). When acetonitrile was used as solvent the conversion was greatly enhanced, reaching completion when the BSA-promoted procedure was employed although the enantioselectivity remained unchanged. On changing solvent to DMF, an improved conversion was again seen at the higher reaction temperature but a slight decrease in enantioselectivity was apparent (entry 6).

The fact that low enantioselectivities were obtained using palladium complexes derived from Quinazolinaps **3a** and **3b** is consistent with the presence of a bulky substituent in the 2-position of the quinazoline ring. Low to moderate enantio-differentiation had been observed in the case of the similarly sized 2-(phenyl)-Quinazolinap **2e**, although the rate of reaction was not as slow for **2e**, with some reactions reaching completion after a couple of hours.[8] Similar reaction times were recorded for the other members of the Quinazolinap ligand series, **2a–f**, all of which possess alkyl groups as the 2-substituent.[10] Hence, the retardation of reaction rate seen when ligands **3a** and **3b** were employed could possibly be attributed to electronic alterations to the catalytic complex due to the presence of the electron-withdrawing 2-pyridyl and 2-pyrazinyl substituents. The possible hemi-labile nature of these substituents, evident in the crystal structures obtained in the present study, Figures 1 and 2, may also be a factor in hindering the progress and stereochemical outcome of the reaction.

Table 4. Palladium-catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with 2-(2-pyrazinyl)-Quinazolinap **3b**

Entry	Method	Solvent	Time (d)	Temperature (°C)	Conv. (%)[a]	Ee (%)[b]
1	A[c]	CH_2Cl_2	5	0	29	37 (*S*)
2	A	MeCN	5	0	25	81 (*S*)
3	B	MeCN	5	0	36	42 (*S*)
4	A	DMF	5	0	0	n/a
5	B	DMF	5	0	18	61 (*S*)
6	A	DMF	3	40	60	61 (*S*)
7	A	MeCN	3	40	85	75 (*S*)
8	B	MeCN	3	40	100	45 (*S*)

[a] Conversions determined by ^{1}H NMR.
[b] Enantiomeric excesses of **15** determined by chiral HPLC.
[c] 15-crown-5 added.

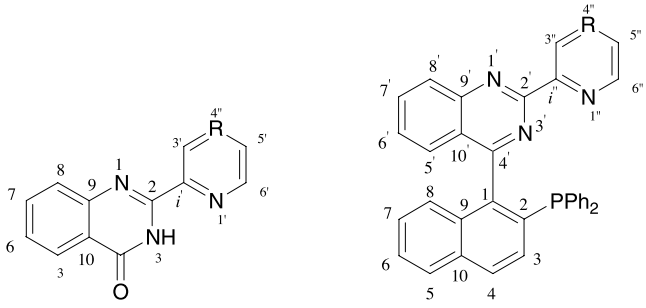
Also noteworthy in the reactions catalysed by (*S*)-2-(2-pyridyl)-Quinazolinap (Table 3), is that, in some instances the (*S*)-enantiomer was formed preferentially. This is the opposite sense of asymmetry to that obtained by Pd-complexes of the less sterically demanding members of the Quinazolinap ligand series (**2a–c**) but was observed in reactions involving the bulky 2-phenyl and 2-*tert*-butyl analogues (**2d–e**).

In conclusion, two new atropisomeric phosphinamine ligands, 2-(2-pyridyl)-Quinazolinap and 2-(2-pyrazinyl)-Quinazolinap were synthesised and resolved via fractional crystallisation of their diastereomeric palladacycles. These ligands were applied in the palladium-catalysed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate by dimethyl malonate. Low conversions and enantioselectivities were obtained with both ligands, possibly due to the hemi-labile nature of the nitrogen atom of the 2-substituent as revealed in the X-ray crystal structures of the Pd-bound diastereomers. Mechanistic studies are currently underway to further investigate both the steric and electronic influences of 2-(2-pyridyl)- and 2-(2-pyrazinyl)-Quinazolinap on the outcome of the allylic alkylation reaction.

5. Experimental

5.1. General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Infrared FT spectrometer. The Microanalytical Laboratory, University College Dublin, performed elemental analyses. Electron impact mass spectra were determined on a VG Analytical 770 mass spectrometer with attached INCOS 2400 data system in the EI mode unless otherwise stated. Electrospray mass spectra were recorded on a Micromass Quattro with electrospray probe. Exact mass ESI mass spectra (HRMS) were measured on a micromass LCT orthogonal time of flight mass spectrometer with leucine enkephalin (Tyr-Gly-Phe-Leu) as an internal lock mass. ^{1}H NMR spectra were obtained on a 300 MHz Varian-Unity spectrometer and a 500 MHz Varian-Unity spectrometer. ^{1}H–^{1}H COSY spectra were recorded on a 300 MHz Varian-Unity spectrometer and a 500 MHz Varian-Unity spectrometer. Chemical shifts are quoted in ppm relative to tetramethylsilane and coupling constants (*J*) are quoted in Hz. $CDCl_3$ was used as the solvent for all NMR spectra unless otherwise stated. 75.4 MHz ^{13}C spectra were recorded on a 300 MHz Varian-Unity spectrometer. Tetramethylsilane was used as the internal standard in all ^{13}C spectra recorded. 121.4 MHz ^{31}P spectra were recorded on a 300 MHz Varian-Unity spectrometer and ^{31}P chemical shifts are reported relative to 85% aqueous phosphoric acid (0.0 ppm). Flash chromatography was performed using Merck Kieselgel 60 (Art. 9385) and aluminium oxide 90, standardized (activity II–III). Merck precoated Kieselgel $60F_{254}$ and alumina (neutral, type E) were used for thin layer chromatography. HPLC analysis was carried out using a Chiralcel OD column (0.46 cm 1.d.×25 cm). Optical rotation values were measured on a Perkin Elmer 241 Polarimeter. All commercially available solvents were purified and dried before use. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride. Where necessary other solvents and reagents (purchased from Aldrich Chemical Co.) used were purified according to the procedures in 'Purification of Laboratory Chemicals'. Pd salts were obtained on loan from Johnson Matthey. Solvents were degassed using three freeze–thaw cycles. Oxygen-free nitrogen was obtained from BOC gases. The following compounds, 2-methoxy-1-naphthylboronic acid,[3] (+)-di-μ-chlorobis{(*R*)-dimethyl[1-(1-naphthyl)ethyl]aminato-C_2,N}dipalladium (II),[24] 1,3-diphenylprop-2-enyl acetate[25] and di-μ-chloro-bis(π-allyl)dipalladium[26] were prepared according to literature procedures. For ease of interpretation of NMR data the following numbering schemes were used for compounds **5** and **3** and related compounds are numbered similarly.



5.1.1. 2-(2-Pyridyl)-4(3*H*)quinazolinone 5a. 2-Cyanopyridine (7.18 g, 6.64 mL, 68.97 mmol) was added to anhydrous methanol (20 mL) under an atmosphere of nitrogen. A solution of sodium metal (0.40 g, 17.40 mmol) in anhydrous methanol (100 mL) was added via cannula. This was stirred at room temperature for 1 h. A solution of anthranilic acid (12.00 g, 87.51 mmol) in dry methanol (125 mL) was added via cannula and the resulting yellow solution stirred at room temperature for a further 45 min. The reaction mixture was then refluxed for 18 h at 85 °C. After cooling to room temperature and then in an ice bath for 1 h a yellow precipitate of 2-(2-pyridyl)-4(3*H*)quinazolinone (11.14 g, 72%) was removed by filtration. On standing overnight, the mother liquor yielded a yellow needle-like precipitate (1.73 g, 11%), which was also collected by filtration, mp 169–171 °C (lit.[27], mp 168.3–168.4 °C); ν_{max} (KBr) 3339 (N–H), 1682 (C=O), 1616 (C=C), 1471 (Ar-H), 1329 (C=N) and 737 (Ar-H) cm^{-1}; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 10.94 (br s, 1H, NH), 8.67 (d, 1H, J=4.8 Hz, $H_{6'}$), 8.59 (d, 1H, J=8.1 Hz, $H_{3'}$), 8.36 (dd, 1H, J_1=7.2 Hz, J_2=1.6 Hz, H_5), 7.92 (dt, J_1=8.1 Hz, J_2=1.6 Hz, H_7), 7.80 (m, 2H, $H_{4'}$, H_8) and 7.50 (m, 2H, H_7, $H_{5'}$); Found: C, 69.64; H, 3.96; N, 19.05. $C_{13}H_9N_3O$ requires C, 69.94; H, 4.06; N, 18.82%.

2-(2-Pyrazinyl)-4(3*H*)quinazolinone **5b** was prepared from pyrazinecarbonitrile on a similar scale and in a similar manner and was obtained in 97% yield as a yellow solid, mp 218–220 °C; ν_{max} (KBr) 3040 (N–H), 1697 (C=O), 1603 (C=C), 1472 (Ar-H) and 766 (Ar-H) cm^{-1}; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 10.63 (br s, 1H, NH), 9.82 (d, 1H, J=1.3 Hz, $H_{3'}$), 8.79 (d, 1H, J=2.5 Hz, $H_{5'}$), 8.65 (d, 1H, J=1.9 Hz, $H_{6'}$), 8.36 (d, 1H, J=7.9 Hz, H_5), 7.85 (m, 2H,

H_7, H_8) and 7.56 (dt, 1H, $J_1=8.1$ Hz, $J_2=1.8$ Hz, H_6); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 161.1, 148.7, 147.3, 146.9, 144.3, 143.8, 142.9, 134.9, 128.3, 128.0, 126.8, 122.6; Found: C, 63.95; H, 3.44; N, 24.85. $C_{12}H_8N_4O$ requires C, 64.28; H, 3.60; N, 24.99%.

5.1.2. 2-(2-Pyridyl)-4-chloroquinazolinone 6a. *N*,*N*-Diethylaniline (4.09 g, 4.39 mL, 27.61 mmol) was added via syringe to 2-(2-pyridyl)-4(3*H*)quinazolinone (4.11 g, 18.41 mmol) in anhydrous benzene (85 mL). This was heated for 5 min at 100 °C to remove water. Phosphorus oxychloride (2.22 g, 1.33 mL, 14.53 mmol) was added via syringe and the resulting deep red solution was refluxed for 4 h at 90 °C after, which time additional phosphorus oxychloride (0.44 g, 0.27 mL, 3.20 mmol) was added. The solution was refluxed for a further 2 h, allowed to cool then washed with iced water (40 mL). The organic layer was then washed sequentially with 20% NaOH (2×30 mL), iced water (30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. The organic solvent was removed in vacuo and the residue was purified by column chromatography (aluminium oxide, cyclohexane until the *N*,*N*-diethylaniline eluted, then 2:1 cyclohexane–ethyl acetate) to give 2-(2-pyridyl)-4-chloroquinazoline (4.45 g, 68%) as a pale yellow powder. The aqueous layers were combined and extracted with dichloromethane. The organic layer was reduced in vacuo to yield a yellow oil, which was purified by column chromatography as above, providing further product to give a total yield of 3.33 g (77%). Mp 120–121 °C (lit.[28], mp 119.7–122.4 °C); ν_{max} (KBr) 3068 (Ar-H), 2922 (Ar-H), 1546 (C=C), 1483 (Ar-H), 1342 (C–N) and 779 (C–Cl) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 8.92 (d, 1H, $J=4.7$ Hz, $H_{6'}$), 8.68 (d, 1H, $J=7.8$ Hz, $H_{3'}$), 8.31 (m, 2H, H_8, H_5), 7.99 (dt, 1H, $J_1=8.5$ Hz, $J_2=1.5$ Hz, H_7), 7.91 (dt, 1H, $J_1=7.9$ Hz, $J_2=1.8$ Hz, $H_{4'}$), 7.75 (t, 1H, $J=8.1$ Hz, H_6) and 7.45 (m, 1H, $H_{5'}$); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 163.1, 158.8, 153.9, 151.8, 150.4, 137.1, 135.1, 129.6, 129.1, 125.8, 125.2, 124.4 and 123.0.

2-(2-Pyrazinyl)-4-chloroquinazoline **6b** was similarly prepared in 56% yield as a yellow solid, mp 178–180 °C; ν_{max} (KBr) 2928 (Ar-H), 1549 (C=C), 1486 (Ar-H), 1342 (C=N) and 758 (C–Cl) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 9.87 (s, 1H, $H_{3'}$), 8.86 (dd, $J_1=2.5$ Hz, $J_2=1.5$ Hz, 1H, $H_{5'}$), 8.74 (d, $J=2.5$ Hz, 1H, $H_{6'}$), 8.35 (d, 1H, $J=7.6$ Hz, H_5), 8.29 (d, 1H, $J=8.1$ Hz, H_8), 8.03 (dt, 1H, $J_1=6.9$ Hz, $J_2=1.5$ Hz, H_7) and 7.80 (dt, 1H, $J_1=8.3$ Hz, $J_2=1.2$ Hz, H_6); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 163.5, 157.8, 151.6, 149.3, 145.9, 145.8, 144.7, 135.5, 129.7, 129.6, 126.0 and 122.7; Found: C, 59.71; H, 2.72; N, 14.66, Cl, 22.89. $C_{12}H_7N_4Cl$ requires C, 59.39; H, 2.91; N, 14.61, Cl, 23.09%.

5.1.3. 2-(2-Pyridyl)-4-(2-methoxynaphthalen-1-yl)-quinazoline 8a. 2-(2-Pyridyl)-4-chloroquinazoline (6.68 g, 27.64 mmol) and tetrakis(triphenylphosphine)palladium (0) (1.10 g, 0.96 mmol) were dissolved in anhydrous, degassed DME (65 mL) in a Schlenk tube under nitrogen and stirred for 1 h to give a yellow solution. 2-Methoxy-1-naphthylboronic acid (5.75 g, 28.46 mmol), in the minimum amount of degassed ethanol (18 mL) was added via syringe resulting in a dark purple solution. Sodium carbonate solution (28.4 mL, 2 M) was added causing the solution to turn green followed by the formation of a white precipitate. The mixture was refluxed at 95 °C for 4 days. The solution was cooled to room temperature and filtered. The solid was washed with dichloromethane and the filtrate reduced in vacuo to give a purple residue, which was redissolved in dichloromethane (100 mL), washed with brine (3×50 mL), dried over magnesium sulfate and the solvent removed in vacuo yielding a dark orange solid. 2-(2-Pyridyl)-4-(2-methoxynaphthalen-1-yl)-quinazoline (7.81 g, 77%) was isolated via column chromatography (aluminium oxide, 2:1 petrol ether–ethyl acetate), mp 204–206 °C; ν_{max} (KBr) 3056 (Ar-H), 1622 (C=N), 1582 (C=C), 1511 (Ar-H), 1341 (C–O), 1249 (C–O) and 789 (Ar-H) cm^{-1}; ^1H NMR (500 MHz): δ ($CDCl_3$) 8.92 (d, 1H, $J=4.5$ Hz, $H_{6''}$), 8.68 (d, 1H, $J=8.1$ Hz, $H_{3''}$), 8.40 (d, 1H, $J=8.4$ Hz, $H_{5'}$), 8.05 (d, 1H, $J=9.1$ Hz, H_4), 7.89 (m, 2H, $H_{7'}$, H_5), 7.81 (dt, 1H, $J_1=7.4$ Hz, $J_2=1.6$ Hz, $H_{4''}$), 7.52 (d, 1H, $J=8.4$ Hz, H_7), 7.44 (m, 2H, H_3, $H_{8'}$), 7.36 (m, 2H, $H_{5''}$, $H_{6'}$), 7.28 (dt, 1H, $J_1=8.7$ Hz, $J_2=1.6$ Hz, H_6), 7.18 (d, 1H, $J=8.4$ Hz, H_8) and 3.77 (s, 3H, OCH_3); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 168.1, 160.1, 155.9, 155.0, 151.5, 150.5, 137.0, 134.1, 133.4, 131.5, 129.9, 129.3, 128.3, 128.0, 127.4, 127.2, 124.9, 124.9, 124.7, 124.7, 124.2, 120.2, 113.6, 56.8; Found: C, 79.06; H, 4.77; N, 11.49. $C_{24}H_{17}N_3O$ requires C, 79.32; H, 4.72; N, 11.56%.

Similarly, 2-(2-pyrazinyl)-4-(2-methoxynaphthalen-1-yl)-quinazoline **8b** was prepared by the coupling of 2-(2-pyrazinyl)-4-chloroquinazoline with 2-methoxy-1-naphthylboronic acid in a 78% yield, mp 202–204 °C; ν_{max} (KBr) 3080 (Ar-H), 2936 (Ar-H), 1620 (C=N), 1541 (C=C), 1512 (Ar-H), 1272 (C–O) and 758 (Ar-H) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 9.90 (s, 1H, $H_{3''}$), 8.85 (deform. T., 1H, $J=1.5$ Hz, $H_{5''}$), 8.69 (d, 1H, $J=2.3$ Hz, $H_{6''}$), 8.39 (d, 1H, $J=8.5$ Hz, $H_{8'}$), 8.08 (d, 1H, $J=9.1$ Hz, H_4), 7.93 (m, 2H, $H_{7'}$, H_6), 7.57 (d, 1H, $J=7.6$ Hz, $H_{5'}$), 7.51 (d, 1H, $J=6.6$ Hz, $H_{6'}$), 7.46 (d, 1H, $J=8.9$ Hz, H_3), 7.33 (m, 2H, H_5, H_7), 7.16 (d, 1H, $J=8.3$ Hz, H_8) and 3.80 (s, 3H, OCH_3); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 186.4, 158.7, 154.8, 151.2, 151.0, 146.3, 145.2, 144.6, 134.4, 133.1, 131.5, 129.6, 129.0, 128.4, 128.2, 127.4, 127.2, 125.0, 124.3, 124.0, 119.5, 113.3, 56.6; Found: C, 75.51; H, 4.49; N, 15.19. $C_{23}H_{16}N_4O$ requires C, 75.81; H, 4.43; N, 15.38%.

5.1.4. 1-[2-(2-Pyridyl)-quinazolin-4-yl]-2-hydroxynaphthalene 9a. 2-(2-Pyridyl)-4-(2-methoxynaphthalen-1-yl)-quinazoline (1.02 g, 2.81 mmol) and aluminium chloride (2.24 g, 16.80 mmol) were refluxed in anhydrous benzene (110 mL) under a nitrogen atmosphere for 3 h. The dark purple mixture was allowed to cool and the pH was adjusted to 4 using 10% HCl. The resulting fine orange precipitate formed was filtered through sintered glass to yield 1-[2-(2-pyridyl)-quinazolin-4-yl]-2-hydroxynaphthalene (0.48 g, 48%). T_{dec} 226 °C; ^1H NMR (300 MHz): δ ($CDCl_3$) 8.92 (d, 1H, $J=4.7$ Hz, $H_{6''}$), 8.72 (d, 1H, $J=8.2$ Hz, $H_{5''}$), 8.33 (d, 1H, $J=8.2$ Hz, $H_{4''}$), 8.00–7.91 (m, 3H), 7.86 (d, 1H, $J=7.8$ Hz), 7.66 (d, 1H, $J=7.8$ Hz), 7.51–7.43 (m, 2H), 7.41 (d, 1H, $J=8.9$ Hz and 7.38–7.32) (m, 3H); *m*/*z* (HRMS, ES) found: 350.1306; $C_{23}H_{16}N_3O$ requires 350.1293.

5.1.5. 1-[2-(2-Pyrazinyl)-quinazolin-4-yl]-2-hydroxynaphthalene 9b. Sodium ethanethiolate (2.41 g, 28.6 mmol)

was added to a solution of 2-(2-pyrazinyl)-4-(2-methoxynaphthalen-1-yl)-quinazoline (4.70 g, 12.90 mmol) in degassed DMF (80 mL) and the red solution refluxed at 120 °C for 3.5 h. After cooling to room temperature, the pH was adjusted to 5 using 10% HCl (3 mL), which caused the solution to turn orange in colour. The solution was allowed to stir for 10 min and a yellow precipitate formed. This was filtered through sintered glass to yield 1-[2-(2-pyrazinyl)-quinazolin-4-yl]-2-hydroxynaphthalene (3.01 g, 66%) as a bright yellow powder. The filtrate was extracted into dichloromethane (100 mL). The organic layer was washed with water (4×100 mL), dried over sodium sulfate and the solvent removed in vacuo giving a dull yellow solid. Recrystallisation of this solid from hot dichloromethane furnished a further 0.80 g of the desired naphthol resulting in a combined yield of 84%. T_{dec} 250 °C; ν_{max} (KBr), 3732 (OH), 3060 (Ar-H), 1563 (Ar-H), 1494 (OH), 1341 (C=N), 1210 (C–O), 763 (Ar-H) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 9.84 (s, 1H, $H_{3''}$), 9.31 (br s, 1H, OH), 8.66 (m, 2H, $H_{5''}$, $H_{6''}$), 8.26 (d, 1H, $J=8.5$ Hz, $H_{8'}$), 7.93 (dt, 1H, $J_1=6.8$ Hz, $J_2=1.5$ Hz, $H_{7'}$), 7.85 (d, 2H, $J=9.0$ Hz, H_4, H_5), 7.68 (d, 1H, $J=8.2$ Hz, $H_{5'}$), 7.48 (dt, 1H, $J_1=6.8$ Hz, $J_2=1.2$ Hz, $H_{6'}$), 7.36 (dt, 1H, $J_1=6.6$ Hz, $J_2=1.5$ Hz, H_6) and 7.25 (m, 3H, H_3, H_7, H_8); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 167.7, 157.2, 154.1, 151.6, 150.0, 145.6, 145.5, 144.2, 134.8, 132.8, 132.1, 129.6, 128.7, 128.4, 128.3, 128.0, 127.4, 126.9, 124.4, 124.2, 123.6, 119.4 and 115.3; Found: C, 74.93; H, 4.13; N, 15.51. $C_{22}H_{14}N_4O$ requires C, 75.41; H, 4.03; N, 15.99%.

5.1.6. 1-[2-(2-Pyridyl)quinazolin-4-yl]-2-naphthyltrifluoromethylsulfonate 10a. 1-[2-(2-Pyridyl)-quinazolin-4-yl]-2-hydroxynaphthalene (0.38 g, 1.10 mmol) and 4-dimethylaminopyridine (0.34 g, 2.75 mmol) were dissolved in dry dichloromethane (20 mL). Trifluoromethanesulfonic anhydride (0.66 g, 0.4 mL, 2.37 mmol) was added and the solution stirred for 20 h under nitrogen. A white precipitate formed, which was removed by filtration. The solid was washed with dichloromethane and the combined filtrates were reduced in vacuo to give a yellow solid. This was purified by column chromatography (aluminium oxide, 2:1 petrol ether–ethyl acetate) to yield 1-[2-(2-pridyl)-quinazolin-4-yl]-2-naphthyltrifluoromethylsulfonate (0.47 g, 78%) as a white solid, mp 176–177 °C; ν_{max} (KBr) 2929 (Ar-H), 1544 (Ar-H), 1405 (–SO_3–), 1219 (–SO_3–), 1135 (C–O) and 828 (Ar-H) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 8.94 (d, 1H, $J=3.8$ Hz, $H_{6''}$), 8.70 (d, 1H, $J=7.9$ Hz, $H_{3''}$), 8.46 (d, 1H, $J=8.6$ Hz, $H_{8'}$), 8.17 (d, 1H, $J=9.1$ Hz, H_4), 8.03 (d, 1H, $J=8.3$ Hz, H_5), 7.97 (dt, 1H, $J_1=6.7$ Hz, $J_2=1.6$ Hz, $H_{7'}$), 7.86 (dt, 1H, $J_1=7.5$ Hz, $J_2=1.8$ Hz, $H_{4''}$), 7.64 (d, 1H, $J=9.1$ Hz, H_3), 7.60 (dt, 1H, $J_1=6.8$ Hz, $J_2=1.3$ Hz, H_6), 7.47 (m, 4H, $H_{6'}$, $H_{5'}$, H_7, $H_{5''}$) and 7.31 (d, 1H, $J=7.5$ Hz, H_8); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 163.8, 159.7, 155.0, 151.6, 150.4, 144.8, 137.1, 134.7, 132.5, 132.4, 132.1, 130.1, 128.5, 128.5, 128.4, 127.5, 127.3, 126.3, 126.2, 124.9, 124.8, 124.0, 119.6; Found: C, 59.58; H, 2.83; N, 8.54; S, 6.76; F, 11.39. $C_{24}H_{14}N_3SF_3O_3$ requires C, 59.87; H, 2.93; N, 8.73; S, 6.66; F, 11.84%.

5.1.7. 1-[2-(2-Pyrazinyl)quinazolin-4-yl]-2-naphthyltrifluoromethylsulfonate 10b. 1-[2-(2-Pyrazinyl)-quinazolin-4-yl]-2-hydroxynaphthalene (1.28 g, 3.64 mmol) and 4-dimethylaminopyridine (1.30 g, 10.81 mmol) were dissolved in dry dichloromethane (40 mL) to give a bright yellow solution. Trifluoromethanesulfonic anhydride (1.53 g, 0.91 mL, 7.28 mmol) was added and the orange solution stirred at room temperature for 48 h under nitrogen. A white precipitate formed, which was removed by filtration. The solid was washed with dichloromethane and the combined filtrates were reduced in vacuo to give a yellow solid. This was purified by column chromatography (aluminium oxide, 2:1 pentane–ethyl acetate) to yield 1-[2-(2-pyrazinyl)-quinazolin-4-yl]-2-naphthyltrifluoromethylsulfonate (1.24 g, 71%) as a white solid, mp 160–162 °C; ν_{max} (KBr) 3070 (Ar-H), 1512 (C=C), 1427 (–SO_3–), 1343 (C=N), 1218 (–SO_3–), 1142 (C–O) and 831 (Ar-H) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 9.91 (s, 1H, $H_{3''}$), 8.87 (app t, 1H, $J=1.6$ Hz, $H_{5''}$), 8.72 (d, 1H, $J=2.3$ Hz, $H_{6''}$), 8.45 (d, 1H, $J=8.5$ Hz, $H_{8'}$), 8.19 (d, 1H, $J=9.1$ Hz, H_4), 8.05 (d, 1H, $J=7.6$ Hz, H_5), 8.00 (dt, 1H, $J_1=7.0$ Hz, $J_2=1.5$ Hz, $H_{7'}$), 7.65 (d, 1H, $J=9.1$ Hz, H_3), 7.54 (m, 4H, $H_{5'}$, $H_{6'}$, H_6, H_7) and 7.31 (d, 1H, $J=8.3$ Hz, H_8); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 164.2, 158.1, 151.4, 150.3, 146.3, 145.6, 144.8, 144.7, 135.1, 132.4, 132.3, 123.0, 129.1, 128.5, 128.5, 127.6, 126.6, 126.1, 124.3 and 119.6; Found: C, 57.05; H, 2.91; N, 11.32; S, 6.95; F, 11.72. $C_{23}H_{13}N_4SF_3O_3$ requires C, 57.26; H, 2.72; N, 11.61; S 6.65; F, 11.81%.

5.1.8. (*R*,*S*)-2-Diphenylphosphino-1-[2-(2-pyridylquinazolin-4)-yl]naphthalene 3a. 1-[2-(2-Pyridyl)quinazolin-4-yl]-2-naphthyltrifluoromethylsulfonate (2.66 g, 5.54 mmol), palladium acetate (0.12 g, 0.55 mmol) and triphenylphosphine (3.34 g, 12.74 mmol) were dissolved under a nitrogen atmosphere in degassed DMF (24 mL). The yellow solution was heated at 115 °C causing it to turn red in colour. The solution was maintained at this temperature, under an atmosphere of nitrogen, for 6 days. The solvent was removed in vacuo. The residue was purified by column chromatography (aluminium oxide, 2:1 petroleum ether–ethyl acetate) to furnish (*R*,*S*)-2-diphenylphosphino-1-[2-(2-pyridylquinazolin-4)-yl]naphthalene (1.68 g, 59%) as a white solid, mp 216–218 °C; ν_{max} (KBr) 3053 (Ar-H), 2921 (Ar-H), 1613 (Ar-H), 1542 (Ph), 1491 (Ph), 1340 (C=N) and 744 (Ar-H) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 8.86 (d, 1H, $J=4.6$ Hz, $H_{6''}$), 8.44 (d, 1H, $J=8.6$ Hz, $H_{3''}$), 7.97–7.87 (m, 3H), 7.75 (d, 1H, $J=7.7$ Hz), 7.56–7.48 (m, 2H), 7.43–7.37 (m, 3H) and 7.34–7.10 (m, 14H); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 169.4, 161.2, 155.2, 151.3, 150.1, 141.8, 141.5, 136.7, 134.6, 134.0, 133.9, 133.7, 133.6, 133.4, 131.8, 129.9, 129.3, 128.5, 128.4, 128.3, 128.1, 127.9, 127.0, 126.8, 126.2, 124.7 and 124.4; ^{31}P NMR (121 MHz): δ ($CDCl_3$) −12.23 ppm. *m/z* (HRMS, ES) 518.1808 $C_{35}H_{25}N_3P$ cation.

(*R*,*S*)-2-Diphenylphosphino-1-[2-(2-pyrazinylquinazolin-4)-yl]naphthalene **3b** was prepared in an analogous fashion via phosphinylation of 1-[2-(2-pyrazinyl)quinazolin-4-yl]-2-naphthyltrifluoromethylsulfonate in a 53% yield after column chromatography on aluminium oxide. Mp 220–222 °C; ν_{max} (KBr) 3050 (Ar-H), 2904 (Ar-H), 1612 (Ar-H), 1564 (Ph), 1546 (Ph), 1340 (C=N) and 744 (Ar-H) cm^{-1}; ^1H NMR (300 MHz): δ ($CDCl_3$) 9.02 (d, $J=1.4$ Hz, 1H, $H_{3''}$), 8.79 (d, $J=2.3$ Hz, 1H, $H_{5''}$), 8.61 (d, $J=2.5$ Hz, 1H, $H_{6''}$), 8.42 (d, $J=8.1$ Hz, 1H, $H_{8'}$), 7.99–7.91 (m, 3H, Ar-H) and 7.55–7.10 (m, 16H, Ar-H); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 170.0, 157.7, 151.2, 150.5, 146.2, 145.2, 144.4,

141.4, 141.0, 136.9, 136.3, 134.8, 134.4, 133.8, 133.5, 132.2–131.9, 130.0, 129.4, 128.7–128.2, 127.1, 127.0, 126.0, 125.5, and 124.7; ^{31}P NMR (121 MHz): δ ($CDCl_3$) −13.20 ppm; *m/z* (HRMS, ES) 519.1754 $C_{34}H_{24}N_4P$ cation.

5.1.9. Resolution of (*R*,*S*)-2-diphenylphosphino-1-[2-(2-pyridylquinazolin-4)-yl]naphthalene. (*R*,*S*)-2-Diphenylphosphino-1-[2-(2-pyridylquinazolin-4)-yl]naphthalene (1.67 g, 3.2 mmol) and (+)-di-μ-chlorobis{(*R*)-dimethyl[1-(1-naphthyl)ethyl]aminato-C_2,N}dipalladium (II) (1.10 g, 1.62 mmol) were dissolved in dry, degassed methanol (110 mL) under an atmosphere of nitrogen and stirred for 18 h. Aqueous potassium hexafluorophosphate (0.65 g, 110 mL water) was added causing a yellow suspension to form. This was stirred for 1 h and water was added (100 mL) and stirring continued for a further 3 h. The mixture was filtered to give an orange solid (2.61 g, 84%). The solid was dissolved in hot butanone and diethyl ethyl until a light suspension had formed. After standing overnight the mixture was filtered and the mother liquor was concentrated in vacuo to yield (*S*,*R*)-**12** as a bright orange solid, (1.86 g, 60%). T_{dec} 200 °C; ν_{max} (KBr) 3060 (Ar-H), 1569 (C=C), 1438 (P-Ph), 1098 (Ar-H) and 841 (P-F) cm^{-1}; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 8.89 (d, 1H, J=8.0 Hz, $H_{6''}$), 8.44 (d, 1H, J=4.3 Hz, $H_{3''}$), 8.25 (dt, 1H, J_1=8.0 Hz, J_2=1.8 Hz, $H_{5''}$), 8.07–7.93 (m, 3H), 7.74 (d, 1H, J=7.6 Hz), 7.66 (t, 1H, J=7.3 Hz), 7.59–6.82 (m, 22H), 4.10 (q, 1H, J=6.0 Hz, C*H*(Me)), 2.06 (s, 3H, NMe), 1.90 (s, 3H, NMe) and 1.26 (d, 1H, J=6.5 Hz, CH(*Me*)); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 165.8, 156.6, 153.9, 152.0, 150.1, 148.8, 147.8, 138.9, 136.7, 135.2, 135.0, 133.1, 132.7, 132.6, 132.6, 131.7, 131.2, 130.1, 129.2, 129.1, 128.9, 128.8, 128.6, 128.4, 128.1, 126.6, 126.5, 126.3, 125.9, 125.1, 124.6, 124.3, 122.9, 71.7 (*C*H(Me)), 51.2 (NMe), 47.3 (NMe) and 20.5 (CH(*Me*)); ^{31}P NMR (121 MHz): δ ($CDCl_3$) 27.61 ppm; −324 (*c* 0.58, $CHCl_3$), *m/z* (HRMS, ES) found: 822.2116; $C_{49}H_{40}N_4PPd$ requires 822.2104.

5.1.10. Resolution of (*R*,*S*)-2-diphenylphosphino-1-[2-(2-pyrazinylquinazolin-4)-yl]naphthalene. (*R*,*S*)-2-Diphenylphosphino-1-[2-(2-pyrazinylquinazolin-4)-yl]naphthalene (0.94 g, 1.8 mmol) and (+)-di-μ-chlorobis{(*R*)-dimethyl[1-(1-naphthyl)ethyl]aminato-C_2,N}dipalladium (II) (0.61 g, 0.9 mmol) were dissolved in dry, degassed methanol (42 mL) under an atmosphere of nitrogen and stirred at 60 °C for 20 h. A white precipitate had formed by this time, which was removed by filtration and washed with a small amount of cold methanol to give (*R*,*R*)-**13** (0.49 g, 28%). T_{dec} 240 °C; ν_{max} (KBr) 3057 (Ar-H), 2919, (Ar-H), 1569 (C=C), 1545 (C=C), 1434 (P-Ph), 1098 (Ar-H) and 747 (Ar-H) cm^{-1}; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 9.65 (s, 1H, $H_{3''}$), 8.82 (d, 1H, J=2.3 Hz, $H_{6''}$), 8.71 (d, 1H, J=2.3 Hz, $H_{5''}$), 8.18–8.08 (m, 3H), 7.97–7.79 (m, 5H), 7.57–7.40 (m, 6H), 7.31–7.16 (m, 8H), 6.95 (appt, 2H), 6.70 (d, 1H, J=8.7 Hz), 6.19 (d, 1H, J=8.2 Hz), 5.93 (t, 1H, J=6.1 Hz) 4.12 (q, 1H, J=5.6 Hz, C*H*(Me)), 2.83 (s, 3H, NMe), 1.93 (d, 3H, J=6.1 Hz, CH(*Me*)) and 1.63 (s, 1H, NMe); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 168.9, 164.5, 157.4, 150.9, 150.7, 148.8, 148.1, 146.0, 145.2, 144.6, 138.2, 138.1, 135.7, 135.6, 153.4, 134.4, 133.4, 132.3, 132.3, 131.1, 130.6, 130.4, 130.3, 128.9, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.3, 127.2, 127.0, 126.2, 125.4, 125.2, 123.9, 123.5, 123.0, 72.8 (*C*H(Me)), 50.6 (NMe), 48.6 (NMe) and 23.5 (CH(*Me*)); ^{31}P NMR (121 MHz): δ ($CDCl_3$) 27.61 ppm; +89 (*c* 0.69, $CHCl_3$), *m/z* (HRMS, ES) found: 823.2048; $C_{48}H_{40}N_5PPd$ requires 823.2056.

To the orange filtrate, was added aqueous potassium hexafluorophosphate and the yellow suspension was stirred at room temperature for 18 h. Water (50 mL) was added and stirring continued for 1 h. The orange solid was filtered off, dissolved in hot butanone and diethyl ether was added until a light suspension formed. The suspension was left to stand overnight, then filtered. The mother liquor was reduced in vacuo to yield (*S*,*R*)-**14** as a bright orange solid, (0.97 g, 56%), mp 230–232 °C; ν_{max} (KBr) 3056 (Ar-H), 2868 (Ar-H), 1562 (C=C), 1437 (P-Ph), 1098 (Ar-H) and 842 (P–F) cm^{-1}; ^{1}H NMR (300 MHz): δ ($CDCl_3$) 10.06 (d, 1H, J=2.0 Hz, $H_{3''}$), 8.87 (s, 1H, $H_{6''}$), 8.45 (s, 1H, $H_{5''}$), 8.17 (d, 1H, J=8.4 Hz), 8.09–7.97 (m, 3H), 7.75–7.63 (m, 3H), 7.52–6.83 (m, 19H), 4.12 (q, 1H, J=6.0 Hz, C*H*(Me)), 2.13 (s, 3H, NMe), 1.97 (s, 3H, NMe) and 1.26 (d, 3H, J=3.7 Hz, CH(*Me*)); ^{13}C NMR (75 MHz): δ ($CDCl_3$) 166.4, 154.9, 151.4, 150.0, 149.1, 148.2, 149.1, 148.2, 147.6, 147.0, 142.1, 137.0, 135.1, 133.2, 132.7, 132.3, 132.3, 132.0, 131.4, 130.7, 129.4, 129.1, 128.9, 128.8, 128.7, 128.1, 126.7, 126.5, 126.4, 126.0, 125.3, 124.8, 124.5, 123.2, 123.0, 122.3, 72.2 (*C*H(Me)), 51.3 (NMe), 47.4 (NMe) and 20.8 CH(*Me*)); ^{31}P NMR (121 MHz): δ ($CDCl_3$) 28.97 ppm; −249 (*c* 0.74, $CHCl_3$), *m/z* (HRMS, ES) found: 822.2018; $C_{48}H_{39}N_5PPd$ requires 822.1978.

5.1.11. (*S*)-2-Diphenylphosphino-1-[2-(2-pyridylquinazolin-4)-yl]naphthalene. *Compound* (*S*,*R*)-**12** (0.62 g, 0.65 mmol) and 1,2-bis(diphenylphosphino)ethane (0.257 g, 0.65 mmol) were dissolved in dichloromethane under an atmosphere of nitrogen and stirred at room temperature for 2 h. The solvent was almost all reduced in vacuo to a yellow oil, which was purified using a short aluminium oxide column (pentane–ethyl acetate 2:1) to give (*S*)-diphenylphosphino-1-[2-(2-pyridylquinazolin-4)-yl] naphthalene as a white solid (0.29 g, 85%), +319 (*c* 0.3, $CHCl_3$), and identical in all other respects to the racemic diphenyl phosphine.

(*R*)-diphenylphosphino-1-[2-(2-pyrazinylquinazolin-4)-yl] naphthalene was similarly isolated from (*R*,*R*)-**13**as a white solid in a 95% yield, +8.0 (*c* 0.55, $CHCl_3$), and identical in all other respects to the previously prepared racemic sample.

5.1.12. Allylic alkylation procedures. *Method A*. (*S*)-2-(2-pyridyl)- or (*R*)-2-(2-pyrazinyl)-Quinazolinap (0.006 mmol) and di-μ-chloro-bis(π-allyl)dipalladium (0.0025 mmol) were placed in a Schlenk tube under an atmosphere of nitrogen. Dry, degassed solvent was added (0.3 mL) and the mixture stirred for 10 min. To this was added a solution of 1,3-diphenylprop-2-enyl acetate (0.063 g, 0.250 mmol) in dry, degassed solvent (0.2 mL). The suspension was stirred for 10 min and then sodium dimethyl malonate (0.042 g, 0.275 mmol) was added and also, if required, 15-crown-5 (55 μL, 0.275 mmol). Reaction progress was monitored by TLC (pentane–diethyl ether 2:1). The reactions were stirred at room temperature for 3 days, or at 0 °C for 5 days, before being quenched by the addition of acetic acid (0.1 mL). The solvent was reduced in vacuo and water (25 mL) was added.

The reaction mixture was extracted into diethyl ether (25 mL), washed with water (25 mL) then brine (25 mL), dried over $MgSO_4$, filtered and the solvent removed in vacuo to give a yellow oil. The % conversion was calculated using ^1H NMR of the crude product. The product was purified on preparative silica plates (pentane–diethyl ether 2:1) to afford (*R*)- or (*S*)-methyl-2-carbomethoxy-3,5-diphenylpent-4-enoate **15** as a colourless oil.[20] ^1H NMR (300 MHz): δ ($CDCl_3$) 7.34–7.20 (10H, m, Ar-H), 6.47 (1H, d, $J=15.82$ Hz, H_3), 6.34 (1H, dd, $J=15.82$, 8.35, H_2), 4.27 (1H, dd, $J=10.84$, 8.49 Hz, H_1), 3.95 (1H, d, $J=10.84$ Hz, C*H*(CO_2Me)$_2$), 3.70 (3H, s, OMe) and 3.52 (3H, s, OMe). The enantiomeric excess was determined by chiral HPLC [Daicel (Chiracel OD) column, 0.46 cm I.D.×25 cm], pentane–isopropanol 99:1, 0.3 mL/min, $R_t=(R)-42$ min, $(S)-45$ min.

Method B. (*S*)-2-(2-pyridyl)- or (*R*)-2-(2-pyrazinyl)-Quinazolinap (0.006 mmol) and di-μ-chloro-bis(π-allyl)dipalladium (0.0025 mmol) were placed in a Schlenk tube under an atmosphere of nitrogen. Dry, degassed solvent was added (0.3 mL) and the mixture stirred for 10 min. To this was added a solution of 1,3-diphenylprop-2-enyl acetate (0.063 g, 0.250 mmol) in dry, degassed solvent (0.2 mL). Potassium acetate (0.005 mmol) was added and the suspension was stirred for 10 min. Dimethyl malonate (31.5 μL, 0.275 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (68 μL, 0.275 mmol) were added and the reactions stirred at room temperature for 3 days, or 0 °C for 5 days. The work-up and determination of conversion and enantioselectivity were the same as described for method A.

5.2. X-ray analysis of (*S*,*R*)-12

Crystal data for (*S*,*R*)-**12**·1.5(CH_2Cl_2): $[C_{49}H_{40}N_4PPd]^+[PF_6]^-\cdot 1.5(CH_2Cl_2)$, from dichloromethane/diethylether, $M_r=1094.58$, orange prism, crystal size: 0.04×0.09×0.16 mm^3; $a=32.1529(6)$ Å, $b=12.7212(3)$ Å, $c=11.7891(3)$ Å, $\beta=104.120(1)°$, $V=4676.3(2)$ $Å^3$, $T=100$ K, monoclinic, space group *C* 2 (No. 5), $Z=4$, $\rho_{calcd}=1.555$ g cm^{-3}, $F(000)=2220$, Nonius Kappa CCD diffractometer, λ(Mo K_α)=0.71073 Å, $\mu=0.702$ mm^{-1}, 39,890 measured and 17,396 independent reflections ($R_{int}=0.068$), 14,603 with $I>2\sigma(I)$, $\theta_{max}=33.14°$, $T_{min}=0.933$, $T_{max}=0.979$, direct methods (SHELXS-97) and least-squares refinement (SHELXL-97) on F_o^2, both programs from G. Sheldrick, University of Göttingen, 1997; 302 parameters, Flack parameter 0.00(2), one of the dichloromethane solute molecules is disordered about a two-fold axis, H atoms riding, Chebyshev type weights, $R_1=0.0533$ ($I>2\sigma(I)$), $wR_2=0.1200$ (all data), $\Delta\rho_{max/min}=0.816/-0.850$ e $Å^{-3}$. CCDC 265942.[1]

5.3. X-ray analysis of (*S*,*R*)-14

Crystal data for (*S*,*R*)-**14**·$C_4H_{10}O$: $[C_{48}H_{39}N_5PPd]^+[PF_6]^-\cdot C_4H_{10}O$, from chloroform/diethylether, $M_r=1042.3$, orange-red prism, crystal size: 0.02×0.06×0.11 mm^2; $a=8.9132(1)$ Å, $b=22.5067(3)$ Å, $c=12.0303(1)$ Å, $\beta=103.079(1)°$, $V=2350.75(5)$ $Å^3$, $T=100$ K, monoclinic, space group $P2_1$ (No. 4), $Z=2$, $\rho_{calcd}=1.473$ g cm^{-3}, $F(000)=1068$, Nonius KappaCCD diffractometer, λ(Mo K_α)=0.71073 Å, $\mu=0.532$ mm^{-1}, 64011 measured and 14940 independent reflections ($R_{int}=0.038$), 14207 with $I>2\sigma(I)$, $\theta_{max}=30.99°$, $T_{min}=0.956$, $T_{max}=0.989$, direct methods (*SHELXS*−97) and least-squares refinement (*SHELXL*-97) on F_o^2, both programs from G. Sheldrick, University of Göttingen, 1997; 631 parameters, Flack parameter −0.03(1), the diethylether solute is disordered over two positions, H atoms riding except for the solute where they are absent, Chebyshev type weights, $R_1=0.0259$ ($I>2\sigma(I)$), $wR_2=0.0615$ (all data), $\Delta\rho_{max/min}=0.440/-0.376$ e $Å^{-3}$. CCDC 265943.[1]

Data for the crystal structures of (*S*,*R*)-**12**·1.5(CH_2Cl_2) and (*S*,*R*)-**14**·$C_4H_{10}O$ can be obtained free of charge on quotation of the CCDC deposition numbers 265942 and 265943 via www.ccdc.cam.ac.uk/conts/retrieving.html (or) from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223-336-033; or e-mail: deposit@ccdc.cam.ax.uk.

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Reversal of aryl bromide reactivity in Pd-catalysed aryl amination reactions promoted by a hemilabile aminophosphine ligand

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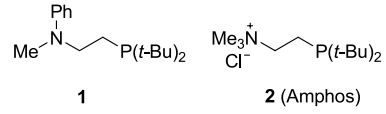
Abstract—Incorporation of a hemilabile amino group with a bulky, electron-rich phosphorus ligand led to a reversal in the order of aryl bromide reactivity in Pd-catalysed aryl amination reactions.

1. Introduction

Electron-rich, sterically bulky alkylphosphines constitute the majority of ligands that promote palladium-catalysed cross-coupling reactions under mild reaction conditions. The remarkable reactivity has been attributed to the ability of these bulky ligands to provide highly coordinatively unsaturated, nucleophilic palladium catalytic precursors.[1]

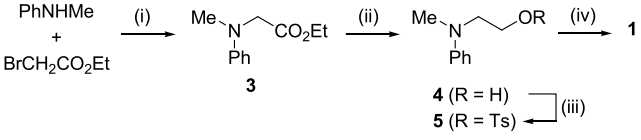
As part of our continued effort to develop nitrogen–phosphorus hybrid ligands for transition-metal mediated catalysis,[2] the aminophosphine ligand **1** was synthesised and its catalytic activity examined. We are particularly interested in exploring potential beneficial effect(s) of introducing a hemilabile nitrogen donor on catalyst activity and/or stability. Combining a bulky di-*tert*-butylphosphine moiety with a hemilabile tertiary amine donor, it is structurally similar to the Amphos ligand (**2**), which has been found to promote Suzuki, Sonogashira, and Heck couplings of aryl bromides in aqueous solvents.[3] The quaternarised amino functionality is not expected to coordinate to the palladium metal centre, but improves the water-solubility of the palladium catalysts, which may be recovered and recycled without any lost of activity (Fig. 1).

The aminophosphine **1** can be prepared expediently in four steps (Scheme 1): *N*-Methylaniline was alkylated with bromoethylacetate to give the amino ester **3**. This was reduced and the resultant amino alcohol was transformed into amino tosylate **4**. Finally, a nucleophilic substitution by di-*tert*-butylphosphide furnished the product **1** as a dense oil. To facilitate handling, the ligand was precipitated and stored as the white crystalline HCl salt, which is remarkably stable to air and moisture—a solution of **1**·HCl may be left exposed to air at room temperature for at least 24 h without any significant oxidation (^{31}P NMR spectroscopy).



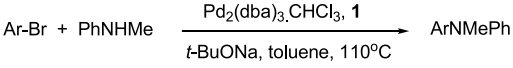
1 **2** (Amphos)

Figure 1. Sterically bulky aminophosphine ligands.



Scheme 1. Preparation of ligand **1**. (i) Na_2CO_3, EtOH; (ii) $LiAlH_4$, THF; (iii) TsCl, pyridine; (iv) (a) *t*-Bu_2PH, *t*-BuLi.

Ligand **1** was subsequently employed in a number of palladium-catalysed reactions, including the amination of aryl bromides (Scheme 2), where the reaction between the sterically bulky *N*-methylaniline with a number of aryl bromides (4-bromoacetophenone, 4-bromobenzonitrile,



Scheme 2. Pd-catalysed aryl amination reaction.

Keywords: Palladium catalysis; PN ligands; Aryl amination; Aryl bromides.
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bromobenzene and 4-bromoanisole) was examined. Despite our initial expectations, no reaction was observed at ambient temperature. This could be due to the coordination of the nitrogen donor group and/or the amine substrate, which suppresses the formation of the reactive coordinatively unsaturated Pd(0) species for the initial oxidative addition step.[†]

As an elevated reaction temperature was necessary to enable catalytic turnover, 1,1′-bis(diphenylphosphino)ferrocene (dppf), previously reported to be an effective ligand for the aryl amination of primary amines,[4] was employed as a comparison, to gauge the catalytic efficiency of ligand **1** and to discount the involvement of catalytic active palladium colloids (Table 1).[5] Under the adopted reaction conditions, dppf is an ineffective ligand for the coupling of this secondary amine. At 1 mol% catalytic loading, less than 12% of products were obtained in 21 h, irrespective of the electronic nature of the aryl halide ligand (Table 1, entries 1–4). In contrast, ligand **1** gave better yields of products (entries 5–12).

Table 1. Pd-catalysed aryl amination reactions (Scheme 2)[a]

Entry	Ar-Br	Ligand	Pd:L[b]	Yield %[c]
1	4-NCC_6H_4Br	dppf	1:1.1	11
2	4-$MeOCC_6H_4Br$	dppf	1:1.1	—
3	PhBr	dppf	1:1.1	7
4	4-$MeOC_6H_4Br$	dppf	1:1.1	9
5	4-NCC_6H_4Br	1	1:1.1	36
6	4-NCC_6H_4Br	1	1:0.8	34
7	4-$MeOCC_6H_4Br$	1	1:1.1	29
8	4-$MeOCC_6H_4Br$	1	1:0.8	21
9	PhBr	1	1:1.1	80
10	PhBr	1	1:0.8	66
11	4-$MeOC_6H_4Br$	1	1:1.1	83
12	4-$MeOC_6H_4Br$	1	1:0.8	93

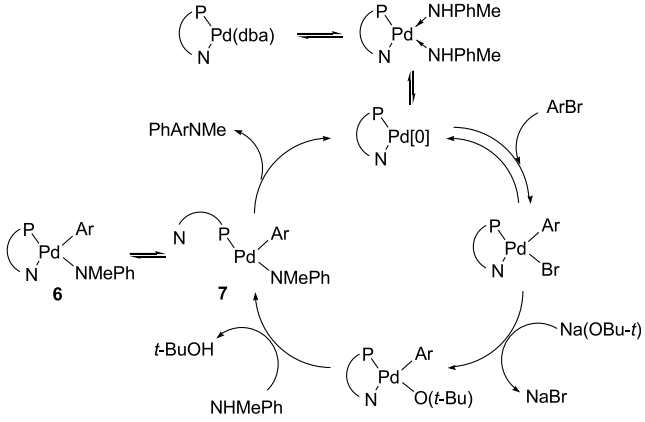
[a] Reaction conditions: $Pd_2(dba)_3 \cdot CHCl_3$, ligand, aryl halide (1 equiv), *N*-methylaniline (1 equiv) and sodium *tert*-butoxide (1.5 equiv) in toluene at 110 °C, 21 h (reaction time unoptimised).
[b] Metal-to-ligand ratio (mol%).
[c] Isolated yield after column chromatography. Duplicated to within 5%.

It is a well-established fact that electron-deficient aryl bromides are 'privileged' substrates in palladium catalysis, as they undergo cross-coupling reactions much more readily than electron-rich aryl bromides. In particular, 4-bromoacetophenone demonstrably undergo cross-coupling reactions with exceptionally high TON's even in the absence of any added ligand, thus has been discounted as a useful benchmark for the evaluation of new catalysts.[6] In light of this, we were surprised to find that ligand **1** imposes an unexpected pattern of reactivity in the aryl amination reactions: electron-deficient substrates, 4-bromoacetophenone and 4-bromobenzonitrile, gave very low yield of products under these reaction conditions (<40%, entries 5 and 7). Conversely, electronically-neutral (bromobenzene) and the electron-rich (4-bromoanisole) aryl bromide substrates gave much higher yields under identical conditions (>80%, entries 9 and 11).

As the yields are equally low for the electron-deficient substrates, complexation of the nitrile moiety to the metal centre is not regarded as a major factor under these reaction conditions. Crucially, in both cases, recovered aryl bromide substrates accounted for the mass balance, that is the low yields were not due to competitive side reactions (e.g., dehalogenation).

These observations clearly contradict the established trends of palladium-catalysed aryl amination reactions, where electron-withdrawing substituents on the aryl moiety enhances the rate of turnover in both the bond-breaking (oxidative addition of aryl halide to the Pd precursor) and bond-making (reductive elimination of arylpalladium amido intermediate) steps.[7]

In our earlier work,[2] we have demonstrated that the hemilability of nitrogen–phosphorus ligands are highly sensitive to the electronic nature of the palladium metal centre. Furthermore, in a recent study by Hartwig et al., 3-coordinate [(L)Pd(Ar)(NAr'_2)] complexes were reported to undergo much faster (irreversible) reductive elimination than their corresponding 4-coordinate [$(L)_2$Pd(Ar)(NAr'_2)] complexes in the C–N bond forming step.[8] Hence, a slight modification of the conventional aryl amination catalytic cycle[9] is proposed, to accommodate the hemilability of the PN ligand (Scheme 3). Following the initial oxidative addition reaction, a series of ligand exchanges occur, leading to the formation of 3- and/or 4-coordinated arylpalladium amido complexes (**6** and **7**), depending on the coordination mode of the PN ligand. In the presence of an electron-rich aryl moiety, the electron density and Lewis acidity of the palladium(II) metal centre is enhanced, which discourages the coordination of the π-basic nitrogen donor. This favours the formation of the complex **7**, which undergoes faster C–N bond formation to furnish the product.



Scheme 3. Proposed catalytic cycle involving ligand **1**.

Further credence to this theory is provided by the effect of the metal-to-ligand ratio. Lowering the ratio have very little effect on the reactions involving electron-deficient aryl bromides (Table 1, entries 5 vs 6, and 7 vs 8), but led to a marked improvement in the reaction of 4-bromoanisole (entries 11 and 12). This fits with the conjecture that excess

[†] Indeed, in the absence of the amine substrate, ligand **1** is able to promote slow catalytic turnover in the Suzuki–Miyaura cross-coupling between aryl bromides and aryl boronic acids at 25 °C. Compared to the catalytic activity of Amphos **2**, which catalyses the C–C bond forming reactions in 1–2 h,[3] the involvement of the hemilabile amino group in the catalytic cycle is also clearly implicated.

ligand could lead to the formation of a 4-coordinate [L_2Pd(Ar)(NMePh)] complex, thus inhibiting the formation of the more reactive metal complex. Interestingly, lowering the *M*:*L* ratio led to a decrease in yield for the reaction involving the bromobenzene substrate (entries 9 and 10). The reason for this observation is unclear at this stage—the presence of a slight excess of the ligand could have improved the catalyst's stability, as was observed for Amphos ligands. However, the operation of a competitive side reaction cannot be ruled out entirely, as it is difficult to quantify formation of the dehalogenated product (benzene).

In summary, the incorporation of a hemilabile amino functionality with sterically bulky, electron rich di-*tert*-butylphosphine aminophosphine led to a very unusual pattern of reactivity in the palladium-catalysed aryl amination of aryl halides, contradicting the conventional notion of 'activated' and 'unactivated' aryl bromides in cross-coupling reactions. The serendipitous discovery will be exploited in the design of ligands for chemoselective catalysis. Further studies on the coordination and catalytic chemistry of this and related aminophosphine ligands will be conducted in our future work.

2. Experimental

2.1. General

THF was freshly distilled under N_2 from sodium benzophenone. Toluene, CH_2Cl_2 and *n*-hexane were freshly distilled from CaH_2 also under N_2. Triethylamine was distilled under Ar from CaH_2 and stored over KOH pellets. Commercially available chemicals were purchased from Aldrich, Avocado, BDH, Fluka, Lancaster or Strem chemical companies, which were used as received, unless otherwise stated. Tris-(dibenzylideneacetone)dipalladium-(chloroform), $Pd_2(dba)_3\cdot(CHCl_3)$, was prepared by established procedure.[10] Air- or moisture- sensitive reactions were carried out under inert atmosphere (N_2 or Ar) using standard Schlenk line techniques. Glassware was oven-dried overnight. Melting points were determined on electrothermal Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using Bruker AM 360, AVANCE 400 and 500 spectrometers in $CDCl_3$. ^{1}H NMR and ^{13}C NMR spectra were referenced to tetramethylsilane (TMS) while ^{31}P NMR spectra were referenced to H_3PO_4 (external standard). Chemical shifts are recorded in parts per million (δ, ppm) downfield to TMS or H_3PO_4. Coupling constants are given in Hertz (*J* Hz). The following abbreviations are used to describe multiplicity: s-singlet, t-doublet, t-triplet, q-quartet, m-multiplet, dd-double doublet, dt-double triplet, td-triple doublet. Mass spectra (MS) were recorded by the mass spectrometry service within the university of London's intercollegiate research services (ULIRS) or EPSRC MS services at university of swansea, Wales. Elemental analyses were carried out by elemental analysis service, London metropolitan university.

2.1.1. (Methyl-phenyl-amino)-acetic acid ethyl ester, 3. Ethyl bromoacetate (6.65 mL, 60 mmol, 1.1 equiv) was added slowly at room temperature to a solution of *N*-methylaniline (5.9 mL, 54 mmol, 1.0 equiv) in EtOH (100 mL). The reaction mixture was stirred at room temperature for 30 min before Na_2CO_3 (19.4 g, 183 mmol, 1.5 equiv) was added and refluxed overnight. After cooling to room temperature, the solution was concentrated by evaporation and diluted with 30 mL of Et_2O. The precipitated salts were removed by filtration through Celite, which were thoroughly rinsed with Et_2O and CH_2Cl_2. The filtrate was acidified by the addition of 1 M aqueous HCl (pH=1). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$ and evaporated to furnish a dark oil. The crude product was purified by distillation under reduced pressure to yield the ester was obtained as a pale yellow oil (9.73 g, 93%). Bp: 90 °C, 1.0 mmHg (lit.[11] 90–92 °C, 0.2 mmHg); ν (thin film)/cm^{-1} 1742 (C=O); δ_H (360 MHz, $CDCl_3$) 1.31 (3H, t, J=7.1 Hz, CH_2CH_3), 3.13 (3H, s, NCH_3), 4.12 (2H, s, NCH_2), 4.24 (2H, q, J=7.1 Hz, CH_2CH_3), 6.79 (2H, d, J=8.7 Hz, H_{ortho}), 6.85 (1H, t, J=7.4 Hz, H_{para}), 7.33 (2H, dd, J=7.4, 8.7 Hz, H_{meta}); δ_C (90.5 MHz, $CDCl_3$) 14.7 (s, CH_2CH_3), 39.9 (s, NCH_3), 54.9 (s, NCH_2), 61.2 (s, CH_2CH_3), 112.7 (s, C_{ortho}), 117.7 (s, C_{para}), 129.6 (s, C_{meta}), 149.4 (s, C_{ipso}), 171.4 (s, CO).

2.1.2. *N*-(2-Hydroxyethyl)-*N*-methyl-aniline 4.[12] In a two-necked round bottom flask fitted with a condenser, lithium aluminium hydride (2.9 g, 75 mmol, 2.0 equiv) was suspended in 30 mL of freshly distilled THF. The reaction mixture was cooled down to 0 °C, and the ester **3** (7.3 g, 37 mmol, 1.0 equiv) was added dropwise. The solution was stirred at room temperature for 1 h before being refluxed for 4 h. After cooling to 0 °C, the excess reducing agent was destroyed carefully by the alternate addition of H_2O and 15% aqueous NaCl. The resultant white solid was removed by filtration through a pad of Celite, which was washed repeatedly with Et_2O. The filtrate was separated and the aqueous layer extracted with diethyl ether (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to yield the amino alcohol as a pale yellow liquid, which was employed in the next step without any further purification (5.2 g, 92%); δ_H (360 MHz, $CDCl_3$) 2.07 (1H, br s, OH), 2.85 (3H, s, CH_3), 3.35 (2H, t, J=5.8 Hz, NCH_2), 3.68 (2H, t, J=5.8 Hz, CH_2O), 6.65 (1H, t, J=7.2 Hz, H_{para}), 6.70 (2H, d, J=8.3 Hz, H_{ortho}), 7.15 (2H, dd, J=7.2, 8.3 Hz, H_{meta}); δ_C (90.5 MHz, $CDCl_3$) 39.2 (s, CH_3), 55.8 (s, NCH_2), 60.4 (s, CH_2O), 113.4 (s, C_{ortho}), 117.6 (s, C_{para}), 129.6 (s, C_{meta}), 150.4 (s, C_{ipso}).

2.1.3. *N*-(2-tosylethyl)-*N*-methyl-aniline, 5.[13] *p*-Toluenesulfonyl chloride (4.5 g, 23 mmol, 1.4 equiv) was added slowly to 11 mL of ice-cooled pyridine. The resulting orange solution was allowed to warm to room temperature. After 30 min, the reaction mixture was cooled to −10 °C (ice-acetone bath), whereupon **4** (2.4 g, 16 mmol, 1.0 equiv) was added portionwise over 30 min. The mixture was allowed to warm to room temperature and stirred for 2 h. The resultant slurry was poured into an ice-water (40 mL), stirred for 30 min and CH_2Cl_2 (30 mL) were then added. The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were treated with 4 M aqueous HCl until the pH was acidic

(4–5, pH paper). The solution was washed with brine (30 mL), saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$) and evaporated to furnish a yellow oil (3.7 g, 75%); δ_H (360 MHz, $CDCl_3$) 2.31 (3H, s, CH_3), 2.77 (3H, s, NCH_3), 3.49 (2H, t, $J=6.1$ Hz, NCH_2), 4.06 (2H, t, $J=6.1$ Hz, CH_2O), 6.47 (2H, d, $J=8.2$ Hz, tol), 6.60 (1H, t, $J=7.3$ Hz, Ph_{para}), 7.10 (2H, dd, $J=7.3$, 8.6 Hz, Ph_{meta}), 7.18 (2H, d, $J=8.2$ Hz, tol), 7.61 (2H, d, $J=8.6$ Hz, Ph_{ortho}); δ_C (90.5 MHz, $CDCl_3$) 22.0 (s, CH_3), 39.3 (s, NCH_3), 51.6 (s, NCH_2), 67.5 (s, CH_2O), 112.5 (s, Ph_{ortho}), 117.3 (s, Ph_{para}), 128.3 (s, tol), 129.6 (s, Ph_{meta}), 130.2 (s, tol), 133.1 (s, tol), 145.3 (s, Ph_{ipso}), 150.2 (s, tol).

2.1.4. [2-Di-(*tert*-butyl)-phosphinoethyl]-*N*-methylaniline, 1. Di-*tert*-butylphosphine (1.0 g, 6.8 mmol, 1.1 equiv) was placed in an oven dried Schlenk tube with 10 mL of degassed Et_2O. The solution was cooled down at 0 °C and a solution of *tert*-butyllithium (1.5 M in pentane, 5.5 mL, 1.3 equiv) was added dropwise. The reaction was allowed to warm to room temperature. After 1 h, it was cooled to 0 °C and 1.0 equiv of the tosylate **5** (1.9 g, 6.2 mmol) was added slowly. After stirring at 0 °C for 30 min, the reaction mixture was warmed to room temperature and stirred for a further 3 h, whereupon the colour changed from yellow to orange (completion of the reaction was monitored by recording the ^{31}P NMR spectrum of the reaction aliquot). The reaction mixture was quenched by the addition of 2.0 mL of freshly distilled MeOH. The solvent was then removed in vacuo. Distilled toluene (20 mL) was added, stirred and the resulting solution was filtered into a pre-weighed Schlenk tube. The solvent was evaporated under vacuum to give a pale oil. Ten cubic centimetres of degassed petroleum ether were added, the solution was stirred at room temperature and evaporated to furnish an oily solid. In order to facilitate the handling of this ligand, the corresponding ammonium salt was formed, achieved by dissolving the oily solid in degassed Et_2O, followed by addition of a few drops of degassed concd. HCl. Upon cooling, the ammonium salt precipitated, which was collected and dried in vacuo. Yield: 91% (1.39 g, pale dense oil). Although the crystalline ligand may be handled in air without any problems, it is stored under an inert atmosphere. Mp (HCl salt) 160–162 °C; Found: C, 72.99; H, 10.73; N, 5.09. $C_{17}H_{30}NP$ requires C, 73.12; H, 10.75; N, 5.02%; δ_H (360 MHz, $CDCl_3$) 1.06 (18H, d, $^3J_{PH}=11.2$ Hz, CH_3), 1.53 (2H, td, $^2J_{PH}=4.8$ Hz and $^3J_{HH}=9.0$ Hz, NCH_2CH_2P), 2.86 (3H, s, CH_3), 3.43 (2H, td, $^3J_{PH}=4.3$ Hz and $^3J_{HH}=9.0$ Hz, NCH_2CH_2P), 6.60 (2H, d, $J=8.6$ Hz, *Ph*), 7.07 (1H, d, $J=7.4$ Hz, *Ph*), 7.14 (2H, dd, $J=7.4$, 8.6 Hz, *Ph*); δ_C (90.5 MHz, $CDCl_3$) 18.3 (d, $^1J_{PC}=23.0$ Hz, CH_2P), 30.1 (d, $^2J_{PC}=13.5$ Hz, CH_3), 31.7 (d, $^1J_{PC}=19.0$ Hz, CMe_3), 38.6 (s, CH_3), 54.3 (d, $^2J_{PC}=39.3$ Hz, NCH_2), 112.8 (s, C_{meta}), 116.6 (s, C_{para}), 129.7 (s, C_{ortho}), 149.0 (s, C_{ipso}); δ_P (146 MHz, $CDCl_3$) +25.7; *m/z* (FAB) 280.2 (MH^+), 145 ($M^+ - C_9H_{12}N$), 134 ($C_9H_{12}N^+$), 77 ($C_6H_5^+$), 57 ($C_4H_9^+$).

2.2. Pd-catalysed aryl amination reaction

Sodium *tert*-butoxide (387 mg, 4 mmol, 1.5 equiv) and a magnetic stirrer bar were introduced into a Schlenk tube, which was repeatedly purged and filled with dry N_2. *N*-Methylaniline (286 mg, 2.67 mmol, 1 equiv), the relevant aryl bromide (1 equiv) and toluene (1 mL) were added to generate a reaction mixture. Meanwhile, $Pd_2(dba)_3 \cdot CHCl_3$ (13.8 mg, 0.013 mmol, 0.5 mol%), ligand **1**·HCl (9.5 mg, 0.030 mmol, 1.1 equiv) and sodium *tert*-butoxide (0.032 mmol) were weighed into a separate vessel and dissolved in warm toluene (1 mL). The solution of the catalyst precursor was transferred via syringe into the reaction vessel, which was heated at 100 °C for 21 h. After cooling, the reaction mixture was diluted with EtOAc (20 mL) and filtered to remove any insoluble material. The solvents were evaporated, and the residue was subjected to column chromatography (flash silica gel) using ethyl acetate/hexane as eluent.

2.2.1. *N*-(4-acetophenone)-*N*-methylaniline.[14] δ_H (360 MHz, $CDCl_3$) 7.83 (2H, d, $J=9.0$ Hz, $H_{meta'}$), 7.44 (2H, dd, $J=8.4$, 7.3 Hz, H_{meta}), 7.25 (1H, t, $J=8.4$ Hz, H_{para}), 7.24 (2H, d, $J=7.3$ Hz, H_{ortho}), 6.77 (2H, d, $J=9.0$ Hz, $H_{ortho'}$), 3.40 (3H, s, NCH_3), 2.53 (3H, s, $COCH_3$).

2.2.2. *N*-(4-Cyanophenyl)-*N*-methylaniline.[15] δ_H (360 MHz, $CDCl_3$) 7.40–7.30 (4H, m, H_{meta}), 7.18 (1H, t, $J=7.4$ Hz, H_{para}), 7.13 (2H, d, $J=7.0$ Hz, H_{ortho}), 6.64 (2H, d, $J=11.0$ Hz, H_{ortho}), 3.27 (3H, s, NCH_3).

2.2.3. Methyl diphenylamine.[16] δ_H (360 MHz, $CDCl_3$) 7.20 (4H, dd, $J=8.5$, 7.3 Hz, H_{meta}), 6.90 (4H, d, $J=8.5$ Hz, H_{ortho}), 6.70 (2H, t, $J=7.3$ Hz, H_{para}), 3.20 (3H, s, NCH_3).

2.2.4. *N*-(4-Methoxyphenyl)-*N*-methylaniline.[17] δ_H (360 MHz, $CDCl_3$) 7.24 (2H, dd, $J=9.0$, 7.4 Hz, H_{meta}), 7.15 (2H, d, $J=9.0$ Hz, $H_{meta'}$), 6.95 (2H, d, $J=9.0$ Hz, $H_{ortho'}$), 6.87 (2H, d, $J=9.0$ Hz, H_{ortho}), 6.85 (1H, t, $J=7.4$ Hz, H_{para}), 3.70 (3H, s, OCH_3), 3.15 (3H, s, NCH_3).

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Halogenated-2-pyrones in Sonogashira cross-coupling: limitations, optimisation and consequences for GC analysis of Pd-mediated reactions

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Abstract—The Sonogashira couplings of 4-bromo-6-methyl-2-pyrone (**5**) with phenylacetylene, mediated by $Pd(PPh_3)_2Cl_2$ in the presence of a CuI co-catalyst, have been investigated in detail. The concentration of Pd dramatically influences the product yield, with lower Pd-loadings favouring higher conversions and purer cross-coupled product. A post reaction time-dependence in product conversion is seen in samples quenched solely on silica-gel (eluted with CH_2Cl_2). The effect is mirrored in reactions employing 4-nitro-bromobenzene (**14**) and to a lesser extent (*E*) and (*Z*)-ethyl 3-iodo-2-propenonate (**16**) under similar conditions. A more efficient quenching system (using excess dppe) has been developed to enable accurate determinations in product conversions. Alternatively, solvent and base (Et_3N) removal in vacuo, or quench with saturated aqueous ammonium chloride, prevents further turnover in Sonogashira coupling. An ESI-MS study on samples eluted through silica was undertaken to probe the nature of the soluble Pd/Cu species. The Sonogashira cross-coupling of 4-chloro- and 6-chloro-2-pyrone (**18** and **20**, respectively) has further been investigated. The former undergoes successful coupling, however the latter decomposes in polar aprotic and protic solvents under standard conditions, through a chlorine substitution process, making Pd-mediated reactions problematic.

1. Introduction

Pd-Catalyzed carbon–carbon and carbon-heteroatom bond-forming processes represent some of the most important and routinely applied reactions in synthetic chemistry.[1] Heck,[2] Negishi,[3] Sonogashira,[4] Stille,[5] Suzuki[6] and the recently developed Hartwig–Buchwald[7] cross-coupling reactions represent key examples. Some of these processes have been comprehensively used in benchmarking transition metal catalysts, particularly in Heck and Suzuki coupling, where high catalyst activity, low catalyst loadings, catalyst recycling, prolonged catalyst lifetime and selectivity are important. The synthesis of biaryl compounds is integral to establishing the efficacy of new Pd-catalysts, particularly given the importance attached to these feedstocks in diverse industrial and academic applications. Heterocyclic derivatives have become the focus of attention in both materials and pharmaceutical arenas, and new catalysts should be broadly evaluated against these derivatives as well as more traditional reactions testing their capacity to produce biaryl derivatives. Indeed, even with the current armory of catalysts described in the literature to date, limitations are known for many heterocyclic compounds.

We are interested in catalyst discovery for cross-coupling processes and the employment of unusual heterocyclic frameworks, for example, 2-pyrones (parent 2-pyrone is structure I, Fig. 1), an unsaturated six-membered oxygenated ring system, which exhibits both aromatic and alkenic chemical properties (the latent polarities are shown in II).

The ring-system is an interesting choice, representing a heterocyclic substrate (electrophilic or nucleophilic) for employment in cross-coupling processes.[8] The 2-pyrone motif is found in many naturally occurring compounds,

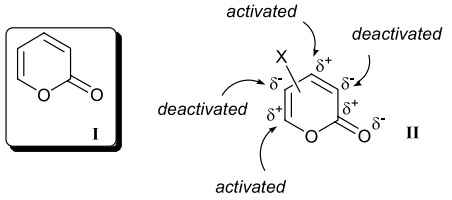

Figure 1. Parent 2-pyrone (**I**) and simple latent polarities in 2-pyrone (**II**).

Keywords: Palladium; Cross-coupling; Sonogashira.
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which display a range of beneficial and exploitable biological and medicinal effects (Fig. 2).[9] Non-natural substituted 2-pyrones (**1** and **4**), synthesized using cross-coupling processes, have been shown to be effective inhibitors of specific types of human ovarian carcinoma (A2780) and human chronic myelogenous leukemia (K562) cell lines (in an in vitro cell culture system).[10] Simple substituted 2-pyrones (**2** and **3**) exhibit anti-fungal and anti-bacterial inhibitory activity. Derivatives of **4** also exhibit pronounced solvatochromism in fluorescence, which could be used to study the biological mode of action of these compounds.[11] Furthermore, transition metal carbonyl complexes, containing the 2-pyrone ring-system, that are η^1-carbonyl[12] and η^4-diene[13] coordinated, undergo Suzuki coupling reactions. The latter complexes possess useful biological properties.[14]

The application of halogenated 2-pyrones in cross-coupling processes has attracted considerable recent interest. 4-Bromo-6-methyl-2-pyrone **5** can be cross-coupled reasonably well in Negishi, Sonogashira and Suzuki coupling processes.[15] In preliminary studies, our group has detailed a useful protocol for the Suzuki coupling of 3-bromo-4-methoxy-6-methyl-2-pyrone **6** and 5-bromo-4-methoxy-6-methyl-2-pyrone **7** with several organoboronic acids.[16] The studies extend on the seminal work carried out by Pleixats and Moreno-mañas.[17] In Suzuki coupling of **6**, hydrodebromination occurs as a minor side-reaction, presumably due to the more forcing conditions. Cho and co-workers have reported extensively on the cross-coupling reactions of 3,5-dibromo-2-pyrone, which undergoes facile regioselective Stille coupling reactions with aryl, heteroaryl and vinyl stannanes to produce various 3-substituted-5-bromo-2-pyrones.[18] Similar regioselectivity for the 3-position is reported in Sonogashira coupling,[19] Suzuki coupling[20] and amination reactions.[21] Other halogenated 2-pyrones in cross-coupling processes include 6-chloro-2-pyrone,[22] 5-iodo-6-substituted-2-pyrones[23] and 3-bromo-5-iodo-2-pyrones.[24] Meinwald and co-workers have coupled 3-methyl-5-bromo-2-pyrone to an alkylzinc reagent, which was a key step in the synthesis of the cockroach sex pheromone, supellapyrone (5-(2′*R*,4′*R*-dimethylheptanyl)-3-methyl-2-pyrone).[25] A reversal in the polarity of the 2-pyrone led to 3-(trimethylstannyl)-5-bromo-2-pyrone being used as an effective organometallic reagent, which facilitates incorporation of aryl groups at the 3-position.[26] Further, stannylated variants at the 3- and 5-position of 2-pyrone are known.[27] The Negishi coupling of 5-(iodozinc)-2-pyrones have been reported.[28] 3-Cuprio-2-pyrone is a well known organometallic 2-pyrone—a surprisingly poor nucleophile—described by Posner and co-workers,[29] although its use in Pd-coupling processes has not been described to the best of our knowledge. Suzuki coupling of 2-pyrone-5-boronate with aryl and heteroaryl halides and triflates is known,[30] and a high yielding route to bufadienolide type steroids was achieved via Suzuki coupling of steroid vinyl triflates with this boronate.[31] 4-Methoxy-6-methyl-3-chlorozinco-2-pyrone reacts with aryl- and vinyl halides.[32] In the same report, 4-bromo-2-pyrone reacted with organozinc compounds such as aryl-, heteroaryl- and ethynyl-zinc chlorides to give the corresponding coupled products.

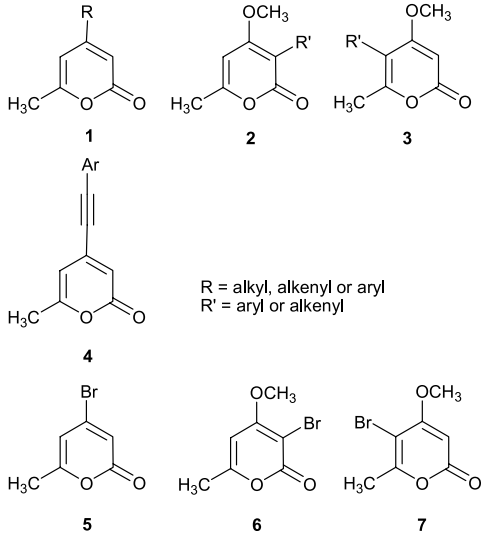


Figure 2. Biologically active non-natural 2-pyrones and halogenated 2-pyrone precursors.

For the majority of these coupling processes, relatively high catalyst loadings were employed, for example, 2.5–6 mol%, under relatively classical conditions. In view of the recent interest in active and selective Pd catalyst systems and in the diverse applications of 2-pyrones, the Sonogashira couplings of **5** and related derivatives have been reassessed. This has led us to more active systems for these substrates using standard Pd(II) precatalysts. Whilst conducting these experiments it has been established that sampling reaction mixtures for GC analysis must be performed with caution. Reaction samples are commonly quenched by passage through a silica plug. However, we demonstrate for **5**, 4-nitrobromobenzene **14** and *Z*- and *E*-ethyl 3-iodo-2-propenonate **16** that continued Sonogashira alkynylation occurs in samples 'quenched' with silica alone. A more efficient quenching system has thus been created for these activated substrates. The Sonogashira couplings of 4-chloro- and 6-chloro-2-pyrone (**18** and **20**, respectively) are further discussed.

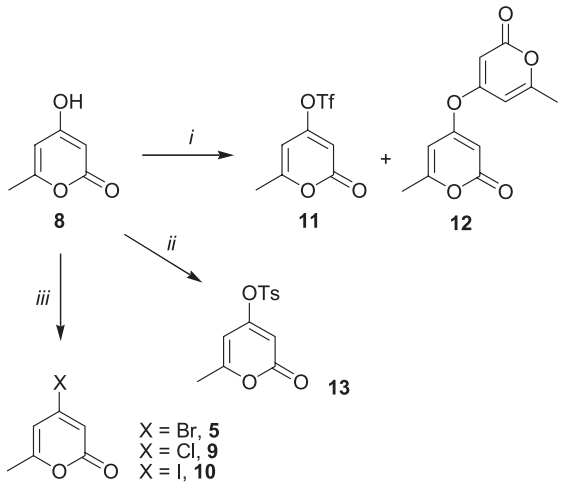
2. Results

The first reactions of interest are Sonogashira couplings of halogenated 2-pyrones shown in Scheme 1.

2.1. Synthesis of halogenated 2-pyrone precursors

Compound **5** was synthesized by bromination of 4-hydroxy-6-methyl-2-pyrone using tetra-*n*-butylammonium bromide (TBAB) and P_2O_5 in toluene at 100 °C with essential vigorous mechanical stirring.[33] The yield of the reaction appears somewhat dependent on efficient mixing (varies between 10 and 91% in our hands).

4-Iodo-6-methyl-2-pyrone **10** was synthesised using a similar procedure, but employing tetra-*n*-butyl ammonium iodide (TBAI), in place of TBAB, in 13% yield. 4-Chloro-6-methyl-2-pyrone was accessed by reaction of **8** with $POCl_3$ to give **9** in 27% yield. We have been unable to optimise these poor yields. The triflate **11** was accessed by reaction of



Scheme 1. Synthesis of 4-halogenated-6-methyl-2-pyrones and related derivatives. Reagents and conditions: (i) $PhN(OTf)_2$, K_2CO_3, THF, 60 °C; (ii) TsCl, Pyr., CH_2Cl_2, rt, 3 h; (iii) for X=Br or I, TBAB or TBAI, P_2O_5, toluene, 100 °C, for X=Cl, $POCl_3$ (excess), 25 °C, 15 h, then 100 °C, 2 h.

8 with *N*-phenyltriflimide in 81% yield. The reaction was accompanied by the formation of **12** (11%), presumably formed by reaction of unreacted **8** with **11**. The tosylate **13** was accessed in 68% yield by reaction of **8** with tosyl chloride in the presence of pyridine (3 equiv) in CH_2Cl_2.

2.2. Sonogashira coupling reactions

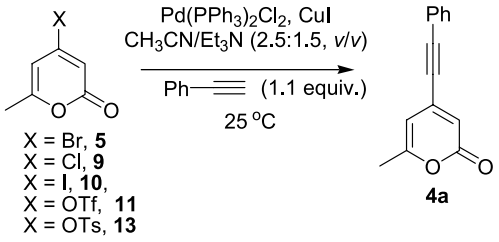
In our first studies on the reactions of **5** with terminal acetylenes we chose relatively high catalyst loadings (2.5–6.0 mol%) and reflux conditions for several hours.[15] The reaction of **5** with phenylacetylene to give **4a** represents our benchmark. In terms of monitoring the progress of reaction, TLC analysis was hampered by almost identical R_f values of product and substrate.

High-resolution gas chromatography (HRGC) analysis was therefore employed to follow the extent of reaction. On comparing the reactions of **5**, **9**–**11** and **13**, we noticed that the reactions were proceeding rapidly at room temperature with 2.5 mol% Pd loading (entry 1, Table 1, Scheme 2). It had previously been shown that $Pd(PPh_3)_2Cl_2$ (6 mol%) was a poor precatalyst for Sonogashira coupling with various

Table 1. Sonogashira coupling of 4-halogenated-6-methyl-2-pyrones

Entry	Substrate	% Conv.[a]/TON[b]		
		2.5 mol% Pd/Cu[c]	0.25 mol% Pd/Cu[d]	0.025 mol% Pd/Cu[e]
1	R=Br, **5**	99(88)/39	99(97)/396	61 (49)/2440
2	R=Cl, **9**[f]	99 (−)/39	99 (−)/396	—
3	R=I, **10**	92 (68)/37	90 (79)/360	48 (41)/1920
4	R=OTf, **11**	89 (56)/36	83 (72)/332	—
5	R= OTs, **13**[f]	95 (41)/38	62 (31)/248	—

Reagents and conditions are as for Scheme 2. Concentration =0.1 M (w.r.t. to halogenated 2-pyrone).
[a] Conversion (%) determined by HRGC against an internal standard. Numbers in parenthesis are yields after purification.
[b] TON=turnover number calculated from HRGC yield.
[c] Reaction time=0.25 h.
[d] Reaction time=3 h.
[e] Reaction time =18 h.
[f] Reaction carried out at 60 °C.



Scheme 2. Sonogashira coupling of 4-halogenated-6-methyl-2-pyrones.

terminal acetylenes, leading to only trace quantities of the coupled products.[15c] Refluxing at this higher Pd loading under the reaction conditions accelerates the agglomeration of Pd and ultimately precipitation of Pd black.[34] This led us to probe the reactivity of this precatalyst at lower catalyst loadings at 25 °C. An improved yield was obtained at 0.25 mol% Pd loading; similar results were observed for both substrates **5** and **9** (entries 1 and 2). The more activated substrate **10** furnishes lower yields of cross-coupled product (entry 3). A higher yield is again seen at 0.25 mol% Pd (79%). The same trend is apparent with triflate **11** (entry 4). Difficulties were encountered purifying **4a** from the reaction using tosylate **13** (entry 5). In selected examples, **5** and **10** demonstrate higher turnover numbers at 0.025 mol% Pd loading, although fail to reach completion. The turnover frequencies (TOFs) were not calculated, as conversion points were not taken in the initial linear portions of the reaction profiles—a comparison of the final TOFs would be misleading (the differences in the reaction times should be noted against Pd/Cu loading).

Recrystallisation of crude **4a** is sufficient at 0.25 mol% Pd/Cu catalyst loadings; whereas at 2.5 mol% Pd/Cu, purification is required by flash chromatography (Pd black and $POPh_3$ are the main problem). Photographs of the reactions at 2.5 and 0.25 mol% Pd loading illustrate a common problem in Pd cross-coupling chemistry: clear differences are presented in Figure 3.

Prior to addition of phenylacetylene the solutions remain a clear orange colour, which is more intense for the higher catalyst loading (frame A). On addition of phenylacetylene, the solutions at both catalyst loadings become black immediately (frame B). On complete loss of **5**, the lower catalyst loading shows no sign of precipitated Pd black (frame C).

It has been determined that reactions of **5** can be performed in the presence of air, albeit in a closed vessel, although purified solvents are required for good yields (note:

Figure 3. Photographs from Sonogashira coupling reactions of **5** with phenylacetylene at 2.5 mol% Pd/Cu (Left tube) and 0.25 mol% Pd/Cu (Right tube): Frame A, $t=0$ (no PhC≡CH added); Frame B, $t=5$ min (PhC≡CH added); Frame C, $t=8$ h (complete conversion).

commercial Et_3N contains significant quantities of water, which appears to cause problems with **5**).

Of interest, while investigating these reactions vide supra, we uncovered a time dependence in product conversions for quenched samples analysed by GC. These results are summarised below.

2.2.1. Consequences for gas chromatographic analysis of the Sonogashira alkynylation of halogenated 2-pyrones. The representative reaction chosen for closer analysis was that of **5** with phenylacetylene to give **4a** using 0.25 mol% Pd/Cu at 25 °C (the reaction is pseudo-first order with respect to **5**—an excess of phenylacetylene was employed).[35] Samples for GC analysis were quenched by passage through a small plug of silica, eluted with CH_2Cl_2. The results of repeated GC analysis of a 'quenched' sample, withdrawn from the reaction mixture after 1 h and stored at 25 °C, are shown in Figure 4. A clear and reproducible time-dependence in product conversion was seen. After storing the sample for 3 h, an additional ~15% substrate conversion was noted. In order to confirm that the striking effect arose from the presence of residual Pd/Cu species in the eluted sample, a solution of 1,2-bis(diphenylphosphino)ethane (dppe) in CH_2Cl_2 was added to samples immediately after their elution through the silica adsorbent.

Although it is known that dppe can be employed as an activating ligand for cross-coupling processes,[36] it is clear in this case, that it completely eliminated continued reaction within stored samples, presumably by irreversibly binding Pd(0) species, which are thereby unable to promote the catalytic reaction. The importance of quenching samples for GC analysis is evident from examining reaction profiles obtained during the alkynylation of **5** (Fig. 5).

The silica/dppe tandem quenching protocol reveals that a conventional silica treatment introduces a systematic error of ca. 10% in calculated GC conversions (response factors for substrate, product, symmetrical 1,3-diyne—the homo-coupling product—and internal standard have been taken into consideration). This finding also has implications for initial rates and associated turnover frequencies from studies wherein adsorption onto silica gel represents the sole quenching step.

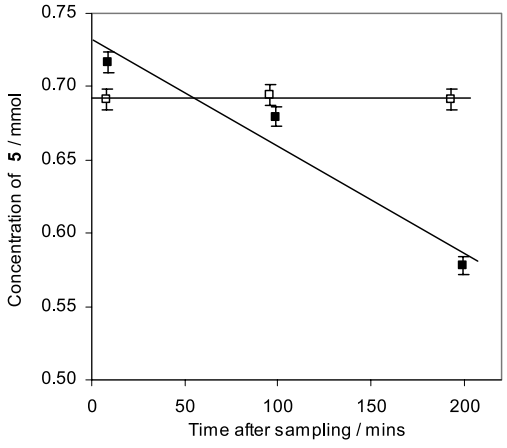


Figure 4. A graph showing the consumption of **5** (0.25 mol% Pd/Cu) in a sample prepared for GC analysis—sampling at specified times (withdrawn from reaction mixture at 0.5 h): ■ reaction sample quenched with a silica-plug and elution with CH_2Cl_2; □ reaction sample quenched with a silica-plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial.

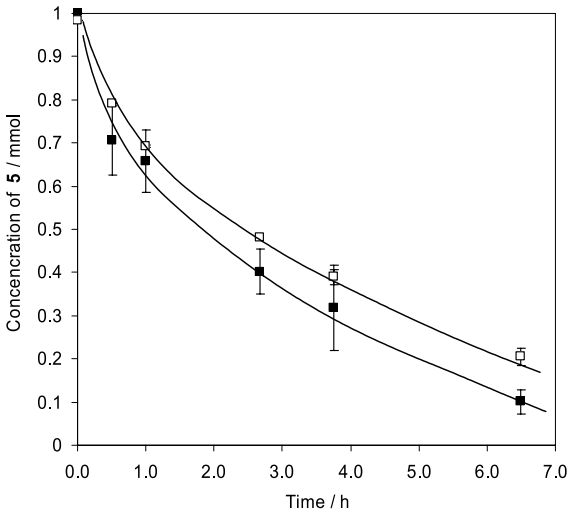


Figure 5. Reaction profiles showing the consumption of **5** (0.25 mol% Pd/Cu) with phenylacetylene at specified times (triplicate samples for each sample time were run by GC): ■ Reaction sample quenched with a silica-plug and elution with CH_2Cl_2; □ Reaction sample quenched with a silica-plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial.

Generally the adsorption capacity of Kieselgel silica-gel (typically >0.1 mmol Pd g^{-1}) vastly exceeds the Pd and Cu content of each reaction sample (0.08 μmol). Thus, the observations made at 0.25 mol% Pd/Cu catalyst loading do not reflect overloading of the silica plugs.[37]

A visible difference is seen for reactions quenched by silica alone and those reactions quenched using the silica/dppe combination at 0.25 mol% Pd/Cu catalyst loading (Fig. 6). A higher catalyst loading (10-fold) intensifies the colour difference, ultimately indicating that the Pd-species has changed in the presence of dppe. The theoretical Pd and Cu content of a withdrawn sample from the reaction mediated with 2.5 mol% Pd is ca. 0.80 μmol.[38]

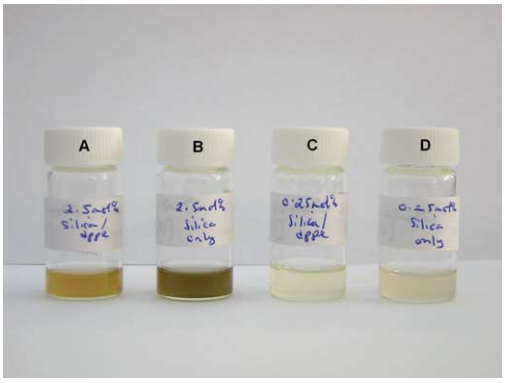


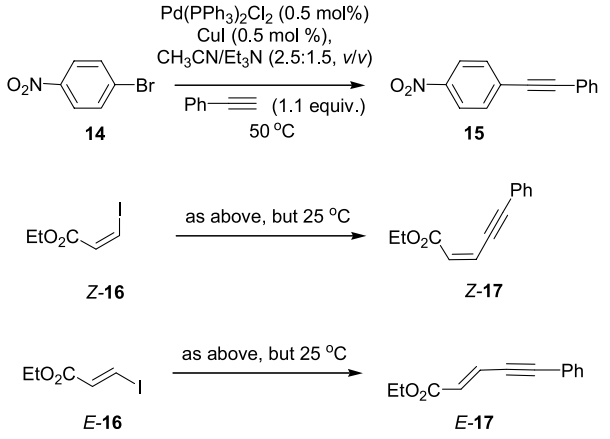
Figure 6. Sample A: Quenched by silica with added dppe (2.5 mol% Pd); Sample B: Quenched by silica without dppe (2.5 mol% Pd); Sample C: Quenched by silica with added dppe (0.25 mol% Pd); Quenched by silica without dppe (0.25 mol% Pd). Note: samples darken over time (precipitation of Pd).

Recently, electrospray mass spectrometry (ESI-MS), which is a soft-ionization technique, has been used to detect short-lived reactive organometallic intermediates in catalytic processes.[39] ESI-MS permits use of dilute solutions, for example, reaction mixtures. The technique has been used in Pd-catalyst screening[40] and for the determination of the mechanism of the Heck reaction using aryldiazonium salts.[41] ESI-MS analysis (in −ve mode) of sample B indicated the presence of two ions *m/z* 682 (100%) and 636 (81%). The observed isotopic pattern for 636 fits the formula $C_{34}H_{26}PCuPd$, which is tentatively assigned as $[PPh_3PdCu(PhC{\equiv}C)_2H]^-$. We did not observe the formation of a $PdBr_3^-$ species, nor any related phosphine ligated anionic Pd species; the former species has been detected through ESI-MS analysis of the Heck reaction by de Vries and co-workers (under phosphine-free conditions).[42] In the +ve mode, two major ions were observed *m/z* =967 (100%) and 921 (20%), which could be one of several bimetallic species containing Pd and Cu.[43]

Analysis of sample A by ESI-MS (in +ve mode), shows two major ions *m/z* 1027 (53%) and 875 (100%), which are assigned as $[Pd(dppe)(PPh_3)_2]^+$ and $[Pd(dppe)(PPh_3)_2{-}C_{12}H_{10}]^+$, respectively.

It is conceded that residual Et_3N/CH_3CN solvent from the sample could be hampering the adsorption of Pd/Cu onto silica. Moreover, Et_3N is required for Sonogashira coupling, although Cu(I) is not. Indeed, a similar trend is seen in reactions conducted with Pd alone. If one removes the base/solvent from the sample in vacuo prior to GC analysis, product conversion remains constant over several hours, representing a valid quenching method in itself for these Sonogashira alkynylation reactions. Samples can also be quenched by treatment with a saturated aqueous solution of NH_4Cl in open air, followed by extraction into CH_2Cl_2 or EtOAc. This procedure allows for elimination of Cu and the accurate determination of product conversions.

To assess whether this effect was generic to other activated substrates, the reactions of **14** with phenylacetylene to give **15**, and the cis- and trans- isomers of ethyl 3-iodo-2-propenoate[44] (*Z*-**16** and *E*-**16**) with phenylacetylene to give *Z*-**17** and *E*-**17**, respectively, were investigated (Scheme 3). Slightly higher 0.5 mol% Pd/Cu catalyst loadings were employed, using the conditions described for **5**. In the reaction of **14**, a clear time-dependence in product conversion was seen in GC samples quenched by silica alone, mirroring the observations with **5** (Fig. 7). The addition of dppe to samples eluted through silica again inhibits further catalysis. The silica/dppe tandem quenching protocol likewise reveals that a conventional silica treatment introduces a systematic error for this substrate in calculated GC conversions (ca. 20%).



Scheme 3. Other Sonogashira couplings assessed for further reaction after work-up by silica treatment alone.

The importance of quenching samples for GC analysis is again evident from the examining reaction profile obtained during the alkynylation of **14** (Fig. 8).[45]

For higher catalyst loadings (5 mol%), the errors were larger (Fig. 9). In samples where excess dppe was added, turnover is still seen to be occurring, albeit the numbers are within the error generally associated with GC. In the sample where solvent and base were removed in vacuo, negligible turnover was observed.

For Sonogashira coupling of *Z*-**16** and *E*-**16** with phenylacetylene to give *Z*-**17** and *E*-**17**, respectively, similar trends were seen. These reactions took approximately 6 h to reach completion. For the non-dppe quenched reaction (using *Z*-**16**), 7% further conversion was seen by GC analysis (after 1 h reaction time) over a 3 h period after passage through silica. Insignificant turnover was seen with added dppe.

2.2.2. Effect of copper loading in Sonogashira coupling. The effect of Cu(I) loading was also assessed for the Sonogashira coupling of **5** with phenylacetylene to give **4a** (Fig. 10 and Table 2). The turnover frequency (TOF) improves with increasing Cu:Pd ratios. Based solely on the consumption of **5**, it appears that reactions are more efficient at higher Cu(I) loadings. However, the isolated yields, after column chromatography, dramatically decreases past 0.5 mol% Cu(I) (with respect to the 0.25 mol% Pd catalyst loading). More oxidative coupled product (1,3-diyne) is observed at 1.94 mol% Cu(I) loading, which could be promoted by oxygen or by the formation of the

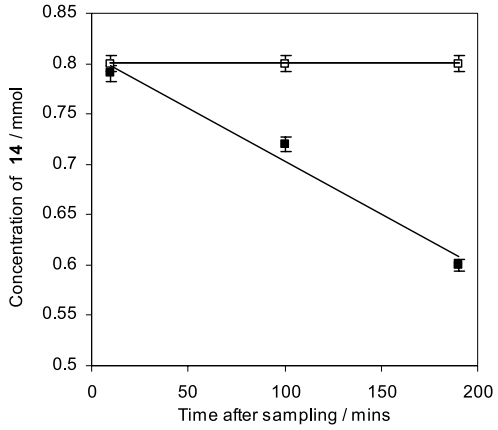


Figure 7. A graph showing the consumption of **14** (0.5 mol% Pd/Cu) in a sample prepared for GC analysis—sampling at specified times (taken from reaction mixture at 1.5 h): ■ reaction sample quenched with a silica-plug and elution with CH_2Cl_2; □ reaction sample quenched with a silica-plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial. (amount of dppe:Pd ~ 4:1).

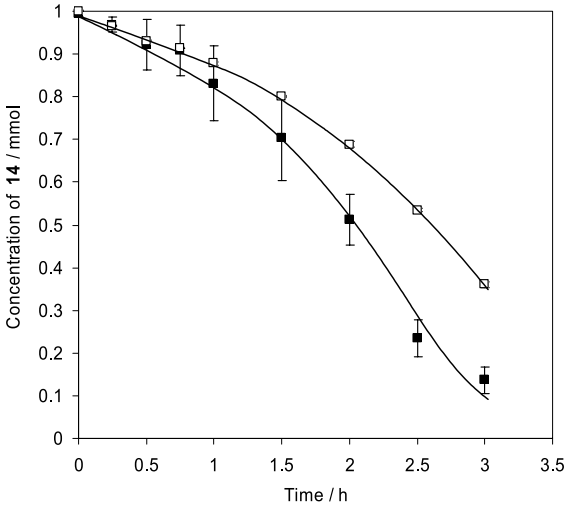


Figure 8. Reaction profiles showing the consumption of **14** (0.5 mol% Pd/Cu) with phenylacetylene at specified times (triplicate samples for each sample time were run by GC): ■ reaction sample quenched with a silica-plug and elution with CH_2Cl_2; □ reaction sample quenched with a silica-plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial.

hydrodebrominated 2-pyrone.[46] We have not detected the latter compound by GC/MS. Other side reactions must account for the complete consumption of **5**, but lower isolated yields of **4a**. The benefit gained from employing increased loadings of Cu(I) with respect to Pd presumably stems from the in situ formation of higher concentrations of alkynylcuprate. It is unlikely that Cu(I) is acting as a phosphine scavenger, and promoting the transmetallation step in the catalytic cycle, in this polar-solvent combination. However, Cu(I) could influence the stability and reactivity of Pd interemediates, for example, in bimetalic species.

With this new information to hand, various other terminal acetylenes were coupled with **5** to provide several substituted acetylene 2-pyrones (**4b–f**), allowing the effect of lower catalyst loadings on other terminal acetylenes to be

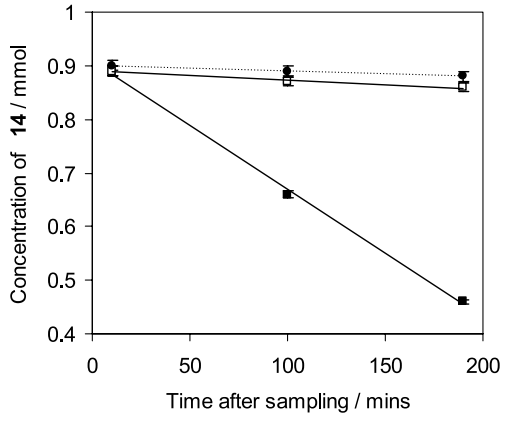


Figure 9. A graph showing the consumption of **14** (5 mol% Pd/Cu) in a sample prepared for GC analysis—sampling at specified times (taken from reaction mixture at 0.25 h): ■ reaction sample quenched with a silica-plug and elution with CH_2Cl_2; □ reaction sample quenched with a silica-plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial (amount of dppe:Pd ~ 4:1); ● reaction sample was concentrated in vacuo (ensuring complete removal of Et_3N) and then re-dissolved in CH_2Cl_2 (dotted line).

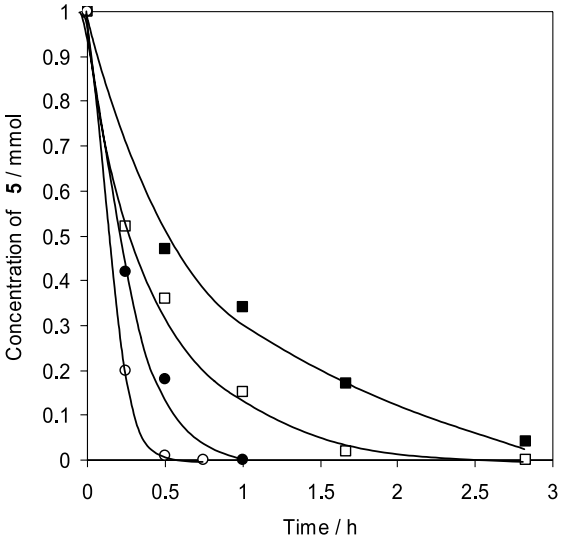


Figure 10. Consumption of **5** in Sonogashira coupling with phenylacetylene to give **4a**. Using identical conditions as Scheme 2. $Pd(PPh_3)_2Cl_2$ (0.25 mol%) was employed. ■ CuI (0.25 mol%); □ CuI (0.5 mol%); ● CuI (0.94 mol%); ○ CuI (1.94 mol%).

assessed (Table 3). Throughout the series of examples, higher yields are observed at 0.25 mol% Pd/Cu loadings (entries 1–6). The reactions do slow down at 0.025 mol% Pd/Cu loadings. However, significant conversions were still recorded. The excellent reactivity of 1-ethynyl-1-cyclopentanol, 1-ethynyl-1-cyclohexanol and 1-ethynyl-1-hydroxyfluorene towards **5** is notable (entries 3–5)—these results compare favourably with phenylacetylene. The formation of a Pd(II)(η^1-4-2-pyrone)alkoxide species could account for the increased reactivity, although we have not detected any carbonyl products that could result from a β-carbon elimination pathway, if such species were formed. Ethynylferrocene coupled with **5** to give **4f** in 59% yield (entry 6). Lower loadings were not recorded for this reaction as incomplete conversion was seen at 0.25 mol% Pd/Cu loading.

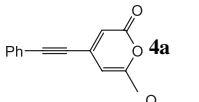
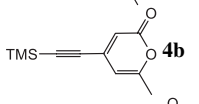
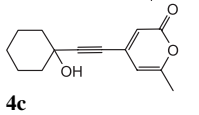
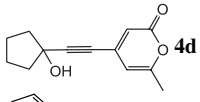
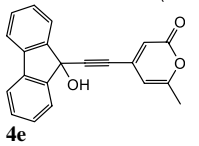
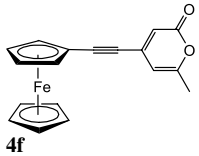
Crystals amenable to X-ray diffraction studies were grown from an ether layered solution of CH_2Cl_2 containing **4f**. The structure is shown in Figure 11 and confirms the proposed structural connectivity. A slight deviation in planarity is observed for the 2-pyrone ring with respect to the acetylene moiety. The bonding in the 2-pyrone is substantially localised, as seen in unsubstituted 2-pyrone.[47] The O(1)–C(15) (1.380(5)), C(13)–C(14) (1.349(5)) and C(13)–C(17) (1.431(5)) bonds in **4f** are slightly longer (in unsubstituted 2-pyrone: 1.384(3), 1.339(4) and 1.424(4) Å, respectively).

Table 2. Effect of Cu(I) loading on Sonogashira coupling of **5**→**4a**[a]

Entry	CuI loading/ mol%[b]	Turnover frequency (TOF)/mol h^{-1}	Isolated yield of coupled product (**4a**)/%
1	0.25 (1:1)	420	>99
2	0.50 (2:1)	510	97
3	0.94 (3.8:1)	640	78
4	1.94 (7.8:1)	1280	54

[a] As for Figure 9; TOF were calculated from the initial linear portion of the reaction profiles, normalised to the molar Pd content.
[b] The ratio in brackets represents the Cu:Pd ratio.

Table 3. Sonogashira coupling of **5** at low Pd/Cu catalyst loadings

Entry	Coupled product	% Conv./TON		
		10 wt% Pd/C, 4 mol % Cu[a]	0.25 mol% Pd/Cu[b]	0.025 mol% Pd/Cu[c]
1	 **4a**	74/37	97/388	61/2440
2	 **4b**	82/41	89/356	58/2320
3	 **4c**	84/42	98/392	46/1840
4	 **4d**	61/31	85/340	54/2160
5	 **4e**	90/45	97/388	62/2480
6	 **4f**	—	59/118[d]	—

[a] Isolated yields obtained using 10 wt% Pd/C (2 mol% Pd), PPh_3 (2.5 mol%), CuI (4 mol%), Et_3N/CH_3CN (2.5:1.5), 3 h, reflux.
[b] Reagents and conditions: as for Scheme 2 and Table 1, but using 0.5 mol% CuI (3 h reaction time).
[c] As for footnote b, but using 0.05 mol% CuI for 15 h.
[d] Pd (0.5 mol%) was employed for this reaction.

The C(11)≡C(12) bond (1.193(5)) is shorter and the adjacent single bonds longer (C(10)–C(11) and C(12)–C(13): 1.419(5) and 1.429(5), respectively) in **4f** than in the same bonds in 4-[4′-(*N*,*N*-dimethylaminophenyl)ethynyl]-6-methyl-2-pyrone.[11]

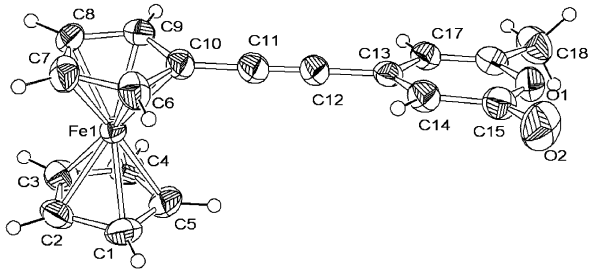


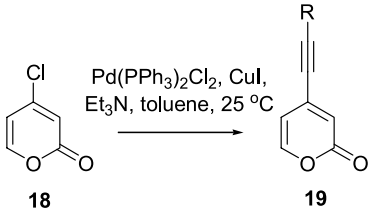
Figure 11. X-ray structure for complex **4f**. Thermal elipsoids are shown at 50% probability level.

2.3. Sonogashira coupling of 4-chloro and 6-chloro-2-pyrone

To our knowledge, the Sonogashira coupling of 4-chloro-2-pyrone with terminal acetylenes remains unreported (**18**→**19**). Using similar reaction conditions described for 6-chloro-2-pyrone **20**,[22] several terminal acetylenes were evaluated for Sonogashira coupling (Table 4). The reaction of phenylacetylene with **18** gave **19a** in 62% yield (entry 1). The product was accompanied by substantial quantities of the 1,3-diyne (26%), which is formed from either oxygen or a hydrodechlorination process. We have not detected or isolated the volatile 2-pyrone that would result from the latter side-reaction. The yield (82%) of **19a** was improved by heating to 60 °C, which also reduced the amount of 1,3-diyne formed. Although the room temperature protocol gave a high yield of **19c** from reaction of **18** with 1-pentyne (entry 3), all further reactions were low yielding (entries 2, 4–6). This was to some extent based on incomplete reaction. Thus, reactions at 60 °C gave improved yields throughout the series. Here, trimethylsilylacetylene was more reactive than 1-hexyne, 1-heptyne and 1-octyne, reaching completion at 60 °C in 3 h.

Comments on the cross-coupling reactions of **20**: The reaction of **20** with trimethylsilylacetylene to give **21a** has been reported (Scheme 4).[22]

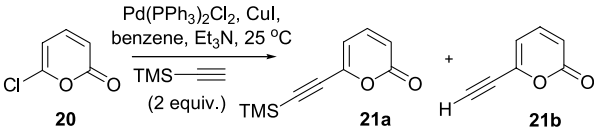
Table 4. Sonogashira coupling of **18**[a]



18 **19**

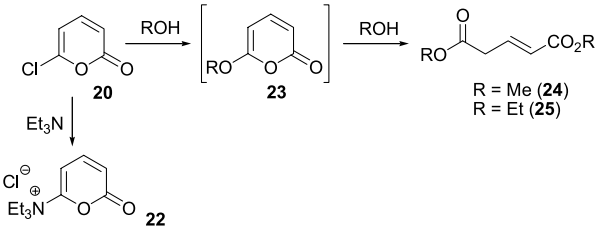
Entry	Coupled product	% Conv. (25 °C)	% Conv. (60 °C)
1	R=Ph, **19a**	62[b]	82[c]
2	R=TMS, **19b**	25 (47)	68[d]
3	R=$(CH_2)_2CH_3$, **19c**	72 (84)	85[c]
4	R= $(CH_2)_3CH_3$, **19d**	32 (48)	79[c]
5	R= $(CH_2)_4CH_3$, **19e**	20 (31)	81[c]
6	R= $(CH_2)_4CH_3$, **19f**	24 (50)	69[c]

[a] Reagents and conditions: $(PPh_3)_2PdCl_2$ (5 mol%), CuI (3 mol%), Et_3N (3 equiv), toluene, 21 h. Number in brackets is the yield based on recovered **18**.
[b] Phenylacetylene dimer yield (26%).
[c] After 21 h.
[d] After 3 h.



Scheme 4. Sonogashira alkynylation of 6-chloro-2-pyrone **20**.

Benzene or toluene may be used as solvent, with Et_3N employed as base. We were unable to accomplish these couplings, until further information was disclosed.[48] The instruction required for successful coupling is to add slowly a solution of Et_3N (1.5 equiv) in benzene over 1.5 h 0 °C, then allowed to warm to room temperature and stirred for 21 h. In our hands, however, using these conditions, we obtained a mixture of **21a** and **21b** in 21 and 16% yield, respectively. These yields are also variable. Previous studies in our research group[49] showed that **20** decomposes in many organic solvents, the exception being toluene (dry or wet), benzene, $CHCl_3$ (ethanol-free) and hexane (Scheme 5).



Scheme 5. Decomposition products derived from **20**.

The decomposition to other products was established by monitoring the decay of solutions of **20** with time by UV spectroscopy. The rapid decomposition in benzene containing 1% Et_3N ($\lambda_{max}=303$ nm) is shown in Figure 12 ($t^{1}/_{2}=19$ min at 25 °C). The solvent/base combination mimics the Sonogashira reaction conditions in the absence of Pd, Cu and terminal acetylene. Note: negligible decomposition was observed in the absence of Et_3N. The new product is **22** ($\lambda_{max}=361$ nm), confirmed by ^{1}H NMR and MS.

The rapid decomposition in many solvents (see Fig. 13) accounts for the difficulties that we encountered in undertaking Sonogashira couplings, as well as in many types of Stille and Suzuki couplings under standard[50] and less standard conditions.[51] We believe that a one-step phosphine-catalyzed annulation between aldehydes and ethyl allenoate represents the most versatile method for the formation of 6-substituted 2-pyrones at the present time.[52]

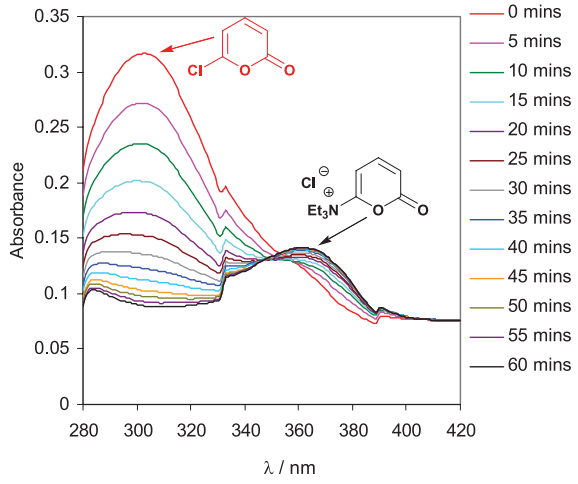


Figure 12. Decomposition of 6-chloro-2-pyrone **20** in benzene containing 1% Et_3N at 25 °C.

3. Discussion and conclusions

In this paper, the Sonogashira coupling of 4-halogenated-6-methyl-2-pyrones with terminal acetylenes has been reinvestigated. Previous experiments showed that relatively high loadings of $Pd(PPh_3)_2Cl_2$ (6 mol%)/CuI (4 mol%) were hampering the coupling process for several terminal acetylenes at reflux. Pd agglomeration and precipitation was the major problem. Lowering the catalyst loading to ca. 0.25–0.5 mol% Pd/Cu has ultimately shown that this previously ineffective catalyst combination promoted Sonogashira coupling with an identical solvent/base system and reactant concentration at 25 °C. In uncovering this it was established that sampling reaction mixtures of **5**, as well as **14** and *E*/*Z*-**16**, which were analysed by GC, should be performed with some caution. Passage of reaction samples through a silica plug and eluting with CH_2Cl_2 is not sufficient to quench further reaction—an implication for other activated substrates, particularly with respect to Pd-catalyst screening, where misleading results could be collected. Efficient quenching systems for these substrates are: (1) quench GC sample by addition of a CH_2Cl_2 solution containing excess dppe (w.r.t. the total theoretical Pd concentration in sample); (2) concentrate the GC sample in vacuo, and then redisolve in CH_2Cl_2; (3) quench the reaction sample by addition of saturated aqueous NH_4Cl (in air), then extract into CH_2Cl_2.

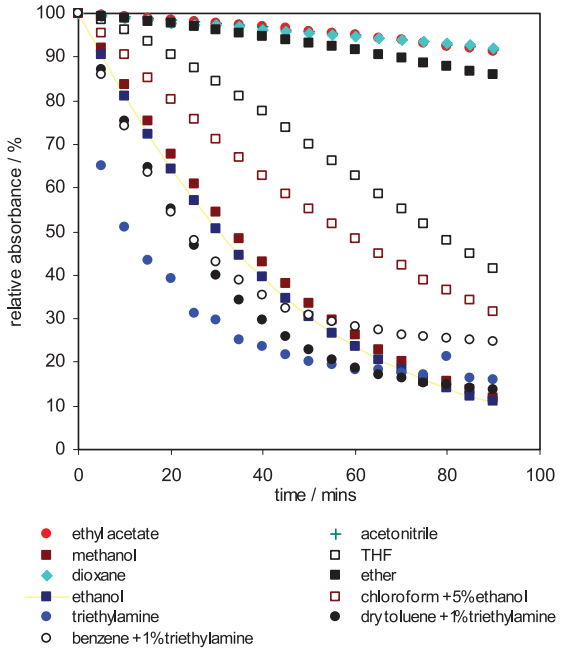


Figure 13. Decomposition of 6-chloro-2-pyrone **20** against various solvents at 25 °C (decay monitored by UV spectroscopy).

We have shown that relatively low catalyst loadings can be used to produce 4-alkynyl-6-methyl-2-pyrones—good turnover numbers can be accomplished with the standard $Pd(PPh_3)_2Cl_2$/CuI catalyst combination. This catalyst system still remains the most popular for Sonogashira coupling; here we have demonstrated that lower catalyst loadings maybe used to ease purification of the coupled products.

Finally, the first Sonogashira couplings on **18** have been conducted. In comparison with **20**, **18** is considerably less reactive under identical Sonogashira conditions, requiring 60 °C and extended reaction times (compared to 25 °C for **20**). The decomposition of **20** represents a hindrance in Sonogashira coupling, and as a consequence the conditions described by Bellina et al.,[22b] which were elegantly applied in target directed synthesis, are key to successful coupling. We have determined that other coupling processes on this 2-pyrone have limited utility.

4. Experimental

4.1. General details

All solvents were dried prior to use and stored under an argon atmosphere. Acetonitrile and triethylamine were distilled from calcium hydride and stored in the dark. Phenylacetylene was purchased from Aldrich and redistilled (stored in the dark at 0 °C). 1,2-Bis(diphenylphosphino) ethane (dppe) was purchased from Avocado. CuI was purchased from Aldrich and used as received. PE refers to petroleum ether (40–60 °C), EtOAc to ethyl acetate and ether to diethyl ether. $Pd(PPh_3)_2Cl_2$ was prepared from $PdCl_2$ in refluxing DMSO and PPh_3 (2 equiv).[53] Ethynylferrocene was synthesised according to a known procedure.[54] Compounds **5**,[15c] **11**,[15c] **21a**[22b] and **21b**[22b] have been previously reported.

Analysis of reaction samples was performed using a Varian CP-3800 GC equipped with a CP-8400 Autosampler. Separation was achieved using a DB-1 column (30 m×0.32 mm, 0.25 μm film thickness) with carrier gas flow rate of 3 mL min^{-1} and a temperature ramp from 50 to 250 °C at 20 °C min^{-1}. The injection volume was 1 μL with a split ratio of 50.

4.2. Synthesis of halogenated 2-pyrones

4.2.1. 4-Chloro-6-methyl-2-pyrone (9). To a two necked flask (100 mL) fitted with a reflux condenser and a calcium chloride drying tube, 4-hydroxy-6-methyl-2-pyrone (2.01 g, 0.016 mol) was dissolved in phosphorous oxychloride (15 mL, 0.160 mol) and stirred overnight at room temperature. The temperature was raised to 100 °C over the course of 2.5 h, and maintained at this temperature for a further 2 h. The reaction was allowed to cool and poured onto ice (100 g), extracted with ether (2×100 mL) and EtOAc (2×100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo. Purification by sublimation (60 °C; 7 mbar) onto a liquid nitrogen cold finger, afforded the title compound as a white crystalline solid (613 mg, 27%). Mp 82–84 °C, lit. 85 °C;[55] δ_H (400 MHz, $CDCl_3$) 6.22 (1H, s, H5), 6.06 (1H, s, H3), 2.26 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 162.59 (4°), 161.12 (4°), 151.76 (4°), 110.99 (CH), 106.13 (CH), 19.85 (CH_3); ν_{max} (CH_2Cl_2, cm^{-1}) 1734 (C=O), 1630, 1554; *m/z* (CI) 162/164 ($M+NH_4^+$, Cl^{35}/Cl^{37}, 62), 145/147 (MH^+, Cl^{35}/Cl^{37}, 100).

4.2.2. 4-Iodo-6-methyl-2-pyrone (10). 4-Hydroxy-6-methyl-2-pyrone (5.08 g, 40 mmol), P_2O_5 (13.63 g, 96 mmol) and tetra-*n*-butylammonium iodide (16.25 g, 44 mmol) were heated to reflux and stirred vigorously for 6 h. The reaction was cooled to room temperature and the resulting upper toluene layer was collected. The remaining mixture was extracted with toluene (2×75 mL) and the combined organic layers washed with and saturated aqueous NaCl (150 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo. Recrystallisation from hot PE afforded the title compound as a cream solid (1.3 g, 13%). Mp 70–72 °C; δ_H (400 MHz, $CDCl_3$) 6.75 (1H, s, H5), 6.35 (1H, s, H3), 2.21 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 161.25 (4°), 159.94 (4°), 121.97 (4°), 115.35 (CH), 113.0 (CH), 19.84 (CH_3); ν_{max} (CH_2Cl_2, cm^{-1}) 1726 (C=O), 1616, 1538; *m/z* (EI) 236 (M^+, 16%); HRCI *m/z* exact mass calculated for $C_6H_6O_2I$ (MH^+): 236.9413. Found: 236.9411.

4.2.3. 4-Tosyloxy-6-methyl-2-pyrone (13). 4-Hydroxy-6-methyl-2-pyrone (1.26 g, 0.01 mol) and pyridine (2.4 mL, 0.03 mol) were stirred for 0.5 h at 0 °C in CH_2Cl_2 (30 mL). *p*-Toluenesulfonyl chloride (2.1 g, 0.011 mol) was dissolved in CH_2Cl_2 (30 mL) and added dropwise over 0.5 h. The mixture was allowed to warm to 25 °C and stirred for 16 h. H_2O (50 mL) was added and the product extracted into EtOAc (3×50 mL). The combined organic layers were washed with 1 M HCl (50 mL), H_2O (50 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo. Recrystallisation from hot ethanol afforded the title compound as pale pink crystals (1.90 g, 68%). δ_H (400 MHz, $CDCl_3$) 7.78 (2H, m, C_6H_4), 7.36 (2H, m, C_6H_4), 5.97 (1H, m, H5), 5.78 (1H, m, H3), 2.44 (3H, s, C_6H_4–CH_3), 2.20 (3H, s, py-CH_3); δ_C (100 MHz, $CDCl_3$) 164.23, 162.87, 161.92, 146.68, 131.51, 130.24, 128.33, 100.72, 100.59, 21.76 (CH_3), 20.13 (CH_3); *m/z* (EI) 280 (M^+, 50); ν_{max} (CH_2Cl_2, cm^{-1}) 1742, 1645, 1574, 1387, 971. This data is consistent with that reported.[56]

4.3. Experiments for gas chromatographic analysis of Sonogashira cross-coupling reactions

Sonogashira procedure-using silica-plug quench only. 4-Bromo-6-methyl-2-pyrone **5** (0.189 g, 1 mmol) and $PdCl_2(PPh_3)_2$ (1.9 mg, 0.25 mol%) was placed in a Radleys carousel reactor vessel and flushed with nitrogen. Hexadecane (11.3 mg, 0.05 mmol) was added as an internal standard. Dry CH_3CN (5 mL) and dry Et_3N (3 mL) was added via syringe. Stirring was switched on at this point and a zero-point sample taken for GC analysis, then CuI (0.5 mg, 0.25 mol%) and phenylacetylene (139 μL, 1.2 equiv) were added immediately (phenylacetylene last). The reaction was kept under nitrogen and followed by GC analysis. *Sample quenching*. (1) Using silica-plug and dppe quench: elution of the analysis sample through silica-gel, 1,2-bis(diphenylphosphino)ethane (dppe) in CH_2Cl_2

(100 μL, 3.3 mM) was added immediately. (2) Using silica-plug and concentration in vacuo: As above for standard silica quench, but all solvents were removed in vacuo. Sample was then immediately taken up in CH_2Cl_2 for GC analysis. (3) The sample was treated with a saturated aqueous solution of NH_4Cl (0.5 mL), which was then extracted with EtOAc (1 mL). The organic layer was dried ($MgSO_4$) and then analysed by GC.

4.4. Standard Sonogashira coupling (preparative)

The characterisation data for compounds **4a–e** have been previously reported.[15c]

Using standard Schlenk techniques: 4-bromo-6-methyl-2-pyrone **5** (0.189 g, 1 mmol) and $Pd(PPh_3)_2Cl_2$ (1.9 mg, 0.25 mol%) were placed in a Schlenk tube purged with N_2. Dry CH_3CN (5 mL) and dry Et_3N (3 mL) was added via syringe. Phenylacetylene (139 μL, 1.2 equiv) and CuI (0.5 mg, 0.25 mol%) was added. The solvents were removed in vacuo and the residue dissolved in diethyl ether (10 mL) or CH_2Cl_2 (the latter for more polar compounds). The organic phase was washed with 10% aqueous HCl (1×5 mL), water (1×5 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. For arylacetylenes, the products could be recrystallised from hot hexane. For the other terminal acetylenes, purification was usually done by flash chromatography using hexane/EtOAc or hexane/CH_2Cl_2 solvent mixtures.

4.4.1. 4-Ethynylferrocene-6-methyl-2-pyrone (4f). Synthesised by the standard procedure, using 0.25 mol% of $Pd(PPh_3)_2Cl_2$ and 0.5 mol% CuI (conducted on a 1 mmol scale w.r.t. **5**). Purification was performed by chromatography using hexane first, to remove unreacted ethynylferrocene, followed by a hexane–CH_2Cl_2 (9/1) mixture to remove unreacted **5**; increasing the polarity to 1:1 gave the product as a red solid (0.22 g, 59%). A small amount of this was crystallised from CH_2Cl_2. Mp 129–130 °C; δ_H (400 MHz, $CDCl_3$) 6.21 (1H, s, H5), 5.99 (1H, s, H3), 4.52 (2H, br s, Cp), 4.34 (2H, br s, Cp), 4.24 (5H, s, Cp), 2.23 (3H, s, CH_3); δ_C NMR (100 MHz, $CDCl_3$) 19.8 (CH_3), 62.4 (Cp), 70.2 (Cp), 70.4 (Cp), 72.3 (Cp), 82.8 (C≡C), 100.5 (C≡C), 105.6 (C3), 113.1 (C5), 139.7 (C4), 161.7 (C6), 162.7 (C2); ν_{max} (KBr, cm^{-1}) 3105, 2921, 2847, 2206, 1703 (C=O), 1621, 1536, 1315, 1213, 960, 808 cm^{-1}; *m/z* (CI) 319 (M^+, 100%); HRCI *m/z* exact mass calculated for $C_{18}H_{15}O_2Fe$ (MH^+): 319.0421. Found: 319.0421.

The characterisation data for *E*- and *Z*-5-phenyl-2-penten-4-ynoic acid ethyl ester (*E*-**17** and *Z*-**17**) agrees with that reported in the literature.[36a]

4.4.2. Sonogashira coupling of 4-chloro-2-pyrone (18). To a degassed solution of 4-chloro-2-pyrone (50 mg, 0.38 mmol, 1 equiv) and terminal acetylene (0.42 mmol, 1.1 equiv) in toluene (2 mL), under a nitrogen atmosphere, was added Et_3N (0.16 mL, 1.15 mmol, 3 equiv), followed by $Pd(PPh_3)_2Cl_2$ (1.3 mg, 1.9×10^{-6} mol, 5 mol%) and CuI (0.2 mg, 1.1×10^{-6} mol, 3 mol%). The solution was allowed to stir for 21 h at the temperature indicated in Table 4. After this time, the mixture was concentrated in vacuo. Purification by column chromatography on silica using hexane–ethyl acetate (9/1–7/3), gave the coupled products as crystalline solids or viscous oils.

4.4.3. 4-Phenylethynyl-2-pyrone (19a). The title compound was isolated as a brown solid. Mp 94–96 °C; R_f=0.55 (hexane/ethyl acetate, 7:3 v/v); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, m, Ph), 7.36–7.55 (5H, br m, Ph and H6), 6.45 (1H, m, H3), 6.25 (1H, dd, ^4J=1.6 Hz, ^3J=5.3 Hz, H5); δ_C (100 MHz, $CDCl_3$) 161.2, 151.0, 138.2, 130.3, 128.7, 121.2, 118.1, 108.2, 99.4, 85.1; ν_{max} (CH_2Cl_2, cm^{-1}) 2927, 2853, 2218, 1726, 1631, 1535, 1176, 1118; *m/z* (CI) 214 ($M+NH_4^+$, 25), 197 (MH^+, 100); HRCI *m/z* exact mass calculated for $C_{13}H_9O_2$ (MH^+): 197.0602. Found: 197.0600.

4.4.4. 4-Trimethylsilyethynyl-2-pyrone (19b). The title compound was isolated as a yellow solid. Mp 102–104 °C; R_f=0.59 (hexane/ethyl acetate, 7:3 v/v); δ_H (400 MHz, $CDCl_3$) 7.34 (1H, dd, ^5J=1.0 Hz, ^3J=5.4 Hz, H6), 6.32 (1H, br s, H3), 6.10 (1H, dd, ^4J=1.5 Hz, ^3J=5.4 Hz, H5), 0.19 (9H, s); δ_C (100 MHz, $CDCl_3$) 149.9, 139.0, 117.8, 107.1, 105.5, 100.7, 98.6, −1.59; ν_{max} (CH_2Cl_2, cm^{-1}) 2962, 2340, 2167, 1762 (C=O), 1735, 1420, 1317, 1215, 1200, 1026; *m/z* (CI) 192 ([MH^+], 11), 177 ([M^+-CH_3], 100); HRCI *m/z* exact mass calculated for $C_{10}H_{13}O_2Si$ (MH^+): 193.0684. Found: 193.0678.

4.4.5. 4-Pentynyl-2-pyrone (19c). The title compound was isolated as a brown oil. R_f=0.45 (hexane/ethyl acetate, 7:3 v/v); δ_H (400 MHz, $CDCl_3$) 7.37 (1H, dd, ^5J=1.0 Hz, ^3J=5.4 Hz, H6), 6.30 (1H, br s, H3), 6.11 (1H, dd, ^4J=1.6 Hz, ^3J=5.4 Hz, H5), 2.40 (2H, t, ^3J=7.0 Hz, $CH_2(3')$), 2.23 (2H, m, $CH_2(4')$), 1.02 (3H, t, ^3J=7.3 Hz, $CH_3(5')$); δ_C (100 MHz, $CDCl_3$) 158.5, 150.8, 139.1, 137.0, 117.9, 108.7, 102.0, 21.7, 21.6, 13.6; ν_{max} (CH_2Cl_2, cm^{-1}) 2937, 2360, 2229, 1726 (C=O), 1632, 1536, 1427, 1230; *m/z* (CI) 180 ($M+NH_4^+$, 5), 163 (MH^+, 100); HRCI *m/z* exact mass calculated for $C_{10}H_{11}O_2$ (MH^+): 163.0759. Found: 163.0756.

4.4.6. 4-Hexynyl-2-pyrone (19d). The title compound was isolated as a red oil. δ_H (400 MHz, $CDCl_3$) 7.33 (1H, dd, ^5J=1.0 Hz, ^3J=5.4 Hz, H6), 6.29 (1H, m, H3), 6.06 (1H, dd, ^4J=1.5 Hz, ^3J=5.4 Hz, H5), 2.38 (2H, t, ^3J=7.0 Hz, $CH_2(3')$), 1.54 (2H, m, $CH_2(4')$), 1.43 (2H, m, $CH_2(5')$), 0.88 (3H, t, ^3J=7.3 Hz, $CH_3(6')$); δ_C NMR (100 MHz, $CDCl_3$) 161.4, 150.7, 139.0, 132.1, 117.8, 108.6, 102.3, 30.0, 21.9, 19.31, 13.5; ν_{max} (CH_2Cl_2, cm^{-1}) 2935, 2875, 2340, 2229, 1726 (C=O), 1632, 1536, 1427, 1224, 1154; *m/z* (CI) 194 ($M+NH_4^+$, 17), 177 (MH^+, 100); HRCI *m/z* exact mass calculated for $C_{11}H_{13}O_2$ (MH^+): 177.0915. Found: 177.0912.

4.4.7. 4-Heptynyl-2-pyrone (19e). The title compound was isolated as a red oil. δ_H (400 MHz, $CDCl_3$) 7.31 (1H, dd, ^5J=0.9 Hz, ^3J=5.4 Hz, H6), 6.25 (1H, br s, H3), 6.06 (1H, ^4J=1.5 Hz, ^3J=5.4 Hz, H5), 2.35 (2H, t, ^3J=7.0 Hz, $CH_2(3')$), 1.74 (2H, m, $CH_2(4')$), 1.26 (4H, m, $CH_2(5'$ and $6')$), 0.85 (3H, t, ^3J=7.1 Hz, $CH_3(7')$); δ_C (100 MHz, $CDCl_3$) 171.0, 161.3, 138.9, 117.7, 108.6, 102.3, 30.9, 27.6, 22.0, 19.5, 13.8; ν_{max} (CH_2Cl_2, cm^{-1}) 2903, 2341, 2256, 1725 (C=O), 1632, 1562, 1452, 1381, 1170, 1096. *m/z* (CI)

208 ($M+NH_4^+$, 8), 191 (MH^+, 100); HRCI *m/z* exact mass calculated for $C_{12}H_{15}O_2$ (MH^+): 191.1072. Found: 191.1070.

4.4.8. 4-Octynyl-2-pyrone (19f). The title compound was isolated as a red oil. δ_H (400 MHz, $CDCl_3$) 7.31 (1H, dd, $^5J=1.0$ Hz, $^3J=5.4$ Hz, H6), 6.24 (1H, br s, H3), 6.07 (1H, dd, $^4J=1.6$ Hz, $^3J=5.4$ Hz, H5), 2.36 (2H, t, $^3J=7.0$ Hz, $CH_2(3')$), 1.51 (2H, m, $CH_2(4')$), 1.30 (2H, m, $CH_2(5')$), 1.23 (4H, m, $CH_2(6'$ and $7')$), 0.83 (3H, t, $^3J=6.9$ Hz, $CH_2(8')$); δ_C (100 MHz, $CDCl_3$) 160.5, 149.7, 138.1, 116.8, 107.7, 101.5, 30.2, 27.6, 27.0, 21.5, 18.6, 13.1; ν_{max} (CH_2Cl_2, cm^{-1}) 2961, 2932, 2860, 2228, 1726 (C=O), 1631, 1536, 1457, 1313, 1158; *m/z* (CI) 222 ($M+NH_4^+$, 11), 205 (MH^+, 100); HRCI *m/z* exact mass calculated for $C_{13}H_{17}O_2$ (MH^+): 205.1228. Found: 205.1225.

4.4.9. 6-(Triethylammonium)-2-pyrone chloride (22). δ_H (400 MHz, $CDCl_3$) 7.19 (1H, t, $^3J=8.3$ Hz, H4), 5.30 (1H, d, $^3J=8.7$ Hz, H5), 5.03 (1H, d, $^3J=7.9$ Hz, H3), 3.33 (6H, q, $^3J=7.1$ Hz, $3\times CH_2$) 1.15 (9H, t, $^3J=7.1$ Hz, $3\times CH_3$); *m/z* (CI) 196 (M^+, 61), 168 ($M-CH_2CH_3^+$, 100).

4.4.10. (*E*)-Dimethyl pent-2-ene-dioate (24). δ_H (400 MHz, $CDCl_3$) 6.99 (1H, td, $^3J=7.3$, 15.8 Hz, H3), 5.92 (1H, td, $^4J=1.5$ Hz, $^3J=15.7$ Hz, H2), 3.70 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.23 (2H, dd, $^3J=1.5$, 7.3 Hz, $CH_2(4)$); δ_C NMR (100 MHz, $CDCl_3$) 170.28, 166.29, 139.87, 124.41, 52.26, 51.72, 37.28. *m/z* (CI) 176 ($M+NH_4^+$, 100).

4.4.11. (*E*)-Diethyl pent-2-ene-dioate (25). δ_H (400 MHz, $CDCl_3$) 6.98 (1H, td, $^3J=7.2$, 15.7 Hz, H3), 5.90 (1H, td, $^4J=1.5$ Hz, $^3J=15.7$ Hz, H2), 4.16 (4H, m, $2\times CH_2$), 3.20 (2H, dd, $^3J=1.5$, 7.2 Hz, $CH_2(4)$), 1.25 (6H, m, $2\times CH_3$); δ_C NMR (100 MHz, $CDCl_3$) 169.93, 165.91, 139.74, 124.73, 61.23, 60.55, 37.544, 14.28, 14.21; *m/z* (CI) 204 ($M+NH_4^+$, 100).

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Sonogashira reaction of aryl halides with propiolaldehyde diethyl acetal catalyzed by a tetraphosphine/palladium complex

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Abstract—All-*cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/$[PdCl(C_3H_5)]_2$ efficiently catalyzes the Sonogashira reaction of propiolaldehyde diethyl acetal with a variety of aryl bromides and chlorides. A minor electronic effect of the substituents of the aryl bromide was observed. Similar reaction rates were observed in the presence of activated aryl bromides such as 4-trifluoromethylbromobenzene and deactivated aryl bromides such as bromoanisole. Turnover numbers up to 95,000 can be obtained for this reaction. Even aryl chlorides and heteroarylbromides or chlorides have been successfully alkynylated with this catalyst. Moreover, a wide variety of substituents on the aryl halide such as fluoro, trifluoromethyl, acetyl, benzoyl, formyl, nitro, dimethylamino or nitrile are tolerated.

1. Introduction

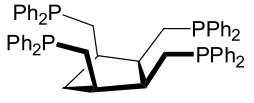
Substituted arylpropiolaldehydes bearing various substituents on the aromatic ring are of great biological interest and are also useful reagents in organic synthesis.[1] The Sonogashira palladium-catalyzed reaction[2] of aryl and heteroaryl halides with propiolaldehyde diethyl acetal is a very powerful method for the synthesis of these arylpropiolaldehydes. However, most of the results have been obtained with very reactive but expensive aryliodides[3–9] and the procedures reported for this reaction require relatively high catalysts loadings (1–10%).[3–12] If the catalytic load of palladium complex could be reduced to a significantly smaller level, this reaction would be much more practical.[13]

In recent years, several thermally stable palladium catalysts have been successfully used for Sonogashira reaction.[14] However, to our knowledge, only triphenylphosphine ligand has been used for the coupling of aryl halides with propiolaldehyde diethyl acetal.[4,5] But this phosphorus ligand can be labile under some coupling conditions especially at elevated temperature and gave palladium black, which is generally inactive. To our knowledge, low-catalyst loading Sonogashira reactions with propiolaldehyde diethyl acetal have not been described.

In order to find more efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand, Tedicyp[15] (Fig. 1). We have reported recently several results obtained in allylic substitution,[15] Suzuki cross-coupling,[16] and Heck reactions.[17] We have also reported the Sonogashira reaction[18] using Tedicyp as ligand in the presence of sterically congested arylbromides,[18b] with arylchlorides[18d] or using alkynols.[18c] Here, in order to further establish the requirements for a successful Sonogashira reaction, we wish to report on the reaction of several aryl and heteroaryl halides with propiolaldehyde diethyl acetal using Tedicyp as ligand.

2. Results and discussion

For this study, based on previous results,[18] DMF was chosen as the solvent and potassium carbonate as the base. The reactions were performed at 130 °C under argon in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst. For the reactions performed with aryl bromides or iodobenzene 5% of copper(I) iodide was added as co-catalyst (Scheme 1). The reactions with aryl chlorides were performed without CuI. We have reported recently that for such substrates with our catalyst the presence of CuI often



Tedicyp

Figure 1.

Keywords: Sonogashira reaction; Aryl bromides; Palladium; Catalysis; Tetraphosphine.
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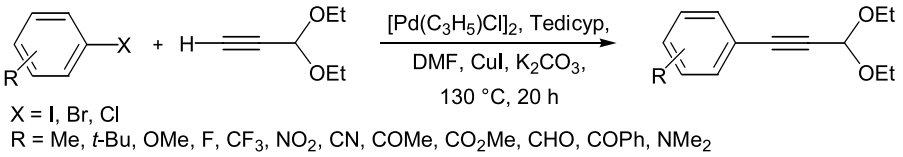


Scheme 1.

led to the formation of side-products such as the dimerization of the alkyne.[18b]

First, we have investigated the Sonogashira reaction of several *para*-substituted aryl bromides with propiolaldehyde diethyl acetal. The results presented in Table 1 disclose a minor effect of the substituents of the aryl bromide. In most cases the reaction performed with propiolaldehyde diethyl acetal proceeds very smoothly in the presence of 0.01% catalyst. We observed that turnover numbers of 6100–95,000 can be achieved with this catalyst for activated substrates such as 4-bromoacetophenone, 4-bromobenzaldehyde, 4-bromobenzophenone, 4-bromobenzonitrile, and 4-fluorobromobenzene (Table 1, entries 2–16). With the deactivated aryl bromides: 4-bromotoluene, 4-*t*butylbromobenzene and 4-bromoanisole slightly lower TONs of 700–10,000 were obtained (Table 1, entries 17–21). The least reactive aryl bromide for this reaction was 4-dimethylaminobromobenzene, but a complete conversion for a ratio substrate/catalyst of 1000 was observed (Table 1, entry 24). The similar TONs obtained with 4-bromobenzophenone and 4-*t*butylbromobenzene (6100 and 9200, respectively) seems to indicate that the oxidative addition of aryl bromides to palladium is not the rate-limiting step of the reaction with this catalyst.

Then, the reaction with propiolaldehyde diethyl acetal was applied to several *meta*- and *ortho*-substituted aryl bromides (Table 2), to aryl chlorides (Table 3) and also to a few heteroaryl halides (Table 4).

The influence of the presence of *meta* and *ortho* substituents on the aryl bromide on the reaction rate is reported in Table 2. As expected very similar TONs were obtained with *meta*-substituted aryl bromides than with the *para*-substituted substrates (Table 2, entries 1–5). *ortho*-Substituents on the aryl bromides generally have a more important effect on the reactions rates of Sonogashira reaction.[18] However, with propiolaldehyde diethyl acetal high TONs were obtained in most cases with the *ortho*- and di-*ortho*-substituted aryl bromides. We observed that the coupling of 2-bromobenzaldehyde, methyl 2-bromobenzoate, 2-bromobenzonitrile, 2-trifluoromethylbromobenzene or 2-fluorobromobenzene proceeds in the presence of 0.01% catalyst (Table 2, entries 8–15). Even the deactivated 2-bromoanisole gave good results in the presence of 0.01% catalyst. Again this observation is also consistent with our suggestion that the rate-limiting step does not involve oxidative addition of the aryl bromide (Table 2, entries 19 and 20).

With 2-bromoacetophenone the formation of an unexpected product was observed (Scheme 2, Table 2, entries 6 and 7). When a ratio substrate/catalyst of 1000 was used, the expected alkynylation product **19a** was obtained together with an other compound, which appears to be **19b**. This

Table 1. Palladium–Tedicyp catalyzed Sonogashira reaction with propiolaldehyde diethyl acetal and aryl halides (Scheme 1)

Entry	Aryl halide	Ratio substrate/catalyst	Product	Yield (%)[a]
1	Iodobenzene	10,000	**1**	100 (92)
2	4-Bromoacetophenone	10,000	**2**	100 (94)
3	4-Bromoacetophenone	100,000	**2**	95
4	4-Bromobenzaldehyde	10,000	**3**	100 (94)
5	4-Bromobenzophenone	1000	**4**	100 (91)
6	4-Bromobenzophenone	10,000	**4**	61
7	Methyl 4-bromobenzoate	1000	**5**	100 (90)
8	Methyl 4-bromobenzoate	10,000	**5**	92
9	4-Bromonitrobenzene	1000	**6**	100 (94)
10	4-Bromonitrobenzene	10,000	**6**	78
11	4-Bromobenzonitrile	10,000	**7**	100 (91)
12	4-Bromobenzonitrile	100,000	**7**	92
13	4-Trifluoromethylbromobenzene	10,000	**8**	100 (90)
14	3,5-bis(Trifluoromethyl)bromobenzene	10,000	**9**	100 (92)
15	4-Fluorobromobenzene	1000	**10**	100 (88)
16	4-Fluorobromobenzene	10,000	**10**	76
17	4-Bromotoluene	1000	**11**	98 (90)
18	4-Bromotoluene	10,000	**11**	70
19	4-*t*Butylbromobenzene	10,000	**12**	100 (92)
20	4-Bromoanisole	10,000	**13**	82 (74)
21	4-Bromoanisole	—[b]	**13**	0
22	2-Bromo-6-methoxynaphthalene	1000	**14**	100 (94)
23	2-Bromo-6-methoxynaphthalene	10,000	**14**	94
24	4-Dimethylaminobromobenzene	1000	**15**	100 (89)

Conditions: Pd–Tedicyp catalyst, ArX (1 equiv), propiolaldehyde diethyl acetal (2 equiv), CuI (0.05 equiv), K_2CO_3 (2 equiv), DMF, 130 °C, 20 h.
[a] GC and NMR conversion; yields in parenthesis are isolated.
[b] Reaction performed with CuI and without Pd catalyst.

Table 2. Palladium–Tedicyp catalyzed Sonogashira reaction with propiolaldehyde diethyl acetal and *meta*- or *ortho*-substituted aryl bromides (Schemes 1 and 2)

Entry	Aryl halide	Ratio substrate/catalyst	Product	Yield (%)[a]
1	3-Bromoacetophenone	10,000	**16**	100 (90)
2	3-Bromoacetophenone	100,000	**16**	50
3	3-Bromonitrobenzene	1000	**17**	100 (89)
4	3-Bromonitrobenzene	10,000	**17**	90
5	3-Bromotoluene	1000	**18**	100 (92)
6	2-Bromoacetophenone	250	**19c**	100 (80)[b]
7	2-Bromoacetophenone	1000	**19a**+**19c**	100 (45 and 42)[b,c]
8	2-Bromobenzaldehyde	10,000	**20**	100 (91)
9	Methyl 2-bromobenzoate	1000	**21**	100 (90)
10	Methyl 2-bromobenzoate	10,000	**21**	67
11	2-Bromobenzonitrile	1000	**22**	100 (87)
12	2-Bromobenzonitrile	10,000	**22**	90
13	2-Trifluoromethylbromobenzene	10,000	**23**	100 (91)
14	2-Fluorobromobenzene	1000	**24**	100 (93)
15	2-Fluorobromobenzene	10,000	**24**	55
16	2-Bromotoluene	1000	**25**	100 (90)
17	1-Bromonaphthalene	1000	**26**	100 (94)
18	1-Bromonaphthalene	10,000	**26**	68
19	2-Bromoanisole	1000	**27**	100 (88)
20	2-Bromoanisole	10,000	**27**	85
21	2,6-Difluorobromobenzene	250	**28**	90 (84)
22	2,6-Difluorobromobenzene	1000	**28**	50
23	2,4,6-Trimethylbromobenzene	1000	**29**	100 (89)
24	2,4,6-Trimethylbromobenzene	10,000	**29**	88
25	2,6-Diethyl-4-methylbromobenzene	1000	**30**	100 (88)
26	9-Bromoanthracene	1000	**31**	100 (90)
27	9-Bromoanthracene	10,000	**31**	40

Conditions: Pd–tedicyp catalyst, ArBr (1 equiv), propiolaldehyde diethyl acetal (2 equiv), CuI (0.05 equiv), K_2CO_3 (2 equiv), DMF, 130 °C, 20 h.
[a] GC and NMR conversion; yields in parenthesis are isolated.
[b] Before filtration on silica gel **19b** was observed (see Scheme 2).
[c] The formation of a mixture of **19a** (45%) and **19c** (42%) (see Scheme 2) was observed.

reaction performed with a ratio substrate/catalyst of 250 led exclusively to **19b**. Acidic treatment or filtration on silica gel of this compound gave the corresponding aldehyde **19c**. The formation of similar cyclization products has already been described for the palladium-catalyzed reactions of 2-iodobenzoic acid or 2-iodobenzyl alcohol and terminal alkynes.[19]

Next, we tried to evaluate the difference of reaction rate between mono- and di-*ortho*-substituted aryl bromides, and we observed that even very hindered aryl bromides could be coupled efficiently with propiolaldehyde diethyl acetal (Table 2, entries 21–27). For example, with 2,4,6-trimethylbromobenzene or 9-bromoanthracene the expected adducts were obtained in 89 and 90% yields, respectively, in the presence of 0.1% catalyst (Table 2, entries 23–27).

Then, the reactivity of a few aryl chlorides was studied (Table 3). These reactions were performed without CuI as co-catalyst. With electron-poor aryl chlorides such as 4-chloroacetophenone, 4-chloronitrobenzene or 4-chlorobenzonitrile the alkynylation products were obtained in good yields in the presence of 1% catalyst (Table 3, entries 1–7). On the other hand the electron-rich 4-chloroanisole led to the adduct **13** in a very low TON of 17 (Table 3, entry 8). Thus, the oxidative-addition of the aryl chlorides be the rate-limiting step of the reaction.

Finally, we have investigated the Sonogashira reaction of nine heteroaryl halides. The results are summarized in Table 4. We have observed in Tables 1 and 2 that with aryl bromides the oxidative addition to the palladium complex is probably not the rate-limiting step of the reaction with this catalyst. Pyridines or quinolines are π-electron deficient.

Table 3. Palladium–Tedicyp catalyzed Sonogashira reaction with propiolaldehyde diethyl acetal and aryl chlorides (Scheme 1)

Entry	Aryl halide	Ratio substrate/catalyst	Product	Yield (%)[a]
1	4-Chloroacetophenone	100	**2**	97 (87)
2	4-Chlorobenzaldehyde	100	**3**	100 (90)
3	4-Chlorobenzaldehyde	250	**3**	100
4	4-Chloronitrobenzene	100	**6**	100 (89)
5	4-Chloronitrobenzene	250	**6**	55
6	4-Chlorobenzonitrile	100	**7**	100 (87)
7	4-Trifluoromethylchlorobenzene	100	**8**	100 (87)
8	4-Chloroanisole	100	**13**	17

Conditions: Pd–Tedicyp catalyst, ArCl (1 equiv), propiolaldehyde diethyl acetal (2 equiv), K_2CO_3 (2 equiv), reactions performed without CuI, DMF, 130 °C, 20 h.
[a] GC and NMR conversion; yields in parenthesis are isolated.

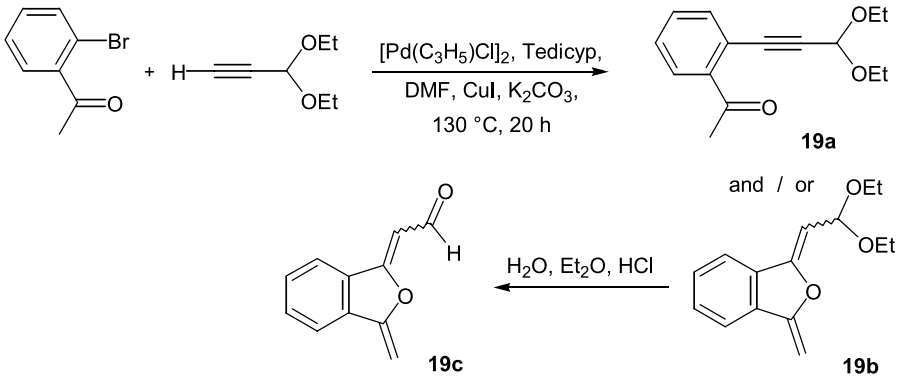
Table 4. Palladium–Tedicyp catalyzed Sonogashira reaction with propiolaldehyde diethyl acetal and heteroaryl halides (Scheme 1)

Entry	Aryl halide	Ratio substrate/catalyst	Product	Yield (%)[a]
1	2-Bromopyridine	1,000	**32**	100 (89)
2	2-Bromopyridine	10,000	**32**	100
3	2-Chloropyridine	100	**32**	100[b]
4	2-Chloropyridine	250	**32**	65[b]
5	3-Bromopyridine	10,000	**33**	100 (93)
6	2-Chloroquinoline	100	**34**	100 (90)[b]
7	2-Chloroquinoline	250	**34**	66[b]
8	3-Bromoquinoline	1000	**35**	100 (94)
9	3-Bromoquinoline	10,000	**35**	52
10	4-Bromoisoquinoline	10,000	**36**	100 (90)
11	5-Bromopyrimidine	1000	**37**	100 (90)
12	5-Bromopyrimidine	10,000	**37**	100
13	2-Bromothiophene	1000	**38**	100 (88)
14	2-Bromothiophene	10,000	**38**	95
15	3-Bromothiophene	100	**39**	100 (90)
16	3-Bromothiophene	1000	**39**	100

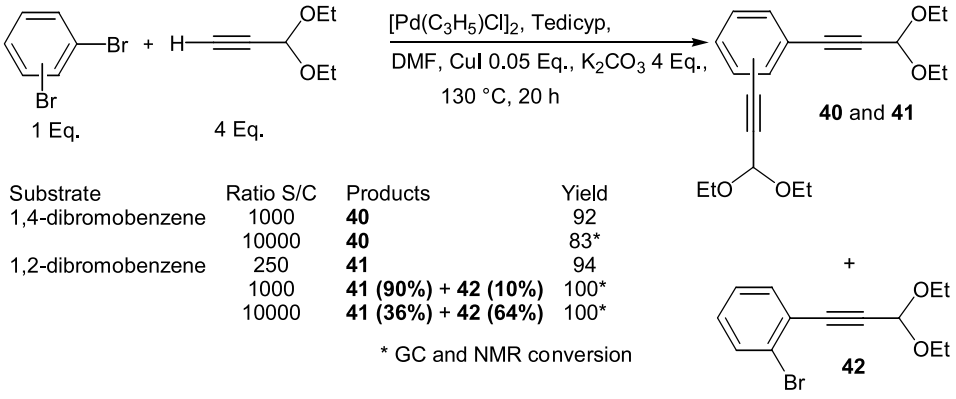
Conditions: Pd–Tedicyp catalyst, ArX (1 equiv), propiolaldehyde diethyl acetal (2 equiv), CuI (0.05 equiv), K_2CO_3 (2 equiv), DMF, 130 °C, 20 h.
[a] GC and NMR conversion; yields in parenthesis are isolated.
[b] Reactions performed without CuI.

Thiophenes or furanes are π-electron excessive. If the oxidative-addition is rate-limiting, the reactions should be slower with thiophenes or furanes than with pyridines or quinolines. In the presence of 2-bromopyridine, 3-bromopyridine, 3-bromoquinoline, 4-bromoisoquinoline, and 5-bromopyrimidine the reactions were performed successfully with 0.1–0.01% catalyst (Table 4, entries 1, 2, 5, and 8–12). Similar reactions rates were observed with 2-bromothiophene and 3-bromothiophene (Table 4, entries 13–16). These results seem to confirm that the oxidative addition of the aryl bromides to palladium is not the rate-limiting step of this reaction. The two heteroaryl chlorides: 2-chloropyridine and 2-chloroquinoline were also successfully alkynylated, but the presence of 0.4% catalyst was required (Table 4, entries 3, 4, 6, and 7).

The synthesis of 1,4- and 1,2-bis(3,3-diethoxyprop-1-ynyl)-benzene **40** and **41** from 1,4- and 1,2-dibromobenzene using 4 equiv of propiolaldehyde diethyl acetal also proceeds in good yields (Scheme 3). With 1,4-dibromobenzene, the



Scheme 2.



Substrate	Ratio S/C	Products	Yield
1,4-dibromobenzene	1000	**40**	92
	10000	**40**	83*
1,2-dibromobenzene	250	**41**	94
	1000	**41 (90%) + 42 (10%)**	100*
	10000	**41 (36%) + 42 (64%)**	100*

* GC and NMR conversion

Scheme 3.

monoaddition product was not observed and the diaddition product **40** was selectively obtained in 92% yield in the presence of 0.1% catalyst. On the other hand, with 1,2-dibromobenzene, if the diaddition product was selectively obtained in the presence of 0.4% catalyst, mixtures of mono and diaddition products **41** and **42** were obtained when ratios substrate/catalyst of 1000 and 10,000 were used. The slower reaction rate observed with 1,2-dibromobenzene probably comes from steric reasons.

In summary, we have established that the Tedicyp–palladium system provides an efficient catalyst for the coupling of aryl bromides with propiolaldehyde diethyl acetal. The uses of this Pd–tetraphosphine catalyst allow the use of low-catalyst loading. This reaction can be performed with as little as 0.01% catalyst with most of the aryl bromides. Due to the high price of palladium, the practical advantage of such low catalyst loadings can become increasingly important for industrial processes. A wide range of functions such as methoxy, fluoro, acetyl, formyl, benzoyl, carboxylate, nitro, nitrile or dimethylamino on the aryl bromide are tolerated. The steric hindrance of the aryl bromide has a minor effect on the reaction rates. Lower TONs were obtained for the coupling of aryl chlorides. With these substrates the use of 1% catalyst was necessary. Some heteroaromatic substrates such as bromo- or chloropyridines, a bromopyrimidine or bromothiophenes have also been used successfully. Moreover, propiolaldehyde diethyl acetal is commercially available and this is a practical advantage of this reaction.

3. Experimental

3.1. General remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMF analytical grade was not distilled before use. Potassium carbonate (99+) was used. Commercial propiolaldehyde diethyl acetal was used without purification. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ^{1}H and ^{13}C spectrum were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in ppm relative to $CDCl_3$ (7.25 for ^{1}H NMR and 77.0 for ^{13}C NMR). Flash chromatography were performed on silica gel (230–400 mesh). GC and NMR yields in Tables 1–4 are conversions of the aryl halides into the product calculated with GC and ^{1}H NMR spectrum of the crude mixtures.

3.1.1. Preparation of the Pd–tedicyp catalyst. An oven-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (30 mg, 81 μmol) and Tedicyp (140 mg, 162 μmol). Anhydrous DMF (10 mL) were added, then the solution was stirred at room temperature for 10 min. The appropriate catalyst concentration was obtained by successive dilutions. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25 (w=80 Hz), 19.4 (w=110 Hz).

3.2. General procedure

In a typical experiment, the aryl halide (1 mmol), propiolaldehyde diethyl acetal (0.256 g, 2 mmol or 0.512 g 4 mmol, see Tables 1–4 and Scheme 3), K_2CO_3 (0.276 g, 2 mmol or 0.552 g 4 mmol, see Tables 1–4 and Scheme 3) and CuI for the reactions performed with aryl bromides (0.01 g, 0.05 mmol) were dissolved in DMF (3 mL) under an argon atmosphere. The prepared Pd–Tedicyp catalyst complex (see Tables 1–4) was then transferred to the reaction flask via cannula. The reaction mixture was stirred at 130 °C for 20 h. Then, the product was extracted three times with Et_2O or CH_2Cl_2. (For compound **19c**, the mixture was acidified with an HCl solution (pH 6) then the product was extracted three times with Et_2O). The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

3.2.1. 1-Phenyl-3,3-diethoxyprop-1-yne 1. From iodobenzene (0.204 g, 1 mmol), product **1** was obtained in 92% (0.187 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.26 (m, 3H), 5.42 (s, 1H), 3.73 (m, 2H), 3.60 (m, 2H), 1.21 (t, 6H, J=7.1 Hz).

3.2.2. 1-(4-Acetylphenyl)-3,3-diethoxyprop-1-yne 2. From 4-bromoacetophenone (0.199 g, 1 mmol), product **2** was obtained in 94% (0.231 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, 2H, J=8.4 Hz), 7.52 (d, 2H, J=8.4 Hz), 5.46 (s, 1H), 3.77 (m, 2H), 3.65 (m, 2H), 2.55 (s, 3H), 1.24 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 136.7, 132.0, 128.1, 126.6, 91.6, 87.5, 84.1, 61.0, 26.5, 15.0; $C_{15}H_{18}O_3$: Calcd C, 73.15; H, 7.37. Found: C, 72.97; H, 7.43.

3.2.3. 1-(4-Formylphenyl)-3,3-diethoxyprop-1-yne 3. From 4-bromobenzaldehyde (0.185 g, 1 mmol), product **3** was obtained in 94% (0.218 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.79 (d, 2H, J=7.8 Hz), 7.60 (d, 2H, J=7.8 Hz), 5.48 (s, 1H), 3.76 (m, 2H), 3.62 (m, 2H), 1.23 (t, 6H, J=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 135.8, 132.4, 129.4, 128.0, 91.6, 88.2, 84.0, 61.1, 15.0; $C_{14}H_{16}O_3$: Calcd C, 72.39; H, 6.94. Found: C, 72.47; H, 7.09.

3.2.4. 1-(4-Benzoylphenyl)-3,3-diethoxyprop-1-yne 4. From 4-bromobenzophenone (0.261 g, 1 mmol), product **4** was obtained in 91% (0.280 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.70 (m, 4H), 7.60–7.52 (m, 3H), 7.45 (t, 2H, J=7.2 Hz), 5.49 (s, 1H), 3.79 (m, 2H), 3.66 (m, 2H), 1.25 (t, 6H, J=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 137.3, 137.1, 132.5, 131.7, 129.9, 129.8, 128.3, 125.9, 91.6, 87.2, 84.2, 61.0, 15.0; $C_{20}H_{20}O_3$: Calcd C, 77.90; H, 6.54. Found: C, 77.67; H, 6.74.

3.2.5. 1-(4-Methoxycarbonylphenyl)-3,3-diethoxyprop-1-yne 5. From methyl 4-bromobenzoate (0.215 g, 1 mmol), product **5** was obtained in 90% (0.236 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 2H, J=8.3 Hz), 7.52 (d, 2H, J=8.3 Hz), 5.48 (s, 1H), 3.89 (s, 3H), 3.77 (m, 2H), 3.65 (m, 2H), 1.27 (t, 6H, J=7.2 Hz).

3.2.6. 1-(4-Nitrophenyl)-3,3-diethoxyprop-1-yne 6. From 4-bromonitrobenzene (0.202 g, 1 mmol), product **6** was obtained in 94% (0.234 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, J=8.5 Hz), 7.59 (d, 2H, J=8.5 Hz), 5.48 (s, 1H), 3.77 (m, 2H), 3.65 (m, 2H), 1.26 (t, 6H, J=7.2 Hz).

3.2.7. 1-(4-Cyanophenyl)-3,3-diethoxyprop-1-yne 7. From 4-bromobenzonitrile (0.182 g, 1 mmol), product **7** was obtained in 91% (0.209 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 2H, J=8.5 Hz), 7.53 (d, 2H, J=8.5 Hz), 5.47 (s, 1H), 3.77 (m, 2H), 3.65 (m, 2H), 1.26 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.4, 131.9, 126.7, 118.2, 112.2, 91.5, 88.7, 83.2, 61.1, 15.0; $C_{14}H_{15}NO_2$: Calcd C, 73.34; H, 6.59. Found: C, 73.21; H, 6.47.

3.2.8. 1-(4-Trifluoromethylphenyl)-3,3-diethoxyprop-1-yne 8. From 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), product **8** was obtained in 90% (0.245 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 4H), 5.51 (s, 1H), 3.83 (m, 2H), 3.68 (m, 2H), 1.29 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2, 130.5 (q, J=32.4 Hz), 125.6, 125.2 (q, J=3.8 Hz), 123.8 (q, J=274.2 Hz), 91.6, 86.8, 83.6, 61.1, 15.0; $C_{14}H_{15}F_3O_2$: Calcd C, 61.76; H, 5.55. Found: C, 61.66; H, 5.34.

3.2.9. 1-[3,5-Bis(trifluoromethyl)phenyl]-3,3-diethoxyprop-1-yne 9. From 3,5-bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol), product **9** was obtained in 92% (0.313 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 2H), 7.81 (s, 1H), 5.48 (s, 1H), 3.83 (m, 2H), 3.68 (m, 2H), 1.27 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0 (q, J=34.5 Hz), 131.8, 124.5, 122.8 (q, J=272.3 Hz), 122.2 (m), 91.5, 88.0, 81.9, 61.2, 15.0; $C_{15}H_{14}F_6O_2$: Calcd C, 52.95; H, 4.15. Found: C, 52.80; H, 4.39.

3.2.10. 1-(4-Fluorophenyl)-3,3-diethoxyprop-1-yne 10. From 4-fluorobromobenzene (0.175 g, 1 mmol), product **10** was obtained in 88% (0.196 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, 2H, J=5.5, 8.5 Hz), 6.97 (t, 2H, J=8.5 Hz), 5.44 (s, 1H), 3.78 (m, 2H), 3.62 (m, 2H), 1.24 (t, 6H, J=7.2 Hz).

3.2.11. 1-(4-Tolyl)-3,3-diethoxyprop-1-yne 11. From 4-bromotoluene (0.171 g, 1 mmol), product **11** was obtained in 90% (0.196 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, J=8.2 Hz), 7.09 (d, 2H, J=8.2 Hz), 5.47 (s, 1H), 3.80 (m, 2H), 3.64 (m, 2H), 2.32 (s, 3H), 1.25 (t, 6H, J=7.2 Hz).

3.2.12. 1-(4-*tert*-Butylphenyl)-3,3-diethoxyprop-1-yne 12. From 4-*t*butylbromobenzene (0.213 g, 1 mmol), product **12** was obtained in 92% (0.239 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 2H, J=8.4 Hz), 7.34 (d, 2H, J=8.4 Hz), 5.50 (s, 1H), 3.83 (m, 2H), 3.68 (m, 2H), 1.32 (s, 9H), 1.27 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 131.6, 125.2, 118.3, 91.5, 85.4, 83.7, 60.9, 34.8, 31.2, 15.1. This compound was characterized by deprotection into the corresponding aldehyde.[20]

3.2.13. 1-(4-Anisyl)-3,3-diethoxyprop-1-yne 13. From 4-bromoanisole (0.187 g, 1 mmol), product **13** was obtained in 74% (0.173 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, 2H, J=8.4 Hz), 6.81 (d, 2H, J=8.4 Hz), 5.46 (s, 1H), 3.80 (m, 2H), 3.79 (s, 3H), 3.64 (m, 2H), 1.26 (t, 6H, J=7.2 Hz).

3.2.14. 2-(3,3-Diethoxy-prop-1-ynyl)-6-methoxynaphthalene 14. From 2-bromo-6-methoxynaphthalene (0.237 g, 1 mmol), product **14** was obtained in 94% (0.267 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.65 (m, 2H), 7.45 (dd, 1H, J=8.5, 1.5 Hz), 7.13 (dd, 1H, J=8.7, 2.4 Hz), 7.06 (d, 1H, J=2.4 Hz), 5.53 (s, 1H), 3.85 (s, 3H), 3.83 (m, 2H), 3.68 (m, 2H), 1.29 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 134.3, 131.8, 129.2, 128.8, 128.2, 126.6, 119.3, 116.6, 105.6, 91.8, 85.6, 83.9, 60.8, 55.1, 15.0; $C_{18}H_{20}O_3$: Calcd C, 76.03; H, 7.09. Found: C, 75.81; H, 7.31.

3.2.15. 1-(4-Dimethylaminophenyl)-3,3-diethoxyprop-1-yne 15. From 4-dimethylaminobromobenzene (0.200 g, 1 mmol), product **15** was obtained in 89% (0.220 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, 1H, J=8.9 Hz), 6.59 (d, 1H, J=8.9 Hz), 5.47 (s, 1H), 3.81 (m, 2H), 3.64 (m, 2H), 2.94 (s, 6H), 1.26 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 132.9, 111.5, 108.4, 92.0, 86.4, 82.1, 60.7, 40.0, 15.1. This compound was characterized by deprotection into the corresponding aldehyde.[21]

3.2.16. 1-(3-Acetylphenyl)-3,3-diethoxyprop-1-yne 16. From 3-bromoacetophenone (0.199 g, 1 mmol), product **16** was obtained in 90% (0.222 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.87 (d, 1H, J=8.0 Hz), 7.62 (d, 1H, J=8.0 Hz), 7.38 (t, 1H, J=8.0 Hz), 5.46 (s, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 2.56 (s, 3H), 1.23 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 137.0, 136.0, 131.8, 128.6, 128.3, 122.4, 91.6, 85.4, 84.0, 61.0, 26.5, 15.0; $C_{15}H_{18}O_3$: Calcd C, 73.15; H, 7.37. Found: C, 73.41; H, 7.18.

3.2.17. 1-(3-Nitrophenyl)-3,3-diethoxyprop-1-yne 17. From 3-bromonitrobenzene (0.202 g, 1 mmol), product **17** was obtained in 89% (0.222 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.15 (d, 1H, J=8.3 Hz), 7.73 (d, 1H, J=8.3 Hz), 7.48 (t, 1H, J=8.3 Hz), 5.46 (s, 1H), 3.79 (m, 2H), 3.63 (m, 2H), 1.24 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 137.4, 129.3,

126.5, 123.6, 123.4, 91.5, 87.0, 82.4, 61.0, 15.0; $C_{13}H_{15}NO_4$: Calcd C, 62.64; H, 6.07. Found: C, 62.47; H, 5.84.

3.2.18. 1-(3-Tolyl)-3,3-diethoxyprop-1-yne 18. From 3-bromotoluene (0.171 g, 1 mmol), product **18** was obtained in 92% (0.201 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.17 (t, 1H, J= 7.8 Hz), 7.11 (d, 1H, J=7.8 Hz), 5.46 (s, 1H), 3.81 (m, 2H), 3.64 (m, 2H), 2.30 (s, 3H), 1.25 (t, 6H, J=7.2 Hz).

3.2.19. 1-(2-Benzoylphenyl)-3,3-diethoxyprop-1-yne 19a. From 2-bromoacetophenone (0.199 g, 1 mmol), product **19a** was obtained in 45% (0.111 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, 1H, J=1.1, 7.5 Hz), 7. 57 (dd, 1H, J=1.2, 7.6 Hz), 7.44 (dt, 1H, J=1.1, 7.5 Hz), 7.36 (dt, 1H, J=1.2, 7.6 Hz), 5.52 (s, 1H), 3.84 (s, 3H), 3.80 (m, 2H), 3.69 (m, 2H), 1.25 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 134.4, 132.3, 131.6, 130.3, 128.4, 122.3, 91.8, 89.3, 83.6, 60.9, 52.1, 15.1; $C_{15}H_{18}O_3$: Calcd C, 73.15; H, 7.37. Found: C, 73.44; H, 7.58. The formation of **19b** was also observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.45 (m, 2H), 7.40–7.30 (m, 2H), 5.61 (d, 1H, J= 7.6 Hz), 5.27 (d, 1H, J=7.6 Hz), 4.77 (d, 1H, J=2.6 Hz), 4.47 (d, 1H, J=2.6 Hz), 3.75 (m, 2H), 3.60 (m, 2H), 1.23 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 153.3, 133.4, 133.3, 130.1 (CH), 129.9 (CH), 120.8 (2CH), 97.2 (CH), 96.1 (CH), 82.5 (=CH_2), 61.3 (CH_2), 15.2 (Me). After HCl hydrolysis of **19b**, **19c** was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (d, 1H, J=8.3 Hz), 7.67 (m, 2H), 7.59 (t, 1H, J=7.6 Hz), 7.51 (t, 1H, J=7.6 Hz), 5.75 (d, 1H, J=8.1 Hz), 5.15 (d, 1H, J=3.2 Hz), 5.09 (d, 1H, J=3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 166.3, 157.2, 133.8, 132.5, 132.4, 130.3, 122.1, 120.8, 99.5, 88.0.

3.2.20. 1-(2-Formylphenyl)-3,3-diethoxyprop-1-yne 20. From 2-bromobenzaldehyde (0.185 g, 1 mmol), product **20** was obtained in 91% (0.211 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.89 (d, 1H, J=7.4 Hz), 7.55 (m, 2H), 7.44 (t, 1H, J=7.4 Hz), 5.52 (s, 1H), 3.80 (m, 2H), 3.66 (m, 2H), 1.23 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 136.1, 133.6, 133.5, 129.1, 127.1, 125.2, 91.6, 91.4, 80.6, 61.2, 15.0; $C_{14}H_{16}O_3$: Calcd C, 72.39; H, 6.94. Found: C, 72.17; H, 6.70.

3.2.21. 1-(2-Methoxycarbonylphenyl)-3,3-diethoxyprop-1-yne 21. From methyl 2-bromobenzoate (0.215 g, 1 mmol), product **21** was obtained in 90% (0.236 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J=1.5, 7.7 Hz), 7.56 (dd, 1H, J=1.5, 7.5 Hz), 7.43 (dt, 1H, J=1.5, 7.7 Hz), 7.34 (dt, 1H, J=1.5, 7.5 Hz), 5.50 (s, 1H), 3.87 (s, 3H), 3.82 (m, 2H), 3.66 (m, 2H), 1.23 (t, 6H, J=7.2 Hz).

3.2.22. 1-(2-Cyanophenyl)-3,3-diethoxyprop-1-yne 22. From 2-bromobenzonitrile (0.182 g, 1 mmol), product **22** was obtained in 87% (0.200 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, 1H, J=7.8 Hz), 7.50 (m, 2H), 7.41 (t, 1H, J=7.8 Hz), 5.49 (s, 1H), 3.81 (m, 2H), 3.64 (m, 2H), 1.25 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.7, 132.6, 132.3, 128.9, 125.7, 117.1, 115.4, 91.5, 90.7, 80.9, 61.2, 15.0; $C_{14}H_{15}NO_2$: Calcd C, 73.34; H, 6.59. Found: C, 73.60; H, 6.71.

3.2.23. 1-(2-Trifluoromethylphenyl)-3,3-diethoxyprop-1-yne 23. From 2-trifluoromethylbromobenzene (0.225 g, 1 mmol), product **23** was obtained in 91% (0.248 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.44 (t, 1H, J= 7.6 Hz), 7.40 (t, 1H, J=7.4 Hz), 5.49 (s, 1H), 3.81 (m, 2H), 3.66 (m, 2H), 1.26 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.6, 131.8 (q, J=30.7 Hz), 131.3, 128.5, 125.7 (q, J=4.9 Hz), 123.3 (q, J=274.0 Hz), 120.2 (q, J=2. 1 Hz), 91.7, 90.1, 80.8, 61.0, 15.0; $C_{14}H_{15}F_3O_2$: Calcd C, 61.76; H, 5.55. Found: C, 61.50; H, 5.72.

3.2.24. 1-(2-Fluorophenyl)-3,3-diethoxyprop-1-yne 24. From 2-fluorobromobenzene (0.175 g, 1 mmol), product **24** was obtained in 93% (0.207 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, 1H, J=7.3 Hz), 7.30 (m, 1H), 7.06 (m, 2H), 5.49 (s, 1H), 3.82 (m, 2H), 3.65 (m, 2H), 1.26 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (d, J=252.4 Hz), 133.6, 130.5 (d, J=7.7 Hz), 123.8 (d, J=3.3 Hz), 115.4 (d, J=21.7 Hz), 110.5 (d, J=15.4 Hz), 91.7, 89.5, 78.6, 61.0, 15.0; $C_{13}H_{15}FO_2$: Calcd C, 70.25; H, 6.80. Found: C, 70.01; H, 6.69.

3.2.25. 1-(2-Tolyl)-3,3-diethoxyprop-1-yne 25. From 2-bromotoluene (0.171 g, 1 mmol), product **25** was obtained in 90% (0.197 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, 1H, J=7.4 Hz), 7.20 (m, 2H), 7.12 (t, 1H, J=7.1 Hz), 5.53 (s, 1H), 3.83 (m, 2H), 3.66 (m, 2H), 2.44 (s, 3H), 1.26 (t, 6H, J=7.2 Hz).

3.2.26. 1-(3,3-Diethoxyprop-1-ynyl)-naphthalene 26. From 1-bromonaphthalene (0.207 g, 1 mmol), product **26** was obtained in 94% (0.239 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, 1H, J=8.1 Hz), 7.84 (m, 2H), 7.72 (d, 1H, J=7.3 Hz), 7.57 (t, 1H, J=7.5 Hz), 7.51 (t, 1H, J=7.5 Hz), 7.41 (t, 1H, J=7.5 Hz), 5.64 (s, 1H), 3.90 (m, 2H), 3.73 (m, 2H), 1.29 (t, 6H, J=7.2 Hz).

3.2.27. 1-(2-Anisyl)-3,3-diethoxyprop-1-yne 27. From 2-bromoanisole (0.187 g, 1 mmol), product **27** was obtained in 88% (0.206 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, 1H, J=1.7, 7.5 Hz), 7.25 (dt, 1H, J=1.7, 8.3 Hz), 6.85 (t, 1H, J=8.3 Hz), 6.82 (d, 1H, J=8.3 Hz), 5.49 (s, 1H), 3.81 (s, 3H), 3.79 (m, 2H), 3.64 (m, 2H), 1.24 (t, 6H, J=7.2 Hz).

3.2.28. 1-(2,6-Difluorophenyl)-3,3-diethoxyprop-1-yne 28. From 2,6-difluorobromobenzene (0.193 g, 1 mmol), product **28** was obtained in 84% (0.202 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 1H), 6.87 (m, 2H), 5.50 (s, 1H), 3.83 (m, 2H), 3.65 (m, 2H), 1.24 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (dd, J=5.2, 254.7 Hz), 130.5 (t, J=10.2 Hz), 111.2 (d, J=24.7 Hz), 101.1 (t, J=19.

5 Hz), 94.4, 91.6, 91.3, 61.2, 15.1; $C_{13}H_{14}F_2O_2$: Calcd C, 64.99; H, 5.87. Found: C, 65.13; H, 5.70.

3.2.29. 1-(2,4,6-Trimethylphenyl)-3,3-diethoxyprop-1-yne 29. From 2,4,6-trimethylbromobenzene (0.199 g, 1 mmol), product **29** was obtained in 89% (0.219 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 5.55 (s, 1H), 3.83 (m, 2H), 3.67 (m, 2H), 2.38 (s, 6H), 2.26 (s, 3H), 1.25 (t, 6H, J=7.2 Hz).

3.2.30. 1-(2,6-Diethyl-4-methylphenyl)-3,3-diethoxyprop-1-yne 30. From 2,6-diethyl-4-methylbromobenzene (0.227 g, 1 mmol), product **30** was obtained in 88% (0.242 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 2H), 5.55 (s, 1H), 3.81 (m, 2H), 3.68 (m, 2H), 2.74 (q, 4H, J=7.6 Hz), 2.30 (s, 3H), 1.24 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 138.6, 126.1, 117.3, 92.1, 91.3, 82.5, 60.8, 27.8, 21.5, 15.1, 15.0; $C_{18}H_{26}O_2$: Calcd C, 78.79; H, 9.55. Found: C, 78.99; H, 9.56.

3.2.31. 9-(3,3-Diethoxy-prop-1-ynyl)-anthracene 31. From 9-bromoanthracene (0.257 g, 1 mmol), product **31** was obtained in 90% (0.274 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, 2H, J=8.7 Hz), 8.41 (s, 1H), 7.99 (d, 2H, J=8.5 Hz), 7.59 (t, 2H, J=7.8 Hz), 7.50 (t, 2H, J=7.8 Hz), 5.86 (s, 1H), 4.03 (m, 2H), 3.86 (m, 2H), 1.35 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 130.9, 128.6, 128.3, 126.7, 126.5, 125.6, 115.7, 95.7, 92.3, 81.9, 61.2, 15.2. This compound was characterized by deprotection into the corresponding aldehyde.[22]

3.2.32. 1-(2-Pyridyl)-3,3-diethoxyprop-1-yne 32. From 2-bromopyridine (0.158 g, 1 mmol), product **32** was obtained in 89% (0.183 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 1H, J=4.8 Hz), 7.60 (t, 1H, J=7.7 Hz), 7.43 (d, 1H, J=7.9 Hz), 7.20 (dd, 1H, J=4.8, 7.0 Hz), 5.44 (s, 1H), 3.77 (m, 2H), 3.62 (m, 2H), 1.21 (t, 6H, J=7.2 Hz).

3.2.33. 1-(3-Pyridyl)-3,3-diethoxyprop-1-yne 33. From 3-bromopyridine (0.158 g, 1 mmol), product **33** was obtained in 93% (0.191 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (m, 1H), 8.60 (m, 1H), 7.77 (d, 1H, J=8.0 Hz), 7.26 (m, 1H), 5.50 (s, 1H), 3.82 (m, 2H), 3.67 (m, 2H), 1.28 (t, 6H, J=7.2 Hz).

3.2.34. 1-(2-Quinolyl)-3,3-diethoxyprop-1-yne 34. From 2-chloroquinoline (0.164 g, 1 mmol), product **34** was obtained in 90% (0.230 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, 1H, J=8.1 Hz), 8.07 (d, 1H, J=8.1 Hz), 7.76 (d, 1H, J=8.1 Hz), 7.69 (t, 1H, J=7.7 Hz), 7.53 (t, 1H, J=7.7 Hz), 7.52 (d, 1H, J=8.1 Hz), 5.54 (s, 1H), 3.84 (m, 2H), 3.69 (m, 2H), 1.26 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 142.3, 136.1, 130.0, 129.4, 127.4, 127.3, 127.2, 124.2, 91.7, 84.7, 84.6, 61.2, 15.0; $C_{16}H_{17}NO_2$: Calcd C, 75.27; H, 6.71. Found: C, 75.46; H, 6.97.

3.2.35. 1-(3-Quinolyl)-3,3-diethoxyprop-1-yne 35. From 3-bromoquinoline (0.208 g, 1 mmol), product **35** was obtained in 94% (0.240 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (m, 1H), 8.24 (s, 1H), 8.12 (d, 1H, J=8.2 Hz), 7.74 (d, 1H, J=8.4 Hz), 7.69 (t, 1H, J=7.5 Hz), 7.52 (t, 1H, J=7.5 Hz), 5.52 (s, 1H), 3.82 (m, 2H), 3.67 (m, 2H), 1.27 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 146.9, 138.9, 130.2, 129.3, 127.5, 127.2, 126.9, 115.9, 91.6, 87.6, 82.2, 61.0, 15.0; $C_{16}H_{17}NO_2$: Calcd C, 75.27; H, 6.71. Found: C, 75.28; H, 6.57.

3.2.36. 1-(4-Isoquinolyl)-3,3-diethoxyprop-1-yne 36. From 4-bromoisoquinoline (0.208 g, 1 mmol), product **36** was obtained in 90% (0.230 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (m, 1H), 8.71 (m, 1H), 8.16 (d, 1H, J=8.5 Hz), 7.93 (d, 1H, J=8.2 Hz), 7.74 (t, 1H, J=7.5 Hz), 7.60 (t, 1H, J=7.5 Hz), 5.60 (s, 1H), 3.85 (m, 2H), 3.70 (m, 2H), 1.28 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 146.7, 135.3, 131.1, 127.8, 127.7, 124.8, 91.7, 80.3, 61.0, 15.1; $C_{16}H_{17}NO_2$: Calcd C, 75.27; H, 6.71. Found: C, 75.47; H, 6.60.

3.2.37. 1-(5-Pyrimidolyl)-3,3-diethoxyprop-1-yne 37. From 5-bromopyrimidine (0.158 g, 1 mmol), product **37** was obtained in 90% (0.186 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.78 (s, 2H), 5.47 (s, 1H), 3.77 (m, 2H), 3.63 (m, 2H), 1.24 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.2, 118.5, 91.5, 91.4, 78.2, 61.2, 15.0; $C_{11}H_{14}N_2O_2$: Calcd C, 64.06; H, 6.84. Found: C, 64.00; H, 6.71.

3.2.38. 1-(2-Thienyl)-3,3-diethoxyprop-1-yne 38. From 2-bromothiophene (0.163 g, 1 mmol), product **38** was obtained in 88% (0.185 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.95 (dd, 1H, J=3.8, 4.9 Hz), 5.48 (s, 1H), 3.80 (m, 2H), 3.64 (m, 2H), 1.26 (t, 6H, J=7.2 Hz).

3.2.39. 1-(3-Thienyl)-3,3-diethoxyprop-1-yne 39. From 3-bromothiophene (0.163 g, 1 mmol), product **39** was obtained in 90% (0.189 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 1H, J=3.0 Hz), 7.23 (dd, 1H, J=3.0, 5.1 Hz), 7.12 (d, 1H, J=5.1 Hz), 5.45 (s, 1H), 3.79 (m, 2H), 3.64 (m, 2H), 1.24 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.8, 129.7, 125.6, 120.8, 91.7, 84.0, 80.4, 60.9, 15.0; $C_{11}H_{14}O_2S$: Calcd C, 62.83; H, 6.71. Found: C, 62.95; H, 6.84.

3.2.40. 1,4-Bis(3,3-diethoxy-prop-1-ynyl)benzene 40. From 1,4-dibromobenzene (0.236 g, 1 mmol), product **40** was obtained in 92% (0.304 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 4H), 5.45 (s, 2H), 3.79 (m, 4H), 3.64 (m, 4H), 1.24 (t, 12H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 122.5, 91.7, 86.3, 84.5, 60.9, 15.0; $C_{20}H_{26}O_4$: Calcd C, 72.70; H, 7.93. Found: C, 72.89; H, 7.81.

3.2.41. 1,2-Bis(3,3-diethoxy-prop-1-ynyl)benzene 41. From 1,2-dibromobenzene (0.236 g, 1 mmol), product **41** was obtained in 94% (0.310 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.25 (m, 2H), 5.48 (s, 2H), 3.82 (m, 4H), 3.66 (m, 4H), 1.24 (t, 12H, J= 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3, 128.4, 124.7, 91.7, 88.3, 83.5, 60.9, 15.1; $C_{20}H_{26}O_4$: Calcd C, 72.70; H, 7.93. Found: C, 72.67; H, 7.98. The monoaddition product **42** was also isolated ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, J=7.8 Hz), 7.48 (d, 1H, J=7.8 Hz), 7.28–7.10 (m, 2H), 5.52 (s, 1H), 3.86 (m, 2H), 3.66 (m, 2H), 1.27 (t, 6H, J= 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8, 132.4, 129.9, 126.9, 125.6, 124.2, 91.7, 88.9, 83.5, 61.1, 15.1.

3.3. Registry No.: 1

6142-95-6; **5**, 181419-95-4; **6**, 83758-93-4; **10**, 74929-22-9; **11**, 62358-86-5; **13**, 62358-88-7; **18**, 62358-87-6; **21**, 181419-89-6; **25**, 181419-85-2; **26**, 2375725 (Beilstein Registry Number); **27**, 202391-28-4; **29**, 73057-39-3; **32**, 49836-19-3; **33**, 143952-62-9; **38**, 13781-32-3.

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Comparison between polyethylenglycol and imidazolium ionic liquids as solvents for developing a homogeneous and reusable palladium catalytic system for the Suzuki and Sonogashira coupling

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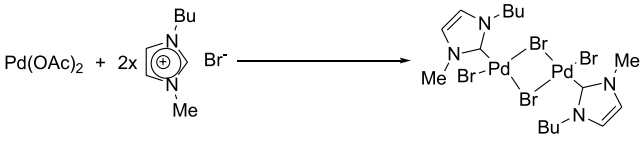
Abstract—The carbapalladacycle complex of 4-hydroxyacetophenone oxime is a highly active palladium catalyst to effect the Suzuki coupling of aryl chlorides and other C–C forming reactions in water. In an attempt to develop a reusable, homogeneous system based on this complex, its stability against prolonged heating in different ionic liquids and polyethylenglycol (PEG) has been studied. It was found that the palladium complex decomposes in water, 1-butyl-1-methylimidazolium hexafluorophosphate and 1-butyl-1-methylimidazolium chloride to form palladium nanoparticles in the first two cases and $PdCl_4^{2-}$ in the third case. In contrast, this cyclic palladium complex was stable upon extended heating in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate and in PEG. The activity of this complex for the Suzuki and Sonogashira correlates with the stability of the complex, the activity in PEG being higher than any of the ionic liquids tested. Although the carbapalladacycle complex also decomposes in PEG upon reaction, the resulting Pd nanoparticles (2–5 nm size) are stabilized by PEG acting as ligand. In this way, a reusable, homogeneous system in PEG has been developed that is able to effect the Suzuki and Sonogashira couplings without the need of copper and phosphorous ligands, working at the open air.

1. Introduction

Imidazolium ionic liquids have been widely used as medium to perform Pd catalyzed C–C bond reactions.[1–6] In precedents related to this work it has been demonstrated that some organometallic palladium complexes act as catalyst precursors rather than being the actual catalyst since they are transformed under reaction conditions into different Pd species.[5,7–11] The nature of these species depends on a large extent on the imidazolium substitution and on the nature of the counter-balancing anion.[6,11,12] Thus, using non-coordinating anions, black Pd nanoparticles are formed, while $PdCl_4^{2-}$ can be stabilized when Cl^- is the counter anion of 1,2,3-trialkylimidazolium ionic liquid.[12] On the other hand, using chloride or bromide salts of 1,3-dialkylimidazolium, a dimeric imidazolidene Pd complex is formed, which can exhibit some activity for the Suzuki and Heck coupling reactions (Scheme 1).

In view of these precedents, it is clear that most Pd complexes considered highly active homogeneous catalysts should be surveyed for stability and considered in principle as suspicious of being precursors of other Pd species that are really the active catalysts for the C–C coupling. In particular, our work focus on carbapalladacycle complex **1**. Carbapalladacycle complex **1** has been reported by Nájera and co-workers as a highly active homogeneous palladium catalyst that is able to promote in water the Suzuki coupling of aryl chlorides and even the coupling of electron-withdrawing aryl fluorides.[13–18] Considering this high activity, it would be of interest to convert this Pd catalyst into a recoverable and reusable catalytic system (Structure 1).

In the present work, we have considered the carbapalladacycle **1** and addressed its stability in different ionic liquids and polyethylenglycol (PEG). The objective is to determine



Scheme 1. Formation of $[Pd_2(\mu\text{-}Br)_2Br_2(C_4C_1)im_2]$.

Keywords: Sonogashira coupling; Carbapalladacycle complex; Polyethyleneglycol; Imidazolium ionic liquids; Suzuki coupling.
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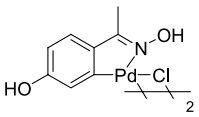


Structure 1. Carbapalladacycle **1** derived from 4-hydroxyacetophenone.

the stability of carbapalladacycle **1** in different liquid media with the target of obtaining a highly active reusable, homogeneous catalytic system for the Suzuki and Sonogashira coupling. We have compared the performance and catalytic activity of **1** in imidazolium ionic liquids with that in polyethyleneglycol and we have found that PEG is a very convenient medium for these Pd catalyzed reactions, allowing the reuse of the catalyst without loss of the catalytic activity. Although complex **1** also decomposes quickly in PEG in the first use, reusability of the system derives from the ability of PEG to stabilize Pd nanoparticles by acting as ligand. PEG has advantages of being a green solvent, with a complete lack of toxicity, large availability, low cost and immiscibility with ethyl ether and other organic solvents.

2. Results and discussion

Firstly, we will comment on the stability of carbapalladacycle **1** in imidazolium ionic liquids and PEG and our attempts to characterize the Pd species derived there from in each case. Secondly, we will compare the reactivity of carbapalladacycle **1** in ionic liquids and PEG.

2.1. Stability of carbapalladacycle complex in ionic liquids and PEG

Imidazolium ionic liquids appear as promising green media for the purpose of developing a homogeneous, reusable catalytic system since they exhibit solubility for a wide range of organic compounds that latter can be separated from the ionic liquid by liquid–liquid extraction using some conventional immiscible organic solvents such as ethyl ether and hexane. Also solid PEG becomes liquid at temperatures higher than 40 °C, exhibits high chemical stability to a wide range of reagents and a high solubility for many organic compounds as well as inorganic salts. Since PEG is immiscible with hexane, ethyl ether and even cold methanol, substrates and reaction products can be recovered by liquid–liquid extraction in hot. The condition to have a reusable homogeneous catalytic system is, as in the case of ionic liquids, that the catalytic species should remain unextracted and active in PEG.

A previous point concerning reusability is the stability of the complex under the reaction conditions, particularly knowing that most carbapalladacyles decompose under reaction conditions to give various Pd species that are finally converted into Pd particles.[7,19] Aimed at studying the stability of complex **1** and the influence of the nature of the ionic liquid on its stability, we submitted **1** to prolonged heating in different imidazolium ionic liquids and PEG and followed the evolution of the system by UV/vis spectroscopy. The heating temperature corresponds to that commonly used in Pd catalyzed reactions.

Complex **1** exhibits in UV/Vis spectroscopy characteristic metal-to-ligand charge transfer bands peaking at 350 and 290 nm. Given the transparency of imidazolium ionic liquids and PEG in the long wavelength regimen of the optical spectrum,[20,21] recording transmission UV/vis spectra can be a simple, suitable spectroscopic technique to follow the persistence of the complex. The list of solvents studied and the result obtained are summarized in Table 1.

Table 1. List of solvents studied and summary of the results obtained after the thermal treatment at 120 °C

Solvent	Time (h)	Stability	Product	Evidence
H_2O	24	No	Pd nanoparticles	Visual darkening UV/vis spectra TEM
(C_1C_4) $imPF_6$	72	No	Pd nanoparticles	Visual darkening UV/vis spectra TEM
(C_1C_4) imCl	24	No	Pd chloride species complexed with imidazolidene	UV/vis spectra HPLC-ESI-MS
$(C_1C_1C_4)$ $imPF_6$	72	Yes	Carbapalladacycle **1**	UV/vis spectra HPLC-ESI-MS
PEG	72	Yes	Carbapalladacycle **1**	UV/vis HPLC-ESI-MS

As it can be seen in the Table 1, heating the complex **1** in water, $(C_1C_4)imPF_6$ and $(C_1C_4)imCl$ lead to the gradual decomposition (hours) of the complex, evidenced by the disappearance of the absorption bands characteristic of complex **1**. Figure 1 shows some selected optical spectra to illustrate the UV/Vis monitoring of carbapalladacycle **1** decomposition. The disappearance of complex **1** is accompanied in two cases by a darkening of the solution. When apparent darkening of the solution occurs, the resulting transmission optical spectrum was compatible either with that of the neutral acetophenone oxime ligand when water was used as solvent or with protonated oxime ligand in the case of $(C_1C_4)imPF_6$. These optical spectra suggest that decomplexation of the carbapalladacycle has occurred and the acetophenone oxime ligand has been formed. TEM images of the black solution after heating carbapalladacycle **1** in water or $(C_1C_4)imPF_6$ (Fig. 2) show

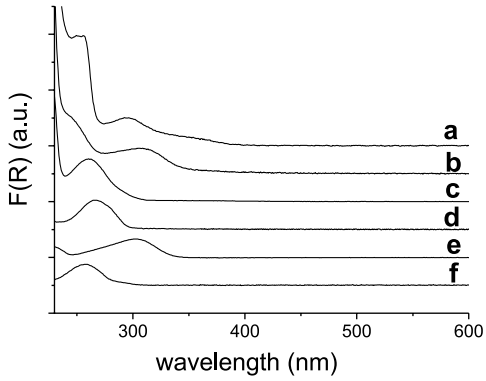


Figure 1. UV/vis spectra recorded in CH_3CN of: (a) complex **1** in $(C_1C_4)imPF_6$ after 2 h of thermal treatment; (b) complex **1** in $(C_1C_4)imPF_6$ after 72 h of thermal treatment; (c) complex **1** in $(C_1C_4)imCl$ after 24 h of thermal treatment; (d) complex **1** in water after 24 h of thermal treatment; (e) acetophenone oxime treated with a 10% v/v HCl; (f) acetophenone oxime.

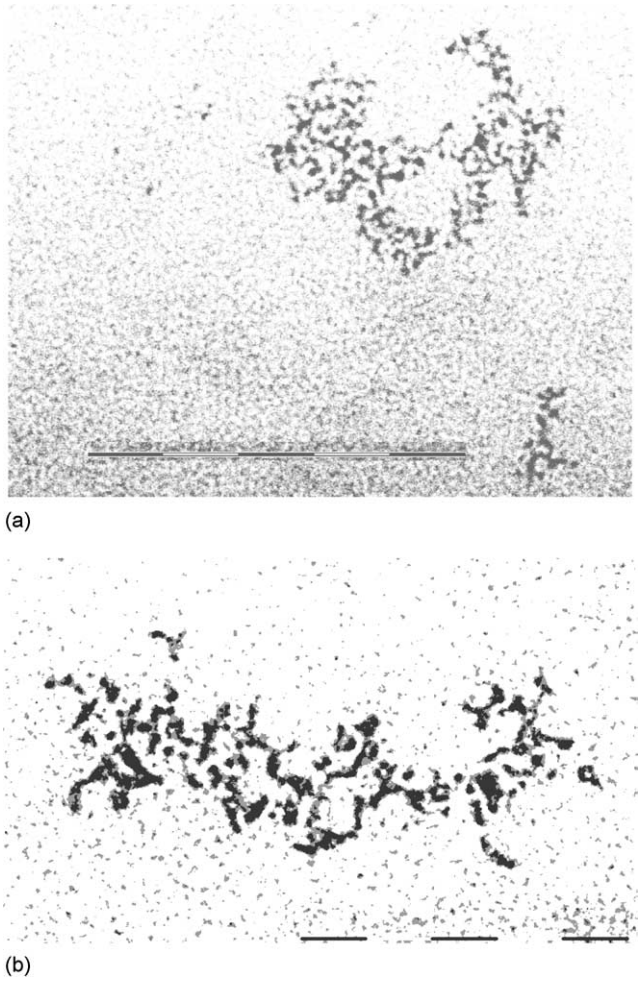


Figure 2. TEM images of Pd nanoparticles formed upon heating a solution of carbapalladacycle **1** in $(C_1C_4)imPF_6$. The scale bar of parts (a) and (b) correspond to 500 and 100 nm, respectively.

the presence of palladium nanoparticles (2–5 nm, Table 1). The possibility of having in addition imidazolium carbene complexes as reported in other cases cannot be disregarded from our data although no evidences from electrospray ionization HPLC-MS (HPLC-ESI-MS) could be obtained (see below).

In contrast to the evolution of complex **1** in water and $(C_1C_4)imPF_6$, decomposition of complex **1** in $(C_1C_4)imCl$ also occurs as evidenced by UV/vis spectroscopy but in this case no darkening of the solution was observed, therefore, formation of Pd metal particles does not seem to occur in $(C_1C_4)imCl$. Using HPLC-ESI-MS we have been able to get evidence of the presence of Pd species being compatible with $PdCl_2$ associated to imidazolidene carbene. It has to be noted that MS is very useful and safe spectroscopic technique to determine the elemental composition of Pd species, since the natural isotopic distribution constitutes a fingerprint revealing the presence of Pd. This is also the case of Cl and, therefore, the structure of $PdCl_2$ associated to imidazolidene carbene is firmly supported by MS.

The evolution of complex **1** in $(C_1C_1C_4)imPF_6$ and PEG was also different as the previous liquids. Thus, heating for prolonged periods in $(C_1C_1C_4)imPF_6$ and PEG (M_W average 6000 Da) does not produce the decomposition of the complex. Figure 3 shows the optical spectra recorded at different heating times showing that the bands of complex **1** at 350 and 290 nm do not decay even after 3 days of heating at 120 °C. The above results suggest that nucleophilic counter anions and the acidity of the H at 2-position of the imidazolium are two factors that eventually produce carbapalladacycle complex instability.

Stability of carbapalladacycle **1** in $(C_1C_1C_4)imPF_6$ after the thermal treatment was also confirmed by HPLC-ESI-MS, in where peaks at *m/z* 297, 338 and 594, containing the characteristic Pd isotopic distribution, were recorded. These peaks can be attributed, respectively, to the carbapalladacycle ligated to one (297 Da) and two (338 Da) CH_3CN and the corresponding dimer of the mono CH_3CN complex (594 Da). CH_3CN is the solvent used in HPLC analyses and the MS spectra would indicate the occurrence of a CH_3CN by Cl^- exchange in complex **1**. It is appropriate to comment here that control experiments by HPLC-ESI-MS in the case of water and $(C_1C_4)imPF_6$ treatment did not allow to detect any Pd peak, suggesting that in those cases in where darkening of the solution occurs, no organometallic complex is present. Importantly, for $(C_1C_4)imCl$ and $(C_1C_1C_4)imPF_6$ in where no darkening of the solution upon thermal treatment was observed, TEM images show that the ionic liquid is free from Pd nanoparticles.

Scheme 2 summarizes the results of our thermal stability study. It is clear that the solvent is not an innocent medium and leads to the decomposition of complex **1**. Water and

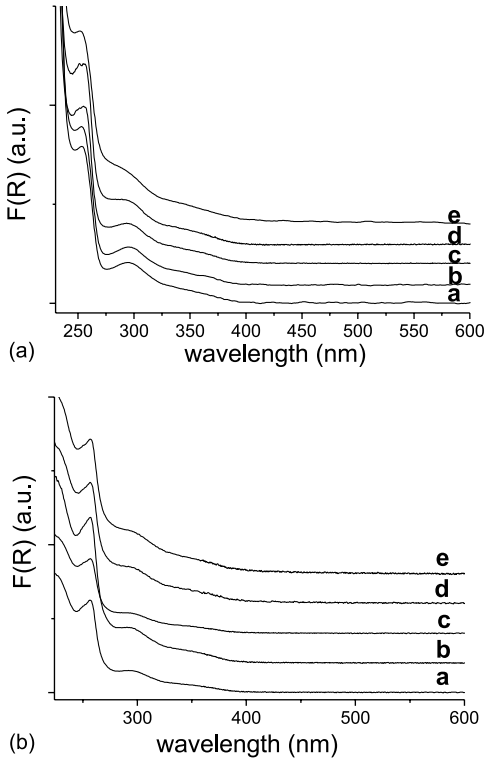
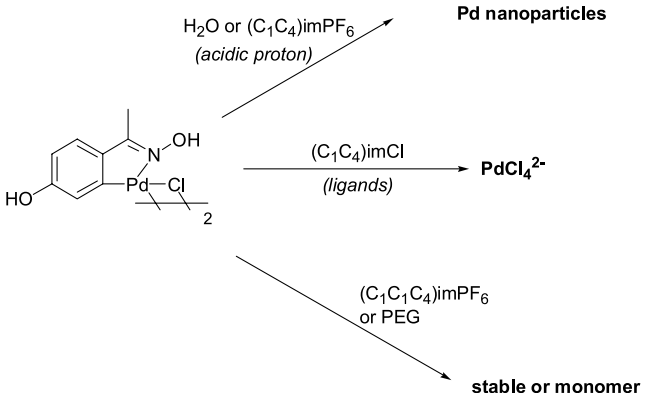


Figure 3. (a) UV/vis spectra of carbapalladacycle **1** dissolved in $(C_1C_1C_4)imPF_6$ recorded in CH_3CN after heating at 120 °C for (a) 2 h; (b) 8 h; (c) 24 h; (d) 48 h; (e) 72 h. (b) UV/vis spectra of carbapalladacycle **1** dissolved in PEG recorded in CH_3CN after heating at 120 °C for (a) 2 h; (b) 8 h; (c) 24 h; (d) 48 h; (e) 72 h.



Scheme 2. Thermal stability of carbapalladacycle **1** in H_2O, imidazolium ionic liquids and PEG.

imidazolium H-2 protons are sufficiently acidic to attack the complex **1** and eventually Pd nanoparticles are formed, unless Pd^{2+} ions are intercepted by Cl^- or other complexing anion. In this regard $(C_1C_1C_4)imPF_6$ is an inert medium. PEG is also an inert medium for **1**. It has to be remarked, however, that in the presence of reactants under real reaction conditions even in inert PEG, decomposition of complex **1** takes place, probably during the reductive elimination of the catalytic cycle (vide infra).

2.2. Comparison of the catalytic activity of species derived from carbapalladacycle 1 in ionic liquids and PEG

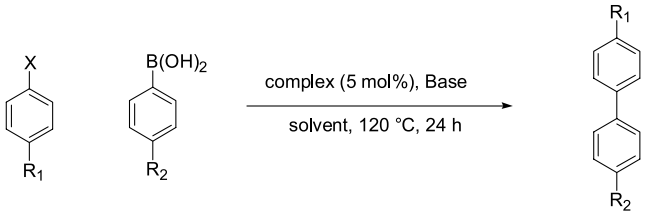
To provide a valid comparison of the catalytic activity of species derived from complex **1** in water, ionic liquids and PEG, we initially studied the Suzuki coupling of 4-chloroacetophenone and phenylboronic acid. Using complex **1** as precursor in water under the reaction conditions previously reported in the literature,[16,17] the expected substituted biphenyl was formed in very high yields. If, instead of a fresh sample of complex **1** in water, the resulting black colloidal suspension obtained after previous thermal decomposition of complex **1** in water is used as catalyst, then also the 4-acetylbiphenyl product is formed but with significantly lower yields (Table 2). This must indicate that, although Pd nanoparticles derived from complex **1** show some activity for the Suzuki coupling, either the complex or atomic Pd species or Pd nanoparticles at early stages are more active catalysts to promote the Suzuki coupling than aged Pd nanoparticles.

In view of this encouraging catalytic performance in aqueous medium, we attempted the same reaction in $(C_1C_4)imPF_6$ and $(C_1C_1C_4)imPF_6$ using CsAcO as base without observing any product formation (Table 2). Furthermore, even using highly reactive iodobenzene as substrate, the corresponding biphenyl was only observed in trace amounts (Table 2). In contrast to this, the use of PEG as solvent and complex **1** as catalyst leads to the corresponding 4-methylbiphenyl with almost complete selectivity and high mass balance, thus showing the superior performance of PEG compared to the series of imidazolium ionic liquids tested.

These promising results using PEG as solvent for Pd C–C coupling reactions were expanded for the Sonogashira cross-coupling between phenylacetylene and substituted halobenzenes. The media studied and the results obtained are summarized in Table 3.

As it can be seen there, using the organometallic complex **1** as catalyst in ionic liquids results, in general, in low to moderate yields depending on whether more active iodo-or a less reactive bromo-benzenes are used as starting materials. If the palladacycle complex **1** is firstly decomposed and, then, the resulting Pd nanoparticles used subsequently for the Sonogashira coupling, worst results are generally obtained. This again indicates that carbapalladacycle **1** or Pd species at early stages of the formation of nanoparticles are more active than the aged Pd nanoparticles themselves. In agreement with this, it is worth commenting from Table 3 that $(C_1C_1C_4)imPF_6$, in where we have previously demonstrated the stability of carbapalladacycle **1**, results in significant higher yield than that of $(C_1C_4)imPF_6$ for the Sonogashira coupling, again in line with the higher activity of the complex **1** compared to aged Pd nanoparticles. In any case, the overall conclusion of the catalytic tests is that imidazolium ionic liquids, particularly those unsubstituted at position C-2, are not suitable as

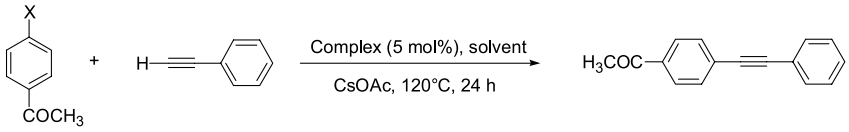
Table 2. Results for the Suzuki coupling of aryl halides with phenylboronic acids in different media



Solvent	X	R_1	R_2	Base	Yield (%)[a]	Mass balance (%)
Water[b]	Cl	$COCH_3$	H	K_2CO_3	78 (8)	>99
					62 (2)[c]	>99
$(C_4C_1)imPF_6$	I	H	CH_3	CsOAc	<5	—
$(C_4C_1C_1)imPF_6$					<5	30
PEG					>99	80

[a] In brackets yield of 4,4′-bisacetylbiphenyl.
[b] TBAB (0.5 equiv) were added, reaction time: 2 h (see Section 3).
[c] After thermal Pd reduction.

Table 3. Results for the Sonogashira coupling of different aryl halides with phenylacetylene in different media



Solvent	X	Solvent/substrate ratio (wt)	Yield (%)	By-products (%)[a]	Mass balance (%)[b]
$(C_4C_1)imPF_6$	I	5	57	5	90
		5	17	2	>99
	Br	5	<5	—	72
		50	0	—	>99
$(C_4C_1C_1)imPF_6$	Br	5	38	—	74
		50	52	1	79
$(C_4C_1)imCl$	Br	5	6	2	27
		50	2	—	38
PEG	Br	5	2	3	79
		50	88	12	20 (84)
		50	>99[c]	—	50
	Br[d]	5	0	2	75
		50	5	3	40
		50	45[c]	—	(80)
	Cl	5	0	—	70
		50	0	18	(75)
		50	25[c]	2	40

[a] Acetophenone and 4,4′-bisacetylbiphenyl.
[b] Extracted with ethyl ether (3 ml×7) at room temperature. In brackets the mass balance value when the products are extracted by stirring the PEG mixture in hot ether for 4 h.
[c] 150°C.
[d] Bromoanisole.

solvents for C–C coupling reactions using carbapalladacycle complex **1**.

In this regard, PEG as solvent showed a better performance that any of the imidazolium ionic liquid studied (see Tables 2 and 3). Thus, using a solvent-to-substrate ratio of 50 and performing the liquid–liquid extraction in hot to recover the reaction products, good mass balances and product yields were obtained starting from 4-bromoacetophenone. Moreover, the system could be reused five times without any decrease in the selectivity of the process.

Since it is known the higher reactivity of electron withdrawing halobenzenes for the C–C cross-coupling reactions, the benchmark to really assess the activity of a Pd catalyst should be either for chloro- and bromobenzenes substituted by electron donor groups. Table 3 contains also data of the activity of carbapalladacycle **1** in PEG using 4-bromoanisole and 4-chloroacetophenone, for which moderate product yields were obtained. It is worth to comment than no conversion at all was observed for the same substrates in any of the imidazolium ionic liquids studied and, thus, PEG is more suitable solvent as those imidazolium ionic liquids tested.

The favourable influence of using a high PEG to substrate ratio can be understood by the need to solubilize completely CsOAc that is the base being used in the process. The ability of PEG to complex large alkali metal ions leading to solubilization of the base is well known.[22] Concerning the reusability, chemical analyses of the extracted solutions indicate the absence of Cs^+ either in ionic liquid or PEG as reaction solvents. However, chemical analyses reveal the presence of significant amounts of Pd in the ionic liquid extracts, while Pd is under the analytical detection limit in the extracts from PEG.

Concerning the relative activity of complex **1** in PEG and water (where complex **1** exhibits the highest initial activity) it has been previously established the positive influence of the solvent polarity on the performance of carbapalladacycle **1**. According to this, carbapalladacycle **1** is initially more active in water, but in water decomposition and formation of Pd black lead to an extensive deactivation that make impossible the reusability of the system. Decomposition of complex **1** under real reaction conditions (in the presence of substrates) also occurs in PEG in the first use of the complex **1** as revealed by TEM. However, the known ability of PEG to act as a ligand plays a positive role stabilizing the Pd nanoparticles and permitting their reuse, although with lower intrinsic activity than in the first run in water. Importantly, TEM images of Pd nanoparticles in PEG after the first and fifth use of complex **1** show no change in the particle size (Fig. 4).

The main advantage of PEG as solvent for the Sonogashira coupling compared to previous literature reports[23,24] is that to achieve good yields of Sonogashira coupling products is not necessary to use noxious copper(I) compounds and expensive phosphorous ligands. Also, the fact that the reaction is carried out in PEG at the open air instead of under inert atmosphere (mainly due to the oxidability of the phosphorus the ligands) is an additional advantage of this process using PEG.

In conclusion, we have established that organometallic carbapalladacycle **1** undergoes extensive decomposition in ionic liquids depending on the substitution and nature of the

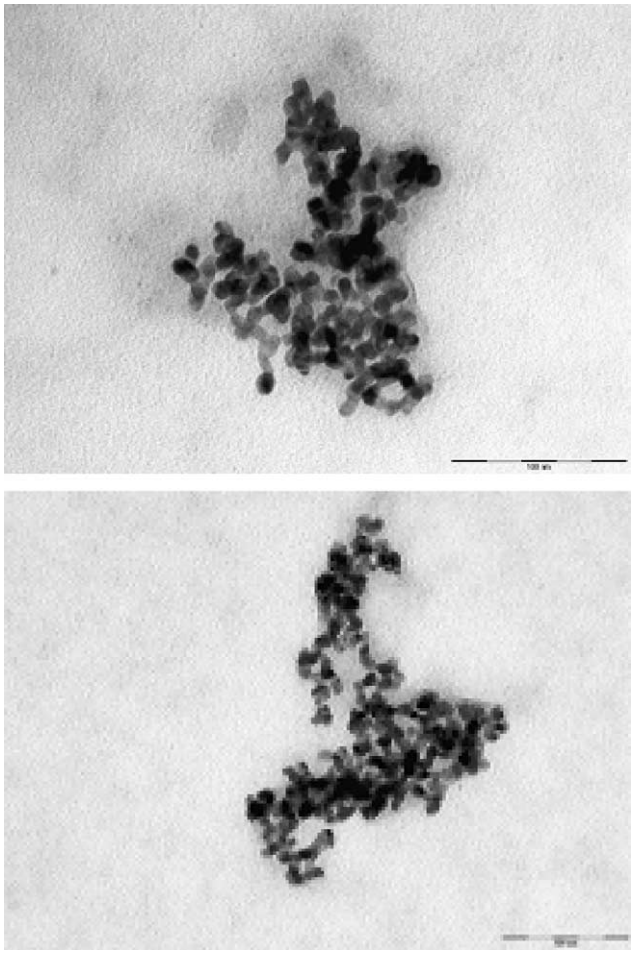


Figure 4. TEM images recorded from a solution containing originally carbapalladacycle **1** in PEG after one (top) or five (bottom) uses as catalyst for the Sonogashira coupling of 4-chloroacetophenone and phenylacetylene. The scale bar of the figures corresponds to 100 nm.

counter ion. In one case, using $(C_1C_1C_4)imPF_6$, no thermal decomposition was observed. However, even in $(C_1C_1C_4)$-$imPF_6$, the catalytic activity is low probably due to a poor CsAcO solubility. This low catalytic activity of $(C_1C_1C_4)$-$imPF_6$ makes the development of a homogeneous and reusable catalytic system for Pd C–C coupling reaction based on complex **1** in imidazolium ionic liquids unpractical. In contrast to the behaviour of ionic liquids, PEG appears as a promising green medium to perform Pd catalyzed reactions. The decomposition of organometallic Pd complex **1** in PEG does not occurs upon prolonged heating, but it occurs under real reaction conditions. However, Pd nanoparticles appears to become stabilized by PEG and, in addition, the CsAcO is fairly soluble in PEG. In this way, a reusable and recoverable, homogeneous Pd system based on PEG had been demonstrated. This has been particularly interesting for the Sonogashira coupling in where no copper salts and P ligands are used.

3. Experimental

3.1. General

Reagents and solvents were obtained from commercial sources and were used without further purification. Gas chromatographic analyses were performed on a HP 5890 instrument equipped with a 25 m capillary column of 5% phenylmethylsilicone. GC/MS analyses were performed on an Agilent 5973N spectrometer equipped with the same column as the GC and operated under the same conditions. ESI-HPLC-MS analyses were performed in an Agilent 1100 equipment with a parallel UV diode array detector using as mobile phase CH_3CN–H_2O (50/50 v/v, flow: 0.7 ml min^{-1}) and diammonium hydrogenphosphate as buffer. ^1H and ^{13}C NMR were recorded in a 300 MHz Bruker Avance instrument using $CDCl_3$, DMSO-d_6 or CD_3OD as solvents and TMS as internal standard. UV/vis spectra were recorded on a Shimadzu spectrophotometer using CH_3CN as solvent. The Pd and Cs content of the extracts was determined by concentrating the solvent under reduced pressure, dissolving the residue in a mixture 1:1 of concentrated HCl/HNO_3 (2.5 mg in ca. 3 ml), diluting the strongly acidic solution in water and measuring by quantitative atomic absorption spectroscopy. Transmission electron microscopy were performed in a Philips equipment after dispersing the sample in CH_2Cl_2 and allowing to evaporate the halogenated solvent.

3.1.1. Procedure for the synthesis of 4-hydroxyacetophenone oxime. 4-Hydroxy-acetophenone (3 g, 0.022 mol) was added to a solution of hydroxylamine hydrochloride (5.13 g, 0.074 mol) and sodium acetate (10.26 g, 0.125 mol) in water (26 ml). The solution was stirred at reflux temperature for 1 h. After that time, diethyl ether was added several times for extraction. The organic phases were dried and the solvent evaporated under vacuum. To the obtained residue, hexane was added and 1-(4-hydroxyphenyl)ethanone oxime started to precipitate as a white solid (3.25 g, 0.0215 mol, 98%). Mp: 146–147 °C. IR (KBr, cm^{-1}): 3324, 1642, 1603, 1514, 1444, 1316, 1240, 1176, 940, 825, 589. ^1H NMR δ_H (ppm, 300 MHz, CD_3OD): 7.49 (2H, d, $J=5$ Hz), 6.77 (2H, d, $J=5$ Hz), 2.18 (3H, s). ^{13}C NMR δ_C (ppm, 300 MHz, CD_3OD): 159.9, 156.7, 130.2, 128.9, 116.5, 12.55. MS (FAB): *m/z* 151. Anal. Calcd for $C_8H_9NO_2$ (151.15): C, 63.5; H, 5.95; N, 9.26. Found: C, 63.19; H, 6.22; N, 9.35.

3.1.2. Procedure for the synthesis of the oxime carbapalladacycle 1. To a solution of Li_2PdCl_4 (524.1 mg, 2 mmol) in methanol (4 ml), a methanolic solution (2 ml) of 4-hydroxyacetophenone oxime (302 mg, 2 mmol) and sodium acetate (0.164 g, 2 mmol) was added. The mixture was stirred at room temperature for 72 h. The mixture was filtered and after adding water (5 ml), the cyclopalladated complex (**1**) starts to precipitate as a yellow solid (75%). Mp: >250 °C. IR (KBr, cm^{-1}): 3429, 1627, 1584, 1472, 1430, 1375, 1326, 1260, 1211, 1037, 873, 799, 608. ^1H NMR δ_H (ppm, 300 MHz, DMSO-d_6): 10.38 (1H, s), 9.88 (1H, s), 9.77 (1H, s) 9.63 (1H, s), 7.3 (2H, s), 7.15 (2H, d, $J=8$ Hz), 6.5 (2H, d, $J=8$ Hz), 2.23 (6H, s). ^{13}C NMR δ_C (ppm, 300 MHz, DMSO-d_6): 167.5, 157.3, 154.7, 133.1, 128.3, 122.1, 111.8, 11.6. MS (FAB): *m/z* 584. Anal. Calcd for $C_{16}H_{16}N_2O_4Pd_2Cl_2$ (584.04): C, 32.87; H, 2.74; N, 4.79. Found: C, 32.12; H, 2.87; N, 4.59.

3.2. Study of the stability of the carbapalladacycle oxime complex in the different solvents

The carbapalladacycle complex **1** (14.6 mg, 0.05 mmol) and

the corresponding solvent (1 g) were magnetically stirred in a pre-heated oil bath at 120 °C. The course of the reaction was periodically followed by stopping the stirring and taking aliquots (100 μl) that were diluted in CH_3CN (ca. 2 ml) and monitored by UV spectroscopy.

3.3. Typical procedure for Sonogashira reactions

The carbapalladacycle complex **1** (14.6 mg, 0.05 mmol, 5 mol%) was placed in a screw capped vial and 4-bromoacetophenone (199 mg, 1 mmol), phenylacetylene (124, 1.2 equiv), cesium acetate (230 mg, 1.2 equiv) and the corresponding solvent (1 g, solvent/aryl halide weight ratio = 5) were added. When the solvent-to-reactive weight ratio was 50 the amount of reagents and catalyst was divided by 5 and 2 g of solvent were used. The resulting mixture was placed in a preheated oil bath at 120 °C under magnetic stirring. After 24 h, the reaction was cooled for 1 min and the resulting mixture extracted with diethyl ether (2 ml×7 times). The combined ether extract was filtered and the solvent removed under reduced pressure. The crude was weighed and analysed by GC using nitrobenzene as external standard, GC–MS and ^1H and ^{13}C NMR.

3.4. Recovery and reuse of the catalyst in PEG

The carbapalladacycle complex (2.9 mg, 0.01 mmol, 5 mol%).) was placed in a round-bottomed flask and 4-bromoacetophenone (39.8 mg, 0.2 mmol), phenylacetylene (26.4 μl, 24.8 mg, 1.2 equiv), cesium acetate (76.8 mg, 2 equiv) and PEG (3.6 g) were added. The mixture was placed in a preheated oil bath at 120 °C and magnetically stirred for 24 h. Then, the reaction was cooled for 1 min and the resulting mixture extracted with diethyl ether (5 ml×7 times). The combined ether extract was filtered and the solvent removed under reduced pressure. The crude was weighed and analysed by GC using nitrobenzene as external standard, GC–MS and ^1H and ^{13}C NMR. The solid mixture was dried under vacuum pump (10^{-1} torr) for 5 min and reused in a next run.

3.5. Typical procedure for Suzuki reactions

The carbapalladacycle complex **1** (5.8 mg, 0.02 mmol, 5 mol%).) was placed in a screw capped vial and 4-chloroacetophenone (52 μl, 62 mg, 0.4 mmol) or iodobenzene (56 μl, 102 mg, 0.5 mmol), phenylboronic acid (61 mg, 0.5 mmol, 1.25 equiv) or 4-tolylboronic acid (81.6 mg, 0.6 mmol), potassium carbonate (69 mg, 0.5 mmol, 1.25 equiv) or cesium acetate (115 mg, 0.6 mmol) and bidistilled water (2 ml, dissolving TBAB (64.5 mg, 0.2 mmol, 0.5 equiv)) or ionic liquids (400 mg) or PEG (400 mg) were added. The mixture was placed in a preheated oil bath at 120 °C and magnetically stirred. *Water as solvent*. After 2 h, the reaction was cooled, diluted in bidistilled water (3 ml) and extracted with ethyl acetate (3× 10 ml). The organic phases were dried using magnesium sulfate, filtered and concentrated under reduced pressure. The resulting crude was analysed by GC and GC–MS using nitrobenzene as external standard. *Ionic liquids or PEG as solvents*. After 24 h, the reaction was cooled for 1 min and the resulting mixture extracted with diethyl ether (2 ml×7 times). The combined ether extract was filtered and the solvent removed under reduced pressure. The crude was weighed and analysed by GC using nitrobenzene as external standard, GC–MS and ^1H and ^{13}C NMR.

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Design of highly active heterogeneous palladium catalysts for the activation of aryl chlorides in Heck reactions

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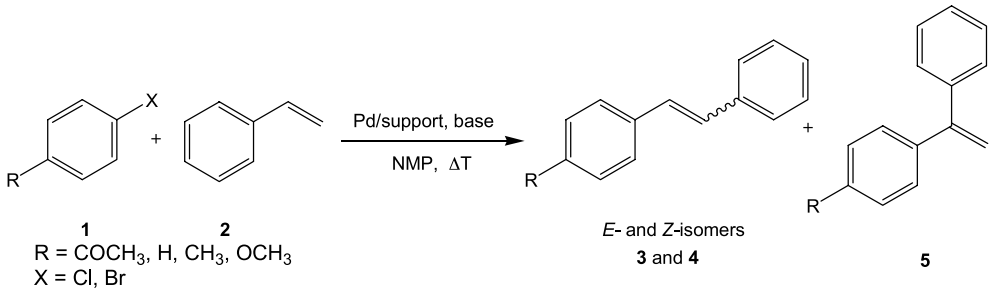
Abstract—In situ generation of highly active palladium species by intermediate dissolution of Pd from solid supported catalysts has been demonstrated to be a very successful approach for the activation of aryl chlorides in Heck reactions. The new 'heterogeneous' Pd catalysts act as reservoir for molecular Pd species with unsaturated coordination sphere in solution. Crucial Pd leaching and re-deposition onto the support can be controlled by optimization of reaction conditions and by the properties of the catalysts. Pd is re-deposited onto the support at the end of the reaction. The catalysts, palladium supported on activated carbon, on various metal oxides or fluorides and Pd complexes in zeolites, are easy to prepare, though the preparation conditions are crucial. The catalysts convert all aryl bromides completely within minutes (TON 100,000). Aryl chlorides (even deactivated ones) are converted with high yields, within 2–6 h. The catalysts belong to the most active ones in Heck reactions at all (including best homogeneous systems) and fulfill all relevant requirements for practical applications in laboratory and industry.

1. Introduction

CC coupling reactions like Heck reactions (Scheme 1) are of growing interest for organic synthesis and fine chemical industry.[1] Advantages of this reaction are a broad availability of aryl bromides and chlorides and the tolerance of a wide variety of functional groups. The Heck reaction is typically catalyzed by Pd complexes in solution. Expensive and often sensitive ligands are necessary to activate Pd and to stabilize it against agglomeration and the formation of Pd black. Accordingly, there have been many efforts to develop new homogeneous systems in the last years.[1]

In addition, several heterogeneous Pd catalysts have been developed in order to overcome typical problems in homogeneous catalysis. The most frequent motivation given is: recovery, recycling, and reuse of the catalyst. However, one of the main and (in our opinion) most important differences between reported homogeneous and heterogeneous systems is the clearly lower activity of the latter catalysts, often being orders of magnitudes lower than that of soluble Pd complexes. This is reflected by the model systems investigated. Typical reports on heterogeneous catalysts focus on aryl iodides and activated aryl bromides as substrates. Reports on the successful activation of



Scheme 1. Heck reaction.

Keywords: CC coupling; Heck reaction; Heterogeneous catalysis; Palladium.
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bromobenzene and in particular of aryl chlorides are very seldom. Most of the reported catalysts that successfully activated aryl chlorides like Pd on activated carbon[2] and layered double hydroxides,[3] Pd complexes bound to polymer matrices[4] or immobilized in porous materials[5] exhibit relevant limitations: they need very long reaction times (several days) or high Pd concentrations for acceptable conversions; restriction on strongly activated aryl chlorides, high selectivity to undesired side products (dehalogenation of the aryl chloride) or a rather complex synthesis of the catalyst itself, which makes it too expensive for possible applications may also be severe problems. Very recently, we have reported that the in situ generation of dissolved Pd species from solid catalysts can be a new and very efficient approach for the activation of aryl chlorides in Heck reactions.[6] Those investigations force of course the discussion on the mechanism of the (heterogeneous) Heck reaction.[7]

While the homogeneous mechanism of the Heck reaction is widely accepted several proposals for the heterogeneous cycle have been made. Several authors suggested a direct interaction between reactants and palladium surface atoms either of supported particles or of colloids in solution as the initial step in the catalytic cycle.[7,8] Shmidt et al.[9] and Arai et al.[10] observed leaching of Pd from the support and claimed these dissolved species to be the active ones. Both performed kinetic investigations on reactions with aryl iodides that indicated a correlation between leaching and reaction rate. In recent years several additional experiments also with non-activated aryl bromides have been reported.[2a,6,7,11] Most of them strongly support this pseudo-homogeneous reaction mechanism and showed that very small amounts of Pd are sufficient for activation of aryl bromides. This interpretation corresponds well with reports of Reetz and de Vries, who achieved similar high activities using 'ligand free' Pd acetate.[12]

With solid catalysts these 'ligand free' active species are generated by dissolution of Pd from the solid. In particular, the determination of the Pd concentration in solution and its correlation with the rate of the Heck reaction were found to be very useful tools for corresponding conclusions.[6,11a] From these observations, the question arose if the control of this leaching process is possible with the aim to speed up the reaction and, which catalyst properties and reaction conditions are the best for the activation of the attractive aryl chlorides by a solid catalyst. This work presents our efforts to elucidate the mechanism of the heterogeneously catalyzed Heck reaction with aryl chlorides. Based on mechanistic insights we optimized heterogeneous Pd catalysts and reaction conditions. As a consequence efficient activation of aryl chlorides became possible by catalysts that are cheap and easily prepared.

2. Results and discussion

2.1. Catalyst preparation

The heterogeneous catalysts presented in this work were specifically prepared to achieve a high dispersion of Pd in oxidation state +II.[11a,13] This has been described and explained to be crucial for high activity and selectivity in Heck reactions of bromobenzene. In order to vary the Pd leaching and re-deposition equilibriums various preparation methods, precipitation of $Pd(OH)_2$ onto different supports, sol-gel techniques and incorporation of Pd(II) complexes into zeolite pores, were used.[14]

2.2. Catalytic activity

The optimized Pd/support catalysts exceed the activity of all heterogeneous catalysts for Heck reactions known so far by at least one order of magnitude. TON of more than 100,000 and TOF up to 39,000 h^{-1} can be achieved with Pd concentrations of less than 0.001 mol% in the Heck reaction of bromobenzene and styrene under standard conditions (NMP, NaOAc, 140 °C, argon atmosphere; Table 1). Comparison of the various support materials did not reveal significant support influences in the reactions. In fact, the high Pd(II) dispersion is found to be crucial also for the present investigations.

Applying exactly the same conditions in the reaction of 4-chloroacetophenone and styrene no conversion is observed. The addition of tetra-*n*-butylammoniumbromide (TBAB) and higher temperature (160 °C) lead to 65% conversion. Addition of TBAB probably prevents Pd agglomeration at this elevated temperature and Br^- can act as a supporting ligand for 'naked' Pd atoms (i.e., the system is now no longer 'ligand free'). Further improvements can be achieved by substitution of the base. While NaOAc leads only to 65% conversion, complete conversion occurs within 2 h using $Ca(OH)_2$ (Fig. 1, Table 2). TON of 10,000–20,000 and TOF of 5000–10,000 h^{-1} are obtained

Table 1. Heck coupling of bromobenzene and styrene

Entry	Catalyst	Catalyst concentration (mol%)	Conversion (%)	Yield **3** (%)	TON[a]	TOF (h^{-1})[b]
1	Pd/TiO_2[c]	0.0011	95	86	87,000	22,000[d]
2	Pd/Al_2O_3[c]	0.0009	96	87	107,000	27,000[d]
3	Pd/TiO_2[c]	0.001	78	71	78,000	39,000
4	Pd/Al_2O_3[e]	0.01	99	94	10,000	5000
5	Pd/AlF_3[c]	0.009	99	93	11,000	5500
6	Pd/MgF_2[c]	0.009	99	93	11,000	5500

Conditions: 10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 10 mL NMP, argon atmosphere, 2 h.
[a] Moles of aryl halide converted/moles of Pd.
[b] TON/h.
[c] Prepared by precipitation of $Pd(OH)_2$ on support.
[d] 4 h reaction time.
[e] Prepared by sol–gel method.

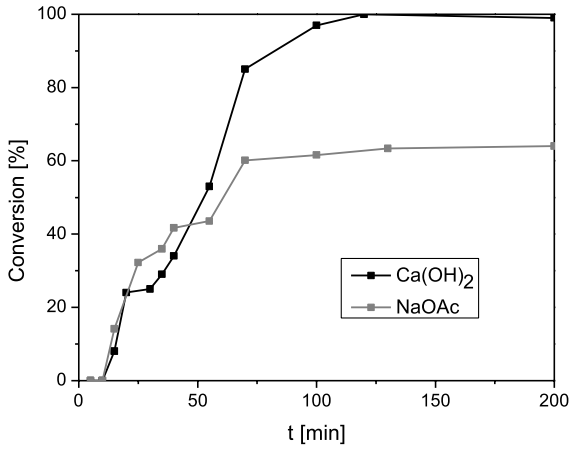

Figure 1. Kinetic investigations: influence of the base on the Heck coupling of 4-chloroacetophenone with styrene. Reaction conditions: 10 mmol 4-chloroacetophenone, 12 mmol styrene, 12 mmol base, 6 mmol TBAB, 10 mL NMP, 0.01 mol% Pd/Al_2O_3 catalyst, 160 °C.

achieved with different other supports, if specific redox conditions were adjusted in the system (Table 2, entries 4–9). Pd re-oxidation by oxygen and/or the support plays a crucial role too. In oxygen atmosphere higher yields could be achieved than in argon atmosphere (Table 2, entries 10, 11). This may be explained by partial re-oxidation of Pd to Pd(II) (lower concentration of Pd(0)) thus preventing Pd agglomeration (Pd black formation).

The use of Pd/NaY and a careful choice of reaction parameters allow the activation and conversion even of deactivated aryl chlorides, like 4-chlorotoluene and 4-chloroanisole, in Heck reactions (Table 2, entries 12, 13). Note, that the selectivity to the Heck products is 100% in all cases and that the problematic dehalogenation which is often found for reactions of aryl chlorides did not occur. We explain this by the controlled prevention of Pd particle formation in the present system (assuming that dehalogenation occurs according to a truly heterogeneous surface mechanism).

Table 2. Heck coupling of aryl chlorides and styrene

Entry	Aryl halide	Catalyst	Catalyst concentration (mol%)	Conversion (%)	Yield **3** (%)
1	4-Chloroacetophenone[a]	Pd/Al_2O_3[b]	0.01	98	90
2	4-Chloroacetophenone[a]	Pd/Al_2O_3[c]	0.01	87	83
3	4-Chloroacetophenone[a]	Pd/NaY[d]	0.005	99	95
4	Chlorobenzene	Pd/Al_2O_3[b]	0.1	45	40[e]
5	Chlorobenzene	Pd/AlF_3[b]	0.1	36	32[e]
6	Chlorobenzene	Pd/Al_2O_3[c]	0.1	33	30[e]
7	Chlorobenzene	Pd/C[f]	0.1	33	32[e]
8	Chlorobenzene	$Pd/Ce/Al_2O_3$[c]	0.1	54	51[e]
9	Chlorobenzene	Pd/CeO_2[b]	0.1	54	51[e]
10	Chlorobenzene	Pd/NaY	0.05	49	45
11	Chlorobenzene	Pd/NaY	0.05	85	83[e]
12	4-Chlorotoluene	Pd/NaY	0.05	40	36[e]
13	4-Chloroanisole	Pd/NaY	0.05	21	19[e]

Conditions: 10 mmol aryl halide, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, argon atmosphere, 6 h.
[a] 2 h reaction time.
[b] Prepared by precipitation of $Pd(OH)_2$ on support.
[c] Prepared by sol–gel method.
[d] Without TBAB.
[e] O_2 atmosphere.
[f] E105 CA/W, Degussa AG.

with different catalysts. In the case of Pd/NaY addition of TBAB can be even renounced.

Kinetic investigations showed that the concentration of the molecular Pd species in solution correlates with the reaction course (Fig. 2). The highly active Pd species are generated in situ. Pd is dissolved from the support, stabilized against agglomeration by dissolution-re-precipitation equilibriums with the surface and re-deposited onto the support at the end of the reaction (after consumption of the aryl chloride).

The conversion of non-activated aryl chlorides like chlorobenzene occurs only satisfactorily if TBAB is added (independent of the support). The best results were achieved with Pd incorporated into the cages of a zeolite (Pd/NaY). Using this catalyst 85% conversion and a yield of 83% of *E*-stilbene were obtained in the Heck reaction of chlorobenzene and styrene within 6 h (TON = 1400, Table 2). This system is particularly suitable to avoid agglomeration of Pd probably by diffusion control. Good results could also be

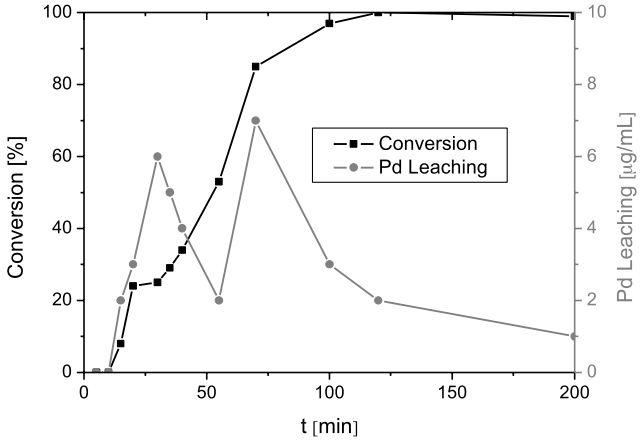

Figure 2. Kinetic investigations and Pd leaching: Heck coupling of 4-chloroacetophenone with styrene. Reaction conditions: 10 mmol 4-chloroacetophenone, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, 0.01 mol% Pd/Al_2O_3 catalyst, 160 °C.

2.3. Pd leaching as a function of reaction time

The progress of the reaction and the Pd content in solution were monitored for different substrates (4-chloroacetophenone, chlorobenzene) and catalysts (Pd/Al_2O_3, Pd/NaY zeolite, Figs. 2 and 3). In all cases the active Pd species are generated by dissolution from the support. They are stabilized against agglomeration by dissolution-re-precipitation equilibriums with the surface and re-deposited onto the support at the end of the reaction. For chlorobenzene and Pd/NaY zeolite catalysts Pd is dissolved (concentration reaches maximum after 20 min) and the conversion of chlorobenzene starts. The Pd content in solution decreases with the degree of aryl chloride consumed. The Pd concentrations in solution and the course of the reaction depend on catalyst, substrate, temperature, base, solvent, and additives. The maximum absolute amount of Pd in solution is higher for the optimized reaction system and chlorobenzene compared to 4-chloroacetophenone. Obviously the lower concentration in the latter case (controlled by the chosen reaction parameters) is not sufficient to activate the less reactive chlorobenzene. Even small divergences of the Pd content in solution correlated with fluctuations in the reaction course (Fig. 3). The divergences of the Pd concentration in solution may be due to the experimental procedure (disturbances/interruptions by the withdrawal of samples from the reaction mixture) or due to differences in the single reaction vessels (see Section 4). Note, that also the zeolite system shows leaching of Pd into bulk solution during the reaction. Obviously, the reaction takes place outside the zeolite pores. Pd leaves the pore system, catalyzes the Heck reaction and diffuses back into the pores (equilibrium).

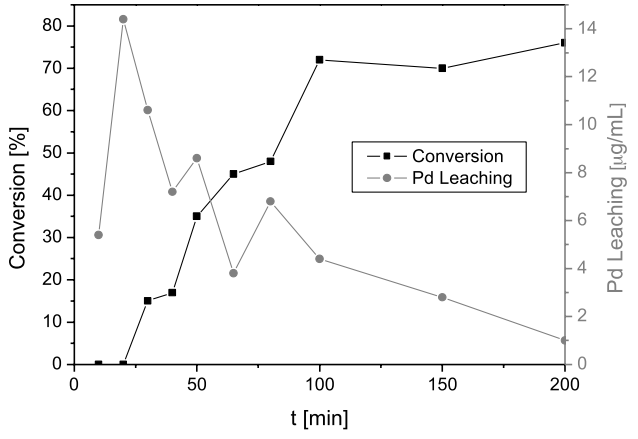

Figure 3. Kinetic investigations and Pd leaching: Heck coupling of chlorobenzene with styrene. Reaction conditions: 10 mmol chlorobenzene, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 6 mmol TBAB, 10 mL NMP, 0.05 mol% Pd/NaY catalyst, 160 °C, O_2 atmosphere.

2.4. Catalyst recycling and reuse

The catalysts were recyclable several times. This is illustrated by the reaction of bromobenzene and styrene. Only a slight decrease in activity emerges in the second run (86% conversion). In the third run, still 69% conversion is achieved (Table 3). The decrease is caused by a partial reduction of Pd(II) to Pd(0) and a lower Pd dispersion after re-deposition. In contrast to observations with activated aryl bromides made by de Vries et al.,[15] reactivation of the catalyst by I_2 or Br_2 was not possible.

Table 3. Heck coupling of bromobenzene and styrene–catalyst recycling experiments

Entry	Run	Conversion (%)	Yield **3** (%)
1	1	98	90
2	2	86	80
3	3	69	62

Conditions: 10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 10 mL NMP, argon atmosphere, 140 °C, 6 h, 0.2 mol% Pd/Al_2O_3.

3. Conclusions

Pd supported on various oxides, fluorides and activated carbon and incorporated into zeolites can be an extremely active and selective catalyst for Heck reactions. The catalytic systems combine extremely high activity, short reaction times, and high selectivity in Heck reactions of aryl bromides and chlorides with the advantages of easy and complete Pd separation and recovery. The activity is comparable to the very best homogeneous catalyst systems. The heterogeneous catalysts are stable against air and moisture, no inert atmosphere and no expensive ligands are necessary. They are easy to prepare, the preparation conditions are crucial (high dispersion and +II oxidation state of Pd, certain water content, no thermal treatment or pre-reduction). Pd complexes ($[Pd(NH_3)_4]^{2+}$) incorporated into the pore system of zeolites (NaY) represent the best catalytic performances. Side reactions (dehalogenation) and Pd black formation can be excluded.

The development of these simple catalysts was possible by enlightenment of the reaction mechanism and corresponding careful optimization as well as choice of reaction parameters and catalyst properties. The highly active Pd species are generated in situ by intermediate dissolution of Pd from the solid support. The 'heterogeneous' Pd catalysts act as a reservoir for coordinative unsaturated molecular Pd species in solution. Pd is re-deposited onto the support at the end of the reaction. These processes are crucial and immanent components of the catalytic cycle, which obviously also involves heterogeneous reactions (oxidative addition of aryl halide to surface palladium atoms initializing dissolution). The Pd amount in solution correlates with the reaction rate and is strongly influenced by the reaction conditions. Solvent, temperature, substrates, base, additives, and atmosphere must be adjusted carefully. Experiments monitoring the Pd concentration in solution as a function of reaction rate were the most valuable tools for corresponding mechanistic studies. Pd leaching is a precondition for high activity and selectivity of heterogeneous catalysts in Heck reactions.

4. Experimental

4.1. General procedure for catalysis experiments

Reactions were performed in sealed pressure tubes after 5 min of purging with argon. Educts and solvents were used non-dried.

Filtered samples were extracted with water/CH_2Cl_2 and dried over $MgSO_4$. Products were identified by GC/MS. Conversions and yields were quantified by GLC using diethylene glycol dibutylether as internal standard ($\Delta_{rel} = \pm 5\%$).

4.2. Typical reaction conditions for Heck reactions with bromobenzene

10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, about 0.001 mol% Pd/support, 10 mL NMP (1-methyl-2-pyrrolidone), $T = 140$ °C, 2–4 h.

4.3. Typical reaction conditions for Heck reactions with aryl chlorides

10 mmol aryl chloride, 12 mmol styrene, 12 mmol $Ca(OH)_2$, 0.01–0.1 mol% Pd/support, 10 mL NMP, $T = 160$ °C, 2–6 h.

4.4. Typical reaction procedure for kinetic investigations

Sixteen identical experiments were performed in 16 pressure tubes as described above. At defined times the reactions were quenched. For Pd leaching 5 mL of the filtered sample were evaporated. Pd content of the residue was analyzed by flame AAS.

4.5. Recycling experiments

10 mmol bromobenzene, 15 mmol styrene, 12 mmol NaOAc, 0.2 mol% Pd/Al_2O_3, 10 mL NMP, $T = 140$ °C, $t = 6$ h. After the reaction was finished, the catalyst was washed three times with CH_2Cl_2 and re-used.

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Aryl alkynylation versus alkyne homocoupling: unprecedented selectivity switch in Cu, phosphine and solvent-free heterogeneous Pd-catalysed couplings

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Abstract—Sonogashira reaction and oxidative dimerisation of terminal alkynes are among the most relevant and attractive C–C bond forming transformations in the metallo-catalysed cross-coupling scenario. Often, the homocoupling reactions of substituted acetylenic derivatives are concomitant to the Sonogashira pathway and time-consuming optimization procedures are required in order to reach satisfactory levels of selectivity. In this paper, the potential of a class of Pd-complexes loaded to mesoporous silica gel in promoting the Sonogashira reaction between aryl acetylenes and iodoarenes is underlined. This family of heterogeneous organo-palladium systems allows the desired cross-coupled compounds to be isolated in excellent yield under very mild conditions. In fact, the absence of organic solvents, copper(I) co-catalyst and phosphane ligands, (which are easily oxidisable and whose preparation has a heavy environmental impact), in conjunction with the low catalyst loading ([Pd] 0.1–1 mol%) and its recoverability, stresses the environmental benefits of the protocol. The Sonogashira/homocoupling selectivity proved to be function of the haloarene employed. As a matter of fact, while iodoarenes bearing EWG (electron withdrawing groups) on the phenyl ring underwent smoothly the Sonogashira pathway, electron-rich iodobenzenes showed opposite behaviour by mainly furnishing the homocoupling product. The use of bromoarenes provided solely the homocoupling product in excellent yield without themselves being consumed. This is despite that fact that the catalysts used activate bromoarenes equally as well as iodoarenes in both Heck and Suzuki systems. Kinetic investigations revealed a highly temperature-dependent profile, which indicates strongly that the reaction takes place at the surface. Finally, the full heterogeneous character of the catalytically active species as well as the reusability of the immobilised Pd-complex were confirmed by hot-filtration test and by multiple reuses of the supported catalyst in subsequent Sonogashira cross-couplings.

1. Introduction

Palladium(0)/(II) catalysed C–C forming processes through cross-coupling reactions are among the most employed organic transformations by academic as well as industrial communities for the syntheses of key structural motifs in pharmaceuticals, agrochemicals and material science.[1]

In this field, Sonogashira reactions[2] and acetylenic couplings[3] (Glaser-type processes) cover a large area of scientific interests being remarkably straightforward for the one-pot synthesis of challenging C–C bonds such as Csp–Csp and Csp–Csp[2].

After the seminal papers published by Sonogashira[4] and Glaser,[5] many efforts have been devoted toward the development of milder, catalytic and more environmentally friendly protocols for both homo- and heterocoupling of terminal alkynes. In this regard, the easy separation and recycling of the Pd(0)/(II) catalyst after the reaction workup would increase the feasibility of the transition metal cross-coupling transformation even in large scale fine-chemical applications.[6] This approach in fact, would minimise the contamination of organic reaction mixtures by the catalyst with a consequent significant advantage in terms of time-demanding purification procedures.[7] Therefore, an ever-increasing number of heterogeneously as well as so-called 'semiheterogeneously' catalysed Sonogashira protocols appear periodically in the literature. Among them, homogeneous two-phase catalysis,[8] heterogeneous biphasic catalysis,[9] Pd-loaded porous glass,[10] palladium-loaded carbon or alumina,[11] palladium-grafted on MCM-41,[12] zeolite (NaY-type)-entrapped Pd systems,[13] polymer-supported

Keywords: C–C coupling; Heterogeneous catalysis; Kinetics; *N*-ligands; Palladium.
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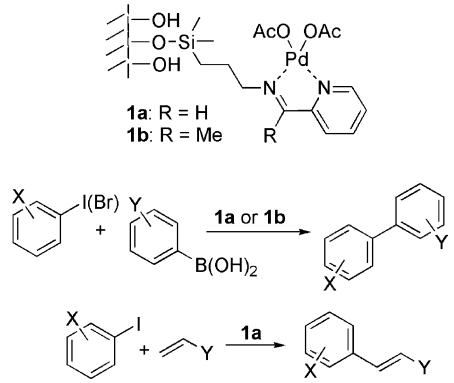
Pd-ligand complexes,[14] recoverable dendritic-Pd complexes[15] and Pd-nanoparticles[16] are some representative examples of recoverable catalytic systems effectively applied to the Sonogashira coupling. However, most of the above listed studies require the presence of co-catalysts (Cu(I) salts), alkyl/aryl phosphanes as stabilizers of the Pd-catalysts and harsh conditions, such as high temperatures, in order to guarantee satisfactory chemical conversions. In this paper, we wish to present our recent findings in the development of a new and effective protocol for the Sonogashira coupling by using a versatile class of silica-supported Pd-complexes. Recently, we have reported on the efficiency of *N*,*N*-chelated[17] Pd(II) complexes of organically modified commercial mesoporous silica gel (**1a–b**, Scheme 1) as promoting agents for Suzuki and Heck cross-couplings, working equally effectively for both iodo- and bromoarenes.[18]



Scheme 1. Silica gel supported palladium catalysts for Suzuki and Heck cross-coupling reactions.

The design/control of the catalytic properties of heterogeneous metal-based systems is an intriguing perspective for many organic/inorganic chemists. In this context, of particular relevance is the use of hybrid organic–inorganic materials through the employment of organically modified inert supports. In fact, the organic counterpart of the catalytic system usually allows the electrical properties of the metal centre to be adequately predicted and tuned. The proposed catalytic approach proved its effectiveness in promoting cross-couplings between a number of aryl iodides with terminal aromatic acetylenes under solvent, copper and phosphane-free conditions (conv. 44–98%).[19] Interestingly, the use of relatively low reaction temperature (70 °C), low catalyst loading ([Pd]$\leq$1 mol%) and the absence of copper salts as co-catalysts,[20] disfavours side reactions of the terminal alkynes. Moreover, the usual requirement for a careful anaerobic atmosphere in copper-free methodologies is not needed, making the strategy very attractive from a practical point of view.[21]

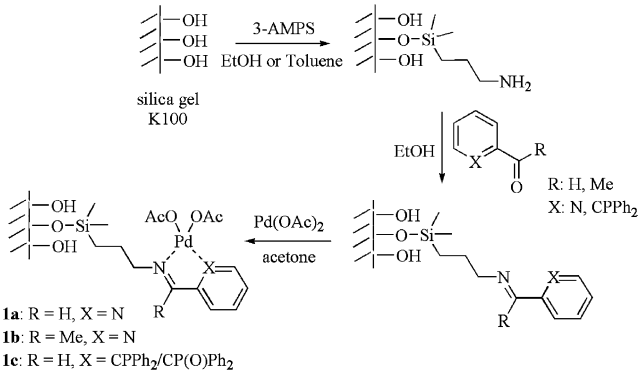
Although good functional group tolerance was recorded for electron-poor aryl partners (halogens, COMe, NO_2, CO_2H, CF_3), the use of substituted iodophenols furnished unexpected results in terms of chemoselectivity between Sonogashira reaction and Glaser-type homocoupling. In particular, when 4-iodophenol was employed, the diphenyldiacetylene became the main reaction outcome (isolated yield 92%), the heterocoupled compound being detected only in traces from the GC analysis of the crude reaction mixture. The solubilization and leaching of palladium from inert supports is commonly observed in Pd-heterogeneous mediated processes.[22] However, we ruled out the presence of a concomitant homogeneous catalysis by hot-filtration test and by adding fresh doses of reactants to the supernatant reaction solution once the solid is filtered off.

Detailed mechanistic investigations of heterocatalysed organic transformations are usually challenging tasks to accomplish. In these cases in fact, both thermodynamic and kinetic parameters are usually functions of several chemical as well as physical phenomena. Here we present a careful evaluation of several reaction parameters by monitoring the reaction profiles of the Sonogashira coupling between phenylacetylene and 2-fluoroiodobenzene (probe reaction) versus time and by separately investigating the adsorption of the reaction partners onto the surface of the catalysts.

2. Results and discussion

2.1. Preparation of the catalysts

The ready availability in discrete amounts of this class of catalysts, in conjunction with the key fine-tuning of the steric as well as electronic properties of the palladium centre, represent some of the peculiarities of the organically modified silica gel supported catalysts **1a–b**. As already described,[18] the functionalisation of the activated Kiesegel 100 was readily accomplished in two steps namely: (i) anchoring of the 3-AMPS (aminopropyl(trimethoxy)silane) linkage in EtOH/rt or toluene/reflux; (ii) synthesis of the desired Schiff base by using the corresponding 2-carbonyl-pyridine in EtOH at rt (Scheme 2). The presence of bound organics was confirmed by diffuse reflectance infrared spectroscopy (DRIFTS).



Scheme 2. Synthetic strategy for the preparation of the silica gel loaded palladium catalysts **1a–c**.

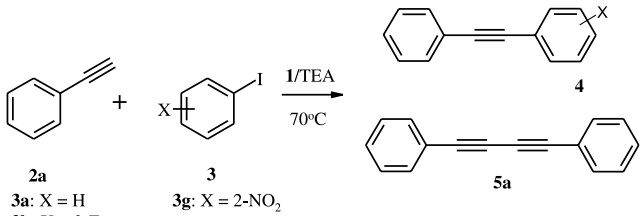
These analyses displayed the sharp peaks of the C=N stretching vibration in the range 1639–1647 cm^{-1}. Then the complexation of the $Pd(OAc)_2$ with the bidentate ligand-grafted silica was carried out in reagent grade acetone at rt leading to Pd-loadings, after repeated conditioning and washing procedures,[18] of 0.1–0.3 mmol/g. In our efforts to monitor the influence of the coordinating heteroatoms on the activity of the catalyst we used analogous synthetic

conditions to prepare the new *N*,*P*-chelated palladium complex **1c**. In this case, the 2-(diphenylphosphane)benzaldehyde was employed for the imine synthesis. Elemental analysis of the isolated catalyst revealed that 0.56 mmol/g were effectively anchored on the inert support surface and with a Brunauer-Emmett-Teller (BET) surface area of 248 m^2/g. The solid state ^{31}P MAS NMR analysis of the *N*,*P*-chelating ligand showed the presence of two main phosphorus-containing species ascribable to the simultaneous presence of the desired complex **1c** (^{31}P δ: −9.0 ppm) and the related phosphinyl (P═O, ^{31}P δ: 36.3 ppm) species (major compound) derived from the combined oxidising effect of oxygen and silica gel on the phosphino ligand.[23] The effectiveness of **1c** in catalysing the Sonogashira cross-coupling (vide infra) is not surprising due to the high aptitude of hemilabile (P═O)-containing ligands in promoting metallo-catalysed organic reactions.[24]

2.2. Sonogashira reaction versus homocoupling process

In preliminary attempts addressed towards the optimization of the protocol, we have taken into account the Sonogashira reaction between PhI (**3a**, 2 equiv) and phenylacetylene (**2a**, 1 equiv) in the presence of catalyst **1a** ([Pd] 1 mol%) and by using an excess of triethylamine (TEA) (3 equiv) as the base. After 12 h stirring at 70 °C, the use of an internal standard technique revealed 87% conversion (based on the starting PhCCH), with the desired cross-coupled product **4a** being the major product with respect to the homocoupled alternative **5a** (13:1, Table 1, entry 1).

Table 1. Heterogenous catalysed cross-coupling reaction[a]



2a

3: **3a**: X = H; **3b**: X = 3-F; **3c**: X = 2-F; **3d**: X = 4-F; **3e**: X = 4-COMe; **3f**: X = 4-NO_2; **3g**: X = 2-NO_2; **3h**: X = 3-NO_2; **3i**: C_6F_5I; **3j**: X = 3-Cl/4-NO_2; **3k**: X = 2-Cl/5-CF_3

Entry	3	Conv. [%][b]	4:5a ratio[c]
1	**3a**	87	13:1
2	**3a**	98[d]	8:1
3	**3b**	>98	>50:1
4	**3b**	>98[d]	12:1
5	**3b**	60[e]	16:1
6	**3c**	95 (91%)[f]	18:1
7	**3d**	87 (85%)[f]	19:1
8	**3e**	>98	35:1
9	**3f**	>98	50:1
10	**3g**	>98	25:1
11	**3h**	>98	50:1
12	**3i**	40	3.5:1
13	**3j**	78	16:1
14	**3k**	85	50:1

[a] All the reactions were carried out under air, **2a**/**3**/TEA/[Pd] 1:2:3:0.01, unless otherwise specified. Reaction time 12 h.
[b] Based on the **2** conversion. Determined by GC-analysis with undecane as the internal standard.
[c] Determined by GC-analysis on the reaction crude.
[d] CuI (5 mol%) was used as the co-catalyst.
[e] 1:1 Ratio of **2a** and **3b** was used.
[f] Isolated yield.

Interestingly, by carrying out the same reaction in the presence of 5 mol% of CuI as the co-catalyst and in comparable reaction time, the conversion recorded was higher (98%) but with reduced selectivity (**4a**:**5a** 8:1, entry 2). An analogous trend was also observed in the cross-coupling with 3-fluoroiodobenzene (**3b**) that, in absence of CuI, gave rise to **4b** in quantitative yield (>98%) and higher selectivity (>50:1, entry 4 vs 3). Moreover, the employment of an excess of iodo-partner proved to be essential in order to guarantee satisfactory conversions. In fact, by running the Sonogashira coupling between **2a** and **3a** as a means of 1:1 ratio, **4a** was isolated only in 60% conversion after comparable reaction time (12 h, entry 5).

In an attempt to clarify the generality of the catalytic protocol, a range of electron-poor aryl iodides were tested under the optimal reaction conditions. The tolerance toward numerous spectator functional groups was observed and in particular NO_2, CO_2H, COMe, halogens as well as CF_3 mono- and disubstituted iodobenzenes smoothly coupled with PhCCH affording the desired cross-coupling compounds in high yields (78–98%) and excellent cross versus homo selectivity. Also sterically congested *ortho*-substituted iodoarenes such as **3c**, **3g** and **3k** readily reacted with **2a** in a highly efficient manner (yield: 95, 98 and 85%, respectively). Only in the case of iodopentafluorobenzene (**3i**) did the optimal reaction conditions afford the asymmetric diarylacetylene (**4i**) in moderate yield (44%, entry 12).

Then, by considering the cross-coupling alkynylation of 2-F–PhI (**3c**) with PhCCH as the model reaction, a comparative study through the family of the heterogeneous catalysts **1a–c** was performed ([Pd]: 1 mol%).[25] The reaction profiles for the catalytic species **1a–c** (conversion vs time) were monitored by GC and depicted in Figure 1.

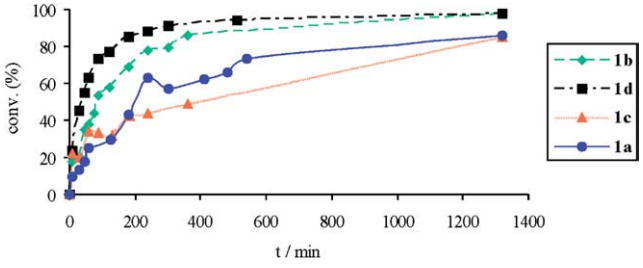
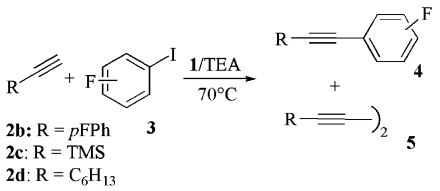


Figure 1. Reaction profiles showing the **4c** formation at specified times for the Sonogashira coupling between **2a** and **3c** catalysed by **1a–d**.

Interestingly, the ketoimine derived Pd-complex **1b**, proved to be the most effective catalyst among the silica-loaded species, furnishing quantitative yield in **4c** (5 h) as the single compound (**4c**:**5a** >50:1). On the other hand, the *N*/*P*(*O*)-containing complex (**1c**) catalysed the probe reaction with no noticeable differences from the aza-analogous **1a**, while the reaction appeared significantly slower with respect to the use of **1b**. Finally, a slightly drop in selectivity was also observed (**4c**:**5a**, 13:1).[26]

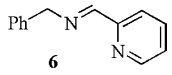
Table 2. Screening of acetylenes in the cross-coupling reaction: the catalyst loading[a]



Entry	Cat./[%]	2/3	Conv. [%][b]	4:5 ratio[c]
1	**1a**/1	**2b/3c**	81	8:1
2	**1b**/1	**2b/3c**	>98%	15:1
3	**1a**/1	**2c/3c**	13	1:1
4	**1b**/1	**2c/3c**	13	1:1
5	**1a**/1	**2d/3c**	—[d]	—[d]
6	**1a**/1	**2a/3b**	>98	>50:1
7	**1a**/0.5	**2a/3b**	85	>50:1
8	**1a**/0.25	**2a/3b**	75	>50:1
9	**1a**/0.1	**2a/3b**	72	>50:1

[a] All the reactions were carried out under air with reaction time 12 h.
[b] Based on the conversion of **2**. Determined by GC-analysis with undecane as the internal standard.
[c] Determined by GC-analysis on the reaction crude.
[d] No reaction.

The decreased activity of immobilised catalysts, in comparison to the analogous homogeneous catalysts, is among the main drawbacks usually encountered in heterogeneous catalysis. To have some insight into this aspect the homogeneous Pd-catalyst **1d**, derived by the in situ complexation of $Pd(OAc)_2$ and 2-pyridine aldoimine **6**,[27] was synthesised and tested in the Sonogashira reaction (Fig. 1). Interestingly, the homogeneous version of the model Sonogashira reaction showed a conversion profile broadly similar (conv.>98%, 3 h) to that recorded with the catalyst **1b**, stressing the catalytic effectiveness of the present Pd-supported system.



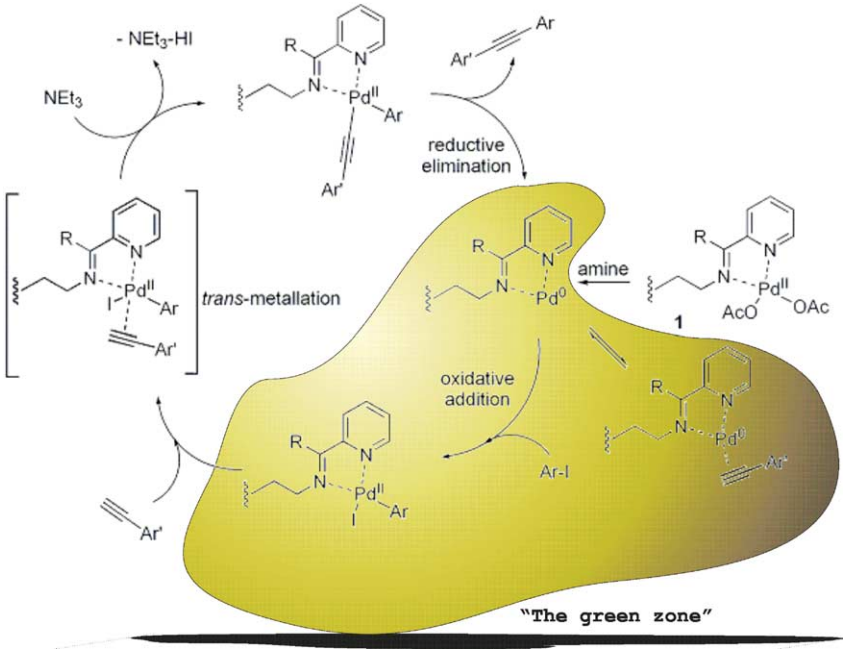
Having tested the reaction conditions for several aryl iodides we turned our attention to other acetylenes (**2b–c**) with **3c**. From the data collected in Table 2 (entries 1–5), it appears clear that while substituted arylethynes such as **2b** proved to be a suitable partners for the present cross-coupling reaction (entries 1, 2), terminal aliphatic alkynes (**2c–d**) underwent the Sonogashira reaction to poor extents and disappointing selectivity (entries 3–5).

This finding confirms the typical acetylene reactivity order aryl-CCH>R_3Si–CCH>alkyl–CCH.[16a] Also with the fluoro substituted **2b**, the Pd-complex **1b** showed the highest activity by guaranteeing the formation of **4bc** in >98% yield and 15:1 hetero- versus homocoupling selectivity.

The practical usefulness of the protocol was further stressed by running the coupling between **2a** and **3b** in the presence of decreasing catalyst loading (Table 2, entries 6–9). In particular, **4b** was isolated in satisfactory yield (72%) and in excellent chemoselectivity (>50:1), even when the palladium content was dropped to 0.1 mmol%.

Haloarenes bearing electron-withdrawing groups are generally classified as 'activated' halo derivatives for cross-coupling procedures, the oxidative addition of the [Pd(0)] into the C–X band being more favoured (Scheme 3).[1d]

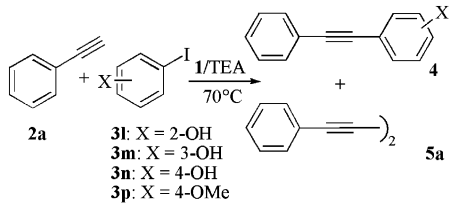
On the other hand, electron-rich aryl halides show a remarkably diminished reactivity leading to minimal conversions and requiring harsher experimental conditions to give satisfactory results. However, in demonstrating the



Scheme 3. Pictorial mechanism representation of the heterogeneously catalysed Sonogashira reaction.

applicability of this protocol to electron-rich aryl halides, we reacted 2-iodophenol (**3l**) with **2a** in the presence of both **1a** and **1b**. Noticeably, the desired cross-coupled product **4al** was isolated in excellent yields (up to 98%) and good selectivity (up to 9:1, entry 2, Table 3).

Table 3. Influence of electron-rich iodophenols in the chemoselectivity of the heterogeneously catalysed Pd-coupling[a]



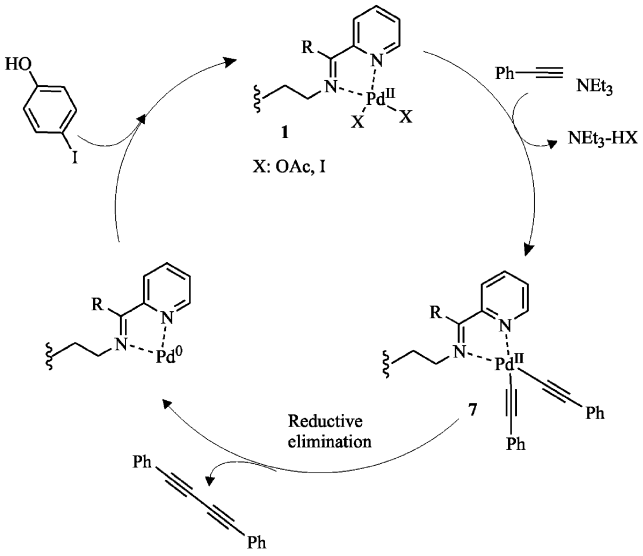
Entry	Cat./[%]	3/[%]	Conv. [%][b]	4:5a ratio[c]
1	**1a**	**3l**/200	93	1.2:1
2	**1b**	**3l**/200	>98 (87%)[d]	9:1
3	**1c**	**3l**/200	82	1:2.4
4	**1b**	**3m**/200	>98	1:1.2
5	**1b**	**3n**/200	86	1:50
6	**1b**	**3n**/100	60	1:50
7	**1b**	**3n**/50	35	1:50
8	**1b**	**3n**/20	>10	1:50
9	**1b**	**3p**/200	—[e]	—[e]

[a] All the reactions were carried out under air with reaction time 12 h.
[b] Based on the **2a** conversion. Determined by GC-analysis with undecane as the internal standard.
[c] Determined by GC-analysis on the reaction crude.
[d] Isolated yield.
[e] No reaction.

However, a gradual and unexpected inversion in chemoselectivity toward the formation of the diyne **5a** was observed, with 3-iodophenol (**3m**) and 4-iodophenol (**3n**) (entries 4–5). In particular, 1,4-diphenylbutadiyne **5a** was the only product obtained in quantitative isolated yield with **3n**. In this case in fact, the phenol-unit was not found to be part of the final product and partially recovered from the final crude. No other products from this reaction partner (e.g., dehalogenated phenol) could be detected.

Even if we do not have a clear mechanism picture yet, we hypothesise that the lower aptitude of electron-rich aryl halides towards metallo-oxidative insertions, in combination with the decelerating effect[28] of Pd-alkyne coordination (depicted in 'the green zone' of Scheme 3)[29] to the initial cross-coupling step could be co-responsible for this unexpected chemoselectivity. Probably, under the present reaction conditions, **3n** simply acts as the reoxidant of Pd(0) to Pd(II)[30–32] and the presence of dialkynylpalladium(II) intermediates (**7**) can be postulated during the reaction mechanism (Scheme 4).[3b,28f]

To gain some insights into this hypothesis we carried out dimerisation reactions of **2a** in the presence of variable amount of **3n** (entries 6–8). An excess of iodophenol proved to be crucial in order to guarantee a satisfactory catalytic turnover, as a matter of fact, by using 20 mol% of **3n** the homocoupling worked but only sluggishly. Moreover, the homocoupling reaction failed when iodoanisole (**3p**) was employed (Table 3, entry 9) and this finding strongly supports the key role of **3n** in restoring the catalytically



Scheme 4. Hypothesis of reaction mechanism for the heterogeneous Pd-catalysed homocoupling of PhCCH.

active Pd species by oxidising the intermediate Pd(0) adduct to the catalytically active Pd(II).

To the best of our knowledge, this represents the first example of heterogeneously catalysed alkyne dimerisation with an unprecedented dependence of the reaction selectivity (cross vs homo) on the organo halide partner. On the other hand, by using 2-iodophenol (**3l**) we suggest that the proximity of the two arene substituents may favour the classic Sonogashira pathway via coordinating interactions between the phenol/ate moiety of **3l** and the palladium during the dissociation of the coordinated alkyne as well as the oxidative insertion.

2.3. Mechanistic investigation

A kinetic analysis of the reaction has been carried out at 55, 65 and at 72 °C. At the highest temperature, the reaction proceeds smoothly, and the data fit well with a second order process (Fig. 2). This is true of both the heterogeneous process with **1a** as well as the homogeneous analogue **1d**

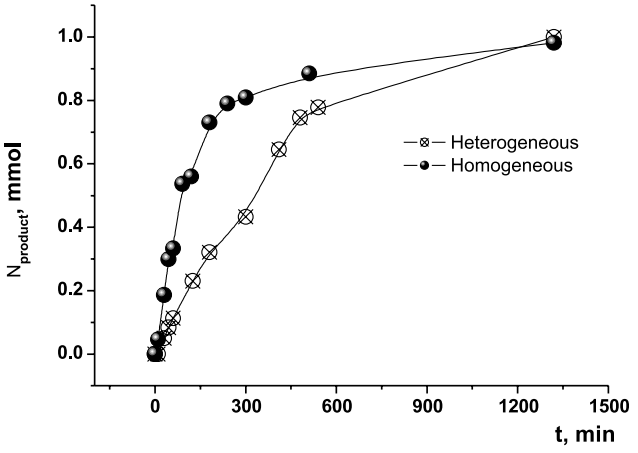


Figure 2. Kinetic profile of the reaction between 2 mmol **3c**, 1 mmol PhCCH in the presence of 3 mmol Et_3N; $T=345$ K; 10 mg **1a**.

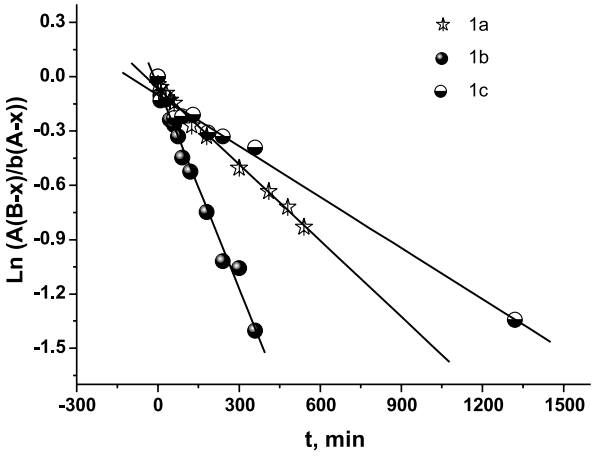


Figure 3. Kinetic profile of the reaction between 2 mmol **3c**, 1 mmol PhCCH in the presence of 3 mmol Et_3N; $T=345$ K; 10 mg **1**. Good fit to second order kinetics is obtained for each of the catalysts **1a–c**.

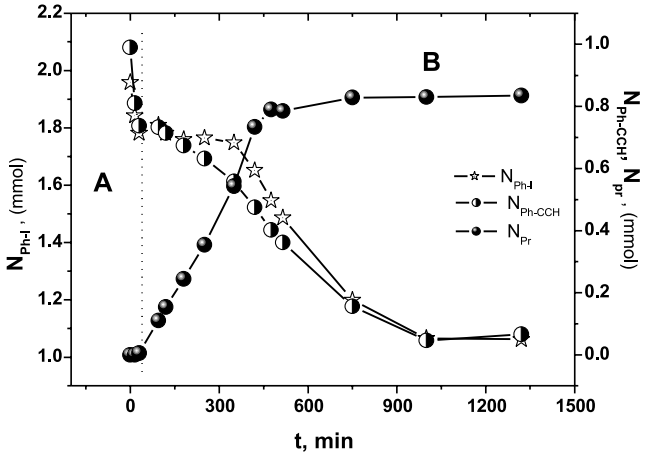


Figure 4. Kinetic profile of the reaction between 2 mmol **3c** and 1 mmol PhCCH in the presence of 3 mmol Et_3N; $T=338$ K; 10 mg **1a**.

(Fig. 3). In this case, there is no significant influence of adsorbency or diffusion to or from the catalyst surface.

In contrast, the behaviour noted for the 55 and 65 °C runs is quite different, and here the reaction is dominated by the adsorption of reagents. From Figure 4, we can see that there is a rapid adsorption of both reagents. Table 1 quantifies this phenomenon for catalysts **1a**, **1b** and **1c**. As can be seen, the quantities adsorbed are substantial (and correspond to more than the pore volume of the catalyst) below 70 °C, and are similar for all three catalysts. Likewise, there is a slight preponderance of the acetylene partner in this surface layer. This indicates that there is a multi-layer adsorption inside the pores of the catalyst and on the external surface, leading to an increase in the hydrodynamic radius of the catalyst particles. Such a phenomenon is well established in fluid dynamics, and a relatively thick surface layer might be expected for the viscous, solvent-free systems in question here. The presence of such a surface-associated layer is reminiscent of the concept of supported phase catalysis.[33]

The reduction in quantity adsorbed as temperature increases is marked and consistent with the switch in kinetic behaviour noted, with diffusion being the dominant factor at lower temperatures, while the catalytic process dominates the kinetics at the highest temperature.

The fact that the quantities adsorbed are similar for the three different catalysts indicate that it is the silica itself, and not the catalytic site, which is the overriding factor in the adsorbency behaviour. Such a dramatic change in adsorbency with temperature might be expected, given the relatively weak forces at play.

The kinetics observed for the lower temperature systems reflect this change in adsorbency. After the initial adsorption, there is a lag phase of ca. 30 min where no product is observed in the liquid phase. It is likely that product is indeed forming but is retained in the supported phase. After this lag phase, there is a steady depletion of the acetylene from the liquid phase into the supported phase and a concomitant release of the products into solution. The iodoarene concentration scarcely drops during this period, but more rapidly afterwards as the compositions of the liquid phase and the supported phase change. The order of reaction during this period is close to zero (Table 4). This decrease in reaction order could be due to the saturation of catalytic sites with reagent due to the adsorption of several layers of reagents.

It is interesting to note that the kinetic parameters of the reaction change dramatically with temperature in the same way as the adsorbency changes. This kinetic data therefore, is strong evidence for the catalysis taking place at the catalyst surface.

Table 4. Summary of adsorption experiments

Catalyst	T, °C	Δ^{ads}_{PhCCH}			Δ^{ads}_{PhI}			n_{pr}	k_2
		mmol/g	g	ml	mmol/g	g	ml		
1a	55	20	2.04	2.2	16	3.0	1.5	0.2	—
	62	12	1.2	1.3	10	1.88	0.98	0.5	—
	70	0	0	0	0	0	0	2	$1.4\ 10^{-3}$
1b	55	20	2.04	2.2	17	3.20	1.67	0	—
	62	18	1.83	1.97	13	2.44	1.27	0	—
	70	0	0	0	0	0	0	2	$0.9\ 10^{-3}$
1c	55	21	2.14	2.30	18	3.38	1.76	0.34	
	62	16	1.63	1.75	10	1.88	0.98	0.2	—
	70	0	0	0	0	0	0	2	$3.7\ 10^{-3}$

n_{pr}, the order of reaction calculated by product; Δ^{ads}_{PhCCH}, amount of PhCCH adsorbed on the surface; Δ^{ads}_{PhI}, amount of PhI adsorbed on the surface; measurements made at the start of the reaction as described in Section 3.6.

2.4. Heterogeneous activity and catalyst reuse

In order to ascertain whether the catalysts were behaving in a truly heterogeneous manner, we repeated several reactions and filtered the catalysts under optimal reaction conditions, and allowed the reactions to continue in the absence of catalyst. No additional conversion was seen in any case after filtration of the catalyst (the rate of a non-catalysed reaction was also determined to be zero. Furthermore, small fractions of liquid were removed from reactions, which were underway, rapidly filtered and added to a fresh mixture of different coupling partners and base. In these cases, the fresh mixture did not react, indicating that no catalytic activity could be ascribed to the liquid aliquot from the first reaction. On the other hand, the first reaction continued, indicating that the solid catalyst remained active (see Section 4).

Again, we turn our attention to the reusability of the present Pd-supported catalysts. To this purpose, the Sonogashira cross-coupling between **2a** and **3c** was used as the model reaction. Despite the high catalytic activity of **1b** (0.1 mol%) in the first and second reuse (conv.$>$99%, after 5 and 24 h, respectively), a partial loss of catalytic activity was observed in the third catalytic cycle, requiring longer reaction times for complete conversions and furnishing **4c** in 53% after 24 h.

3. Conclusion

In summary, this work gives evidence that readily synthesisable palladium complexes supported on organically modified mesoporous silica can be advantageously employed to promoted solvent, phosphane and copper-free Sonogashira reactions as well as homocoupling of acetylenes. This class of heterogeneous Pd-catalysts allows for a rapid access to a wide range of compounds with a remarkable chemoselectivity that proved to be also dependent on the organo-halide employed in the C–C bond forming reaction. To the best of our knowledge, this represents the first example of catalytic acetylenic coupling mediated by immobilised Pd-complexes. The kinetic behaviour of the catalysts is complex and very temperature dependent, with lower temperatures being dominated by adsorption/desoprtion processes, and zero order kinetics within an adsorbed layer. Higher temperatures give more 'normal' second order kinetic profiles, which correlate well with the adsorption behaviour. Finally, both stability and reusability of the catalytic system were addressed and proved, stressing the 'greenness' of the present C–C coupling strategy.

4. Experimental

4.1. General

Chemicals were obtained from Aldrich, Merck and Lancaster and used as received. The amount of Pd loaded on the surface of the silica was determined by atomic absorption spectroscopy. The thermal analysis was performed using a Netzsch 409 STA with a temperature ramp rate of 10 °C/min. The intermediates for the synthesis of the catalysts were analysed (C–H and C═N bonds) by DRIFTS by using a Bruker Equinox 55 FTIR spectrometer using an environmental diffuse reflectance cell. The binding energy of palladium in the catalysts was determined by XPS using a Kratos AXIS HSi instrument equipped with a charge neutraliser and a Mg Kα X-ray source. The pore size distribution and BET surface area were determined by using a Beckman Coulter SA 3100 porosimeter with dinitrogen as an adsorbate. Pd loadings were carried out on samples by acid digestion followed by ICP analysis at the university of Newcastle.

4.2. Materials and methods

All the reactions were carried out under air. All the commercially available reagents were used without further purification.

4.3. Synthesis of the catalysts

Pd-catalysts **1a–b**. The procedures for the grafting of ligands on the silica surface and for the preparation of the Pd-supported catalysts have been already described in Ref. 18.

Pd-catalyst **1c**. One gram of 3-AMP-silica were treated with 0.5 mmol (145 mg) of 2-PPh_2-benzaldehyde in 50 mL of absolute EtOH under air. The mixture was stirred under reflux for 18 h. Then, the pale yellow solid was recovered by filtration, washed with EtOH and then dried under air at 90 °C overnight. DRIFTS (KBr) ν: 1647 cm^{-1}; ^{31}P MAS NMR (162 MHz): δ −9.0 (br, $ArPPh_2$), 36.6 (br, $ArP(O)Ph_2$). The immobilised Pd-complex **1c** was synthesised by stirring at rt for 16 h, 1 g of organically modified silica and $Pd(OAc)_2$ (112 mg, 0.5 mmol) in acetone (25 mL). The recovered brown solid was conditioned for a total of 30 h (3×3 h each refluxing in toluene, EtOH, CH_3CN and 1×3 h in xylene at 130 °C) in order to remove any physisorbed palladium. [Pd] loading: 0.11 mmol/g; BET surface area: 235 m^2/g, DRIFTS (KBr) ν: 1605 cm^{-1}.

4.4. General procedure for the heterogeneous Pd-catalysed Sonogashira reaction

A two-necked flask equipped with a condenser was charged with the alkyne (**2**, 1 mmol), TEA (3 mmol, 418 μL), undecane (1 mmol, 110 μL) and the desired iodoarene (2 mmol). The mixture was pre-heated to 70 °C into an oil bath when the Pd-supported catalyst ([Pd] 1 mol%) was added. The reaction was kept stirred overnight at 70 °C when the colour of the solution gradually turned to deep red. After cooling, the catalyst was easily recovered by filtration and subsequently washed with MeOH and gently dried under vacuum (70 °C) before reusing. The filtrate was analysed by GC and the use of internal standard technique allows the reaction yields to be determined. All the Sonogashira and dimerisation products were characterised by GC–MS analysis and compared with reported analytical data.[34] [GC–MS: **4a** M^+178; **4b** M^+196; **4c** M^+196; **4d** M^+196; **4e** M^+220 (205, $-CH_3$, 177, $-COCH_3$); **4f** M^+223 (193, 177); **4g** M^+223 (193, 177); **4h** M^+223 (193, 177); **4i** M^+344; **4j** M^+259, 257 (229, 227; 213, 211); **4k** M^+282, 280; **5a** M^+202.] In addition selected examples were

isolated by chromatography-in all cases their isolated yields correlated extremely well with their GC yields.

4.4.1. 2-Fluorodiphenylethyne (4c). Table 1, entry 6: yield 91%; white solid, 45–47 °C (Flash chromatography: *c*-Hex:Et_2O 98:2.) GC–MS: 85 (13), 98 (11), 144 (8), 175 (12), 196 (100). ^{1}H NMR (300 MHz, $CDCl_3$): 7.45–7.55 (m, 3H), 7.18–7.33 (m, 4H), 7.00–7.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 162.9 (d, J=250.5 Hz), 133.5, 131.4, 130.1, 128.6, 128.1, 123.2, 122.5, 115.0, 112.0, 94.5, 82.9.

4.4.2. 4-Fluorodiphenylethyne (4d). Table 1, entry 7: yield 85%; white solid, 108–111 °C (Flash chromatography: *c*-Hex: Et_2O 98:2.) GC–MS: 51 (15), 98 (10), 144 (7), 169 (11), 196 (100). ^{1}H NMR (300 MHz, $CDCl_3$): 7.52–7.60 (m, 4H), 7.34–7.38 (m, 3H), 7.12–7.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 162.8 (d, J=249.8 Hz), 133.7, 131.6, 128.0, 123.1, 119.5, 115.5, 89.1, 88.7.

4.4.3. 2-Hydroxydiphenylethyne (4l). Table 3, entry 2: yield 87%; white solid, 45–48 °C (Flash chromatography: *c*-Hex:Et_2O 90:10.) GC–MS: 82 (10), 165 (50), 194 (100). ^{1}H NMR (300 MHz, $CDCl_3$): 6.88–7.15 (m, 4H), 7.22–7.55 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 156.2, 131.5, 131.4, 130.0, 128.6, 128.1, 122.3, 120.1, 114.9, 109.7, 96.7, 83.1.

4.5. Heterogeneous versus homogeneous catalysis

A model Sonogashira reaction between **2a** and **3b** was carried out in the presence of **1a** ([Pd]: 0.26 mmol/g, 1 mol%]. After 2 h stirring at 70 °C the catalyst was rapidly filtered off (hot filtration technique) and the reaction mixture (10% conversion at that time) was allowed to stir at 70 °C overnight. After 18 h the monitoring of the reaction outcome provided a conversion of 10%. To test the activity of the catalyst that was removed, fresh cross-coupling partners (**2a**, **3b**) were added to a TEA solution of catalyst. After 16 h at 70 °C the conversion in **4b** was found to be >98%.

4.6. Kinetic study

A typical GC kinetics experiment was performed as reported for the general Sonogashira procedure using undecane as the internal standard. All reactions were carried out at 70±1 °C. Aliquots (20 μL) were withdrawn by syringe at regular period of time, diluted with Et_2O, filtered and rapidly analysed by GC to determine the actual reaction conversion.

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Pd/C-mediated coupling of aryl halides with terminal alkynes in water☆

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Abstract—2-Aminoethanol facilitated the alkynylation of aryl halides (Sonogashira reaction) under palladium/charcoal–copper catalysis in water affording a mild and practical method for the synthesis of arylalkynes. A variety of terminal alkynes were coupled with aryl iodides and bromides possessing no hydrophilic functional groups to give the coupled products in good to excellent yields.

1. Introduction

Transition metal-catalyzed cross-coupling reactions rank among the most important processes for constructing new carbon–carbon bonds.[1] Over the past 25 years, palladium-catalyzed coupling of terminal alkynes with the aryl halide (Sonogashira coupling)[2a] has become a most attractive and powerful tool for C(sp^2)–C(sp) bond forming reaction.[2b] This reaction can be applied to the substrates carrying various functional groups (thereby eliminating the protection–deprotection sequences as well as functional group transformations) and has found wide application in the synthesis of valuable compounds such as natural products and drugs including the construction of complex enediyne antibiotics.[2c–e] The reaction, in general, is carried out with a large excess of a secondary or tertiary alkyl amine as a solvent/co-solvent and therefore, application of this protocol especially to large scale preparations often leads to environmental pollution due to the volatile nature of these amines.[3a] Moreover, the use of copper salts often led to Glaser-type homocoupling of the terminal alkyne.[3b–f] Nevertheless, this palladium-catalyzed reaction has been investigated extensively to improve the reaction conditions[4] and an impressive variety of modifications have been reported thus far. This includes the use of a variety of additives,[5] solvents,[6] phase-transfer catalysts,[7] new catalysts system[8] including copper-free versions,[9] biphasic versions,[10] use of hydrogen atmosphere to suppress the homocoupling of the terminal alkynes,[11] polymer supported Pd-triazine complex,[12a] solid supported Pd-catalyst[12b] etc. In addition to the copper salts use of other metal co-catalysts such as zinc, tin, boron or aluminium has also been reported.[13a–c] Very recently microwave mediated transition-metal free Sonogashira coupling has been reported.[14]

The use of aqueous media in palladium-catalyzed reactions have become popular[15] because water based synthetic processes are inherently safer (water is non-toxic and non-flammable) as well as inexpensive. Moreover, it does not require dry solvents and products can easily be isolated by extraction, which greatly facilitates the operation. Thus the use of water in palladium-catalyzed reactions represents one of the most economically and environmentally viable options for many organic transformation. Its use is particularly more beneficial in the cross coupling reaction of peptides (e.g., 4-IC_6H_5CONHR, where R represents a peptide chain) with alkyne ligands for the construction of biomolecule-based systems where poor solubility of the reactants often prevent the reaction to be performed in common organic solvents.[15n] Thus, the use of water-soluble catalysts[15g] and water-soluble phosphine ligands, for example, sulfonated phosphines[15f] has been investigated. The initial account of palladium-catalyzed alkylations of small molecules in aqueous media was reported by Casalnuovo and Calabrese in 1990.[15g] Since then several examples of cross-coupling reactions have been demonstrated in aqueous media.[15l–m] Generally these reactions were found to be effective with aryl iodides and activated aryl bromides, typically at high temperature. While a variety of Pd(II) complexes in combination with triarylphosphines, sterically demanding trialkylphosphines, sterically demanding *N*-heterocyclic carbenes or ligands that form

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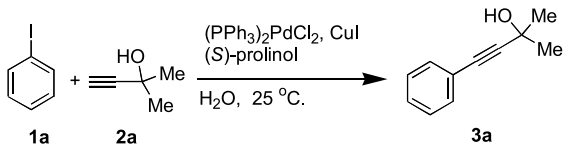
palladacycles have been successfully employed for the coupling of aryl halides with terminal alkynes in common organic solvents at room temperature, the use of Pd/C–CuI–PPh_3 as catalyst system[16] for efficient Sonogashira coupling has not been exploited well until recently.[17] When compared with the most frequently used expensive palladium catalysts [e.g., $Pd(PPh_3)_4$, $(PPh_3)_2PdCl_2$, $Pd(OAc)_2/PPh_3$ etc.], Pd/C-based methods have an economic advantage and hence remain attractive in large or industrial scale applications. Nevertheless, most of the aqueous Pd-catalyzed reactions are usually carried out in an aqueous-organic media and a co-solvent, such as acetonitrile[15f] or DME.[17g] Due to our continuing interest in the palladium-catalyzed reactions[18] we have recently shown that Sonogashira coupling could be carried out in water in the presence of $(PPh_3)_2PdCl_2$ and CuI at 25 °C affording a high yield of arylalkyne (Scheme 1).[18c] Subsequently, we have developed a mild and efficient method for the synthesis of 2-substituted benzo[*b*]furans via Pd/C-catalyzed C–C bond forming reaction in water.[19a] These procedures, however, involve the use of an expensive and chiral reagent, that is, (*S*)-prolinol. Moreover, for our ongoing drug discovery program on the development of various alkynyl substituted heterocyclic structures[19b] we required an efficient and practical method for the synthesis of arylalkynes, especially 3-aryl substituted alkynols.[19c] Accordingly, we now wish to report a general Pd/C catalyzed synthesis of arylalkynes using 2-aminoethanol[20a–b] as a cheaper amine base in water.[20c] Since arylalkynes are useful intermediates for the synthesis[21] of various biologically active compounds as well as drugs, for example, HMG-CoA reductase inhibitor Atrovastatin lactone[21c] or COX-2 inhibitor rofecoxib[21d] (Fig. 1) for the treatment of hypercholesterolemia and inflammatory diseases, respectively, we envisioned that this process could offer an increased scope of aryl and heteroaromatic alkyne formation to the researchers working especially in the field of medicinal and process chemistry.

2. Results and discussion

Our initial effort was devoted to the selection of a suitable amine base for efficient Sonogashira coupling in water. We therefore, studied the influence of amine bases possessing hydroxyl group on the coupling of iodobenzene (**1a**) with 2-methylbut-3-yn-2-ol (**2a**) in the presence of Pd/C–PPh_3–CuI as a catalyst system in water (Table 1). We reasoned that due to the presence of hydrophilic group these amines would exhibit better water miscibility as well as lower volatility than triehylamine and would facilitate the coupling reaction in water. Accordingly, the model coupling reaction of **1a** with **2a** was performed in the presence of few hydroxy amines chosen based on their physical properties as well as triethylamine. Triethylamine, known to give high yields of coupled product when the Sonogashira reaction is carried out in an organic solvent (e.g., THF, dioxane, acetonitrile or DMF), afforded only low yield of product in our case (Entry 1, Table 1). However, an essential improvement in yield was achieved when (*S*)-prolinol (Entry 2, Table 1) or 2-aminoethanol (Entry 3, Table 1) was used in place of triethylamine. The halide **1a** was consumed completely after 9 h in both cases and the coupled product **3a** was isolated in 81 and 78% yield, respectively. The use of 4-hydroxypiperidine was also found to be equally effective (Entry 4, Table 1) as **3a** was isolated in 76% yield in this case. Nevertheless, we preferred to choose 2-aminoethanol to continue our investigation further because of its lower cost. Although copper-free Sonogashira reaction has been realized using appropriate palladium complexes, no product was detected in the present Pd/C-mediated coupling of **1a** with **2a** in the absence of CuI (Entry 5, Table 1).

The absence of PPh_3 also retarded the coupling reaction significantly under the conditions studied. The reaction was carried out at 80 °C as decrease in temperature afforded low yield (34%) of product even after 24 h (Entry 6, Table 1). No coupled product was detected when the reaction was



Scheme 1. $(PPh_3)_2PdCl_2$–CuI catalyzed reaction of iodobenzene with terminal alkyne **2a** in water.

Table 1. Effect of amine bases on the Pd/C-mediated coupling reaction of **1a** with **2a** in water[a]

Entry	Base (reaction time)	Temp. (°C)	Yield (%)[b]
1	Et_3N (12 h)	80	59[c]
2	(*S*)-Prolinol (12 h)	80	81
3	2-Aminoethanol (9 h)	80	78
4	4-Hydroxypiperidine (9 h)	80	76
5	2-Aminoethanol (9 h)	80[d]	n.d.[e]
6	2-Aminoethanol (24 h)	60	34

[a] Reactions were carried out by using **1a** (1.0 equiv), **2a** (1.5 equiv), Pd/C (0.04 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv), base (3 equiv) in water.
[b] Isolated yields.
[c] Three equivalents of Et_3N was used.
[d] The reaction was performed in the absence of CuI.
[e] n.d., not detected.

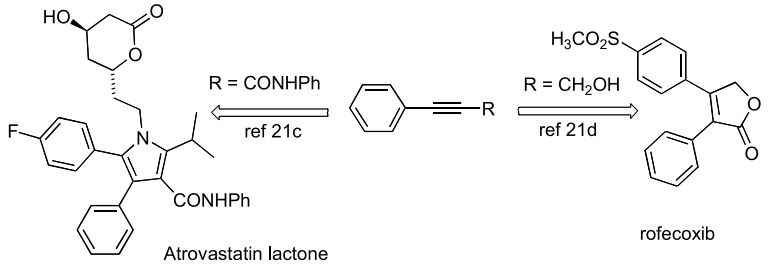


Figure 1. Uses of arylalkynes in drug synthesis.

performed at room temperature even for 2 days. These observations clearly indicate in situ generation of a new Pd(0) species from Pd/C–PPh_3 at higher temperature, which actually catalyzed the cross-coupling reaction. Notably, the present coupling reaction in water was found to be selective as no significant dimerization of terminal alkynes was observed during the course of our reaction.

Having optimized the present methodology, we chose to investigate the coupling of a variety of terminal alkynes with aryl halides in water. When aryl halide **1** was treated with 1–2 equiv of terminal alkyne (**2**, R = alkyl, hydroxyalkyl, aryl etc.) in water in the presence of 10% Pd/C (0.04 equiv), PPh_3 (0.20 equiv), CuI (0.05 equiv) and 2-aminoethanol (3 equiv) under nitrogen, aryl alkynes **3** were obtained as desired products in good to excellent yields. Results of this study are summarized in Table 2.

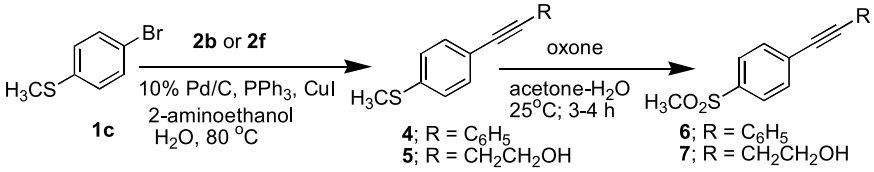
In general we have chosen aryl halides that do not possess hydrophilic functional groups. This clearly ruled out the possibility of effective Sonogashira coupling aided by the enhanced solubility of the aryl halides in water in the presence of a base. Thus, aryl iodides/bromides were reacted with terminal alkynes under the present reaction conditions (Table 2). Remarkably, the base sensitive ester group was not affected in this aqueous Sonogashira coupling (Entry 2, Table 2). Aryl iodides are known to react readily under the normal Sonogashira coupling condition and were found to be the same in the present case. However, aryl bromides are available in far greater number and their use more economical. We thus employed an array of commercially available aryl bromides bearing a variety of substituents (Entries 3–10, Table 2), for example, electron donating (Me, SMe) or withdrawing groups ($COCH_3$, CHO) for the coupling reactions. We were particularly interested in the synthesis of 4-acyl substituted arylalkynes as this moiety was found to be an integral part of biologically active compound such as human farnesyltransferase inhibitor 4-[1-hydroxy-3-(3′-methoxy-5-pentanoyl-biphenyl-2-yl)-1-(3-methyl-3*H*-imidazol-4-yl)-prop-2-ynyl]-benzonitrile.[21f] Like aryl iodides, all the bromides used were found to be equally effective in terms of yields and the respective substituents were well tolerated in this coupling reaction. Yields were not affected drastically due to the presence of either electron-donating (Entries 3–5 and 11, 12, Table 2) or withdrawing groups (Entries 6–10, Table 2). Notably, aryl bromides were found to be less reactive in the solventless, microwave-assisted Sonogashira coupling using Pd–CuI–PPh_3/KF–Al_2O_3 as catalyst system.[12b] Their reactivity was also found to be low in *t*-Bu-Amphos/$Pd(OAc)_2$ mediated Sonogashira coupling in water[15k] or dependent on the choice of the base in $(PPh_3)_4$Pd–CuI mediated coupling reaction in water.[20c] Thus we have achieved similar levels of reactivity with aryl iodides and bromides towards the palladium-mediated alkynylation of arenes that have been reported in organic solvents.[18b] However, chlorobenzene failed to react with terminal alkynes when employed under the present reaction conditions.

While most of the terminal alkynes used for the present coupling reaction in water alone were hydrophilic in nature, the use of at least one hydrophobic alkyne, for example, phenyl acetylene was examined and was found to afford good yield of products (Entries 2 and 10, Table 2). The overall process displays generality as well as good functional group tolerability. Base sensitive functional groups like ester, ketone and aldehyde group is well tolerated under the condition studied and the reaction is relatively insensitive to the electronic characteristics of a substitutent.

Of the several examples shown in Table 2, compound **3k** is the precursor of (*S*)-2-(6-methoxy-2-naphthyl)propanoic acid, a non-steroidal anti-inflammatory agent commonly known as naproxen, used for the treatment of inflammatory diseases.[21a] However, its preparation via conventional Sonogashira coupling[21a] was incompatible to the industrial production. Our procedure reported herein should find application for the synthesis of **3k** in large scale thereby in the preparation of various types of 2-arylpropenoic acids. Similarly, compound **3e** has been utilized for the synthesis of incrustoporin [3-(*p*-tolyl)-5-ethyl-5*H*-furan-2-one, an antifungal antibiotic isolated from *Incrustoporia carneola*] and was prepared via a multi-step procedure.[21g] We have also investigated the Pd/C-mediated coupling-cyclization of *o*-iodophenol with phenylacetylene in the presence of 2-aminoethanol where effective Sonogashira coupling was favored due to the enhanced solubility of the aryl halides in water in the presence of a base to produce a 75% yield of 2-phenyl benzo[*b*]furan.[22] To demonstrate the applicability of this process in the large scale preparation of aryl alkynes we prepared compounds **6** and **7**[23] on 5 g scale using the conditions used for the synthesis of **3c** (Table 1), as a key synthetic step (Scheme 2).

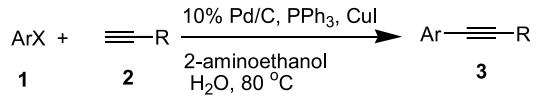
3. Conclusion

In conclusion, we have described a general and practical procedure for the synthesis of a variety of arylalkynes via Pd/C-mediated cross-coupling in water. Application and scope of the methodology along with its limitations has also been described. The process is free from the use of expensive palladium complexes, hazardous as well as expensive organic co-solvents and volatile amine bases. The methodology is equally effective for the Sonogashira coupling of aryl iodides and bromides. The reaction proceeds well with activated and electron rich aryl



Scheme 2. Synthesis of arylalkynes **6** and **7**.

Table 2. Pd/C catalyzed synthesis of aryl alkynes in aqueous media[a]



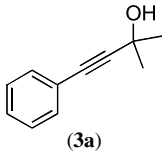
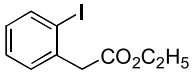
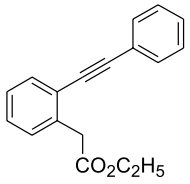
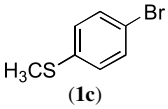
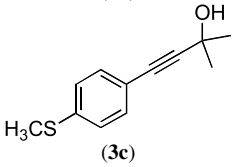
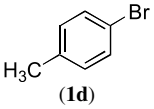
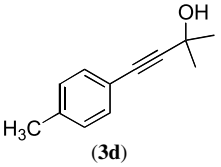
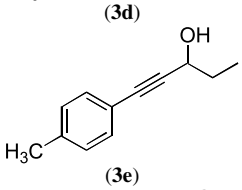
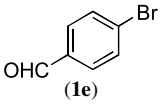
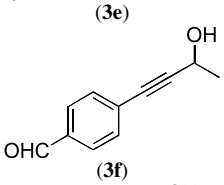
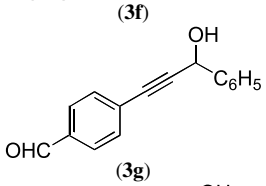
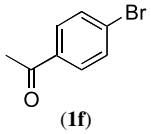
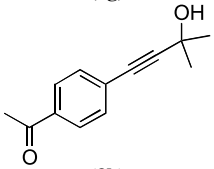
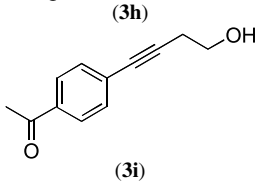
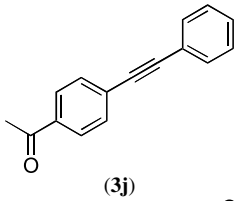
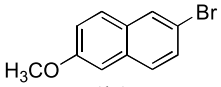
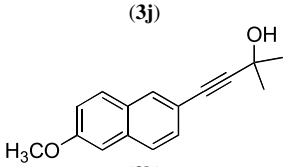
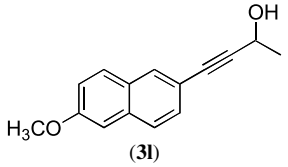
Entry	Substrate (**1**); ArX=	Alkynes (**2**); R=	Reaction time (h)[b]	Products[c] (**3**)	Yield (%)[d]
1	 (**1a**)	$C(CH_3)_2OH$ **2a**	9	 (**3a**)	78
2	 (**1b**)	C_6H_5 **2b**	15	 (**3b**)	93
3	 (**1c**)	**2a**	8	 (**3c**)	77
4	 (**1d**)	**2a**	9	 (**3d**)	84
5	(**1d**)	$CH(OH)CH_2CH_3$ **2c**	6	 (**3e**)	77
6	 (**1e**)	$CH(OH)CH_3$ **2d**	10	 (**3f**)	85
7	(**1e**)	$CH(OH)C_6H_5$ **2e**	9	 (**3g**)	59
8	 (**1f**)	**2a**	9	 (**3h**)	69
9	(**1f**)	CH_2CH_2OH **2f**	5.5	 (**3i**)	85

Table 2 (*continued*)

Entry	Substrate (**1**); ArX=	Alkynes (**2**); R=	Reaction time (h)[b]	Products[c] (**3**)	Yield (%)[d]
10	(**1f**)	**2b**	5	 (**3j**)	72
11	 (**1g**)	**2a**	15	 (**3k**)	80[e]
12	(**1g**)	**2c**	15	 (**3l**)	82[e]

[a] All reactions were carried out by using **1** (1.0 equiv), **2** (1.5 equiv), 1:5:1 ratio of Pd/C:PPh_3:CuI, 2-aminoethanol (3 equiv) in water.
[b] The reaction was monitored by TLC.
[c] Identified by ^1H NMR, ^{13}C NMR, IR, MS.
[d] Isolated yields.
[e] 1:1 acetonitrile–H_2O was used.

bromides. Both hydrophobic and hydrophilic terminal alkynes reacted well and no significant side reaction such as dimerization of terminal alkynes was observed during the course of our reaction. As far as we know, in spite of a large number reports on useful and effective modifications of Sonogashira reaction, no successful examples of Pd/C-mediated synthesis of arylalkynes in water have been reported. Due to the operational simplicity as well as easy isolation and purification procedures for the products the methodology appears to be a useful alternative to the conventional Sonogashira reaction. The process is also expected to be useful in the construction of novel biomolecule-based systems via transition metal mediated cross-coupling strategy in water. Current work is focused on extending the scope and generality of this methodology.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed in dried glassware under a nitrogen atmosphere. All the solvents used were commercially available and distilled before use. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (SRL 230–400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solutions on Varian Gemini 200 MHz spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta=0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in Hertz. Infrared spectra were recorded on a Perkin-Elmer 1650 FT-IR spectrometer. UV spectra were recorded on Shimadzu UV 2100S UV–vis recording spectrophotometer. Melting points were determined using a Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data was generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. Purity was determined by HPLC (AGIL-AUTO) using the condition specified in each case: column, mobile phase (range used), flow rate (range used), detection wavelength, retention times. Microanalyses were performed using Perkin-Elmer 2400 C H N S/O analyzer. All the aryl halides and terminal alkynes used are commercially available.

4.1.1. Synthesis of arylalkynes: a typical procedure for the synthesis of 4-(3-hydroxybut-1-ynyl)benzaldehyde (3f). A mixture of *p*-bromobenzaldehyde (0.5 g, 2.7 mmol), 10% Pd/C (0.11 g, 0.103 mmol), PPh_3 (0.14 g, 0.53 mmol), CuI (0.025 g, 0.13 mmol) and 2-aminoethanol (0.48 g, 8 mmol) in H_2O (10 mL) was stirred at 25 °C for 30 min under nitrogen. To this was added butyn-2-ol (0.2 g, 4.0 mmol) slowly and the mixture was then stirred at 80 °C for 10 h. The mixture was cooled to room temperature, diluted with EtOAc (60 mL) and filtered through Celite. The filtrate was collected, washed with cold water (2×50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by column chromatography (hexane–EtOAc) to afford the desired product as yellow oil (85% yield); ^1H NMR (200 MHz, $CDCl_3$) δ 10.0 (s, 1H, CHO), 7.82 (d, $J=$ 8.3 Hz, 2H), 7.56 (d, $J=7.9$ Hz, 2H), 2.29 (q, $J=7.5$ Hz, 1H, CH), 1.75 (s, 1H exchangeable, OH), 1.58 (d, $J=$

6.6 Hz, 3H, CH_3); IR (KBr, cm^{-1}) 3385, 1700 (CHO); MS (CI, *i*-Butane) 175 ($M^+ + 1$, 100%), 157 ($M^+ - 17$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.7 (CHO), 135.3, 132.0 (2C), 129.4 (2C), 128.9, 95.2 (C_{sp}), 82.8 (C_{sp}), 58.5 (CH), 23.7 (CH_3); HPLC 98.9%, Inertsil ODS 3V (250×4.6 mm) mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 280 nm, retention time 9.02 min; found C, 75.79; H, 5.80; $C_{11}H_{10}O_2$ requires C, 75.84; H, 5.79%.

4.1.2. 2-Methyl-4-phenyl-3-butyn-2-ol[18c] (3a) Light yellow solid; yield 78%; DSC 51.8 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.33–7.27 (m, 3H), 1.94 (br s, exchangeable with D_2O, 1H, OH), 1.64 (s, 6H, $2CH_3$); IR (KBr, cm^{-1}): 3357, 2982; MS (CI, *i*-Butane): 143 ($M^+ - 17$, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.5 (2C), 128.1 (2C), 128.0, 122.7, 93.9 (C_{sp}), 81.9 (C_{sp}), 65.4 (CMe_2OH), 31.3 (2C, CH_3); HPLC 99.60%, Inertsil ODS 3V (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 240 nm, 14.6 min.

4.1.3. (2-Phenylethynylphenyl)acetic acid ethyl ester (3b). Low melting solid; yield 93%; ^1H NMR (200 MHz, $CDCl_3$) δ 7.57–7.50 (m, 2H), 7.38–7.25 (m, 7H), 4.16 (q, $J_1=14.1$ Hz, $J_2=7.1$ Hz, 2H), 3.90 (s, 2H, CH_2), 1.22 (t, $J=3.7$, 3.3 Hz, 3H, CH_3); IR (KBr, cm^{-1}): 2215 (w, –C≡C–), 1735 (C=O); MS (CI, *i*-Butane) 265 ($M^+ + 1$, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2 (C=O), 136.4, 131.9, 131.5 (2C), 129.8, 128.5, 128.3 (2C), 127.1, 126.5, 123.5, 123.3, 93.8 (C_{sp}), 87.4 (C_{sp}), 60.8 (CMe_2OH), 40.2 (CH_2), 14.1 (CH_3); found C, 81.58; H, 6.18; $C_{18}H_{16}O_2$ requires C, 81.79; H, 6.10%.

4.1.4. 2-Methyl-4-(4-methylsulfanylphenyl)-3-butyn-2-ol[24a] (3c) Yellow solid; yield 77%; DSC 71.20 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, $J=8.3$ Hz, 2H), 7.16 (d, $J=8.3$ Hz, 2H), 2.48 (s, 3H, SCH_3), 2.03 (br s, 1H, OH), 1.66 (s, 6H, $2CH_3$); IR (KBr, cm^{-1}): 2987; MS (CI, *i*-Butane) 207 (M^+), 189 ($M^+ - 17$,100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.1, 131.8 (2C), 125.7 (2C), 118.9, 93.8 (C_{sp}), 81.7 (C_{sp}), 65.5 (CMe_2OH), 31.4 (2C, CH_3), 15.2 (CH_3); HPLC 99.40%, Inertsil ODS 3V (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 210, retention time 17.9 min.

4.1.5. 2-Methyl-4-(4-methylphenyl)-3-butyn-2-ol[17a] (3d) Yellow liquid; yield 84%; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (d, $J=8.1$ Hz, 2H), 7.19 (d, $J=8.1$ Hz, 2H), 2.34 (s, 3H, CH_3), 1.91 (br s, exchangeable with D_2O, 1H, OH), 1.61 (s, 6H, $2CH_3$); IR (KBr, cm^{-1}): 3356, 2981, 2228 (w, –C≡C–); MS (CI, *i*-Butane) 157 ($M^{+1} - 17$, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 131.4 (2C), 128.9 (2C), 119.6, 93.0 (C_{sp}), 82.1 (C_{sp}), 65.5 (CMe_2OH), 31.4 (2C, CH_3), 21.3 (CH_3); HPLC 99.4%, Inertsil ODS 3V (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 240 nm, retention time 17.6 min.

4.1.6. 1-{4-Methylphenyl}-1-pentyn-3-ol[24b] (3e) Yellow liquid, yield 77%; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (d, $J=8.0$ Hz, 2H), 7.12 (d, $J=8.3$ Hz, 2H), 4.56 (t, $J=5.9$ Hz, 1H, CH), 2.35 (s, 3H, CH_3), 1.82 (m, 2H, CH_2), 1.64 (br s, 1H, OH), 1.08 (t, $J=7.3$ Hz, 3H, CH_3); IR (KBr, cm^{-1}) 3358, 2231 (w, –C≡C–); MS (CI, *i*-Butane) 175 (M^+, 20%), 157 ($M^+ - 17$, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 131.5 (2C), 128.9 (2C), 119.5, 89.3 (C_{sp}), 84.9 (C_{sp}), 64.1 (CH), 30.9 (CH_2), 21.3 (CH_3), 9.4 (CH_3); HPLC 98.18%, Inertsil ODS 3V (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 210 nm, retention time 8.9 min.

4.1.7. 4-{3-Hydroxy-3-phenyl-1-propynyl}-benzaldehyde (3g). Yellow liquid; yield 59%; ^1H NMR (200 MHz, $CDCl_3$) δ 10.00 (s, 1H, CHO), 7.78 (d, $J=15.0$ Hz, 2H), 7.63–7.37 (m, 7H), 5.73 (s, 1H, CH); IR (neat, cm^{-1}) 3414, 1701; MS (CI, *i*-Butane) 237 ($M^+ + 1$, 100%), 219 ($M^+ - 17$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.6 (CHO), 140.2, 135.5, 132.1 (2C), 129.4 (2C), 128.6 (2C), 128.4, 128.2, 126.6 (2C), 92.9 (C_{sp}), 85.3 (C_{sp}), 64.8 (CH); HPLC 94.97%; Hichrom KR100 C18 (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 280 nm, retention time 10.6 min; found C, 81.23; H, 5.15; $C_{16}H_{12}O_2$ requires C, 81.34; H, 5.12%.

4.1.8. 1-[4-(3-Hydroxy-3-methyl-1-butynyl)-phenyl]-1-ethanone[24c–d] (3h) Light brown liquid; yield 69%; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89 (d, $J=8.3$ Hz, 2H), 7.49 (d, $J=8.3$ Hz, 2H), 2.6 (s, 3H, CH_3), 2.18 (br s, exchangeable with D_2O, 1H, OH), 1.64 (s, 6H, $2CH_3$); IR (KBr, cm^{-1}) 3417, 2981, 1681 (C=O); MS (CI, *i*-Butane) 203 (M^+, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.0 (C=O), 136.1, 131.6 (2C), 128.1 (2C), 127.7, 97.3 (C_{sp}), 81.2 (C_{sp}), 65.4 (CMe_2OH), 31.2 (2C, CH_3), 26.5 (CH_3); HPLC 95.10%, Inertsil ODS 3V (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 215 nm, retention time 11.4 min.

4.1.9. 1-[4-(4-Hydroxy-1-butynyl)phenyl]-1-ethanone.[18b,24e] (3i) White solid; yield 85%; DSC 75.47 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, $J=8.3$ Hz, 2H), 7.48 (d, $J=8.4$ Hz, 2H), 2.72 (t, $J=6.4$ Hz, 2H, CH_2), 3.84 (t, $J=6.4$ Hz, 2H, CH_2), 2.59 (s, 3H, CH_3), 1.90 (br s, 1H, OH); IR (KBr, cm^{-1}) 3324, 1680 (C=O); MS (CI, *i*-Butane) 189 ($M^+ + 1$, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.5 (C=O), 135.7, 131.6 (2C), 128.4, 128.1 (2C), 90.5 (C_{sp}), 81.4 (C_{sp}), 60.8 (CH_2OH), 26.4 (CH_3), 23.7 (CH_2); HPLC 99.89%, Inertsil ODS 3V (4.6×250 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 276 nm, retention time 13.1 min.

4.1.10. 1-(4-Phenylethynyl-phenyl)-ethanone.[14,24f] (3j) Off white solid, yield 72%; DSC 99.25 °C (lit.[24f] 96–98 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 7.93 (d, $J=8.5$ Hz, 2H), 7.63–7.52 (m, 5H), 7.36 (t, $J=3.4$ Hz, 2H), 2.61 (s, 3H, CH_3); IR (KBr, cm^{-1}) 2217, 1679 (C=O); MS (CI, *i*-Butane) 221 (M^+, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.2 (C=O), 136.2, 131.7 (2C), 131.6 (2C), 128.8 (2C), 128.4 (2C), 128.2 (2C), 122.6, 92.7 (C_{sp}), 88.6 (C_{sp}), 26.5 (CH_3); HPLC 99.9%, Inertsil ODS 3V (250×4.6 mm), 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 303 nm, 12.5 min.

4.1.11. 4-(6-Methoxy-naphthalen-2-yl)-2-methylbut-3-yn-2-ol[21a] (3k) White solid; yield 80%; mp 118–119 °C (lit.[21a] 119–121 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.65 (d, $J=3.5$ Hz, 1H), 7.67 (d, $J=3.2$ Hz, 1H), 7.42 (d, $J=8.2$ Hz, 1H), 7.20 (s, 1H), 7.10 (d, $J=3.8$ Hz, 1H), 3.90 (s, 3H, OCH_3), 1.90 (br s, 1H, OH), 1.57 (s, 6H, $2CH_3$).

4.1.12. 4-{6-Methoxy-2-naphthyl}-3-butyn-2-ol (3l). White solid; yield 82%; DSC 99.64 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.69 (d, J=3.6 Hz, 1H), 7.66 (d, J=3.0 Hz, 1H), 7.43 (d, J=8.3 Hz, 1H), 7.17 (s, 1H), 7.11 (d, J=3.9 Hz, 1H), 4.80 (q, J=6.3 Hz, 1H, CH), 3.92 (s, 3H, OCH_3), 1.95 (br s, 1H, OH), 1.58 (d, J=6.6 Hz, 3H, CH_3); IR (KBr, cm^{-1}) 3385; MS (CI, *i*-Butane) 227 (M^++1), 209 (M^+−17, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.2, 134.1, 131.3, 129.2, 128.9, 128.3, 126.7, 119.3, 117.4, 105.7, 90.4 (C_{sp}), 84.4 (C_{sp}), 58.8 (OCH_3), 55.2 (CH), 24.4 (CH_3); HPLC 99.93%, Inertsil ODS 3V (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN, 1.0 mL/min, UV 250 nm, retention time 15.5 min; found C, 79.80; H, 6.22; $C_{15}H_{14}O_2$ requires C, 79.62; H, 6.24%.

4.2. Preparation of compound 4 and 5

General procedure. A mixture of *p*-bromothioanisole (5.5 g, 27.0 mmol), 10% Pd/C (1.1 g, 1.03 mmol), PPh_3 (1.4 g, 5.3 mmol), CuI (0.25 g, 1.3 mmol) and 2-aminoethanol (4.8 g, 80.0 mmol) in H_2O (75 mL) was stirred at 25 °C for 30 min under nitrogen. To this was added terminal alkyne **2b** or **2f** (40.0 mmol) slowly and the mixture was then stirred at 80 °C for 8–10 h. The mixture was cooled to room temperature, diluted with EtOAc (200 mL) and filtered through Celite. The filtrate was collected, washed with cold water (2×150 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by crystallization (hexane–EtOAc) to afford the desired product.

4.2.1. 1-(4-Methylsulfanylphenyl)-2-phenylacetylene[24g] (4) Light brown solid, yield 59%; mp 80–82 °C (lit.[24g] 83–84 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.41 (d, J=8.3 Hz, 2H), 7.31–7.20 (m, 5H), 2.49 (s, 3H, SCH_3); IR (neat, cm^{-1}) 1460, 1375; MS (CI, *i*-Butane) 224 (M^+, 100%).

4.2.2. 4-(4-Methylsulfanylphenyl)-3-butyn-1-ol (5). Yellow solid; yield 45%; mp 80–82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (d, J=8.3 Hz, 2H), 7.11 (d, J=8.3 Hz, 2H), 3.80 (t, J=6.3 Hz, 2H, CH_2), 2.70 (t, J=6.3 Hz, 2H, CH_2), 2.47 (s, 3H), 1.97 (br s, exchangeable with D_2O, 1H, OH); IR (neat, cm^{-1}) 3400, 1461; MS (CI, *i*-Butane) 192 (M^+, 60%), 161 (M^+−31, 100%); HPLC 97.6%; Symmetry C18 (250×4.6 mm), mobile phase H_2O/CH_3CN (40:60), 1.0 mL/min, UV 279 nm, retention time 5.08 min; found C, 68.68; H, 6.30; $C_{11}H_{12}OS$ requires C, 68.71; H, 6.29%.

4.3. Preparation of compound 6 and 7

General procedure. To a solution of compound **4** or **5** (36.0 mmol) in acetone (40 mL) was added a solution of oxone (44.0 g, 71.5 mmol) in water (20 mL). The reaction mixture was stirred vigorously for 4 h at 25 °C. After completion of the reaction the solvent was removed under reduced pressure and water (100 mL) was added to the reaction mixture. The mixture was then stirred for 15 min and the solid precipitated was filtered. The crude product was purified by crystallization from hexane–EtOAc to give the desired compound.

4.3.1. 1-(4-Methylsulfonylphenyl)-2-phenylacetylene (6). Light yellow solid; yield 78%; mp 157–158 °C (lit.[24h] 162.5–163.5 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, J=8.8 Hz, 2H), 7.72 (d, J=8.8 Hz, 2H), 7.57–7.28 (m, 5H), 3.09 (s, 3H, SO_2CH_3); IR (neat, cm^{-1}) 1461, 1377; MS (CI, *i*-Butane) 256 (M^+, 100%); HPLC 98.5%; Inertsil ODS 3V (250×4.6 mm), mobile phase H_2O/CH_3CN (40: 60), 1.2 mL/min, UV 308 nm, retention time 11.0 min.

4.3.2. 4-(4-Methylsulfonylphenyl)-3-butyn-1-ol (7). White solid; yield 68%; mp 94–96 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90 (d, J=7.8 Hz, 2H), 7.60 (d, J=8.3 Hz, 2H), 3.80 (t, J=6.3 Hz, 2H, CH_2), 3.0 (s, 3H, SO_2CH_3), 2.70 (t, J=6.3 Hz, 2H, CH_2), 1.75 (br s, exchangeable with D_2O, 1H, OH); IR (neat, cm^{-1}) 3440, 1465; MS (CI, *i*-Butane) 224 (M^+, 50%), 194 (M^+−31, 100%); HPLC 98.67%; Shimpak CLC C8 (250×4.6 mm), mobile phase 0.01 M KH_2PO_4/CH_3CN (60:40), 1.0 mL/min, UV 256 nm, retention time 5.59 min; found C, 58.72; H, 5.40; $C_{11}H_{12}O_3S$ requires C, 58.91; H, 5.39%.

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A simple catalyst system for the palladium-catalyzed coupling of aryl halides with terminal alkynes

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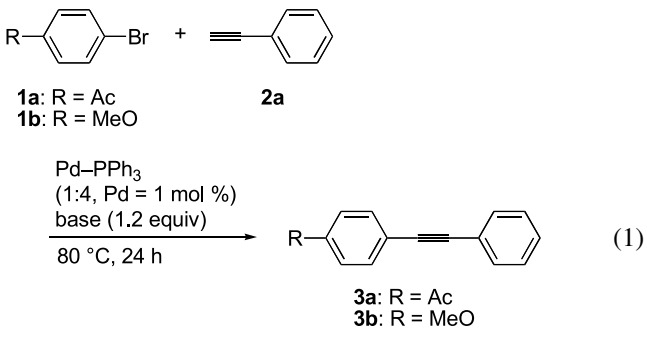
Abstract—A convenient catalyst system consisting of $Pd(OAc)_2$, PPh_3, K_3PO_4 and DMSO was found to be effective for the coupling reaction of aryl halides with terminal alkynes as well as the deacetonative coupling reaction using a 4-aryl-2-methylbut-3-yn-2-ol as a terminal alkyne precursor. An iminophosphine as a ligand worked more effectively for some combination of substrates than triphenylphosphine.

1. Introduction

The palladium-catalyzed alkynylation of aryl and alkenyl halides using terminal alkynes has become one of the most convenient methods to prepare arylalkynes and conjugated enynes,[1,2] which are important precursors for natural products,[3] pharmaceuticals[4] and molecular organic materials.[5] The two earliest studies in this field were reported independently by the Heck's Group[6] and Cassar[7] in 1975. Heck and co-workers used a $Pd(OAc)_2$–PPh_3 complex as a catalyst and triethylamine or piperidine as a base and a solvent, which are based on the Mizoroki–Heck reaction, namely the palladium-catalyzed arylation or alkenylation of alkenes. On the other hand, a palladium catalyst coordinated by PPh_3 in combination with sodium methoxide as a base and DMF as a solvent was disclosed in the Cassar's report. The both methods generally require high temperature (up to 100 °C). Later but in the same year, Sonogashira and Hagihara reported that addition of a catalytic amount of CuI greatly accelerates the reaction to enable the alkynylation at room temperature.[8] Thereafter the Sonogashira–Hagihara coupling, alternatively called simply as to the Sonogashira coupling, had expelled all other protocols from the field of the palladium-catalyzed coupling of aryl or alkenyl halides with terminal alkynes. However, copper-free protocols have recently emerged as matches for the Sonogashira coupling reaction. In 1993, Alami and Linstrumelle found that cyclic amines such as pyrrolidine and piperidine[9] as a base and a solvent enhanced the reaction rate to promote the coupling even at room temperature.[10] Numerous studies on copper-free protocols have followed it, the protocols being called as to the copper-free Sonogashira coupling but not as to the Heck and/or Cassar coupling.

The copper-free protocols thus far reported should be classified into two groups on the basis of reagents used. The first group, which includes the original methods developed by Heck or Cassar, utilizes a simple system consisting of an easily available palladium precursor, a conventional phosphine ligand such as triphenylphosphine, a simple base and a usual solvent. The second group uses expensive and/or elaborated compounds, for example, (1) stoichiometric amount of activators such as silver(I) oxide and ammonium salts,[11] (2) a special medium such as ionic liquids,[12] (3) expensive, difficult to handle ligands such as tri(*t*-butyl)phosphine,[13] or (4) special catalysts such as palladacycles.[14] Most of the methods in the second group achieve higher efficiency and/or wider scope but require one or more compounds that have low accessibility and/or difficulty in handling. Some protocols seem to spoil the



(1)

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Table 1. Palladium-catalyzed coupling of 4-bromoacetophenone or 4-bromoanisole with phenylacetylene[a]

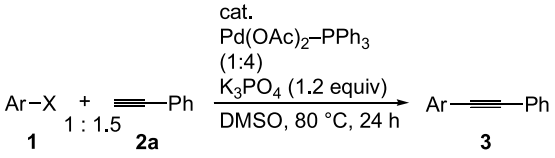
Entry	Aryl bromide	Solvent	Base	**2a/1**	Conv. (%)[b]	Yield (%)[c]
1[d]	**1a**	DMF	NaOMe	1.5	>99	35
2		DMF	NaOMe	1.5	>99	43
3		DMF	K_3PO_4	1.5	>99	83
4		DMSO	K_3PO_4	1.5	>99	89
5		1,4-Dioxane	K_3PO_4	1.5	87	63
6		Toluene	K_3PO_4	1.5	80	56
7		DMSO	Et_3N	1.5	>99	92
8		Piperidine	—	1.5	>99	96
9	**1b**	DMSO	K_3PO_4	1.5	>99	81
10		DMSO	Et_3N	1.5	79	51
11		Piperidine	—	1.5	67	59
12	**1a**	DMSO	K_3PO_4	1.2	>99	87
13	**1b**	DMSO	K_3PO_4	1.2	>99	78

[a] The reaction was carried out in a solvent (1.6 mL) at 80 °C for 24 h using 4-bromoacetophenone or 4-bromoanisole (0.80 mmol), phenylacetylene (1.2 mmol) and a base (0.96 mmol) in the presence of $Pd(OAc)_2$ (8.0 μmol) and PPh_3 (32 μmol).
[b] Determined by the yield of the recovered aryl bromide.
[c] Isolated yield based on the aryl bromide.
[d] A combination of $PdCl_2(PPh_3)_2$ (8.0 μmol) and PPh_3 (16 μmol) was used instead of $Pd(OAc)_2$–PPh_3.

merit to omit the copper catalyst. Consequently, the simplest methods to couple aryl and alkenyl halides with terminal alkynes thus far available should be the following three procedures: (1) the Heck's method with an amine as a base and a solvent,[15] (2) its descendant using a cyclic amine as a base and a solvent reported by Alami and Linstrumelle,[10,16] and (3) the Cassar's method featuring an inorganic base.[17,18] All of these do not require any commercially unavailable reagents except for the substrates themselves. The Cassar's method is hardly explored in contrast that the amine-based methods seem to have become mature. Here, we report a convenient system, based on the Cassar's original report, for the coupling reaction of aryl or alkenyl halides with terminal alkynes, consisting solely of commercially available and easy to handle materials.

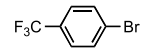
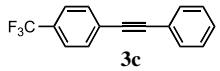
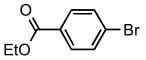
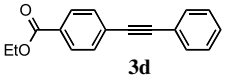
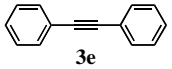
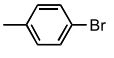
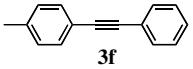
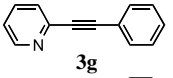
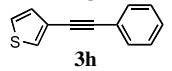
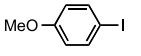
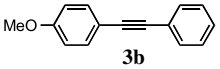
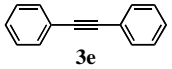
2. Results and discussion

We first examined the effect of bases and solvents in the coupling of 4-bromoacetophenone (**1a**) with phenylacetylene (**2a**) using a catalyst (1 mol%) consisting of a palladium precursor and PPh_3 (4 equiv to Pd) at 80 °C for 24 h (Eq. 1). Under the Cassar's conditions,[7] which employ $PdCl_2(PPh_3)_2$–PPh_3 (1/2) as a catalyst, NaOMe as a base, and DMF as a solvent, the reaction of **1a** with **2a** (1:1.5) afforded only 35% yield of 4-acetylphenyl(phenyl)acetylene



(2)

Table 2. Coupling of aryl halides with phenylacetylene[a]

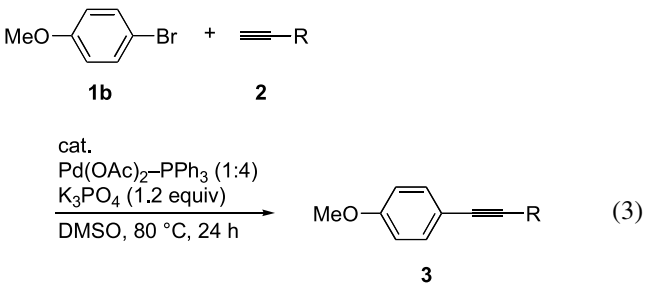
Entry	Aryl halide **1**	Pd (mol%)	Product **3**	Yield (%)[b]
1		3	 **3c**	94
2		3	 **3d**	93
3		1	 **3e**	81
4		1	 **3f**	80
5		1	 **3g**	89
6		3	 **3h**	84
7[c]		3	 **3b**	80
8		3	 **3e**	89

[a] The reaction was carried out in DMSO (1.6 mL) at 80 °C for 24 h using an aryl halide (0.80 mmol), phenylacetylene (1.2 mmol), K_3PO_4 (0.96 mmol), $Pd(OAc)_2$ and PPh_3 (4.0 equiv to Pd).
[b] Isolated yield based on the aryl halide.
[c] The reaction was carried out at 60 °C.

(**3a**) with a complete consumption of **1a** (entry 1 of Table 1). As $Pd(OAc)_2$, a more easily available precursor than $PdCl_2(PPh_3)_2$, in combination with PPh_3 (4 equiv to Pd) scored a comparable yield (entry 2), we used $Pd(OAc)_2$–PPh_3 as a catalyst thereafter. The change of the base from NaOMe to K_3PO_4 raised the yield to 83% (entry 3).[19] Then we compared DMF with other solvents to find that DMSO[20] was rather superior to DMF, and much more effective than 1,4-dioxane and toluene (entries 4–6). Use of triethylamine instead of K_3PO_4 in DMSO, which recalls the Heck's method,[6] also was found to be effective (entry 7), and piperidine as a solvent and a base, the system of Alami and Linstrumelle,[10] was even more efficient (entry 8). However, with these organic bases, an electron-rich aryl halide, 4-bromoanisole (**1b**), coupled sluggishly with **2a** to give only $<60\%$ yield of **3b** after 24 h, whereas K_3PO_4 worked well also with **1b** (entries 9–11). The coupling of **1a** or **1b** with a decreased amount of **2a** resulted in a slightly lower yield (entries 12 and 13).

The protocol can be applied to various combinations of substrates, though some reactions required 3 or 5 mol% of the catalyst for completion within 24 h. Phenylacetylene coupled with phenyl bromides having an electron-withdrawing or -donating group other than acetyl or methoxy at the *para* position in high yields (Eq. 2 and entries 1–4 of Table 2). The reaction is applicable also to heteroaryl bromides in addition to an aryl iodide and a triflate (entries 5–8), where a lower temperature raised the yield in the reaction of an active electrophile such as 4-iodoanisole.

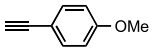
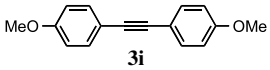
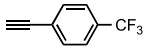
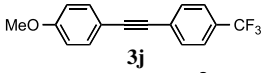
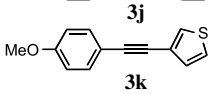
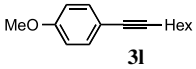
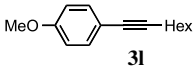
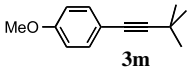
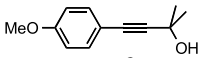
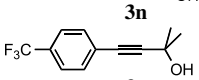
Next, we examined the scope on terminal alkynes in the coupling with 4-bromoanisole (**1b**) (Eq. 3 and Table 3). Phenylacetylenes substituted by an electron-withdrawing or -donating group as well as a heteroarylacetylene also participated in the coupling reaction (entries 1–3). In addition to diarylacetylenes, alkyl(aryl)acetylenes were obtained from aliphatic alkynes (entries 4–6). In the coupling of 1-octyne, use of increased amounts of K_3PO_4 and the alkyne was much more effective than that of an increased amount of the palladium catalyst. The Pd–PPh_3 catalyst is applicable also to the coupling of 2-methylbut-3-yn-2-ol, whose coupling products are known to undergo deacetonation to give terminal alkynes (entry 7).[21] 4-Bromo(trifluoromethyl)benzene also coupled with 2-methylbut-3-yn-2-ol, where a lower reaction temperature was found to be more suitable (entry 8).



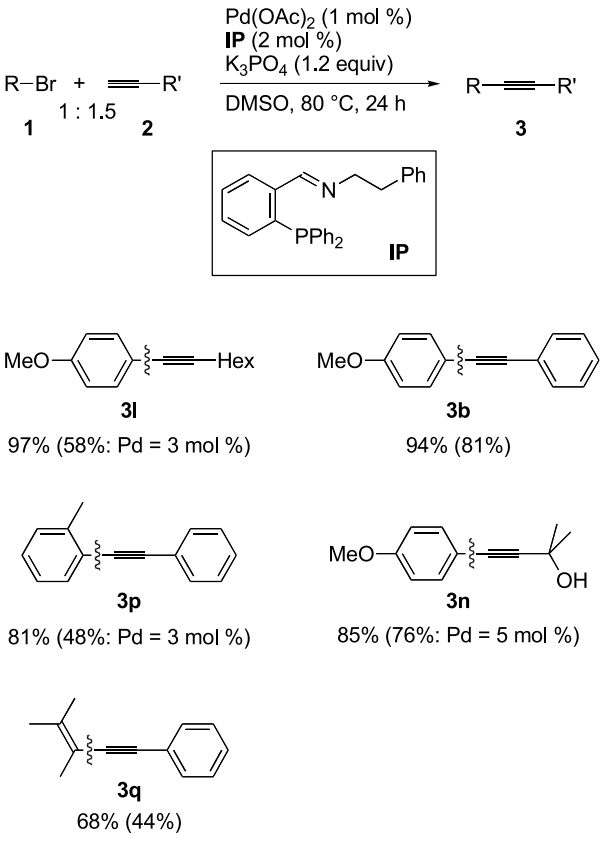
(3)

As we have described thus far, a palladium complex coordinated by triphenylphosphine, one of the most common phosphine ligands, conveniently catalyzes the coupling of various combinations of aryl halides with alkynes. However, sometimes the yields are not sufficient. For such cases, a palladium complex having *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (**IP**)[22] as a ligand was found to be more effective. **IP** can be easily prepared by condensation of 2-(diphenylphosphino)benzaldehyde[23] with 2-phenylethylamine, both of which are commercially available. The results using $Pd(OAc)_2$ and **IP** in a 1:2 ratio compared with those with

Table 3. Coupling of aryl bromides with terminal alkynes[a]

Entry	Alkyne **2**	Pd (mol%)	Product **3**	Yield (%)[b]
1		3	 **3i**	82
2		3	 **3j**	71
3		3	 **3k**	72
4		3	 **3l**	58
5[c]		1	 **3l**	84
6		3	 **3m**	86
7		5	 **3n**	76
8[d]		5	 **3o**	77

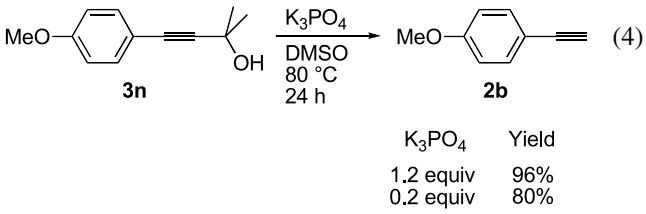
[a] The reaction was carried out in DMSO (1.6 mL) at 80 °C for 24 h using an aryl bromide (0.80 mmol), a terminal alkyne (1.2 mmol), K_3PO_4 (0.96 mmol), $Pd(OAc)_2$ and PPh_3 (4.0 equiv to Pd).
[b] Isolated yield based on the aryl bromide.
[c] K_3PO_4 (1.6 mmol) and 1-octyne (1.6 mmol) were used.
[d] 4-Bromo(trifluoromethyl)benzene was used instead of 4-bromoanisole. Reaction temperature = 70 °C.

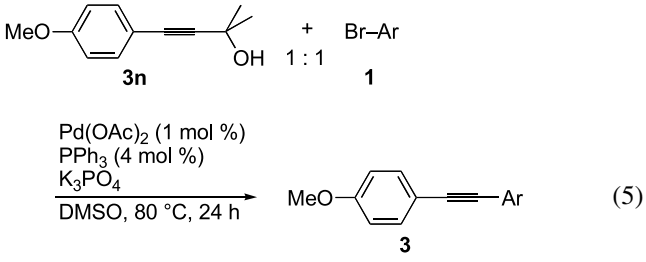


Scheme 1. Palladium–**IP**-catalyzed coupling of organic halides with terminal alkynes. The results using PPh_3 (4.0 equiv to Pd) instead of **IP** are shown in parenthesis.

triphenylphosphine are summarized in Scheme 1. The yield in the coupling of an aliphatic alkyne drastically increased without use of increased amounts of some of the reagents, though the effect of **IP** was not so drastic in the reaction of phenylacetylene. A sterically hindered aryl bromide, 2-methylbut-3-yn-2-ol and an alkenyl bromide also received the benefit of the iminophosphine ligand.

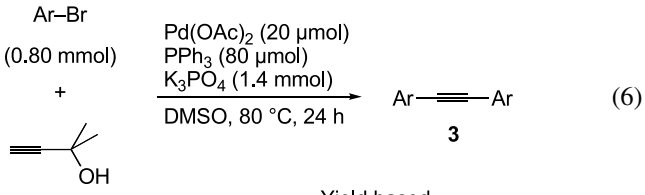
2-Methylbut-3-yn-2-ol can be regarded as a masked acetylene, one of whose acetylenic protons is protected with a hydroxy(dimethyl)methyl group. The protecting group can be removed as acetone by treatment of a base such as KOH or NaOH.[21] We expected that K_3PO_4, the base used in our coupling reaction, also would mediate the deacetonation, and found that arylpropargyl alcohol **3n** underwent deacetonation by treatment of 0.2 or 1.2 equiv of K_3PO_4 in DMSO at 80 °C for 24 h, giving 4-methoxyphenylacetylene in 80% or 96% yield, respectively (Eq. 4). However, any examination aiming the K_3PO_4-mediated deacetonation in the presence of a palladium catalyst failed. Thus, the coupling-deacetonation sequence using 2-methylbut-3-yn-2-ol in combination with 4-methoxyphenyl or 4-(trifluoromethyl)phenyl bromide afforded only a trace amount of the corresponding terminal alkyne,[24] probably because most of them were consumed through the influence of the palladium catalyst. In sharp contrast, in the presence of an aryl bromide, the deacetonation proceeded successfully, being accompanied by the coupling reaction to give diarylacetylenes (Eq. 5). The deacetonative coupling effectively proceeded with phenyl bromide in addition to that having an electron-withdrawing group, whereas the coupling reaction with 4-bromoanisole resulted in a low yield, which was recovered in some extent by using an excess amount of K_3PO_4.



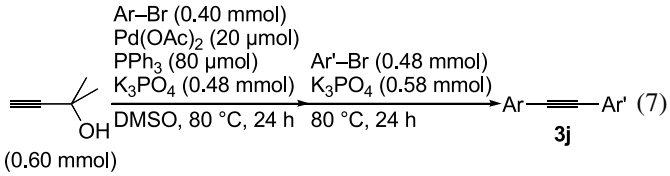


Ar	Amount of K_3PO_4	Yield	Product
Ph	1.2 equiv	84%	**3b**
4-CF_3-C_6H_4	1.2 equiv	93%	**3j**
4-MeO-C_6H_4	1.2 equiv	60%	**3i**
4-MeO-C_6H_4	3.0 equiv	73%	**3i**

Besides the above two-pot reaction consisting of the coupling using 2-methylbut-3-yn-2-ol and the deacetonative coupling, the one-pot version through a coupling-deacetonation-coupling sequence also was found to be possible.[25,26] Symmetrical diarylacetylenes were obtained by treatment of an aryl bromide and 2-methylbut-3-yn-2-ol (2:1.1) with a catalytic amount of $Pd(OAc)_2$–PPh_3 (1/4) and K_3PO_4 at 80 °C for 48 h (Eq. 6). Although the propargyl alcohol coupled twice with 4-(trifluoromethyl)phenyl bromide eliminating acetone in a good yield, the reaction of 4-bromoanisole gave the desired diarylacetylene only in 42% yield, which was accompanied by formation of a considerable amount (ca. 20% estimated by ^1H NMR) of 1-(4-methoxylphenyl)-2-phenylethyne. The phenyl group of the unsymmetrical diarylacetylene must be derived from triphenylphosphine, where the 4-methoxyphenyl group in exchange for the phenyl group should be transferred from the bromine to the phosphorous atom of the phosphine through the palladium.[27] Unsymmetrical diarylacetylenes can be prepared in moderate yields with a similar procedure, where a second aryl bromide as well as two-thirds amount of K_3PO_4 were added after 24 h interval (Eq. 7). The order of adding aryl bromides did not affect so significantly the yields of 1-(4-methoxyphenyl)-2-[4-(trifluoromethyl)-phenyl]ethyne (**3j**).



Ar	Yield based on Ar–Br	Product
4-CF_3-C_6H_4	76%	**3r**
4-MeO-C_6H_4	42%	**3i**



Ar	Ar'	Yield based on Ar–Br
4-MeO-C_6H_4	4-CF_3-C_6H_4	62%
4-CF_3-C_6H_4	4-MeO-C_6H_4	52%

In conclusion, we have disclosed a simple catalyst system, consisting merely of commercially available, relatively inexpensive materials, for the palladium-catalyzed coupling reaction of aryl halides with terminal alkynes. The protocol is not only as simple as the Casser's original method but also shows much wider scope than that, where electron-rich and -poor aryl electrophiles having a bromide, iodide or triflate as a leaving group coupled with various aryl and aliphatic terminal alkynes. Another feature of this protocol is the simple catalyst system applicable also to the deacetonative coupling reaction of α-dimethyl-γ-arylpropargyl alcohols with aryl halides. Symmetrical and unsymmetrical diarylacetylenes can be obtained by simple one-pot procedures from aryl bromides and 2-methylbut-3-yn-2-ol without adding other reagents. We also described efficiency of **IP**, prepared from commercially available reagents in one step, in the present coupling reaction.

3. Experimental

3.1. General

All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique under a nitrogen atmosphere. Nuclear magnetic resonance spectra were taken on a Varian Gemini 2000 (^{1}H, 300 MHz) or a JEOL JNM LA-500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometer using tetramethylsilane (^{1}H and ^{13}C) as an internal standard. Preparative recycling gel permeation chromatography was performed with JAI LC-908 equipped with JAIGEL-1H and -2H using chloroform as an eluent. Unless otherwise noted, reagents were commercially available and used without further purification. Anhydrous DMF, DMA, and DMSO were purchased from Aldrich Chemical Co. and Kanto Chemicals and used as received. Toluene and 1,4-dioxane were distilled from sodium/benzophenone ketyl. 3-Ethynylthiophene[28] and *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine (**IP**)[22a] were prepared according to the literature methods.

3.2. Palladium-catalyzed coupling of aryl halides with terminal alkynes. A general procedure (Tables 2 and 3, and Scheme 1)

A solution of an aryl halide (0.80 mmol), an alkyne (1.2 mmol), $Pd(OAc)_2$, a ligand (PPh_3: 4.0 equiv to Pd, or **IP**: 2.0 equiv to Pd), and K_3PO_4 (204 mg, 0.96 mmol) in DMSO (1.6 mL) was degassed by four freeze-thaw cycles. After stirring at 80 °C for 24 h, water (30 mL) was added and the resulting mixture was extracted with diethyl ether (20 mL×3). The combined organic layer was washed with brine (30 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with PTLC, column chromatography, or gel permeation chromatography gave the corresponding arylalkyne.

3.2.1. 1-(4-Methoxyphenyl)-2-(3-thienyl)ethyne (3k). A pale yellow powder; mp 63–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.84–6.90 (m, 2H), 7.18 (dd, J=5.0, 1.1 Hz, 1H), 7.28 (dd, J=5.0, 3.1 Hz, 1H), 7.42–7.47 (m, 2H), 7.48 (dd, J=3.1, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3, 83.1, 88.8, 114.0, 115.3, 122.6, 125.2, 128.0, 129.9, 133.0, 160.0. Anal. Calcd for $C_{13}H_{10}OS$: C, 72.87; H, 4.70. Found: C, 73.14; H, 4.87.

Other coupling products are the compounds already reported in literature. Their spectroscopic data are as follows.

3.2.2. 1-(4-Acetylphenyl)-2-phenylethyne (3a).[13b] A white powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.35–7.41 (m, 3H), 7.52–7.58 (m, 2H), 7.59–7.65 (m, 2H), 7.92–7.98 (m, 2H).

3.2.3. 1-(4-Methoxyphenyl)-2-phenylethyne (3b).[29] A white powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.85–6.91 (m, 2H), 7.28–7.37 (m, 3H), 7.44–7.53 (m, 4H).

3.2.4. 1-Phenyl-2-[4-(trifluoromethyl)phenyl]ethyne (3c).[30] A white powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.41 (m, 3H,), 7.52–7.58 (m, 2H), 7.60–7.64 (m, 4H).

3.2.5. Ethyl 4-(phenylethynyl)benzoate (3d).[11c] A pale yellow powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, J=7.2 Hz, 3H), 4.39 (q, J=7.2 Hz, 2H), 7.34–7.40 (m, 3H), 7.52–7.62 (m, 4H), 8.00–8.06 (d, J=8.4, 2 H).

3.2.6. Diphenylethyne (3e).[31] A white powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.37 (m, 6H), 7.52–7.56 (m, 4H).

3.2.7. 1-(4-Methylphenyl)-2-phenylethyne (3f).[31] A pale yellow powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.13–7.19 (m, 2H), 7.30–7.39 (m, 3H), 7.40–7.46 (m, 2H), 7.50–7.56 (m, 2H).

3.2.8. 1-Phenyl-2-(2-pyridyl)ethyne (3g).[32] A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.28 (m, 1H), 7.34–7.40 (m, 3H), 7.51–7.56 (m, 1H), 7.58–7.64 (m, 2H), 7.65–7.73 (m, 1H), 8.61–8.65 (m, 1H).

3.2.9. 1-Phenyl-2-(3-thienyl)ethyne (3h).[33] A pale yellow powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, J=4.8,

1.2 Hz, 1H), 7.30 (dd, J=4.8, 2.7 Hz, 1H), 7.32–7.39 (m, 3H), 7.49–7.55 (m, 3H).

3.2.10. Bis(4-methoxyphenyl)ethyne (3i).[26] A yellow powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 6.84–6.90 (m, 4H), 7.42–7.48 (m, 4H).

3.2.11. 1-(4-Methoxyphenyl)-2-[4-(trifluoromethyl)-phenyl]ethyne (3j).[31] A white powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.87–6.93 (m, 2H), 7.46–7.52 (m, 2H), 7.57–7.62 (m, 4H).

3.2.12. 1-(4-Methoxyphenyl)-1-octyne (3l).[34] A pale brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J= 7.0 Hz, 3H), 1.25–1.39 (m, 4H), 1.40–1.51 (m, 2H), 1.53–1.66 (m, 2H), 2.38 (t, J=7.2 Hz, 2H), 3.79 (s, 3H), 6.79–6.82 (m, 2H), 7.28–7.35 (m, 2H).

3.2.13. 1-(4-Methoxyphenyl)-3,3-dimethyl-1-butyne (3m).[35] A pale yellow powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 3.79 (s, 3H), 6.77–6.83 (m, 2H), 7.29–7.35 (m, 2H).

3.2.14. 4-(4-Methoxyphenyl)-2-methylbut-3-yn-2-ol (3n).[34] A pale yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (s, 6H), 1.99 (s, 1H), 3.81 (s, 3H), 6.81–6.86 (m, 2H), 7.32–7.37 (m, 2H).

3.2.15. 4-[4-(Trifluoromethyl)phenyl]-2-methylbut-3-yn-2-ol (3o).[36] A brown powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 6H), 2.03 (s, 1H), 7.49–7.59 (m, 4H).

3.2.16. 1-Phenyl-2-(2-tolyl)ethyne (3p).[31] A brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 7.13–7.21 (m, 1H), 7.22–7.25 (m, 2H), 7.30–7.40 (m, 3H), 7.47–7.58 (m, 3H).

3.2.17. 3,4-Dimethyl-1-phenylpent-3-en-1-yne (3q).[37] A brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 3H), 1.89 (s, 3H), 2.02 (s, 3H), 7.22–7.34 (m, 3H), 7.39–7.45 (m, 2H).

3.3. Deacetonation of 4-(4-methoxyphenyl)-2-methylbut-3-yn-2-ol (Eq. 4)

A solution of 4-(4-methoxyphenyl)-2-methylbut-3-yn-2-ol (**3n**, 76.6 mg, 0.403 mmol) and K_3PO_4 (102 or 16.3 mg, 0.48 or 0.077 mmol) in DMSO (0.80 mL) was degassed by four freeze-thaw cycles. After stirring at 80 °C for 24 h, water (30 mL) was added and the resulting mixture was extracted with diethyl ether (20 mL×3). The combined organic layer was washed with brine (30 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with PTLC (hexane/EtOAc=4:1) gave 4-methoxyphenylethyne.

3.4. Deacetonative coupling of 4-(4-methoxyphenyl)-2-methylbut-3-yn-2-ol with terminal alkynes (Eq. 5)

A solution of 4-(4-methoxyphenyl)-2-methylbut-3-yn-2-ol (**3n**, 76.3 mg, 0.401 mmol), an aryl bromide (0.40 mmol), $Pd(OAc)_2$ (0.90 mg, 4.0 μmol), PPh_3 (4.2 mg, 16 μmol), and K_3PO_4 (102 or 254 mg, 0.48 or 1.2 mmol) in DMSO (0.80 mL) was degassed by four freeze-thaw cycles. After stirring at 80 °C for 24 h, water (30 mL) was added and the resulting mixture was extracted with diethyl ether (20 mL× 3). The combined organic layer was washed with brine (30 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with PTLC (hexane/EtOAc=3:1 for **3b**, 2:1 for **3i**, 4:1 for **3j**) gave **3b**, **3i** or **3j**.

3.5. One-pot synthesis of symmetrical diarylacetylenes from an aryl bromide and 2-methylbut-3-yn-2-ol (Eq. 6)

A solution of an aryl bromide (0.80 mmol), 2-methylbut-3-yn-2-ol (37 mg, 0.44 mmol), $Pd(OAc)_2$ (4.5 mg, 20 μmol), PPh_3 (21 mg, 80 μmol), and K_3PO_4 (309 mg, 1.46 mmol) in DMSO (0.80 mL) was degassed by four freeze-thaw cycles. After stirring at 80 °C for 48 h, water (30 mL) was added and the resulting mixture was extracted with diethyl ether (20 mL×3). The combined organic layer was washed with brine (30 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with column chromatography (hexane for **3r**, hexane/EtOAc=10:1 for **3i**) gave **3r** or **3i**.

3.5.1. Bis[4-(trifluoromethyl)phenyl]ethyne (3r).[13f] A white powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.67 (m, 8H).

3.6. One-pot synthesis of an unsymmetrical diarylacetylene from two different aryl bromides and 2-methylbut-3-yn-2-ol

A solution of an aryl bromide (0.40 mmol), 2-methylbut-3-yn-2-ol (50 mg, 0.60 mmol), $Pd(OAc)_2$ (4.5 mg, 20 μmol), PPh_3 (21 mg, 80 μmol), and K_3PO_4 (102 mg, 0.48 mmol) in DMSO (0.80 mL) was degassed by four freeze-thaw cycles. After stirring at 80 °C for 24 h, another aryl bromide (0.48 mmol) and K_3PO_4 (123 mg, 0.58 mmol) were added. After the reaction mixture was stirred at 80 °C for 24 h, water (30 mL) was added and the resulting mixture was extracted with diethyl ether (20 mL×3). The combined organic layer was washed with brine (30 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by purification with column chromatography (hexane/EtOAc=5:1) gave **3j**.

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References and notes

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Palladium-catalyzed trans-selective alkynylation–alkylation tandem process for the synthesis of (*E*)-3-alkyl-1-trialkylsilyl-3-alken-1-ynes☆

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Abstract—The Pd-catalyzed trans-selective monoalkynylation of 1,1-dihalo-1-alkenes with $XZnC{\equiv}CSiMe_3$, where X is Br or Cl, can proceed generally in excellent yields in the presence of $Pd(DPEphos)Cl_2$ or $Pd(dppf)Cl_2$, and subsequent alkylation with methyl- and ethylzincs can proceed in excellent yields with $\geq 98\%$ retention of configuration in the presence of $Pd(^tBu_3P)_2$ as a catalyst.

1. Introduction and background

Since the first publication of Pd-catalyzed trans-selective monoarylation and monoalkylation of β,β-dichlorostyrenes by Minato, Suzuki, and Tamao,[2] an attractive notion of exploiting this reaction for selective synthesis of trisubstituted alkenes of defined stereochemistry has been pursued by a number of workers[3–5] including the authors' group.[4] The presence of two halogen atoms bonded to one alkenyl carbon atom exerts a few notable influences in the Pd-catalyzed cross-coupling. Firstly, the presence of two geminal halogen atoms renders 1,1-dihaloalkenes more reactive toward Pd complexes than the corresponding monohaloalkenes, thereby making their Pd-catalyzed cross-coupling facile. Secondly, the Pd-catalyzed monosubstitution of 1,1-dihalo-1-alkenes is generally highly trans-selective. The observed trans-selectivity must be largely attributable to steric effects exerted by the carbon substituents of 1,1-dihalo-1-alkenes, which should favor their oxidative addition to Pd away from, or trans to, the carbon substituents in the β position. This effect, however, must be further amplified by a kinetic resolution discussed below. The third noteworthy aspect of the Pd-catalyzed monosubstitution of 1,1-dihalo-1-alkenes is that one of the main side reactions is the unwanted disubstitution during the first substitution.[5] This suggests that the second step of substitution must be significantly accelerated, as compared with the corresponding reaction of the same monohaloalkenes preformed and introduced as free alkenes. Although unwanted, this side reaction must, at the same time, exert a beneficial kinetic resolution leading to a significantly higher level of stereoselectivity for the conversion of 1,1-dihalo-1-alkenes (**1**) into the trans-monosubstitution products (trans-**2**) due to faster trans-substitution of the minor and unwanted cis-**2**-Pd complexes to produce the disubstitution products **3** (Scheme 1).

Prompted by the favorable results reported earlier,[2–5] the development of a synthetic protocol represented by Scheme 2 was initiated several years ago in the authors' group. Whereas trans-selective monosubstitution of 1,1-dihalo-1-alkenes with organometals containing aryl[2,5] and alkenyl[3–5] groups as well as with just one alkylzinc derivative, that is, ^nBuZnCl,[2] and $^nBu_3SnH$[6] had been reported by then, the corresponding trans-selective monoalkynylation had remained unexplored. During the course of this investigation, however, the Pd-catalyzed trans-selective monoalkynylation of 1,1-dibromo-1-alkenes with the use of alkynylzinc derivatives[7] and of terminal alkynes under the Sonogashira conditioins[8] were reported. With $Me_3SiC{\equiv}CZnCl$ as an alkynylating agent, the desired bromoenynes were obtained in 41–66% yields.[7a] Although monoalkynylation of $Ph(CH_2)_2CH{=}CBr_2$ with $Me_3SiC{\equiv}CH$ under the Sonogashira coupling conditions was initially reported to give the desired bromoenyne in 87% yield,[8a] a more recent full paper revised its yield to 68%.[8b] These results are summarized in Scheme 3. Clearly, substantial improvements were desirable.

☆ See Ref. 1.

Keywords: Pd-catalyzed; trans-Selective monoalkynylation; 1,1-Dihalo-1-alkenes; (*E*)-3-Alkyl-1-trialkyulsilyl-3-en-1-ynes; $Pd(^tBu_3P)_2$.
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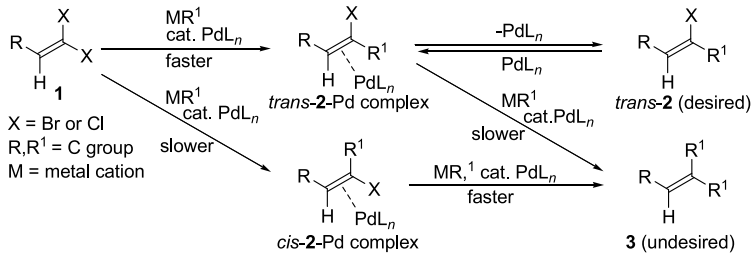
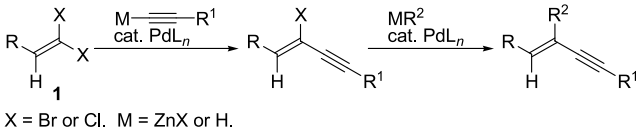
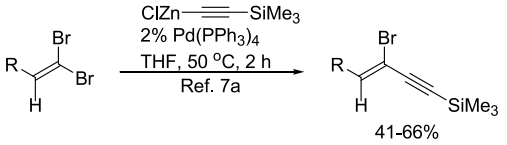
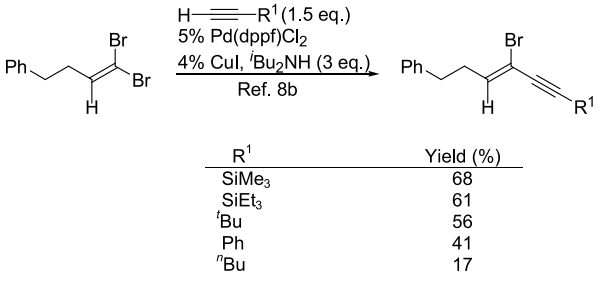


Scheme 1.



Scheme 2.





R^1	Yield (%)
$SiMe_3$	68
$SiEt_3$	61
^{i}Bu	56
Ph	41
^{n}Bu	17

Scheme 3.

The protocol shown in Scheme 2 for the stereoselective synthesis of trisubstituted alkene-containing natural products requires clean and stereospecific alkylation of the monohaloenyne intermediates. Very little was known about this transformation until a few years ago. Just a couple of bromoenynes prepared by Pd-catalyzed trans-selective alkynylation of 1,1-dibromo-1-alkenes with $HC{\equiv}CSiMe_3$ have recently been alkylated with ethyl- and trimethylsilylmethylmagnesium halides in the presence of $Ni(dppp)Cl_2$ as a catalyst in 47–71% yields.[8a] Also known were the reaction of a β-chlorostyrene derivative with ^{n}HexMgBr in the presence of $Pd(PPh_3)_2Cl_2$[2a] and that of a bromostilbene derivative with Me_4Sn in the presence of $Pd_2(dba)_3$ and tris(2-furyl)phosphine (TFP).[5] Attempts to achieve the Ni-catalyzed alkylation of haloalkenes substituted only with the alkyl groups were unsuccessful.[9] It was clear that development of generally satisfactory procedures represented by Scheme 2 would require a detailed full-scale investigation of the Pd-catalyzed alkylation, in particular methylation, of the monohaloenyne intermediates.

2. Results and discussion

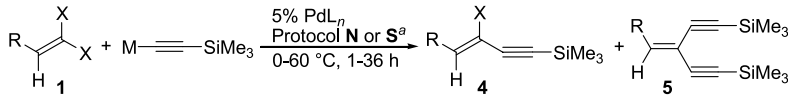
2.1. Pd-catalyzed trans-selective monoalkynylation of 1,1-dihalo-1-alkenes

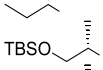
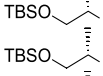
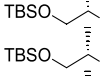
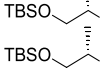
With the goal of developing a highly satisfactory procedure for Pd-catalyzed trans-selective monoalkynylation of 1,1-dihalo-1-alkenes, both the parent $HC{\equiv}CSiMe_3$ for the Sonogashira alkynylation[10,11] and $XZnC{\equiv}CSiMe_3$, where X is Cl or Br, for the Negishi alkynylation[11,12] were chosen as representative alkynylating agents. The $Me_3SiC{\equiv}C$ group can, in principle, be subsequently converted to a variety of alkynyl groups. Moreover, some preliminary results earlier suggested that these reagents might be readily conducive to the development of satisfactory procedures. Both 1,1-dibromo- and 1,1-dichloro-1-alkenes containing ^{n}Hexyl or ^{n}Nonyl, Ph, and $Me_3SiC{\equiv}C$ as representative sp^3-, sp^2-, and sp-hybridized carbon groups, respectively, were chosen as electrophilic substrates. Also chosen were (*S*)-$EtCHMeCH{=}CBr_2$ and (*R*)-$TBSOCH_2CHMeC{=}CBr_2$ as desirable synthons for the syntheses of a variety of natural products including polypropionates. As Pd catalysts, two containing monodentate phosphines, that is, $Pd(PPh_3)_4$ and $Pd(TFP)_2Cl_2$ as well as two containing bidentate phosphines, that is, $Pd(dppf)Cl_2$, where dppf is 1,1′-bis(diphenylphosphino)-ferrocene, and Pd(DPEphos)Cl_2, where DPE is bis(*o*-diphenylphosphinophenyl) ether, were employed.

The experimental results summarized in Table 1 indicate the following. Firstly, Pd complexes containing bidentate phosphines, that is, DPEphos[13] and dppf,[14] are generally more satisfactory catalysts than those containing monodentate phosphines (see Sonogashira alkynylation in entries 1–4, entry 5 vs. entries 6 and 7), even though the latter phosphines can be comparably satisfactory in some less demanding cases (Negishi alkynylation in entries 1 and 2). As long as 1,1-dibromo-1-alkenes and Pd(DPEphos)Cl_2 are used, both Negishi and Sonogashira protocols lead to $\geq$87% yields of the desired products **4** (entries 4, 8, 9, and 12–16). These results are considerably more favorable than those reported previously.[7a,8]

Secondly, despite the statement made above, substantial differences between the two protocols have been observed in cases where 1,1-dichloro-1-alkenes were used as substrates (entries 6, 7, and 10). Whereas the Negishi alkynylation in the presence of Pd(DPEphos)Cl_2 as a catalyst was generally satisfactory for monoalkynylation of 1,1-dichloro-1-alkenes as well, the Sonogashira alkynylation was rather unsatisfactory except in the reaction of $TMSC{\equiv}CCH{=}CCl_2$ (entries 7, 10, and 11).

Table 1. Pd-catalysed alkynylation of 1,1-dihalo-1-alkenes with M–≡–$SiMe_3$[a]

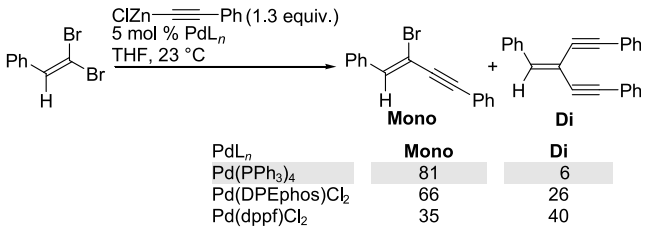


Entry	R	X	PdL_n	Protocol and product yield (%)[b]			
				N		S	
				4	5	4	5
1	Ph	Br	$Pd(PPh_3)_4$	84	14	15	18
2	Ph	Br	$Pd(TFP)_2Cl_2$	87	8	18	43
3	Ph	Br	$Pd(dppf)Cl_2$	89	3	78	3
4	Ph	Br	$Pd(DPEphos)Cl_2$	90 (84)	8	89	8
5	Ph	Cl	$Pd(PPh_3)_4$	61	12	[c]	[c]
6	Ph	Cl	$Pd(dppf)Cl_2$	87 (84)	10	33[d]	10
7	Ph	Cl	$Pd(DPEphos)Cl_2$	84	13	56[e]	4
8	^{n}Nonyl	Br	$Pd(DPEphos)Cl_2$	94 (87)	3	92	6
9	^{n}Hexyl	Br	$Pd(DPEphos)Cl_2$	95 (88)	5	[f]	[f]
10	^{n}Hexyl	Cl	$Pd(DPEphos)Cl_2$	65 (65)	8	26[g]	2
11	Me_3Si–≡	Cl	$Pd(DPEphos)Cl_2$	91 (88)	7	84[h]	12
12		Br	$Pd(DPEphos)Cl_2$	96 (94)	2	[f]	[f]
13		Br	$Pd(DPEphos)Cl_2$	87 (77)	13	90 (74)	10
14		Br	$Pd(dppf)Cl_2$	[f]	[f]	89 (73)	11
15[i]		Br	$Pd(DPEphos)Cl_2$	99 (99)	<1	[f]	[f]
16[j]		Br	$Pd(DPEphos)Cl_2$	99 (86)	<1	[f]	[f]

[a] **N**, Negishi alkynylation with ClZn–≡–$SiMe_3$ in THF at 0–50 °C. See footnote i and j. **S**, Sonogashira alkynylation with H–≡–$SiMe_3$, 5 mol% CuI, $^iPr_2NH$ (2 equiv) in benzene.
[b] By GLC with isolated yields in parentheses.
[c] The experiment was performed, but it needs to be reinvestigated.
[d] Formation of the *E*-isomer in 16% yield was observed.
[e] Formation of the *E*-isomer in 3% yield was detected.
[f] Not performed.
[g] Formation of the *E*-isomer in 6% yield was observed.
[h] Formation of the *E*-isomer in 3% yield was observed.
[i] BrZn–≡–$SiPh_3$ was used.
[j] BrZn–≡–$SiPr_3$ was used.

Thirdly, all Negishi alkynylation reactions shown in Table 1 was >99% stereoselective with no detectable sign of formation of the *E*-isomers. The major side reaction was identified as competitive dialkynylation to produce **5**, the extents of their formation being ≤13% (entries 4 and 7–13). Moreover, formation of **5** was almost completely suppressed by using $BrZnC{\equiv}CSiPh_3$ and $BrZnC{\equiv}CSi^iPr_3$ (entries 15 and 16).

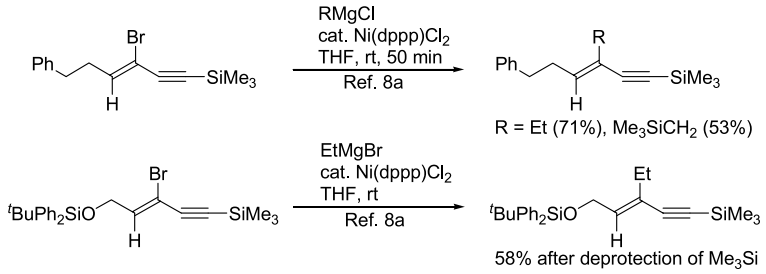
Although attention in this study was focused on Pd-catalyzed monoalkynylation with $HC{\equiv}CSiMe_3$ and its Zn derivatives and related compounds containing bulky silyl groups, a brief investigation of the reactions with other alkynes suggest that the generalization made above may not be extended beyond the scope of this study. Thus, for example, the results summarized in Scheme 4 clearly indicate that, at least in this case, $Pd(DPEphos)Cl_2$ and $Pd(dppf)Cl_2$ are inferior to $Pd(PPh_3)_4$. Clearly, formation of the dialkynylation product is the main side reaction to be avoided. Since the mono/di ratio must be a function of relative rates of the first and second alkynylation steps, maximization of the mono/di ratio would be expected to be a delicate multi-faceted issue. In this regard, however, it is important to be reminded that silylethynylated products can, in principle, be readily converted to many other derivatives via Pd-catalyzed alkynylation[10–12] and many other alkynylation reactions.



Scheme 4.

2.2. Pd-catalyzed alkylation of (*Z*)-3-halo-1-trimethylsilyl-3-alken-1-yns (4)

Prior to this investigation, Pd- or Ni-catalyzed alkylation of internal monobromo- or monochloroalkenes obtainable via trans-selective monosubstitution of 1,1-dihalo-1-alkenes had been reported just for five cases,[2a,5,8a] as described in Section 1. Directly pertinent to this study are three cases of alkylation of 3-bromo-1-trimethylsilyl-3-alken-1-ynes[8a] with alkylmagnesium halides in the presence of $Ni(dppp)Cl_2$ essentially under the conditions reported earlier[2a] (Scheme 5). However, no mention was made about stereoisomer formation. Nor was methylation reported.

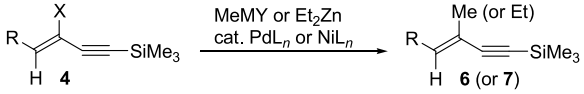


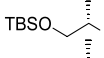
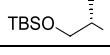
Scheme 5.

In light of some preliminary indications that the presence of proximal π-bonds can significantly facilitate Pd- or Ni-catalyzed cross-coupling, those 3-halo-3-buten-1-ynes that contain an aryl, alkenyl, or alkynyl group bonded to C4 may not serve as representative substrates. So, 3-bromo-1-trimethylsilyl-3-tridecen-1-yne (**4b**) was chosen as a representative 4-alkyl-substituted 3-halo-3-buten-1-yne, and its Pd- or Ni-catalyzed methylation and ethylation were investigated along with several other cases.

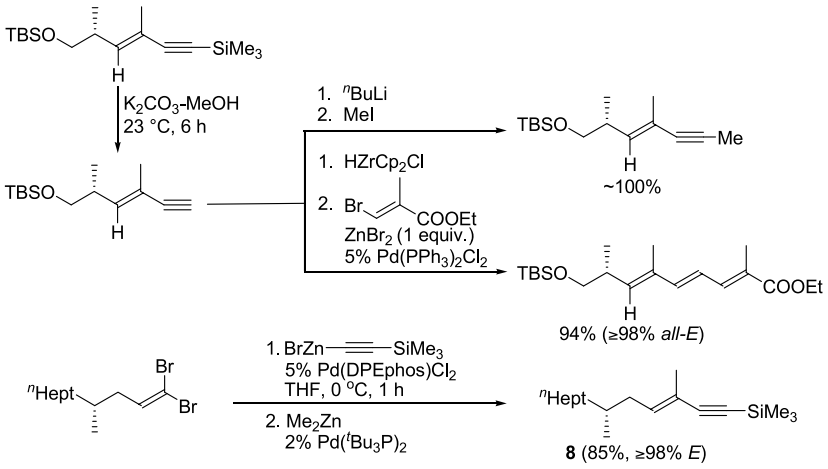
The experimental results summarized in Table 2 indicate the following. Firstly, the reaction of **4b** with MeMgBr with either $Ni(dppp)Cl_2$[8a] or $Pd(PPh_3)_4$ as a catalyst led to 24 and 23% yields of *E* and *Z* stereoisomeric mixtures of **6b** under the reaction conditions employed (entries 1 and 2). Even the use of $Pd(^tBu_3P)_2$, which was later found to be highly satisfactory in alkylation with alkylzincs, (*E*)-**6b** and (*Z*)-**6b** were obtained as a mixture in 31 and 21% yields, respectively (entry 3). Thus, no satisfactory results were obtained with MeMgBr. Furthermore, the results discussed above suggested that *E*–*Z* isomerization could be a serious side reaction to be avoided. In this regard, some of the results reported earlier in related studies[2a,8a] may have to be reexamined. At least two other byproducts were formed in significant quantities, but no attempts were made to identify them. Secondly, the use of Me_2Zn and a catalytic amount of $Ni(dppp)Cl_2$ was also disappointing, producing (*E*)-**6b** and (*Z*)-**6b** in 8 and 10% yields, respectively (entry 4). On the other hand, the use of Pd catalysts led to much high product yields ranging from 61 to essentially 100%. Unfortunately, however, unacceptable mixtures of (*E*)-**6b** and (*Z*)-**6b** were obtained[15] (entries 5–8). Thirdly, the use of $Pd(^tBu_3P)_2$,[16] formed from in situ reaction of Pd_2dba_3 with *t*-Bu_3P (1:2, Pd:*t*-Bu_3P), and not only significantly accelerated the reaction but also suppressed almost fully unwanted stereoisomerization. Both methylation and ethylation of not only **4b** but also several other bromo- and chloroenynes listed in Table 1 have all been converted to ≥98% (*E*)-**6** and (*E*)-**7** in >90% yields (entries 9–21).

Table 2. Methylation or ethylation of (*Z*)-3-halo-1-trimetylsilyl-3-buten-1-ynes with methyl- or ethylzincs in the presence of pd catalysts



Entry	R	X	MeMY or Et_2Zn	PdL_n or NiL_n	Temperature (°C)	Time (h)	Product[a]	Yield[b] (%)	**6/6*Z***
1	^{n}Nonyl	Br	MeMgBr	$Ni(dppp)Cl_2$	23	1	**6b**	24	2/22
2	^{n}Nonyl	Br	MeMgBr	$Pd(PPh_3)_4$	23	3	**6b**	23	5/18
3	^{n}Nonyl	Br	MeMgBr	$Pd(^tBu_3P)_2$	23	1	**6b**	52	31/21
4	^{n}Nonyl	Br	Me_2Zn	$Ni(dppp)Cl_2$	23	1	**6b**	18	8/10
5	^{n}Nonyl	Br	Me_2Zn	$Pd(PPh_3)_4$	50	3	**6b**	101	47/54
6	^{n}Nonyl	Br	Me_2Zn	$Pd(TFP)_2Cl_2$	50	6	**6b**	80	9/71
7	^{n}Nonyl	Br	Me_2Zn	$Pd(dppf)Cl_2$	50	12	**6b**	97	70/27
8	^{n}Nonyl	Br	Me_2Zn	$Pd(DPEphos)Cl_2$	50	8	**6b**	61	18/43
9	^{n}Nonyl	Br	Me_2Zn	$Pd(^tBu_3P)_2$	0	1	**6b**	(93)	>98/2
10	^{n}Nonyl	Br	MeZnCl	$Pd(^tBu_3P)_2$	0	1	**6b**	>95	>98/2
11	^{n}Nonyl	Br	MeZnY[c]	$Pd(^tBu_3P)_2$	0	1	**6b**	>95	>98/2
12	^{n}Hexyl	Br	Me_2Zn	$Pd(^tBu_3P)_2$	23	1	**6c**	(91)	>98/2
13	^{n}Hexyl	Cl	Me_2Zn	$Pd(^tBu_3P)_2$	50	12	**6c**	>95	>98/2
14	^{n}Hexyl	Br	Et_2Zn	$Pd(^tBu_3P)_2$	23	1	**7c**	(93)	>98/2
15	Ph	Br	Me_2Zn	$Pd(^tBu_3P)_2$	0	1	**6a**	(95)	>98/2
16	Ph	Cl	Me_2Zn	$Pd(^tBu_3P)_2$	50	12	**6a**	>95	>98/2
17	Ph	Cl	Et_2Zn	$Pd(^tBu_3P)_2$	50	3	**7a**	(91)	>98/2
18	Me_3Si–≡	Cl	Me_2Zn	$Pd(^tBu_3P)_2$	50	12	**6d**	(94)	>98/2
19		Br	Me_2Zn	$Pd(^tBu_3P)_2$	0	1	**6e**	(94)	>98/2
20		Br	Me_2Zn	$Pd(^tBu_3P)_2$	23	1	**6f**	(95)	>98/2
21		Br	Et_2Zn	$Pd(^tBu_3P)_2$	23	1	**7f**	(99)	>98/2

[a] **a**: R=Ph; **b**: R=^{n}Nonyl; **c**: R=^{n}Hexyl; **d**: R=Me_3Si–≡; **e**: R=EtCHMe; **f**: R=$TBSOCH_2CHMe$.
[b] By GLC with isolated yields in parentheses.
[c] Prepared from MeMgBr and $ZnCl_2$.



Scheme 6.

The protocol developed above appears to be highly dependable and satisfactory. It promises to be particularly useful for the synthesis of trisubstituted alkenes that contain asymmetric carbon centers in the α- or β-position of the 'tail' side[17] of trisubstituted alkenes, as suggested by some model studies shown in Scheme 6. Compound **8** can potentially serve as a convenient intermediate for the synthesis of a potent topoisomerase inhibitor, topostatin.[18]

3. Conclusions

(1) Trans-Selective monoalkynylation of 1,1-dibromo-1-alkenes and1,1-dichloro-1-alkenes with $HC{\equiv}CSiMe_3$ or its zinc derivatives was investigated in detail with $Pd(PPh_3)_4$, $Pd(TFP)_2Cl_2$, $Pd(dppf)Cl_2$, and $Pd(DPEphos)Cl_2$ as catalysts. The results significantly depend on (i) cross-coupling protocols, that is, Sonogashira alkynylation versus Negishi alkynylation, involving the use of different countercations (M); (ii) halogen leaving groups (X), that is, Br versus Cl; (iii) carbon substituents (R) and (iv) catalysts. Under the Negishi alkynylation conditions with $ClZnC{\equiv}CSiMe_3$ as the alkynylating agent, trans-selective monoalkynylation has been achieved in $\geq$84% yields with all 1,1-dibromo-1-alkenes examined and all four Pd-phosphines catalysts used. In the corresponding reactions of 1,1-dichloro-1-alkenes, the use of bidentate phosphine-containing Pd catalysts, has led to the desired monosubstitution products in $\geq$84% yields except in the case of 1,1-dichloro-1-octene where the product yield was 65%.

Under the Sonogashira alkynylation conditions, however, the reactions of 1,1-dichloro-1-alkenes with $HC{\equiv}CSiMe_3$ in the presence of $Pd(DPEphos)Cl_2$ proved to be generally poor, the product yields being 56% or less except in the reaction of $Me_3SiC{\equiv}CCH{=}CBr_2$, where the yield of the desired product was 84%. Even the reactions of 1,1-dibromo-1-alkenes were sluggish and low-yielding with monodentate phosphine-containing Pd catalysts. The use of $Pd(dppf)Cl_2$ and $Pd(DPEphos)Cl_2$, however, proved to be generally very satisfactory.

(2) All of the four Pd-phosphine complexes used for trans-selective monoalkynylation proved to be unsatisfactory for the second-stage alkylation. Also unsatisfactory was $Ni(dppp)Cl_2$. A previously unknown stereoisomerization was shown to be one of the serious side reactions. The use of a bulky trialkylphosphine-containing Pd complex of low election count, that is, $Pd(^tBu_3P)_2$, was found to be critically important. With this catalyst and alkylzincs as alkylating agents, the second stage alkylation for producing **6** and **7** was achieved in >90% yields and in >98% stereoselectivity. Even under these conditions, however, MeMgBr led to disappointing results.

(3) The synthetic protocols developed in this study promise to be useful for the synthesis of trisubstituted alkenes containing proximal asymmetric carbon atoms representing a number of natural products.

4. Experimental

4.1. General

All experiments were conducted under an atmosphere of dry argon. THF and benzene were dried and distilled by the standard methods. $ZnCl_2$ and $ZnBr_2$ were flame-dried under vacuum prior to use. Me_2Zn, Et_2Zn, and $Cl_2Pd(dppf)$ were purchased from Aldrich and used as received. 1,1-Dihalo-1-alkenes were prepared from their corresponding aldehydes by the method of Corey and Fuchs.[19] $Pd(PPh_3)_4$,[20] Cl_2-Pd(DPEphos),[13] and $Pd(^tBu_3P)_2$[16c] were prepared according to the literature procedures. Flash chromatographic separations were carried out on 230–400 mesh silica gel 60. Gas chromatography was performed on an HP 6890 Gas Chromatograph using an HP-5 capillary column (30 m$\times$ 0.32 mm, 0.5 μm film) with appropriate hydrocarbons as internal standards. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova-300 spectrometer. IR spectra were recorded on a Perkin-Elmer Spectrum 2000 FT-IR spectrometer. LRMS and HRMS were obtained on Hewlett Packard 5995 GC-MS and Finnigan MATL95 mass spectrometers, respectively. Microanalyses were performed on a Perkin-Elmer 2400 Series II CHNS/O Analyzer. Optical rotations were measured on an Autopol III automatic polarimeter.

4.2. Palladium-catalyzed trans-selective alkynylation of 1,1-dibromo-1-alkenes with alkynylzincs. Representataive procedure A

4.2.1. (3*Z*)-3-Bromo-1-trimethylsilyl-3-tridecen-1-yne [4b(Br)]. To a solution of (trimethylsilyl)acetylene (118 mg, 1.2 mmol) in THF (5 mL) cooled to −78 °C was added *n*-BuLi (0.5 mL, 2.5 M in hexanes, 1.25 mmol). After 30 min, dry $ZnCl_2$ (164 mg, 1.2 mmol) in THF (5 mL) was added to the reaction mixture at −78 °C. The cooling bath was removed after 15 min, and the resultant mixture was warmed to 23 °C over 30 min. At 0 °C, the zinc reagent prepared and 1,1-dibromo-1-undecene (312 mg, 1.0 mmol) were added to a solution of Pd(DPEphos)Cl_2 (36 mg, 0.05 mmol) in THF (5 mL). The resultant mixture was stirred at 0 °C and monitored by GLC using decane (142 mg, 1 mmol) as an internal standard. After 1 h, GLC analysis indicated that the starting material had been completely consumed, the title compound was formed in 94% yield and the dialkynylation product in 3% yield. The reaction mixture was quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ filtered and concentrated. Flash chromatography (silica gel, hexanes) gave the title compound **4b(Br)**: yield 87%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9H), 0.86 (t, J=6.2 Hz, 3H), 1.2–1.45 (m, 14H), 2.1–2.25 (m, 2H), 6.30 (t, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.31 (3 C), 14.09, 22.67, 27.88, 29.22, 29.30, 29.40, 29.50, 31.89, 31.97, 94.47, 102.33, 102.46, 141.35; IR (neat) 2856, 2155, 1466, 1250 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 314 (5) [M^+]; HRMS calcd for $C_{16}H_{29}BrSi$ [M^+]: 326.1222; found: 326.1220. 1-Trimethylsilyl-3-(trimethylsilyl)ethynyl-3-tridecen-1-yne was obtained as a byproduct in 2% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9H), 0.18 (s, 9H), 0.86 (t, J=6.6 Hz, 3H), 1.2–1.45 (m, 14H), 2.25–2.35 (m, 2H), 6.38 (t, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.13 (6 C), 14.10, 22.67, 28.34, 29.23, 29.31, 29.37, 29.53, 30.79, 31.88, 91.40, 98.30, 99.82, 102.54, 105.83, 152.07; IR (neat) 2856, 2144, 2068, 1465, 1250 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 346 (42) [M^+]; HRMS calcd for $C_{21}H_{38}Si_2$ [M^+]: 346.2512; found: 346.2512.

4.2.2. (*Z*)-3-Bromo-1-trimethylsilyl-3-decen-1-yne [4c(Br)].[21] The title compound was prepared according to representative procedure A except that 1,1-dibromo-1-octene was used in place of 1,1-dibromo-1-undecene as a starting compound: yield 88%; stereoisomeric purity ≥98%; ^{1}H NMR (J=300 Hz, $CDCl_3$) δ 0.18 (s, 9H), 0.87 (t, J=6.9 Hz, 3H), 1.2–1.45 (m, 8H), 2.18 (q, J=7.2 Hz, 2H), 6.30 (t, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.32 (3 C), 14.05, 22.56, 27.84, 28.88, 31.59, 31.96, 94.44, 102.31, 102.42, 141.32; IR (neat) 2143, 1614, 1467, 1251, 1107, 845, 760 cm^{-1}. Anal. Calcd for $C_{13}H_{23}BrSi$: C, 54.34; H, 8.07; Br, 27.81. Found: C, 54.46; H, 8.13; Br, 27.69.

4.2.3. (*Z*)-3-Bromo-4-phenyl-1-trimethylsilyl-3-buten-1-yne [4a(Br)]. The title compound was prepared according to representative procedure A except that 1,1-dibromo-2-phenylethene was used in place of 1,1-dibromo-1-undecene as a starting compound: yield 84%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H), 7.27 (s, 1H), 7.3–7.45 (m, 3H), 7.6–7.7 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.31 (3 C), 96.92, 99.95, 103.71, 128.26, 128.94, 129.24, 134.81, 137.25; MS (EI, 70 eV) *m*/*z* (%) 278 (34), 280 (34) [M^+]. In this reaction 4-phenyl-1-trimethylsilyl-3-(trimethylsilyl)ethynyl-3-buten-1-yne was obtained as a byproduct in 6% yield; ^{1}H NMR (300 MHz, $CDCl_3$) 0.24 (s, 9H), 0.26 (s, 9H), 7.07 (s, 1H), 7.3–7.4 (m, 3H), 7.85–7.9 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.39 (3 C), −0.13 (3 C), 93.36, 101.27, 101.66 103.17, 104.08, 128.18, 129.16, 129.36, 135.40, 145.19; IR (neat) 3064, 3030, 2959, 2149, 1619, 1446 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 296 (100) [M^+]; HRMS calcd for $C_{18}H_{24}Si_2$ [M^+]: 296.1417; found: 296.1420.

4.2.4. (3*Z*,5*S*)-3-Bromo-5-methyl-1-trimethylsilyl-3-hepten-1-yne [4e(Br)]. The title compound was prepared according to representative procedure A except that (3*S*)-1,1-dibromo-3-methyl-1-butene was used in place of 1,1-dibromo-1-undecene as a starting compound: yield 94%; stereoisomeric purity ≥98%; $[\alpha]_D^{23}$ +26.2 (*c* 7.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 0.18 (s, 9H), 0.87 (t, J=7.3 Hz, 3H) 0.97 (d, J=6.7 Hz, 3H), 1.3–1.45 (m, 2H), 2.45–2.5 (m, 1H), 6.08 (d, J=9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.30 (3 C), 11.69, 18.79, 29.03, 38.41, 94.45, 101.08, 102.41, 146.60; IR (neat) 2963, 2137, 2069, 1457, 1250 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 258 (12) [M^+]; HRMS calcd for $C_{11}H_{19}BrSi$ [M^+]: 258.0439; found: 258.0438.

4.2.5. (3*Z*,5*R*)-3-Bromo-6-(*t*-butyldimethylsilyloxy)-5-methyl-1-trimethylsilyl-3-hexen-1-yne [4f(Br)]. The title compound was obtained according to representative procedure A (cross-coupling at 0 °C for 6 h) except that (3*R*)-1,1-dibromo-3-methyl-4-(*t*-butyldimethysilyloxy)-1-butene was used in place of 1,1-dibromo-1-undecene as a starting compound: yield 77%; stereoisomeric purity ≥98%; $[\alpha]_D^{23}$ −6.7 (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.18 (s, 9H), 0.88 (s, 9H), 1.01 (d, J=6.6 Hz, 3H), 2.7–2.85 (m, 1H), 3.45 (dd, J=9.6, 6.0 Hz, 1H), 3.53 (dd, J=9.6, 5.4 Hz, 1H), 6.17 (d, J=9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.38 (2 C), −0.33 (3 C), 15.56, 18.30, 25.88 (3 C), 39.77, 66.06, 94.85, 101.96, 102.31, 143.51; IR (neat) 2144, 1615, 1472, 1251, 1110, 842, 776 cm^{-1}. Anal. Calcd for $C_{16}H_{31}BrOSi_2$: C, 51.18; H, 8.32; Br, 21.28. Found: C, 51.22; H, 8.43; Br, 21.14.

4.2.6. (3*Z*,5*R*)-3-Bromo-6-(*t*-butyldimethylsilyloxy)-5-methyl-1-triphenylsilyl-3-hexen-1-yne [4g(Br)]. The title compound was obtained (1.12 g, 99%, >98% *Z*) as a colorless viscous oil from (3*R*)-1,1-dibromo-3-methyl-4-(*t*-butyldimethylsilyloxy)-1-butene (716 mg, 2.0 mmol), 1.3 equiv of (triphenylsilyl)acetylene, *n*-BuLi, dry $ZnBr_2$ and 5.0 mol% of Pd(DPEphos)Cl_2 by following representative procedure A (cross-coupling at 0 °C for 6 h); $[\alpha]_D^{23}$ + 0.37 (*c* 4.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 1.04 (s, 9H), 1.17 (d, J=6.9 Hz, 3H), 2.9–3.05 (m, 1H), 3.6–3.7 (m, 2H), 6.49 (d, J=9.0 Hz, 1H), 7.45–7.6 (m, 9H), 7.75–7.6 (m, 9H), 7.75–7.8 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.36, −5.35, 15.50, 18.28, 25.90 (3 C), 39.81, 66.06, 89.84, 101.67, 106.41, 128.01 (6 C), 130.05 (3 C), 132.96 (3 C), 135.56 (6 C), 144.92; IR (neat) 2138, 1471, 1257, 1114, 837, 710, 700 cm^{-1}. Anal. Calcd

for $C_{31}H_{37}BrOSi_2$: C, 66.29; H, 6.64; Br, 14.23. Found: C, 66.48; H, 6.64; Br, 14.15.

4.2.7. (3*Z*,5*R*)-3-Bromo-6-(*t*-butyldimethylsilyloxy)-5-methyl-1-triisoproplsilyl-3-hexen-1-yne [4h(Br)]. The title compound was obtained (1.18 g, 86%, >98% *Z*) as a yellow oil from (3*R*)-1,1-dibromo-3-methyl-4-(*t*-butyldimethylsilyloxy)-1-butene (1.07 g, 3.0 mmol), 1.3 equiv of (triisopropylsilyl)acetylene, *n*-BuLi, dry $ZnBr_2$ and 5.0 mol% of Pd(DPEphos)Cl_2 by following representative procedure A (cross-coupling at 0 °C for 6 h); $[\alpha]_D^{23}$ −0.88 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.03 (d, J=6.9 Hz, 3H), 1.08 (s, 21H), 2.7–2.85 (m, 1H), 3.48 (dd, J=9.6, 6.6 Hz, 1H), 3.54 (dd, J=9.6, 5.7 Hz, 1H), 6.14 (d, J=9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.40, −5.35, 11.27, 15.59 (3 C), 18.28, 18.58 (6 C), 25.88 (3 C), 39.70, 66.18, 91.81, 102.35, 104.53, 14280; IR (neat) 2141, 1616, 1471, 1257, 1110, 837, 776, 681 cm^{-1}. Anal. Calcd for $C_{22}H_{43}BrOSi_2$: C, 57.49; H, 9.43; Br, 17.38. Found: C, 57.24; H, 9.26; Br, 17.24.

4.2.8. (*Z*)-3-Bromo-1,4-diphenyl-3-buten-1-yne. The title compound was prepared according to representative procedure A except that 1,1-dibromo-2-phenylethene was used in place of 1,1-dibromo-1-undecene and Pd(PPh_3)$_4$ in place of Pd(DPEphos)Cl_2: yield 78%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3–7.4 (m, 7H), 7.4–7.55 (m, 2H); 7.65–7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.18, 91.10, 100.06, 121.98, 128.26 (2 C), 128.37 (2 C), 128.37 (2 C), 128.87, 128.97, 129.23 (2 C), 131.69 (2 C), 134.92; IR (neat) 3070, 3050, 2193, 1644, 1438, 1266 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 282 (29) [M^+]; HRMS calcd for $C_{16}H_{11}Br$ [M^+]: 282.0044; found: 282.0046.

4.2.9. (3*Z*,6*R*)-3-Bromo-6-methyl-1-trimethylsilyl-3-tridecen-1-yne. The title compound was prepared according to representative procedure A except that (4*R*)-1,1-dibromo-4-methyl-3-undecene was used in palce of 1,1-dibromo-1-undecene: yield 90%; stereoisomeric purity ≥98%; $[\alpha]_D^{23}$ −2.2 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 9H), 0.86 (t, J=6.9 Hz, 3H), 0.89 (d, J=6.7 Hz, 3H), 1.15–1.35 (m, 12H), 1.55–1.65 (m, 1H), 1.95–2.25 (m, 2H), 6.32 (t, J=7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.29 (3 C), 14.10, 19.72, 22.68, 27.07, 29.33, 29.79, 31.88, 32.66, 36.69, 39.19, 94.45, 102.48, 102.87, 140.35; IR (neat) 2926, 2144, 1457, 1250 cm^{-1}.

4.3. Palladium-catalyzed trans-selective alkynylation of 1,1-dichloro-1-alkenes with alkynylzincs. Representative procedure B.

4.3.1. (*Z*)-3-Chloro-1-trimethylsilyl-3-decen-1-yne [4c(Cl)]. To a stirring solution of (trimethylsilyl)acetylene (118 mg, 1.2 mmol) in THF (5 mL) cooled to −78 °C was added *n*-BuLi (0.5 mL, 2.5 M in hexanes, 1.25 mmol). After 30 min, dry $ZnCl_2$ (164 mg, 1.2 mmol) in THF (5 mL) was added to the reaction mixture at −78 °C. The cooling bath was removed after 15 min, and the resultant mixture was warmed to 23 °C over 30 min. To a solution of Pd(DPEphos)Cl_2 (36 mg, 0.05 mmol) in THF (5 mL) were added the zinc reagent prepared and 1,1-dichloro-1-octene (181 mg, 1.0 mmol). The resultant mixture was stirred at 50 °C and monitored by GLC using decane (142 mg, 1 mmol) as an internal standard. After 24 h, GLC analysis indicated that the starting material had been completely consumed, the title compound was formed in 65% yield and the dialkynylation product in 8% yield. The reaction mixture was quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, hexanes) gave the title compound **4c(Cl)**: yield 65%, stereoisomeric purity ≥98%; ^{1}H NMR (J=300 Hz, $CDCl_3$) δ 0.18 (s, 9H), 0.87 (t, J=6.4 Hz, 3H), 1.2–1.45 (m, 8H), 2.15–2.3 (m, 2H), 6.12 (t, J=7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.34 (3 C), 14.05, 22.56, 28.00, 28.90 29.19, 31.59, 93.74, 101.30, 113.54, 138.50; IR (neat) 2858, 2149, 2069, 1457, 1250 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 242 (20); HRMS calcd for $C_{13}H_{23}ClSi$ [M^+]: 242.1258; found: 242.1257.

4.3.2. (*Z*)-3-Chloro-4-phenyl-1-trimethylsilyl-3-buten-1-yne [4a(Cl)]. The title compound was prepared according to representative procedure B except that 1,1-dichloro-2-phenylethene was used in place of 1,1-dichloro-1-octene as a starting compound: yield 84%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H), 6.99 (s, 1H), 7.3–7.4 (m, 3H), 7.6–7.7 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.33 (3 C), 96.01, 102.57, 112.22, 128.36 (2 C), 128.87, 129.55 (2 C), 134.02, 134.39; IR (neat) 3064, 3024, 2962, 2129, 1602, 1442, 1250 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 234 (70) [M^+].

4.3.3. (*Z*)-3-Chloro-1,6-bis(trimethylsilyl)-3-hexen-1,5-diyne [4d(Cl)]. The title compound was prepared according to representative procedure B except that 1,1-dichloro-4-trimethylsilyl-3-buten-1-yne was used in place of 1,1-dichloro-1-octene as a starting compound: yield 88%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 18H), 6.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.50 (3 C), −0.30 (3 C), 99.26, 100.56, 101.18, 108.85, 116.21, 123.10; IR (neat) 3026, 2962, 2147, 1571, 1410, 1252 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 254 (42) [M^+].

4.4. Representative procedure C for Sonogashira alkynylation.[8,10]

4.4.1. (3*Z*,5*R*)-3-Bromo-6-(*t*-butyldimethylsilyloxy)-5-methyl-1-trimethylsilyl-3-hexen-1-yne [4f(Br)]. To a mixture of (3*R*)-1,1-dibromo-3-methyl-4-(*t*-butyldimethylsilyloxy)-1-butene (3.58 g, 10.0 mmol) in benzene (100 mL) was added (trimethylsilyl)acetylene (2.12 mL, 1.47 g, 15.0 mmol), $Cl_2Pd(dppf)\cdot CH_2Cl_2$ (408 mg, 0.5 mmol) or Pd(DPEphos)Cl_2 (358 mg, 0.5 mmol). CuI (76 mg, 0.4 mmol), and diisopropylamine (8.4 mL, 6.07 g, 60.0 mmol) successively at 23 °C. The mixture was stirred for 30 min (GLC analysis indicated that the starting material had been completely consumed, and the title compound was formed in 89% observed with $Cl_2Pd(dppf)\cdot CH_2Cl_2$ or 90% yield observed with Pd(DPEphos)Cl_2 with no indication of the formation of byproducts in more than trace quantities), and then diluted with hexanes, filtered, washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (silica gel, hexanes/ethyl acetate 100:1) afforded the title compound (2.74 g, 73%, >98% *Z*) as a yellow oil.

4.4.2. (*E*)-3-Chloro-4-phenyl-1-trimethylsilyl-3-buten-1-yne [(*E*)-4a(Cl)]. A mixture of $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol), (trimethylsilyl)acetylene (118 mg, 1.2 mmol), and 1,1-dichloro-2-phenylethene (173 mg, 1.0 mmol) in benzene (10 mL) was stirred at 50–60 °C. After 3 h, the reaction mixture was quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (silica gel, hexanes) gave the title compound: yield 60%; stereoisomeric purity ≥97%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.31 (s, 9H), 5.68 (s, 1H), 7.35–7.4 (m, 3H), 7.75–7.8 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.57 (3 C), 100.57, 103.93, 111.71, 128.30 (2 C), 128.38 (2 C), 128.96, 134.10, 136.65; IR (neat) 3064, 3062, 2961, 2147, 1596, 1495, 1252 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 234 (60) [M^+]; HRMS calcd for $C_{13}H_{15}ClSi$ [M^+]: 234.0632; found: 234.0630.

4.5. Palladium-catalyzed stereospecific methylation or ethylation of 3-bromo-1-trialkylsilyl-3-en-1-ynes. Representative procedure D

4.5.1. (*E*)-3-Methyl-1-trimethylsilyl-3-tridecen-1-yne (6b). To a stirred solution of (*Z*)-3-bromo-1-trimethylsilyl-3-tridecen-1-yne (158 mg, 0.5 mmol) in THF (5 mL) was added $Pd(^tBu_3P)_2$ (5.1 mg, 0.01 mmol) and Me_2Zn (0.5 mL, 2.0 M in toluene, 1.0 mmol) at 0 °C. After 60 min, the reaction mixture was carefully quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (silica gel, hexanes) gave **6b**: yield 93%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9H), 0.86 (t, J=6.4 Hz, 3H), 1.2–1.4 (m, 14H), 1.75 (s, 3H), 1.95–2.1 (m, 2H), 5.90 (t, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.10 (3 C), 14.09, 17.02, 22.67, 28.50, 28.93, 29.31 (2 C), 29.49, 29.55, 31.88, 89.63, 108.72, 139.81.

4.5.2. (*E*)-3-Methyl-4-phenyl-1-trimethylsilyl-3-buten-1-yne (6a). The title compound was prepared according to representative procedure D except that (*Z*)-3-bromo-4-phenyl-1-trimethylsilyl-3-buten-1-yne was used in place of (*Z*)-3-bromo-1-trimethylsilyl-3-tridecen-1-yne as a starting compound: yield 95%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 9H), 2.05 (d, J=1.4 Hz, 3H), 6.89 (br, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.04 (3 C), 19.06, 92.70, 109.03, 119.75, 127.22, 128.22 (2 C), 128.95 (2 C), 136.67, 136.92.

4.5.3. (3*E*,5*S*)-3,5-Dimethyl-1-trimethylsilyl-3-hepten-1-yne (6e). The title compound was prepared according to representative procedure D except that (3*E*,5*S*)-3-bromo-5-methyl-1-trimethylsilyl-3-hepten-1-yne was used in place of (*Z*)-3-bromo-1-trimethylsilyl-3-tridecen-1-yne as a starting compound: yield 94%; stereoisomeric purity ≥98%; $[\alpha]_D^{23}$ +44.3 (*c* 4.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 0.15 (s, 9H), 0.82 (t, J=5.6 Hz, 3H), 0.91 (d, J=6.5 Hz, 3H), 1.2–1.4 (m, 2H), 1.75 (d, J=1.3 Hz, 3H), 2.2–2.4 (m, 1H), 5.68 (dd, J=6.9, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.10 (3 C), 11.89, 17.23, 19.99, 29.88, 34.75, 89.54, 108.77, 116.57, 145.44; IR (neat) 2926, 2148, 1249 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 194 (25) [M^+]; HRMS calcd for $C_{12}H_{22}Si$ [M^+]: 194.1491; found: 194.1482.

4.5.4. (3*E*,5*R*)-6-(*t*-Butyldimethylsilyloxy)-3,5-dimethyl-1-trimethylsilyl-3-hexen-1-yne (6f). The title compound was prepared according to representative procedure D except that (3*Z*,5*R*)-3-bromo-6-(*t*-butyldimethylsilyloxy)-5-methyl-1-trimethylsilyl-3-hexen-1-yne was used in place of (*Z*)-3-bromo-1-trimethylsilyl-3-tridecen-1-yne as a starting compound: yield 95%; stereoisomeric purity ≥99%; $[\alpha]_D^{23}$ +14.3 (*c* 1.0, $CHCL_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.15 (s, 9H), 0.86 (s, 9H), 0.94 (d, J=6.6 Hz, 3H), 1.77 (d, J=1.2 Hz, 3H), 2.5–2.6 (m, 1H), 3.34 (dd, J=9.6, 7.2 Hz, 1H), 3.44 (dd, J=9.6, 5.7 Hz, 1H), 5.67 (dd, J=9.6, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.41, −5.35, 0.08 (3 C), 16.63, 17.36, 18.33, 25.92 (3 C) 36.14, 67.23, 90.03, 108.49, 118.20, 141.69; IR (neat) 2145, 1472, 1250, 1121, 843, 776 cm^{-1}. Anal. Calcd for $C_{17}H_{34}OSi_2$: C, 65.73; H, 11.03. Found: C, 65.60; H, 11.14.

4.5.5. (*E*)-3-Ethyl-1-trimethylsilyl-3-decen-1-yne (7c). The title compound was prepared according to representative procedure D except that (*Z*)-3-chloro-1-trimethylsilyl-3-decen-1-yne and Et_2Zn were used in place of (*Z*)-3-bromo-1-trimethylsilyl-3-tridecen-1-yne and Me_2Zn: yield 93%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9H), 0.86 (t, J=6.4 Hz, 3H), 1.05 (t, J=7.5 Hz, 3H), 1.2–1.4 (m, 8H), 1.74 (s, 3H), 2.0–2.15 (m, 4H), 5.87 (t, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.11 (3 C), 13.03, 14.07, 22.61, 23.72, 28.15, 29.00, 29.19, 31.71, 90.73, 107.52, 124.53, 138.72.

4.5.6. (3*E*,5*R*)-6-(*t*-Butyldimethylsilyloxy)-3-ethyl-5-methyl-1-trimethylsilyl-3-hexen-1-yne (7f). The title compound was obtained (321 mg, 99%, >99% *E*) as a yellow oil from (3*Z*,5*R*)-3-bromo-6-(*t*-butyldimethylsilyloxy)-5-methyl-1-trimethylsilyl-3-hexen-1-yne (376 mg, 1.0 mmol), 2.0 mol% of $Pd(^tBu_3P)_2$ (10.2 mg, 0.02 mmol) and Et_2Zn (1.0 mL, 1.0 M in hexanes, 1.0 mmol) by following the representative procedure D; $[\alpha]_D^{23}$ +11.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.15 (s, 9H), 0.87 (s, 9H), 0.95 (d, J=6.3 Hz, 3H), 1.06 (t, J=7.5 Hz, 3H), 2.05–2.2 (m, 2H), 2.5–2.65 (m, 1H), 3.33 (dd, J=9.6, 7.2 Hz, 1H), 3.44 (dd, J=9.6, 5.7 Hz, 1H), 5.64 (d, J=9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.39, −5.33, 0.10 (3 C), 13.38, 17.03, 18.36, 24.13, 25.94 (3 C), 35.87, 67.45, 91.16, 107.30, 125.06, 140.73; IR (neat) 2143, 1472, 1250, 1098, 842, 760 cm^{-1}. Anal. Calcd for $C_{18}H_{36}OSi_2$: C, 66.59; H, 11.18. Found: C, 66.47; H, 11.23.

4.6. Palladium-catalyzed stereospecific methylation or ethylation of 3-chloro-1-trialkylsilyl-3-en-1-ynes. Representative procedure E

4.6.1. (*E*)-3-Methyl-1-trimethylsilyl-3-decen-1-yne (6c). A mixture of (*Z*)-3-chloro-1-trimethylsilyl-3-decen-1-yne (143 mg, 0.5 mmol), $Pd(^tBu_3P)_2$ (12.8 mg, 0.025 mmol), and Me_2Zn (0.5 mL, 2.0 M in toluene, 1.0 mmolo) in THF (5 mL) was stirred at 50 °C for 12 h. The reaction mixture was carefully quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered an concentrated. Flash chromatography (silica gel, hexanes) gave **6c**: yield 91%; stereoisomeric purity ≥98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 9H), 0.86 (t, J=6.3 Hz, 3H), 1.2–1.4 (m, 8H), 1.74 (s, 3H), 2.0–2.1 (m, 2H), 5.92 (t, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 0.08 (3 C), 14.05, 16.99, 22.61 28.50, 28.91, 28.99, 31.71, 89.60, 117.63, 139.72.

4.6.2. (*E*)-3-Methyl-1,6-bis(trimethylsilyl)-3-hexen-1,5-diyne (6d). The title compound was prepared according to representative procedure E except that (*Z*)-3-chloro-1,6-bis(trimethylsilyl)-3-hexen-1,5-diyne was used in place of (*Z*)-3-chloro-1-trimethylsilyl-3-decen-1-yne as a starting compound: yield 94%; stereoisomeric purity $\geq$98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 9H), 0.17 (s, 9H), 1.98 (d, J=1.0 Hz, 3H) 5.78 (d, J=1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.14 (3 C), −0.09 (3 C), 20.31, 98.19, 101.81, 104.69, 106.41, 116.37, 132.15; IR (neat) 2960, 2185, 2144, 1409, 1250 cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 254 (42) [M$^+$]; HRMS calcd for $C_{13}H_{22}Si$ [M$^+$]: 234.1260; found: 234.1255.

4.6.3. (*E*)-3-Ethyl-4-phenyl-1-trimethylsilyl-3-buten-1-yne (7a). The title compound was prepared according to representative procedure E except that (*Z*)-3-bromo-4-phenyl-1-trimethylsilyl-3-buten-1-yne and Et_2Zn were used in place of (*Z*)-3-chloro-1-trimethylsilyl-3-decen-1-yne and Me_2Zn: yield 91%; stereoisomeric purity $\geq$98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.21 (t, J=7.5 Hz, 3H), 2.38 (q, J=7.5 Hz, 2H); 6.90 (br, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.06 (3 C), 13.90, 24.65, 94.05, 107.43, 126.79, 127.22, 128.24 (2 C), 128.76 (2 C), 136.12, 136.60; MS (EI, 70 eV) *m*/*z* (%) 228 (59) [M$^+$]; HRMS calcd for $C_{15}H_{20}Si$ [M$^+$]: 228.1334; found: 228. 1342.

4.7. Miscellaneous transformations

4.7.1. (4*E*,6*R*)-7-(*t*-Butyldimethylsilyloxy)-4,6-dimethyl-4-hepten-2-yne. A mixture of (3*E*,5*R*)-6-(*t*-butyldimethylsilyloxy)-3,5-dimethyl-1-trimethylsilyl-3-hexen-1-yne (1.42 g, 4.57 mmol) and K_2CO_3 (632 mg, 4.57 mmol) in MeOH (23.0 mL) was stirred at 21 °C for 3 h, then treated with aqueous NH_4Cl, extracted with ether, washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the crude (3*E*,5*R*)-6-(*t*-butyldimethylsilyloxy)-3,5-dimethyl-3-hexen-1-yne as a red-orange oil (1.07 g, 98%), which was essentially pure by GLC and NMR and was directly used in the following reaction without further purification. This crude terminal alkyne was then dissolved in THF (20.0 mL) and cooled to −78 °C followed by the addition of *n*-BuLi (1.98 mL, 2.5 M in hexanes, 4.95 mmol). The resultant mixture was stirred at −78 °C for 30 min, warmed to 0 °C and stirred for another 30 min, cooled back to −78 °C followed by the addition of MeI (1.40 mL, 3.19 g, 22.48 mmol) and slowly warmed to 23 °C over 12 h. The reaction mixture was then quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to afford the title compound (1.14 g, 100%, >99% *Z*) as an orange oil; $[\alpha]_D^{23}$ +9.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 0.92 (d, J=6.9 Hz, 3H), 1.75 (d, J=1.5 Hz, 3H), 1.89 (s, 3H), 2.5–2.6 (m, 1H), 3.32 (dd, J=9.9, 7.2 Hz, 1H), 3.42 (dd, J=9.9, 6.3 Hz, 1H), 5.49 (d, J=9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.43, −5.36, −4.05, 16.79, 17.72, 18.30, 25.90 (3 C), 35.92, 67.37, 82.03, 82.62, 118.43, 138.99; IR (neat) 2226, 1634, 1472, 1257, 1101, 838, 776 cm^{-1}. Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18. Found: C, 71.55; H, 11.20.

4.7.2. Ethyl (2*E*,4*E*,6*E*,8*R*)-9-(*t*-Butyldimethylsilyloxy)-2,6,8-trimethyl-2,4,6-nonatrienoate. A mixture of $Cp_2Zr(H)Cl$ (543 g, 2.0 mmol) and (3*E*,5*R*)-6-(*t*-butyldimethylsilyloxy)-3,5-dimethyl-3-hexen-1-yne (238 mg, 1.0 mmol) in THF (3.0 mL) was stirred in the dark at 23 °C for 5 h. GLC analysis indicated a complete and clean hydrozirconation. In another flask containing $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) and THF (2.0 mL) was added DIBAH (0.1 mL, 1.0 M in hexanes, 0.1 mmol) and at 23 °C, and the resultant dark brown homogeneous solution was stirred for 10 min and then treated with ethyl (*E*)-3-bromo-2-methylpropenoate (232 mg, 1.2 mmol) in THF (2.0 mL). The resultant mixture was stirred for 5 min at 23 °C and added via cannula to the dienylzirconium species generated above followed by the addition of dry $ZnCl_2$ (273 mg, 2 mmol) in THF (2.0 mL). The dark brown mixture thus, obtained was stirred at 23 °C for 10 h. GLC analysis indicated a complete and clean reaction. The reaction mixture was carefully quenched with aqueous NH_4Cl, extracted with ether, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (silica gel, hexanes/ethyl acetate 100:1) afforded the title compound (302 mg, 86%, >98% *E*,*E*,*E*) as a slightly yellow oil; $[\alpha]_D^{23}$ +4.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.06 (d, J=1.8 Hz, 6H), 0.91 (s, 9H), 1.02 (d, J=6.6 Hz, 3H), 1.34 (t, J=6.9 Hz, 3H), 1.87 (s, 3H), 2.00 (s, 3H), 2.65–2.8 (m, 1H), 3.4–3.55 (m, 2H), 4.23 (q, J=7.2 Hz, 2H), 5.50 (d, J=9.6 Hz, 1H), 6.44 (d, J=15.0 Hz, 1H), 6.57 (d, J=15.0 Hz, 1H), 7.28 (d, J=12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.43, −5.35, 12.68 (2 C), 14.31, 16.94, 18.28, 25.86 (3 C), 36.04, 60.37, 67.56, 121.71, 125.82, 134.10, 138.90, 140.13, 144.51, 168.52; IR (neat) 1705, 1613, 1472, 1228, 1100, 969, 837, 751 cm^{-1}. Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 67.89; H, 10.02.

Acknowledgements

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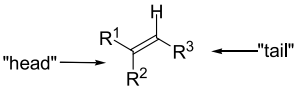
17. For distinguishing the two ends of a trisubstituted alkene, they have been defined as the head and tail, as shown below:



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Tetrahedron

A palladium catalyzed efficient synthesis of γ-methylene-α,β-unsaturated γ-lactones via cyclization of 3,4-alkadienoic acids

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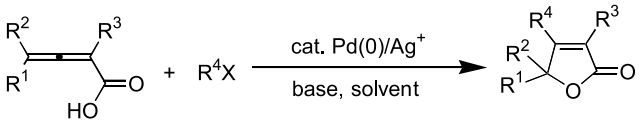
Abstract—An efficient method was developed for the synthesis of γ-methylene-α,β-unsaturated γ-lactones from the Pd-catalyzed cyclization of 3,4-alkadienoic acids. Control experiment shows that the reaction should be carried out under a N_2 atmosphere to ensure the high purity of the products.

1. Introduction

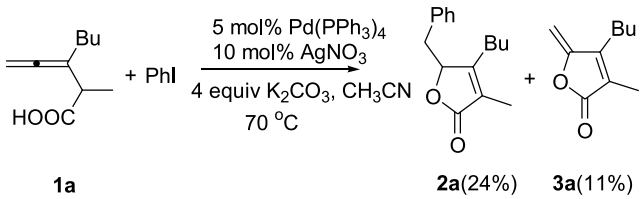
Recently, the chemistry of allenes has been attracting the attention of more and more chemists.[1,2] During the course of our studies on the chemistry of allenes,[3,4] we have developed some new methodologies for the synthesis of butenolides from α-allenoic acids (Scheme 1).[5]



Scheme 1.

2. Results and discussion

When we turned our attention from the α-allenoic acids to the β-allenoic acids **1a**, we found that under the catalysis of $Pd(0)/Ag^+$ the reaction of 2-methyl-3-(*n*-butyl)-3,4-pentadienoic acid with iodobenzene in MeCN afforded not only the coupling-cyclization product **2a** but also 5-methylene-2(5*H*)-furanone **3a** (Scheme 2). Recently, the γ-alkylidene-α,β-unsaturated γ-lactones[6] has also attracted the attention of many organic chemists because of their biological activities[7,8] and versatile use in organic synthesis.[9] When we found product **3a** was obtained in 29% yield in DMF under the catalysis of $Pd(PPh_3)_4$ (entry 1, Table 1), we went on to search a set of reaction conditions for the sole formation of **3a**. When 4 equiv $CuCl_2$ were used instead of PhI, 5-methylene-2(5*H*)-furanone **3a** was afforded under the catalysis of $PdCl_2(PPh_3)_2$ (entry 2, Table 1). However, the product was contaminated by other inseparable by-products. Furthermore, it is lucky for us to observe that when the reaction was conducted under a N_2 atmosphere, **3a** was isolated as the single product in 88% yield with a very high purity (entry 3, Table 1). When $CuBr_2$ was used instead of $CuCl_2$, the reaction was complicated (entry 4, Table 1). In the presence of H_2O or O_2, the purity of the product was also not high (entries 2, 5, and 6, Table 1). When a less amount of $CuCl_2$ was applied, the yield of **3a** was obviously lower (entries 7 and 8, Table 1). Thus, after screening several commonly used catalyst, $PdCl_2(PPh_3)_2$ appeared to be the best (compare entries 9–11 with entry 3, Table 1). The reaction could proceed in the absence of $PdCl_2(PPh_3)_2$ albeit in much lower yield (entry 12, Table 1). Obviously this cyclization reaction can also be mediated by $CuCl_2$ (entry 13, Table 1). In the absence of the base the yield was also low (entry 14, Table 1). When only 3 equiv of K_2CO_3 were added, the product isolated was not pure (entry 15, Table 1). When 5 equiv of $CuCl_2$ were applied, no obvious improvement was observed (entry 16, Table 1). From these results we concluded the best reaction conditions:



Scheme 2.

Keywords: 3,4-Alkadienoic acids; Palladium; $CuCl_2$; Cyclization.
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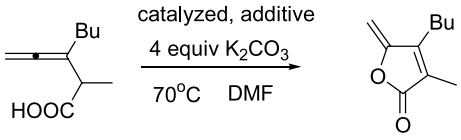
Table 1. Pd-catalyzed cyclization reaction of 2-methyl-3-(*n*-butyl)penta-3,4-dienoic acid **1a**



1a **3a**

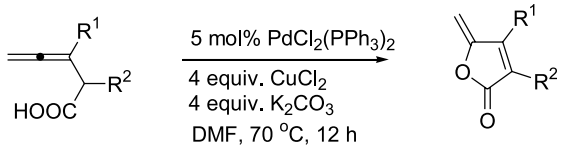
Entry	Catalyst (5 mol%)	Additive (equiv)	Time (h)	Yield of **3a** (%)
1	$Pd(PPh_3)_4$	PhI (1.5)	24	29
2[a]	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	<87[b]
3	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	88
4	$PdCl_2(PPh_3)_2$	$CuBr_2$ (5)	24	complicated
5[c]	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	<50[b]
6[d]	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	<70[b]
7	$PdCl_2(PPh_3)_2$	$CuCl_2$ (2.5)	24	75
8	$PdCl_2(PPh_3)_2$	$CuCl_2$ (0.8)	24	22
9	$PdCl_2$	$CuCl_2$ (4)	24	54
10	$Pd(OAc)_2$	$CuCl_2$ (4)	24	40
11	$PdCl_2(CH_3CN)_2$	$CuCl_2$ (4)	24	34
12	—	$CuCl_2$ (4)	24	60
13	—	$CuCl_2$ (1)	12	18
14[e]	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	70
15[f]	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	<87[b]
16[g]	$PdCl_2(PPh_3)_2$	$CuCl_2$ (4)	12	89

[a] The reaction was exposed to air.
[b] The product is not pure.
[c] The reaction was conducted under 1 atm of pure O_2.
[d] Four equivalents H_2O was added.
[e] No K_2CO_3 was used.
[f] Three equivalents K_2CO_3 were used.
[g] Five equivalents K_2CO_3 were used.

5 mol% $PdCl_2(PPh_3)_2$, 4 equiv of $CuCl_2$, 4 equiv of K_2CO_3 in DMF at 70 °C for 12 h under N_2.

β-Allenoic acids can be conveniently prepared from the hydrolysis of the corresponding β-allenoic acid esters.[10] Subsequently, we studied the scope of this cyclization reaction of β-allenoic acids (Table 2). From the data listed in Table 2, it is obvious that the scope of the reactant is broad: R^1 can be H, alkyl, allyl, Bn or *t*-Bu and R^2 can be H or alkyl. With simple unsubstituted pentadienoic acid, the yield of **3k** (protoanemonin)[7] is 31% by NMR (entry 11, Table 2).

Table 2. $PdCl_2(PPh_3)_2$-catalyzed cyclization reaction of β-allenoic acids **1**



1 **3**

Entry	R^1	R^2		Yield of **3** (%)
1	*n*-Bu	Me	(**1a**)	88 (**3a**)
2	*n*-Bu	H	(**1b**)	78 (**3b**)
3	*n*-Bu	Et	(**1c**)	81 (**3c**)
4	*n*-Bu	*n*-Pr	(**1d**)	84 (**3d**)
5	Me	Me	(**1e**)	64 (**3e**)
6	n-C_7H_{15}	Me	(**1f**)	84 (**3f**)
7	*t*-Bu	Me	(**1g**)	71 (**3g**)
8	Allyl	Me	(**1h**)	66 (**3h**)
9	Bn	Me	(**1i**)	89 (**3i**)
10	H	*n*-Pr	(**1j**)	51 (**3j**)
11	H	H	(**1k**)	31 [a](**3k**)

[a] The yield was determined by NMR using *p*-methoxyiodobenzene as the internal standard.

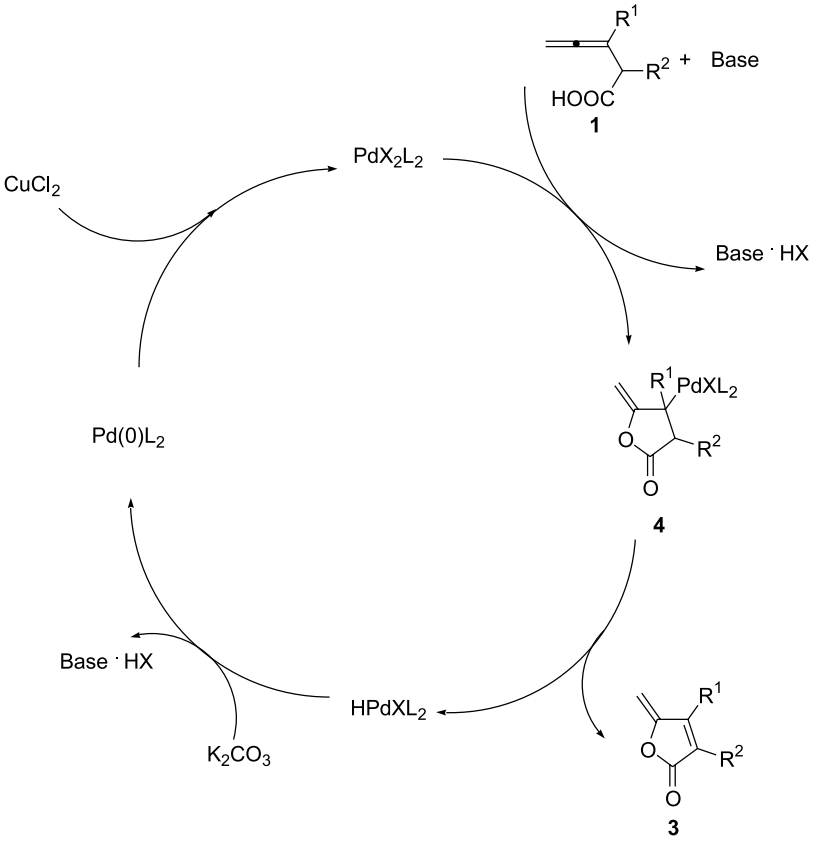
A palladium catalyzed mechanism was proposed for this reaction: *endo*-mode cyclic anti-oxypalladation of the non-terminal carbon–carbon double bonds in the 3,4-allenoic acids would form **4**, which would afford the products **3** via *syn*-β-H elimination, which may be facilitated by the presence of the base and the electron-withdrawing carbonyl group in **4**. The in situ generated palladium hydride species would form Pd(0) species upon its action with K_2CO_3. The catalytically active Pd(II) species would be regenerated via the oxidation with $CuCl_2$ (Scheme 3).

In conclusion, we have described a convenient method for the preparation of the valuable γ-methylene-2(5*H*)-furanones from 3,4-allenoic acids in high yield. The reaction demonstrated high efficiency and regioselectivity. Further studies in this area are being conducted in our laboratory.

3. Experimental

3.1. General procedure for the synthesis of β-allenoic acids 1

Conditions A. A solution of the corresponding β-allenoic acid ethyl ester[10] (6 mmol), and LiOH (288 mg, 12 mmol) was stirred in the mixed solvent of 12 mL of H_2O and 24 mL of MeOH at 30 °C for 3 days. After acidification with 1 N HCl, extraction with ether, drying over anhydrous Na_2SO_4, and evaporation, the mixture was submitted to flash



Scheme 3.

chromatography on silica gel (CH_2Cl_2/MeOH = 10/1) to produce compound **1**.

Conditions B. A solution of the corresponding β-allenoic acid ethyl ester[10] (6.6 mmol) was stirred in the mixed solvent of 27 mL of 20% hydrochloric acid, 20 mL of 1,4-dioxane, and 7 mL of THF at 30 °C for 3 days. After extraction with ether, drying over anhydrous Na_2SO_4, and evaporation, the mixture was submitted to flash chromatography on silica gel (CH_2Cl_2/MeOH = 10/1) to produce compound **1**.

3.1.1. 2-Methyl-3-(*n*-butyl)penta-3,4-dienoic acid (1a). The reaction of the corresponding allenoic acid ester (1044 mg, 5.3 mmol) with LiOH (250 mg, 10.4 mmol) afforded 817 mg (91%) of **1a** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.64 (br s, 1H), 4.85–4.81 (m, 2H), 3.05–2.95 (m, 1H), 2.08–1.93 (m, 2H), 1.47–1.30 (m, 4H), 1.27 (d, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 205.9, 181.3, 103.3, 78.3, 42.1, 30.2, 29.6, 22.3, 15.8, 13.9; IR (neat) 1958, 1711, 1459, 1222 cm^{-1}; MS (*m*/*z*) 168 (M^+, 4.83), 111 (100); HRMS calcd for $C_{10}H_{16}O_2(M^+)$ 168.11503; Found 168.11785.

3.1.2. 3-(*n*-Butyl)penta-3,4-dienoic acid (1b). The reaction of the corresponding allenoic acid ester (1.132 g, 6.2 mmol) with LiOH (314 mg, 13 mmol) afforded 275 mg (29%) of **1b** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.83 (br s, 1H), 4.78–4.70 (m, 2H), 3.03 (t, J = 2.4 Hz, 2H), 2.08–1.99 (m, 2H), 1.48–1.25 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.1, 178.0, 96.7, 76.1, 38.5, 31.2, 29.4, 22.2, 13.8; IR (neat) 1961, 1740 cm^{-1}; MS (*m*/*z*) 154 (M^+, 11.97), 41 (100); HRMS calcd for $C_9H_{14}O_2(M^+)$ 154.09938; Found 154.10058.

3.1.3. 2-Ethyl-3-(*n*-butyl)penta-3,4-dienoic acid (1c). The reaction of the corresponding allenoic acid ester (3654 mg, 17.4 mmol) with LiOH (945 mg, 39.4 mmol) afforded 3060 mg (97%) of **1c** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.52 (br s, 1H), 4.84–4.79 (m, 2H), 2.77 (t, J = 7.5 Hz, 1H), 2.08–1.92 (m, 2H), 1.85–1.71 (m, 1H), 1.69–1.56 (m, 1H), 1.48–1.25 (m, 4H), 0.94 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.2, 180.7, 101.8, 77.8, 49.9, 30.3, 29.5, 23.5, 22.3, 13.9, 12.0; IR (neat) 1957, 1707, 1460, 1219 cm^{-1}; MS (*m*/*z*) 182 (M^+, 1.59), 153 (100); HRMS calcd for $C_{11}H_{18}O_2Na(MNa^+)$ 205.1223; Found 205.1219.

3.1.4. 2-*n*-(Propyl)-3-*n*-(butyl)penta-3,4-dienoic acid (1d). The reaction of the corresponding allenoic acid ester (4613 mg, 20.6 mmol) with LiOH (1198 mg, 50 mmol) afforded 3300 mg (82%) of **1d** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 4.84–4.76 (m, 2H), 2.87 (t, J = 7.5 Hz, 1H), 2.06–1.92 (m, 2H), 1.63–1.52 (m, 1H), 1.45–1.25 (m, 4H), 1.49–1.25 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.2, 180.9, 102.0, 77.8, 48.0, 32.4, 30.2, 29.5, 22.3, 20.6, 13.9, 13.8; IR (neat) 1957, 1708, 1466, 1210 cm^{-1}; MS (*m*/*z*) 196 (M^+, 1.19), 153 (100); HRMS calcd for $C_{12}H_{20}O_2Na(MNa^+)$ 219.1355; Found 219.1377.

3.1.5. 2,3-Dimethylpenta-3,4-dienoic acid (1e). The reaction of the corresponding allenoic acid ester (1.541 g, 10 mmol) with LiOH (480 mg, 20 mmol) afforded 639 mg (51%) of **1e** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (br s, 1H), 4.79–4.72 (m, 2H), 3.08–2.96 (m, 1H), 1.76 (t, J=3.3 Hz, 3H), 1.28 (d, J=6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.5, 181.1, 98.0, 76.3, 42.9, 17.1, 15.5; IR (neat) 1962, 1712, 1456, 1223 cm^{-1}; MS (*m*/*z*) 126 (M^+, 7.53), 111 (100); HRMS calcd for $C_7H_{10}O_2$(M^+) 126.06635; Found 126.06681.

3.1.6. 2-Methyl-3-(*n*-heptyl)penta-3,4-dienoic acid (1f). The reaction of the corresponding allenoic acid ester (1.357 g, 5.7 mmol) with LiOH (297 mg, 12.4 mmol) afforded 639 mg (53%) of **1f** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (br s, 1H), 4.86–4.81 (m, 2H), 3.08–2.95 (m, 1H), 2.14–1.92 (m, 2H), 1.48–1.26 (m, 13H), 0.88 (d, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 205.9, 181.3, 103.4, 78.2, 42.1, 31.8, 30.5, 29.2, 29.1, 27.4, 22.6, 15.8, 14.1; IR (neat) 1958, 1709, 1459, 1221 cm^{-1}; MS (*m*/*z*) 210 (M^+, 3.75), 111 (100); HRMS calcd for $C_{13}H_{22}O_2$(M^+) 210.16198; Found 210.16407.

3.1.7. 2-Methyl-3-(*tert*-butyl)penta-3,4-dienoic acid (1g). The reaction of the corresponding allenoic acid ester (538 mg, 2.7 mmol) with LiOH (145 mg, 5.5 mmol) afforded 143 mg (31%) of **1g** under conditions A: solid; mp 44 °C (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (s, 2H), 3.06 (q, J=6.9 Hz, 1H), 1.29 (d, J=7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 205.3, 181.6, 112.8, 79.1, 37.6, 33.6, 29.0, 18.4; IR (neat) 1950, 1707, 1233 cm^{-1}; MS (*m*/*z*) 169 (M^++1, 93.02), 168 (M^+, 20.46), 153 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found C, 71.46; H, 9.31.

3.1.8. 2-Methyl-3-allylpenta-3,4-dienoic acid (1h). The reaction of the corresponding allenoic acid ester (2745 mg, 15.2 mmol) with LiOH (719 mg, 30 mmol) afforded 553 mg (24%) of **1h** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (br s, 1H), 5.88–5.71 (m, 1H), 5.12–5.02 (m, 2H), 4.88–4.83 (m, 2H), 3.09–2.98 (m, 1H), 2.90–2.73 (m, 2H), 1.28 (d, J=6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.3, 180.9, 135.1, 116.5, 101.6, 78.3, 41.2, 35.7, 15.7; IR (neat) 1958, 1712, 1641 cm^{-1}; MS (*m*/*z*) 153 (M^++1, 38.90), 152 (M^+, 14.13), 107 (100); HRMS calcd for $C_9H_{12}O_2$(M^+) 152.08373; Found 152.08326.

3.1.9. 2-Methyl-3-benzylpenta-3,4-dienoic acid (1i). The reaction of the corresponding allenoic acid ester (1.798 g, 7.8 mmol) with LiOH (402 mg, 16.8 mmol) afforded 1.179 g (75%) of **1i** under conditions A: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (br s, 1H), 7.38–7.15 (m, 5H), 4.87 (br s, 2H), 3.52 (d, J=15.0 Hz, 1H), 3.41 (d, J=15.0 Hz, 1H), 3.03–2.92 (m, 1H), 1.28 (d, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.9, 181.1, 138.7, 129.1, 128.2, 126.4, 102.9, 78.1, 40.6, 38.2, 15.9; IR (neat) 1958, 1705, 1455, 1226 cm^{-1}; MS (*m*/*z*) 202 (M^+, 2.59), 129 (100); HRMS calcd for $C_{13}H_{14}O_2$(M^+) 202.09938; Found 202.09801.

3.1.10. 2-(*n*-Propyl)penta-3,4-dienoic acid (1j). The reaction of the corresponding allenoic acid ester (1693 mg, 10 mmol) afforded 453 mg (33%) of **1j** under conditions B: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.60 (br s, 1H), 5.20 (q, J=3.6 Hz, 1H), 4.80 (d, J=6.9 Hz, 2H), 3.03 (q, J=8.1 Hz, 1H), 1.83–1.72 (m, 1H), 1.64–1.55 (m, 1H), 1.43–1.34 (m, 2H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 208.5, 180.8, 88.7, 76.5, 44.9, 33.9, 20.2, 13.7; IR (neat) 1958, 1709, 1415, 1286, 1208 cm^{-1}; MS (*m*/*z*) 141 (M^++1, 4.15), 97 (100); HRMS calcd for $C_8H_{11}O$(M^+−OH) 123.08099; Found 123.08177.

3.1.11. Penta-3,4-dienoic acid (1k).[11] The reaction of the corresponding allenoic acid ester (2038 mg, 16.2 mmol) afforded 1360 mg (86%) of **1k** under conditions B: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (br s, 1H), 5.23 (pentet, J=6.9 Hz, 1H), 4.79–4.71 (m, 2H), 3.12–3.04 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.3, 178.1, 82.7, 75.9, 33.9; IR (neat) 1960, 1713, 1440 cm^{-1}; MS (*m*/*z*) 98 (M^+, 15.03), 97 (M^+−1, 40.04), 70 (100).

The reaction of **1a** (86 mg, 5.0 mmol), PhI (85 μl, 7.5 mmol), K_2CO_3 (273 mg, 2.0 mmol), $AgNO_3$ (8 mg, 0.05 mmol), and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) in 3 mL of CH_3CN at 70 °C for 33 h produced 30 mg (24%) of **2a** and 9 mg (11%) of **3a** via separation with chromatography on silica gel (petroleum ether/ether=5/1).

3.1.12. 3-Methyl-4-(*n*-butyl)-5-benzyl-2(5*H*)-furanone (2a). Liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 5.09–4.97 (m, 1H), 3.15 (dd, J=3.6, 14.1 Hz, 1H), 2.75 (dd, J=7.5, 14.1 Hz, 1H), 2.53–2.40 (m, 1H), 2.30–2.22 (m, 1H), 1.74 (s, 3H), 1.52–1.22 (m, 4H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.3, 162.5, 135.6, 129.2, 128.3, 126.8, 123.9, 82.1, 38.6, 29.7, 26.4, 22.5, 13.6, 8.5; IR (neat) 1754, 1675, 1455 cm^{-1}; MS (*m*/*z*) 244 (M^+, 0.62), 84 (100); HRMS calcd for $C_{16}H_{20}O_2$(M^+) 244.14633; Found 244.14523.

3.2. General procedure for $PdCl_2(PPh_3)_2$-catalyzed cyclization reaction of β-alleneoic acids 1

Under N_2 atmosphere a solution of **1** (0.5 mmol), $PdCl_2(PPh_3)_2$ (18 mg, 5 mol%), anhydrous $CuCl_2$ (270 mg, 2 mmol), and K_2CO_3 (276 mg, 2 mmol) was stirred in 3 mL of anhydrous DMF at 70 °C for 12 h. The reaction mixture was diluted with ether (50 mL), washed with brine, and dried over anhydrous Na_2SO_4. After evaporation, the residue was submitted to column chromatography on silica gel (petroleum ether/ether=10/1) to produce **3**.

3.2.1. 3-Methyl-4-(*n*-butyl)-5-methylene-2(5*H*)-furanone (3a). The reaction of **1a** (84 mg, 0.5 mmol), $CuCl_2$ (266 mg, 2.0 mmol), K_2CO_3 (277 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 73 mg (88%) of **3a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, J=2.7 Hz, 1H), 4.81 (d, J=2.7 Hz, 1H), 2.44 (t, J=7.5 Hz, 2H), 1.91 (s, 3H), 1.56–1.46 (m, 2H), 1.41–1.30 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.7, 155.2, 150.9, 126.0, 92.5, 31.1, 24.5, 22.6, 13.8, 8.8; IR (neat) 1773, 1648, 1459, 1287 cm^{-1}; MS (*m*/*z*) 167 (M^++1, 10.40), 166 (M^+, 10.40), 124 (100); HRMS calcd for $C_9H_{11}O_2$(M^+−CH_3) 151.0759; Found 151.0785.

3.2.2. 5-Methylene-4-(*n*-butyl)-2(5*H*)-furanone (3b). The reaction of **1b** (74 mg, 0.5 mmol), $CuCl_2$ (267 mg, 2.0 mmol), K_2CO_3 (276 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 57 mg (78%) of **3b**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95–5.92 (m, 1H), 5.13–5.10 (m, 1H), 4.91–4.89 (m, 1H), 2.45 (dt, J=1.2, 7.5 Hz, 2H), 1.66–1.52 (m, 2H), 1.46–1.31 (m, 2H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.2, 159.3, 155.9, 116.6, 94.1, 29.9, 25.7, 22.2, 13.6; IR (neat) 1763, 1651, 1467, 1261 cm^{-1}; MS (*m*/*z*) 153 (M^++1, 21.12), 152 (M^+, 12.22), 110 (100); HRMS calcd for $C_9H_{12}O_2(M^+)$ 152.08373; Found 152.08498.

3.2.3. 3-Ethyl-4-(*n*-butyl)-5-methylene-2(5*H*)-furanone (3c). The reaction of **1c** (92 mg, 0.5 mmol), $CuCl_2$ (282 mg, 2.0 mmol), K_2CO_3 (286 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 74 mg (81%) of **3c**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, J=2.7 Hz, 1H), 4.79 (d, J=2.4 Hz, 1H), 2.42 (t, J=7.5 Hz, 2H), 2.32 (q, J=7.5 Hz, 2H), 1.57–1.46 (m, 2H), 1.44–1.30 (m, 2H), 1.10 (t, J=7.5 Hz, 3H), 0.91 (t, J=6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.1, 155.1, 150.4, 131.3, 92.5, 31.7, 24.3, 22.6, 17.2, 13.7, 12.7; IR (neat) 1772, 1648, 1463, 1296, 1256 cm^{-1}; MS (*m*/*z*) 181 (M^++1, 100); HRMS calcd for $C_{11}H_{16}O_2Na(MNa)^+$ 203.1042; Found 203.1041.

3.2.4. 3-(*n*-Propyl)-4-(*n*-butyl)-5-methylene-2(5*H*)-furanone (3d). The reaction of **1d** (98 mg, 0.5 mmol), $CuCl_2$ (272 mg, 2.0 mmol), K_2CO_3 (278 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 81 mg (84%) of **3d**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, J=2.4 Hz, 1H), 4.79 (d, J=2.7 Hz, 1H), 2.41 (t, J=7.5 Hz, 2H), 2.26 (t, J=7.5 Hz, 2H), 1.58–1.46 (m, 4H), 1.40–1.30 (m, 2H), 0.91 (t, J=7.5 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.2, 155.0, 150.9, 129.9, 92.5, 31.6, 25.7, 24.4, 22.7, 21.4, 13.9, 13.7; IR (neat) 1718, 1648, 1465, 1284 cm^{-1}; MS (*m*/*z*) 195 (M^++1, 32.35), 194 (M^+, 15.12), 123 (100); HRMS calcd for $C_{12}H_{18}O_2(M^+)$ 194.13068; Found 194.13200.

3.2.5. 3,4-Dimethyl-5-methylene-2(5*H*)-furanone (3e). The reaction of **1e** (63 mg, 0.5 mmol), $CuCl_2$ (270 mg, 2.0 mmol), K_2CO_3 (281 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 40 mg (64%) of **3e**: solid; mp 80–81 °C (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, J=2.7 Hz, 1H), 4.79 (d, J=2.7 Hz, 1H), 2.04 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.6, 155.8, 146.6, 126.2, 92.2, 9.9, 8.7; IR (neat) 1763, 1651, 1439, 1285, 1260 cm^{-1}; MS (*m*/*z*) 124 (M^+, 100); HRMS calcd for $C_7H_8O_2(M^+)$ 124.05243; Found 124.05262.

3.2.6. 3-Methyl-4-(*n*-heptyl)-5-methylene-2(5*H*)-furanone (3f). The reaction of **1f** (105 mg, 0.5 mmol), $CuCl_2$ (277 mg, 2.0 mmol), K_2CO_3 (282 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 90 mg (84%) of **3f**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, J=2.1 Hz, 1H), 4.78 (d, J=2.7 Hz, 1H), 2.40 (t, J=7.5 Hz, 2H), 1.88 (s, 3H), 1.53–1.46 (m, 2H), 1.30–1.21 (m, 8H), 0.84 (t, J=6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.7, 155.2, 151.0, 126.0, 92.5, 31.6, 29.4, 29.0, 28.9, 24.8, 22.5, 14.0, 8.8; IR (neat) 1774, 1648, 1466, 1287 cm^{-1}; MS (*m*/*z*) 208 (M^+, 6.83), 124 (100); HRMS calcd for $C_{13}H_{20}O_2(M^+)$ 208.14633; Found 208.14484.

3.2.7. 3-Methyl-4-(*tert*-butyl)-5-methylene-2(5*H*)-furanone (3g). The reaction of **1g** (77 mg, 0.46 mmol), $CuCl_2$ (250 mg, 1.85 mmol), K_2CO_3 (262 mg, 1.90 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 53 mg (71%) of **3g**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (d, J=2.1 Hz, 1H), 5.09 (d, J=2.1 Hz, 1H), 2.08 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.9, 155.5, 154.0, 125.4, 97.0, 34.7, 30.9, 11.3; IR (neat) 1770, 1639, 1464, 1274 cm^{-1}; MS (*m*/*z*) 166 (M^+, 59.06), 123 (100); HRMS calcd for $C_{10}H_{14}O_2Na(MNa)^+$189.0886; Found 189.0894.

3.2.8. 3-Methyl-4-allyl-5-methylene-2(5*H*)-furanone (3h). The reaction of **1h** (77 mg, 0.5 mmol), $CuCl_2$ (269 mg, 2.0 mmol), K_2CO_3 (280 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 50 mg (66%) of **3h**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86–5.72 (m, 1H), 5.15–5.08 (m, 3H), 4.84 (d, J=3.0 Hz, 1H), 3.21 (d, J=6.0 Hz, 2H), 1.92 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.4, 154.8, 147.7, 132.4, 127.1, 117.5, 93.1, 28.9, 8.8; IR (neat) 1782, 1650, 1441, 1287 cm^{-1}; MS (*m*/*z*) 150 (M^+, 36.37), 79 (100); HRMS calcd for $C_9H_{10}O_2Na(MNa^+)$ 173.0573; Found 173.0580.

3.2.9. 3-Methyl-4-benzyl-5-methylene-2(5*H*)-furanone (3i). The reaction of **1i** (101 mg, 0.5 mmol), $CuCl_2$ (264 mg, 2.0 mmol), K_2CO_3 (282 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 90 mg (89%) of **3i**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.13 (m, 5H), 5.08 (d, J=2.7 Hz, 1H), 4.81 (d, J=2.7 Hz, 1H), 3.82 (s, 2H), 1.94 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.3, 154.9, 148.4, 136.5, 128.8, 128.1, 127.4, 126.9, 93.7, 30.6, 9.0; IR (neat) 1770, 1648, 1496, 1454, 1287 cm^{-1}; MS (*m*/*z*) 200 (M^+, 41.10), 84 (100); HRMS calcd for $C_{13}H_{12}O_2Na(MNa^+)$ 223.0729; Found 223.0737.

3.2.10. 3-(*n*-Propyl)-5-methylene-2(5*H*)-furanone (3j). The reaction of **1j** (70 mg, 0.5 mmol), $CuCl_2$ (270 mg, 2.0 mmol), K_2CO_3 (286 mg, 2.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced 36 mg (51%) of **3j**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 5.08 (dd, J=1.2, 2.4 Hz, 1H), 4.76 (d, J=2.4 Hz, 1H), 2.38–2.28 (m, 2H), 1.66–1.54 (m, 2H), 0.95 (t, J=6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.5, 153.9, 136.4, 128.5, 96.5, 27.1, 20.7, 13.6; IR (neat) 1767, 1465 cm^{-1}; MS (*m*/*z*) 138 (M^+, 24.48), 84 (100); HRMS calcd for $C_8H_{10}O_2Na(MNa)^+$ 161.0573; Found 161.0581.

3.2.11. 5-Methylene-2(5*H*)-furanone (3k).[12] The reaction of **1k** (98 mg, 1.0 mmol), $CuCl_2$ (545 mg, 4.0 mmol), K_2CO_3 (550 mg, 4.0 mmol), and $Pd(PPh_3)_4$ (5 mol%) in 3 mL of DMF at 70 °C for 12 h produced **3k** (31%) (determined by NMR using *p*-methoxyiodobenzene as the internal standard).

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Palladium-catalyzed regioselective Heck arylation of electron-rich olefins in a molecular solvent-ionic liquid cocktail

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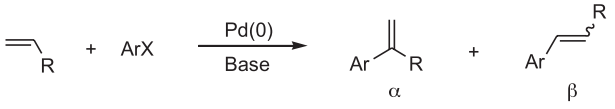
Abstract—We have recently established that highly regioselective Heck arylation of electron-rich olefins can be accomplished with aryl halides without using any halide scavengers in imidazolium ionic liquid solvents. The results presented in this paper show that the benchmark electron-rich olefins vinyl ethers can be readily arylated by aryl bromides in a molecular solvent-ionic liquid cocktail with no compromise on regioselectivity. By introducing a small amount of 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) to DMSO, the arylation reactions of the vinyl ethers **1a–d** by the bromides **2a–j** took place to afford essentially only the α arylated products. The enamide **1e** underwent similar regioselective arylation in the solvent cocktail. In the absence of the ionic liquid, lower regioselectivities were observed. In comparison with the chemistry we have reported so far, the current method reduces considerably the reliance on the volume of ionic liquids used, providing a simpler and more practical synthetic pathway for preparing arylated vinyl ethers and aryl methyl ketones.

1. Introduction

The palladium-catalyzed arylation and vinylation of olefins with aryl halides are well known as the Heck reaction and have proved to be of genuine synthetic utility for carbon–carbon bond formation.[1,2] Although, a great deal of progress has been made in the Heck coupling reactions in the past several years, the olefinic substrates have so far mostly been limited to electronic deficient olefins.[1] With electron-rich olefins, such as silanes, vinyl ethers, and enol amides, there exits an important issue that has not been fully resolved to date, that is the lack of regioselectivity in normal intermolecular Heck reactions.[1a,d-f,3] Such reactions usually give rise to a mixture of α and β substituted olefins and hence, are of only limited synthetic utility (Eq. 1). The problem with regioselectivity can be addressed by using aryl triflates instead of halides or stoichiometric amounts of halide scavengers when aryl halides are used, toxic thallium(I) or costly silver(I) salts being most popular.[3] The effect of the triflates and halide scavengers on the regioselectivity stems from their effect on the reaction pathway. The Heck reaction is believed to proceed via two pathways, one ionic leading to the branched product and the other neutral giving rise to the linear variant (Scheme 1).[3,4] One can easily envision that the ionic pathway will be rendered favorable when triflates or halide scavengers are chosen. However, triflates are thermally labile and in general not commercially available, and the inorganic additives create new problems such as toxicity and high cost. Therefore, it is practically important to develop novel methods, which would allow aryl halides to be used in regioselective arylation of electron-rich olefins with no need for costly or toxic additives.



(1)

In a programme aimed at developing organometallic catalysis in ionic liquids,[5] we disclosed that highly regioselective Heck arylation with aryl halides can be accomplished in imidazolium ionic liquids without recourse to halide scanvegers.[5d,6] In these reactions, pure ionic liquids were used as the bulky solvent. This may create a problem for using the chemistry in various synthetic reactions, as ionic liquid are by no means cheap as solvents and their toxicity and biodegradability are yet to be fully determined.[7] With these concerns in mind, we decided to minimize the amount of ionic liquid used. We now disclose that regioselective arylation of electron-rich olefins can be carried out equally well in a solvent cocktail that contains little ionic liquid. Although molecular solvent-ionic liquid

Keywords: Heck reaction; Electron-rich olefins; Regioselectivity; Ionic liquid; DMSO.
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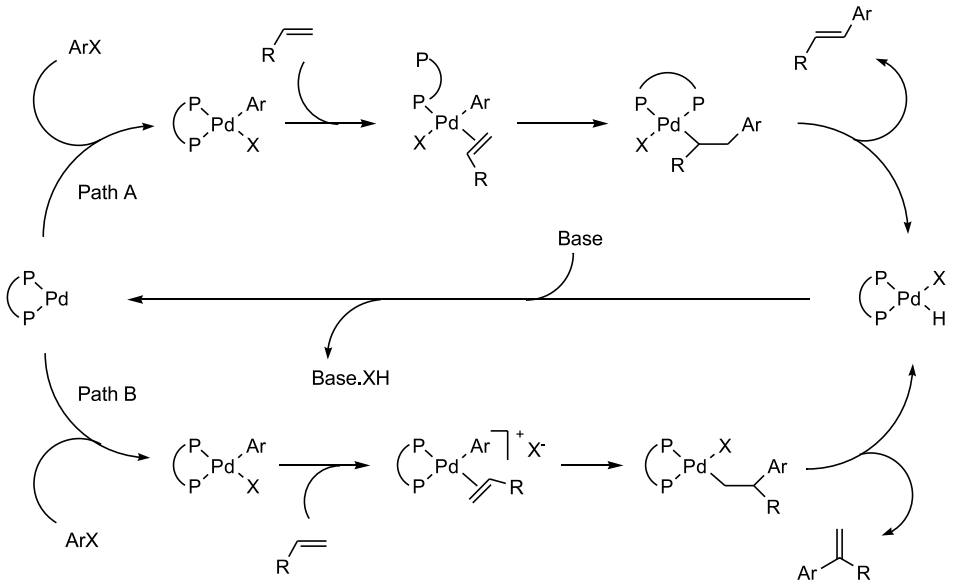


Scheme 1. The neutral and ionic pathways of the Heck reaction.

cocktails have been used in catalysis, ionic liquids act in most instances as the bulky solvents with molecular solvents added mainly to enhance substrate solubilities and/or facilitate catalyst/product separation via phase separation.[8]

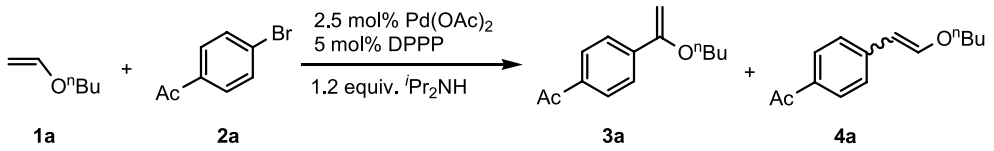
Room temperature ionic liquids such as those based on imidazolium salts have been extensively studied as one of the most promising alternatives to hazardous organic solvents for clean chemical reactions, due to their novel physicochemical properties such as low vapor pressure and tunable solubility for organic or inorganic compounds.[7,9] These solvents are entirely composed of ions; hence, the ionic Heck pathway could be made favorable when an arylation reaction is performed therein. Indeed, shortly after our initial report on the highly regioselective arylation of butyl vinyl ether with aryl bromides in [bmim][BF_4],[5d] Hallberg and co-workers reported similar reactions in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]).[10] High regioselectivities could also be achieved in aqueous DMF, in which water acts as an indispensable polar additive.[11]

2. Results and discussion

In our previous studies into the Heck arylation of electron-rich olefins by palladium catalysis,[5d,6] ionic liquids were used as the sole solvents. A typical arylation reaction at the scale of 1 mmol of substrate would normally require the use of 2 mL of an ionic liquid. To determine if the volume of ionic liquids could be reduced without compromising the regioselectivity at the same time, we examined the arylation of the benchmark electron-rich olefin butyl vinyl ether **1a** by 4-bromoacetophenone **2a** in a DMSO-[bmim][BF_4] solvent cocktail under conditions previously optimized for reactions in neat [bmim][BF_4]. The catalyst was derived in situ from 1 equiv of $Pd(OAc)_2$ and 2 equiv of a diphosphine, 1,3-bis(diphenylphosphino)propane (DPPP). The choice of DMSO as the molecular solvent was based on our observation that it promotes regioselective arylation of enamides in [bmim][BF_4].[6] For comparison, the arylation of **1a** was also carried out in neat DMSO. In a typical reaction, a mixture of **1a**, **2a**, $^{i}Pr_2NH$, $Pd(OAc)_2$, and DPPP was heated in a chosen solvent for 24 h under an inert atmosphere. The products were analyzed by NMR and the results are given in Table 1. As can be seen, in the molecular solvent DMSO, which is often used in the Heck reactions, the reaction afforded an α/β ratio of 86/14 (entry 1). This is consistent with early observations, that is, mixtures of regioisomers result when electron-rich olefins are arylated with aryl halides in molecular solvents.[12] Surprisingly somewhat, when 0.01 ml of [bmim][BF_4] was used as additive, the reaction afforded a better α/β ratio of 91/9 (entry 2). The regioselectivity was further improved when 0.05 ml of [bmim][BF_4] was added (entry 3), and much to our delight, when 0.1 ml of the ionic liquid was introduced to 2 ml of DMSO, **1a** was completely arylated by **2a** to give essentially exclusively the α substituted product **3a** (entry 4); the ^1H NMR spectrum of the reaction mixture after removing the ionic liquid showed no sign of the linear olefin **4a**, indicating that the ionic pathway B becomes overwhelmingly dominated in the presence of even catalytic amount of [bmim][BF_4] (5% volume; ca. 0.5 mmol) in DMSO. Song, Chi and co-worker have recently, reported a method that effects very efficient fluorination of mesylates by KF in a wet mixture of [bmim][BF_4] and CH_3CN, with catalytic amount of ionic liquid being feasible as well albeit less efficient.[8e]

Encouraged by the results above, we extended the scope of additives to other ionic liquids. As is clear, all the additives, [bmim][PF_6], [bmim][NTf_2] and [bdmim][BF_4],[13] promote the regioselectivity in favor of the branched product (entries 5–7). However, the regioselectivity was slightly poorer with these ionic liquids under similar conditions. In contrast, little conversion was observed when the ionic liquid additive was [bmim][Br] (entry 8). This is likely to be due to halide coordination to palladium, which affects the

Table 1. Solvent effect on the Heck arylation of butyl vinyl ether by 4-bromoacetophenone[a]



Entry	Molecular solvent	Ionic liquid (mL)	Conversion (%)[b]	α/β[c]	E/Z[d]
1	DMSO	[bmim][BF_4] (0)	100	84/16	79/21
2	DMSO	[bmim][BF_4] (0.01)	100	91/9	78/22
3	DMSO	[bmim][BF_4] (0.05)	100	98/2	77/23
4	DMSO	[bmim][BF_4] (0.1)	100	>99/1	—
5	DMSO	[bmim][PF_6] (0.1)	100	97/3	63/37
6	DMSO	[bmim][NTf_2] (0.1)	100	95/5	71/29
7	DMSO	[bdmim][BF_4] (0.1)	100	97/3	70/30
8	DMSO	[bmim][Br] (0.1)	5	92/8	—
9	DMSO[e]	None	100	90/10	81/19
10	DMSO[e]	H_2O (0.1)	100	61/39	70/30
11	DMF	[bmim][BF_4] (0)	100	75/25	80/20
12	DMF	[bmim][BF_4] (0.1)	100	94/6	79/21
13	None[f]	[bmim][BF_4] (0.01)	36	>99/1	—
14	None[f]	[bmim][BF_4] (0. 1)	70	>99/1	—
15	DMSO	[$^nBu_4N$][BF_4] (0.2)[g]	100	77/23	80/20
16	DMSO	[$^nBu_4N$][BF_4] (0.5)[g]	100	65/35	76/24

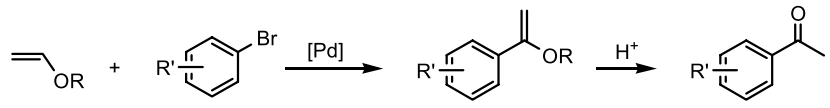
[a] Reaction conditions: 2.0 mmol **1a**, 1.0 mmol **2a**, 2.5 mol% $Pd(OAc)_2$, 5.0 mol% DPPP and 1.2 equiv $^iPr_2NH$ in the solvent cocktail DMSO/DMF (2 mL)+ ionic liquid at 115 °C for 24 h; the product was analyzed by ^1H NMR.
[b] Conversion of **2a** to **3a** and **4a**.
[c] Molar ratio of **3a/4a**; when the product **4a** could not be detected by ^1H NMR, a value of >99/1 was assigned.
[d] Ratio of *trans*/*cis* isomers of **4a**.
[e] Dried DMSO.
[f] 10.0 mmol **1a** and 3.0 mmol $^iPr_2NH$ were used.
[g] The number refers to mmol salt added.

generation of the cationic Pd-olefin species (vide supra), and/or the formation of inactive 1-butyl-3-methylimidazol-2-ylidene complexes of palladium.[14] The DMSO of this study was used as received. Drying the DMSO with molecular sieves resulted in a slightly increased α/β ratio, whilst adding water to the pre-dried DMSO led to its deterioration (entries 9 and 10). In the latter case decomposition of the Pd-DPPP catalyst appeared to occur as judged by the formation of palladium black, which may explain the partial loss of regioselectivity. Significantly improved regioselectivity was also observed when 5% [bmim][BF_4] was introduced into 2 ml of DMF (entries 11 and 12). It was surprising that the reaction proceeded, even without utilizing any molecular solvent, to give rise to exclusively the α substituted product **3a** when 0.01 mL of [bmim][BF_4] was added to the reaction mixture, although it was slow, only affording a 36% conversion (entry 13). However, when the amount of ionic liquid was increased to 0.1 mL, the reaction was accelerated to give a 70% conversion with >99/1 regioselectivity (entry 14). It is noteworthy that in the absence of the ionic liquid, little olefinic product was observed, showing that the ionic liquid plays a pivotal role for the enhanced regioselectivity.

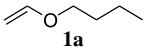
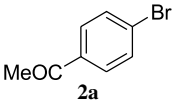
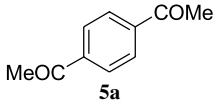
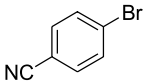
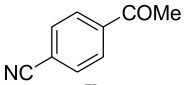
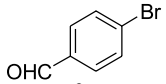
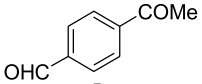
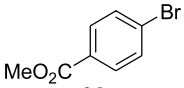
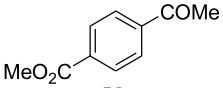
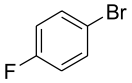
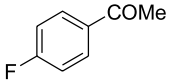
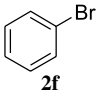
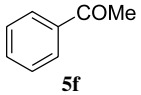
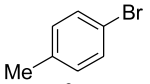
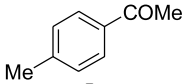
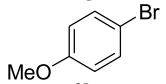
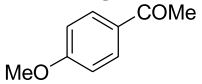
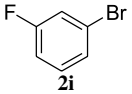
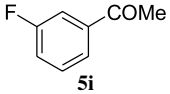
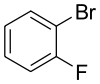
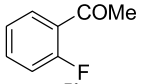
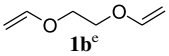
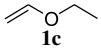
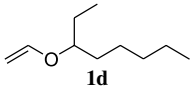
The excellent regioselectivity observed in the DMSO-[bmim][BF_4] solvent cocktail is in line with the arylation proceeding via the ionic pathway that is promoted by the ionic liquid. We have previously shown that amongst various molecular solvents DMSO exerts the best α regiocontrol over the arylation of vinyl ethers; but it could not deliver the same effect as imidazolium ionic liquids.[6] In the present study, DMSO probably plays a role in reinforcing the effect of the ionic liquids, as it is well known to facilitate ligand substitution on square-planar complexes.[15] How the ionic liquids promote the ionic pathway remains unclear, however. Their effects on the α regioselectivity may stem partly from increased ionic strength of the solution, which would be expected to enhance the rate of formation of the ionic palladium species shown in Scheme 1.[16] However, this is somewhat at odds with the observations made when a very small amount of [bmim][BF_4] was added without DMSO (entries 13 and 14), although, one might speculate that those reactions could take place in small droplets of ionic liquid. Furthermore, replacing [bmim][BF_4] with [$^nBu_4N$][BF_4] for the cocktail reaction brought about no improvement in the α/β ratios (entries 15 and 16), suggesting that the primary role of [bmim][BF_4] cannot be ascribed to its effect on the ionic strength. One possibility is the hydrogen bonding of the C^2–H proton with the halide anions,[17,5a] which might facilitate the dissociation of the bromide ion from Pd(II) and hence, the ionic pathway. However, this is not entirely backed by the observation made with [bdmim][BF_4], nor is it consistent with our previous report and that by Dyson.[6,18] Clearly, much remains to be done to delineate the role of the ionic liquids.

On the basis of the above studies, the arylation of **1a** was undertaken in the DMSO-[bmim][BF_4] mixture (20/1 volume ratio) with a variety of aryl bromides in the presence of 2.5 mol% $Pd(OAc)_2$ and 5.0 mol% DPPP. The isolated products were the aryl methyl ketones **5** following acidification of **3**. The results obtained are summarized in Table 2. As can be seen, excellent regioselectivities together with high isolated yields for the ketones **5** were obtained in

Table 2. Heck arylation of vinyl ethers **1a–d** by aryl bromides **2** in DMSO-[bmim][BF_4][a]



1 **2** **3** **5**

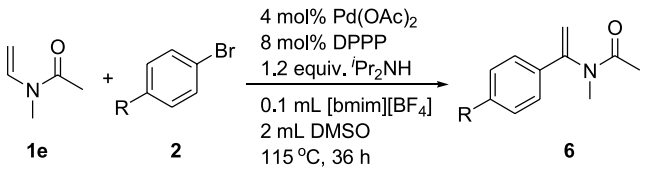
Entry	Olefin	Aryl bromide	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **5a**	92
2	**1a**	 **2b**	 **5b**	88[c]
3	**1a**	 **2c**	 **5c**	89
4	**1a**	 **2d**	 **5d**	94
5	**1a**	 **2e**	 **5e**	96
6	**1a**	 **2f**	 **5f**	95
7	**1a**	 **2g**	 **5g**	87
8	**1a**	 **2h**	 **5h**	84[c]
9	**1a**	 **2i**	 **5i**	82[d]
10	**1a**	 **2j**	 **5j**	81[d]
11	 **1b**[e]	**2a**	**5a**	96
12	 **1c**	**2a**	**5a**	91
13	 **1d**	**2a**	**5a**	85

[a] Reaction conditions: 2.0 mmol **1**, 1.0 mmol **2**, 2.5 mol% $Pd(OAc)_2$, 5.0 mol% DPPP and 1.2 equiv $^iPr_2NH$ in DMSO (2 mL)+[bmim][BF_4] (0.1 mL), at 115 °C for 24 h; all reactions afforded 100% conversion and >99/1 α/β selectivity, as determined by ^1H NMR.
[b] Isolated yield of **5**.
[c] $Pd(OAc)_2$ (4 mol%) and 8 mol% DPPP were used, 36 h.
[d] Thirty six hours.
[e] 0.75 mmol of **1b** was used.

all the reactions in the solvent cocktail, regardless of the nature of the substituents on the aryl rings. Thus, bromobenzenes bearing either strongly electron-withdrawing or electron-donating *p*-substituents, such as –CN or –OMe, all furnished good to excellent isolated yields with α/β ratios of >99/1 (entries 1–8). With either the very electron-withdrawing or donating substituents, –CN or –OMe, the reaction tended to be slower and required a higher catalyst loading, however. With these two substituents, the olefin insertion step or coordination step might be inhibited, leading to slower reactions. Similar arylation reactions can be carried out with *m*- and *o*-substituted bromobenzenes, as demonstrated by the substrates **2i** and **2j** (entries 9 and 10).

The vinyl ethers **1b–d** underwent similar arylation under the same conditions. Examples of arylation of these olefins with **2a** are also seen in Table 2 (entries 11–13). These reactions again furnished >99/1 α/β regioselectivities and over 80% isolated yields for the ketone **5**. Under the given conditions, all the reactions shown in Table 2 went to completion; but shorter times should be possible, since the reaction time was not optimized for each individual reaction. The protocol thus provides a simple, practical supplement to the known methodologies for the synthesis of important aromatic ketones, and particularly to Friedel Crafts acylation, which is neither effective toward electron-deficient arenes nor as regioselective as the current method for the introduction of an acetyl group.[19]

In addition to the vinyl ethers, enamides could also be arylated under the same conditions. A few selected examples concerning the enamide **1e** are given in Eq. 2. The reactions were complete in 36 h, furnishing exclusively the branched product. We have previously shown that **1e** could not be arylated in neat [bmim][BF_4] and the reaction led to a mixture of products when run in neat DMSO.[6] The remarkable regioselectivities observed here suggest that the ionic path B (Scheme 1) is significantly facilitated in the arylation in the presence of even a small quantity of [bmim][BF_4].



2 = **2a** (R = *p*-Ac), **2f** (R = H), **2g** (R = *p*-Me).

100% conversion with α/β >99/1 for all, based on two runs for each.

(2)

3. Conclusions

We have recently developed the ionic liquid method for the highly regioselective Heck arylation of electron-rich olefins with aryl halides by palladium catalysis, circumventing the problems of using halide scavengers, which are often expensive and toxic. We have now shown that the same level of regiocontrol can be delivered for the same reaction by using a molecular solvent-ionic liquid cocktail that contains only a few percent of an ionic liquid, [bmim][BF_4]. This is significant that it substantially reduces the usage of ionic liquids and hence, makes the chemistry more practical for chemical synthesis. The unique regiocontrol observed in the mixed solvent results probably from the promoting effect of the ionic liquid on the ionic pathway, which is generally believed to give rise to the branched olefins. The molecular details of the mechanism remain to be delineated, however.

4. Experimental

All reactions were carried out under a nitrogen atmosphere. 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) was prepared according to the literature method.[20] Following vacuum-drying at 80 °C for 8 h, the ionic liquid was stored under nitrogen at ambient temperature. $AgNO_3$ titration showed the chloride content of the ionic liquid to be below detection limit (<0.2%). Vinyl ethers **1a–d**, aryl halides **2**, $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (DPPP), and diisopropylamine were purchased from Lancaster and Aldrich and were used as received. DMSO was bought from VWR and was used as received (≥99% purity).

An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl halide **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), DPPP (0.05 mmol), DMSO (2 mL) and [bmim][BF_4] (0.1 mL) under nitrogen at room temperature. Following degassing three times, vinyl ether **1** (2.0 mmol) and $^iPr_2NH$ (1.2 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at the desired temperature. After a reaction time of 24 h, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for NMR analysis. To the rest of the mixture, aqueous HCl (5%, 5 mL) was added and following stirring for 0.5 h, CH_2Cl_2 (20 mL) was added. After separation of the organic phase, the aqueous layer was extracted with CH_2Cl_2 (2×20 mL), and the combined organic phase was washed with water until neutrality, dried (Na_2SO_4), filtered, and concentrated in vacuo. The aryl methyl ketone was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99–10/90) as eluant. The identity and purity of the products were established by comparing their NMR, MS and HRMS spectra with the published data,[6] which are available for all the products in this study.

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A practical synthesis of highly functionalized aryl nitriles through cyanation of aryl bromides employing heterogeneous Pd/C: in quest of an industrially viable process

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Abstract—Preparation of aryl nitrile **2a** through classical Rosenmund-von Braun reaction of aryl bromide **1a** resulted in a poor yield (61%) due to a high reaction temperature (165 °C) and a lack of efficient procedure for separating **2a** from a large quantity of heavy metal waste (Cu salts). To address these issues, a practical synthesis of multifunctional aryl nitriles through cyanation of aryl bromides has been developed with heterogeneous Pd/C used as the catalyst. Treatment of aryl bromides **1** with $Zn(CN)_2$ in the presence of Pd/C, Zn, $ZnBr_2$ and PPh_3 in DMA provided aryl nitriles **2** involving those carrying sterically demanding electron-rich substituent in good yields and in highly reproducible manner. The activity of Pd/C is highly dependent on the properties of the Pd/C. Oxidic thickshell type catalyst Pd/C D5 was found to furnish the highest rate acceleration and yield. The use of heterogeneous Pd/C might anchor and disperse Pd over the solid support of the catalyst, at least in the initial stage of the reaction, to assure the formation of monomeric Pd complex without precipitating to inactive Pd black. The use of a slightly excess of $Zn(CN)_2$ (0.6 equiv) and air oxidation of phosphine ligand, after end of the reaction, converted Pd species to insoluble phosphine-free Pd cyanides, from which Pd was recovered in high yield through simple filtration followed by usual recovery process involving combustion.

1. Introduction

Development of an industrially viable process for drug synthesis forces one to consider a number of factors to affect feasibility of the reaction as well as economy of the overall sequence. For protection of the ecology, the reaction with lower environmental impact is required as well. Meanwhile, Pd-catalyzed cross coupling reaction has recently been underscored as a synthetic methodology and its application to large-scale production of chemicals carrying various functional groups has been extensively investigated with some measure of success.[1] As significance of aryl nitriles in the drug synthesis[2] increases, so does the demand for the truly efficient synthetic method. Synthesis of aryl nitriles through Pd-catalyzed cyanation of aryl halides[3] represents one of the most direct approaches to this important class of compounds. In contrast to remarkable leading-edge technologies, accomplished on the Pd-catalyzed C–C and C–X (X=N, O and S) bond forming reaction such as Suzuki–Miyaura coupling, Heck reaction, amination and amidation in the past decade,[1c] Pd-catalyzed cyanation is far from perfect and still needs further investigation for subjecting to scalable and cost-effective preparations. Intensive efforts to improve the reaction have currently been undertaken not only in academia but also in pharmaceutical industries. However, they still pose many challenges, when aimed at applying for commercial-scale production. They need inherently very expensive and/or toxic phosphine ligand or additive. Cyanation of aryl halides carrying sterically demanding electron-rich substituent, such as amino and hydroxyl group, has hardly been accomplished, still posing a big challenge for the practical use. Reported herein is a course of our investigations to develop a more versatile and industrially viable process for the cyanation of aryl bromides.[4]

2. Results and discussion

2.1. Synthesis of aryl nitrile 2a through Rosenmund-von Braum reaction of aryl bromide 1a

Cyanation of aryl bromide was first investigated applying classical Rosenmund-von Braum reaction[5] with 3-bromo-4-hydroxymorpholinobenzamide (**1a**) used as the typical

Keywords: Cyanation; Palladium on charcoal; Cross-coupling reaction; Aryl bromides; Aryl nitriles; Zinc dust; Bromine; Zinc bromide.
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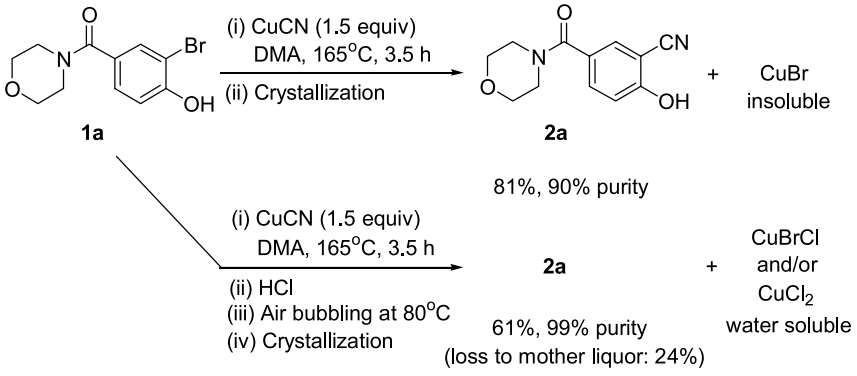


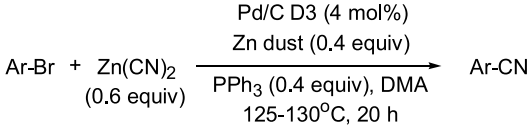
Scheme 1. The Rosenmund-von Braun reaction of **1a** to **2a** and isolation of the product **2a**.

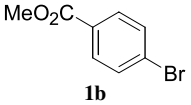
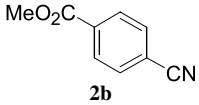
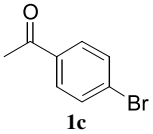
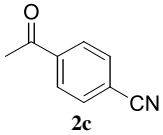
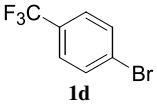
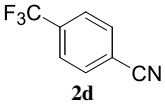
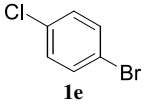
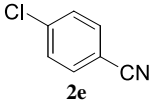
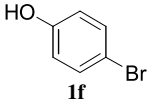
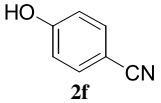
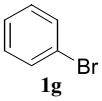
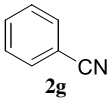
substrate (Scheme 1). Treatment of **1a** with CuCN (1.5 equiv) in DMA at 165 °C for 3.5 h gave desired aryl nitrile **2a** in 93% yield (98% conversion), accompanied by a small amount of hydration byproduct, 3-carbamoyl-4-hydroxymorpholinobenzamide (**3**) (**2a/3**=95:5). Isolation of the product **2a** was initially conducted by direct crystallization of the residue that was obtained by evaporation of DMA. Purity of the resulting **2a** was, however, at most 90%, as it was contaminated with a large amount of insoluble Cu^{I} salts. The use of an alternative workup, involving oxidation of the insoluble Cu^{I} salts to soluble and easy-removable Cu^{II} analogues (CuClBr and/or $CuCl_2$)[6] and subsequent crystallization, provided much purified **2a** (purity: 99%). However, the yield was moderate (61%), because of considerable loss of **2a** to the mother liquor.

2.2. Synthesis of aryl nitrile 2a through cyanation of aryl bromide 1a with $Zn(CN)_2$ employing Pd/C, Zn and PPh_3

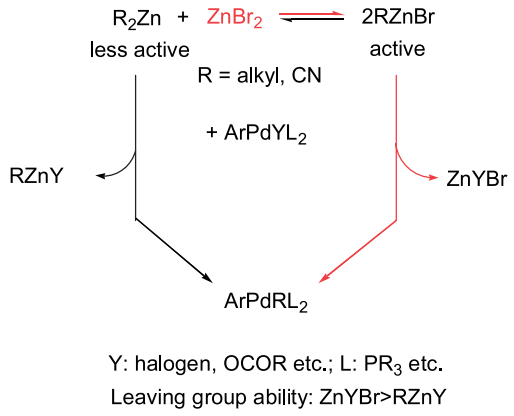
To lower the reaction temperature and to eliminate the formation of a large amount of hazardous Cu salts, we investigated Pd-catalyzed cyanation of aryl bromides as an alternative method. In a series of our synthetic studies of

Table 1. Cyanation of various aryl bromides **1b–g** to aryl nitriles **2b–g** with $Zn(CN)_2$ in the presence of Pd/C D5, Zn and PPh_3



Entry	Substrate **1b–g**	Substrate **2b–g**	Conv. (%)[a]	Assay yield (%)[a]
1[b]	 **1b**	 **2b**	29–100	31–72
2	 **1c**	 **2c**	99	93
3	 **1d**	 **2d**	100	91
4	 **1e**	 **2e**	100	58
5	 **1f**	 **2f**	6	—[c]
6	 **1g**	 **2g**	0	—[c]

[a] Determined by HPLC.
[b] The reaction was conducted at 130–150 °C for 20–24 h.
[c] Not determined.



Scheme 2. Equilibrium of zinc reagents and $Zn(CN)_2$ in the presence of $ZnBr_2$ and their reaction with palladised aryl bromides and carboxylates.

(+)-biotin,[7] we have reported heterogeneous Pd/C-catalyzed Fukuyama reactions, that is, transformations of thiol esters to aldehydes or ketones.[7a–e,k] As an extension of the study, we investigated the synthesis of aryl nitriles through cyanation of aryl bromides employing readily accessible and inexpensive Pd/C.

In our initial study, cyanation of methyl 4-bromobenzoate **1b** was investigated as a typical example. Treatment of **1b** with $Zn(CN)_2$ (0.6 equiv) in the presence of Pd/C D5[8] (oxidic, uniform type, vide infra) (4 mol%), inexpensive PPh_3[9] (0.16 equiv) and Zn dust (0.4 equiv) in DMA at 130–150 °C for 20–24 h was found to provide desired aryl nitrile **2b**. However, the reaction fluctuated widely (31–72%) and overall lacked reproducibility (Table 1, entry 1). The protocol is problematic in scope and limitation as well. While, in the case of electron-deficient aryl bromides **1c–e**, a moderate to high yield of the desired products **2c–e** were similarly obtained, the relatively electron-rich aryl bromides **1f,g** were almost inactive under the same reaction conditions (Table 1, entries 1–4 vs entries 5 and 6). What we had to come up with was an alternative reaction protocol, which is, applicable even with electron-rich aryl bromides and controls reaction precisely for scale-up.

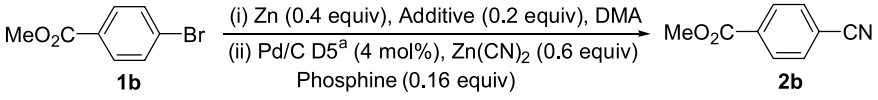
2.3. Synthesis of aryl nitriles 2 through cyanation of aryl bromides 1 with $Zn(CN)_2$ employing Pd/C, Zn, $ZnBr_2$ and PPh_3

As shown in our previous report[7k] on the Fukuyama coupling reaction of zinc reagents with thiol esters, prior addition of Br_2 to Zn dust, that in situ produces $ZnBr_2$, is very effective not only for activation of Zn dust but also for generation of active alkyl zinc halide (RZnBr) through a shift of the Schlenk equilibrium from R_2Zn to RZnBr (Scheme 2, R=alkyl). We envisioned that the Schlenk type equilibrium might occur as well on $Zn(CN)_2$ (Scheme 2, R=CN). Much enhanced activity and solubility would be expected of CNZnBr than $Zn(CN)_2$ because of higher leaving group activity of ZnYBr (Y=halogen or carboxylate anion etc.) compared with CNZnY, both of which are assumed to liberate on reaction with palladium complex, $ArPdYL_2$. The well-documented Pd-deactivation[3k] by coordination with cyanide ion might be suppressed as well through the gradual formation of soluble CNZnBr from fairly insoluble $Zn(CN)_2$.

The reaction was thus conducted with initial addition of Br_2 (0.2 equiv) to the mixture of Zn dust in DMA at 25 °C to activate Zn dust and in situ generate $ZnBr_2$. As expected, with this pre-treatment, the reaction was completed in 3 h at much lower temperature (80 °C) to afford **2b** in 97% yield and in highly reproducible manner (Table 2, entry 2). While the reaction proceeded as well in the presence of other Zn-activating reagents such as I_2, TMSCl or 1,2-dibromoethane that, on treatment with Zn dust, also generates zinc halides (ZnX_2, X=I, Br or Cl[10]), the yield slightly declined (Table 2, entries 3–5). An inferior result (73% yield) was obtained by the addition of $Zn(OAc)_2$, a known efficient activator for the cyanation of aryl halides employing homogeneous Pd catalyst (Table 2, entry 6).[3f] The observation reflects the importance of halide anion (Cl^-, Br^- and I^-)[11] of zinc halides in the cyantaion (vide infra).

Dppf participated similarly well in the cyanation (Table 2, entry 7). In contrast, electron-rich bulky ligands such as P(*o*-tol)$_3$, Cy_3P and *t*-Bu_3P were almost inactive (Table 2, entries

Table 2. Cyanation of **1b** to **2b** with $Zn(CN)_2$ in the presence of Pd/C D5,[a] Zn dust, PPh_3 and various additives



Entry	Phosphine	Additive	Temp (°C)	Period (h)	Conv. (%)[b]	Assay yield (%)[b]
1	PPh_3	None	130–150	20–24	29–100	31–72
2	PPh_3	Br_2	80	3	100	97
3	PPh_3	I_2	80	4	99	92
4	PPh_3	TMSCl	80	3	100	95
5	PPh_3	$Br(CH_2)_2Br$	80	4	100	90
6	PPh_3	$Zn(OAc)_2$	80	7	73	—[c]
7	dppf[d]	Br_2	80	3	100	88
8	P(*o*-tol)$_3$	Br_2	80	3	1	—[c]
9	Cy_3P	Br_2	80	3	0	—[c]
10	*t*-Bu_3P	Br_2	80	3	5	—[c]

[a] Pd/C was purchased from Degussa Japan Co., Ltd.[8]
[b] Determined by HPLC.
[c] Not determined.
[d] Ligand 0.08 equiv was employed.

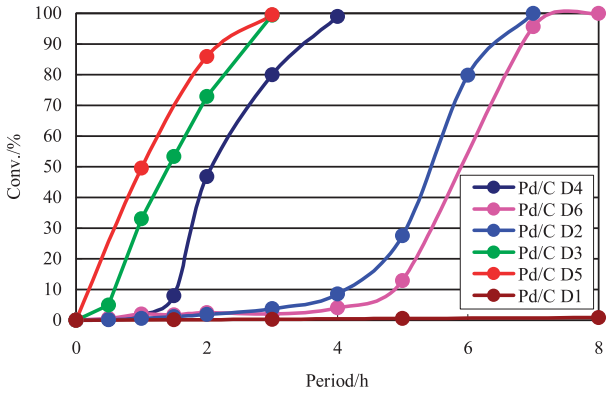


Figure 1. Screen of Pd/C catalyst[8] in the cyanation of **1b** to **2b**. The reaction was conducted by the use of Pd/C (4 mol%), Zn (0.4 equiv), Br_2 (0.2 equiv) and PPh_3 (0.16 equiv) at 80 °C in DMA. Pd/C D1: oxidic, eggshell; Pd/C D2: reduced, eggshell; Pd/C D3: oxidic, uniform; Pd/C D4: reduced, uniform; Pd/C D5: oxidic, thickshell; Pd/C D6: reduced, thickshell.

8–10). For explanation of the inferior result obtained by the addition of *t*-Bu_3P, there are not any possibilities that the remaining Br_2 oxidizes the highly basic phosphine *t*-Bu_3P in preference over less basic PPh_3 and dppf, because Br_2, upon addition to zinc dust, disappears rapidly through reduction to $ZnBr_2$. Although dppf is expensive, PPh_3 is economical in practice and easy to handle, and, hence, it has finally been chosen as the ligand for the cyanation.

The next step is to optimize Pd/C catalyst[8] in the cyanation of **1b** to **2b** (Fig. 1). Among the Pd/C catalysts tested, oxidic thickshell type Pd/C D5, where Pd disperses at 200–500 nm from the surface and having low reduction degree, exhibited the highest activity. In contrast, oxidic eggshell type Pd/C D1, where Pd localizes closer to the surface (50–150 nm), was almost inactive. Somewhat delayed rate acceleration, observed in oxidic uniform type Pd/C D3 as compared with Pd/C D5, might reflect inferior diffusion of the substrate **1b** to the Pd surface in Pd/C D3. The reduced type Pd/C D4, D2 and D6 were much less active than the oxidized counterparts Pd/C D3 and D5, though Pd/C D1 irregularly behaved.

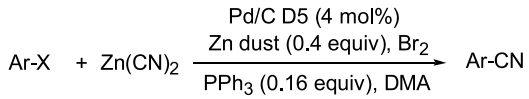
The present cyanation tolerates substantial variation in aryl bromides as the substrates (Table 3). Even aryl bromides **1i**, **1k**, and **1l** carrying electron-donating substituents, that gave poor yields through the reported procedure,[12] furnished the corresponding aryl nitriles **2i**, **2k**, and **2l** in good to excellent yields at slightly higher reaction temperature (115–125 °C) (Table 3, entries 4, 6, and 7). Broad range of functional groups such as acetyl, ester, amino, hydroxyl, and sulfide groups were all compatible with the reaction conditions (Table 3, entries 1, 2, 4, and 6–9). To the best of our knowledge, the successful cyanation of sterically congested electron-rich aryl bromides, such as 2-*N*,*N*-dimethylamino-bromobenzene **1i** and 2-hydroxybromobenzene **1l**, represents the first examples hitherto recorded. However, the present cyanation is limited in scope. It was effective with the aryl bromides but not with less reactive and less expensive aryl chloride such as 4′-chloroacetophenone **1o**. Even prolonged heating the reaction mixture of **1o** at 140 °C provided only 4% conversion (Table 3, entry 10).

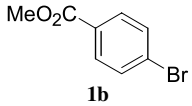
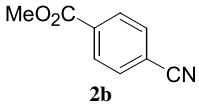
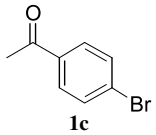
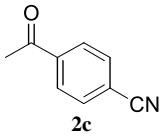
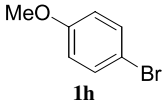
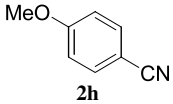
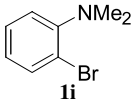
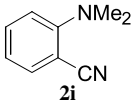
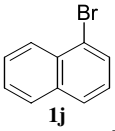
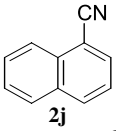
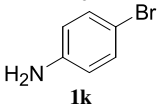
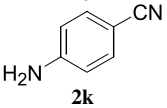
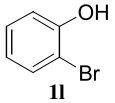
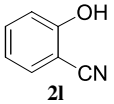
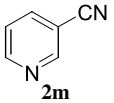
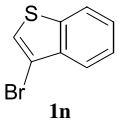
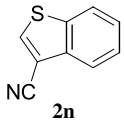
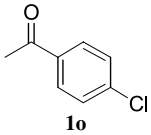
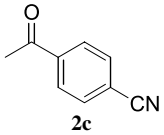
Comparison of the present protocol with those employing homogeneous Pd catalyst was then tested (Table 4). Cyanation of **1a** in the presence of $Pd(OAc)_2$ (5 mol%), PPh_3 (0.2 equiv) and zinc dust (0.56 equiv) required much higher temperature (150 °C) and exhibited an unsatisfying conversion (82%), accompanied by considerable amount of reduction byproduct **4** [**2a/4**=75/25] (Table 4, entry 2). Addition of $ZnBr_2$, that was in situ generated from Zn dust and Br_2, to the system involving $Pd(OAc)_2$, PPh_3 and Zn dust considerably improved the reaction to provide **2a** in a higher yield (87%), though it is still poorer than that employing Pd/C (Table 4, entry 3 vs entries 1 and 2). Because about 30% of the total Pd was consistently dissolved from Pd/C into the solution (vide infra), the reaction was tested by the use of 1.2 mol% (4 mol%×0.3) of $Pd(OAc)_2$. Through this treatment, were observed not only incomplete conversion (44%) but also elevation of the reduction byproduct **4** (**2a/4**=74/26) (Table 4, entry 4). In contrast, conducting the reaction in the presence of the same amount of Pd/C D5 (1.2 mol%) in place of $Pd(OAc)_2$ provided **2a** in a higher selectivity (**2a/4**=91/9), while the conversion (33%) remained almost unchanged (Table 4, entry 5 vs entry 4). Despite for just one substrate **1a**, the present process using Pd/C appears to be superior to the protocols employing homogeneous Pd catalysts.

Clarifying the reaction mechanism of the present cyanation was the next subject for our investigation. There are controversies on the mechanism of the cross coupling reaction employing heterogeneous Pd/C.[13] It is often difficult to identify the actual reaction site and the role of the solid support of Pd/C. When phosphine ligand is added to the reaction mixture, Pd might thoroughly dissolve from the solid support into the solution phase through coordination with phosphine ligand.[14] It implies the reaction might actually occur not on a solid support but in a homogeneous system. If it is true, the use of Pd/C involving activated carbon as the solid support is useless, especially as a device to promote the reaction. However, dependence of the present cyanation on the properties of the Pd/C catalysts, shown in Figure 1, demonstrates that the extent of Pd dispersion in the charcoal matrix does considerably affect the rate of the reaction. Finaly dispersed Pd, which is realized by the use of the thickshell or uniform type catalysts, is responsible for higher activities in the cyanation.[15] The use of heterogeneous Pd catalyst has, therefore, an advantage in that Pd metal is embedded and finely dispersed on the charcoal matrix, which assures the formation of monomeric Pd-phosphine complexes.

The hypothesis on the reaction site of the present cyanation is further supported by the extent of Pd leaching during the reaction. As shown in Figure 2, the concentration of Pd, dissolved in the solution phase, remained almost unchanged all the way from beginning of the reaction [ca. 30% of the initially added Pd (1.2 mol% relative to **1b**)].[16] The reaction was not finished in the presence of 1.2 mol% of $Pd(OAc)_2$ or Pd/C D5 or dissolved 'Pd' (1.2 mol%) obtained through filtration of a mixture of Zn dust (0.6 equiv), Br_2 (0.2 equiv), Pd/C and Ph_3P (0.16 equiv) (Table 4, entries 4 and 5 and Scheme 3). The observations suggest the reaction does not reach to completion only by initially dissolved Pd (1.2 mol%). It needs a help of remaining Pd (2.8 mol%)

Table 3. Cyanation of various aryl halides **1b**, **1c**, **1h–n** to aryl nitriles **2b**, **2c**, **2h–n** with $Zn(CN)_2$ in the presence of Pd/C D5, Zn, $ZnBr_2$ and PPh_3



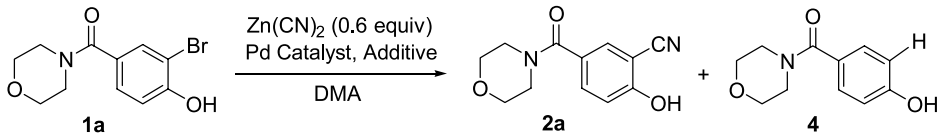
Entry	Substrate	Product	Temp (°C)	Period (h)	Assay yield (%)[a]
1[b]	 **1b**	 **2b**	80	3	97
2[b]	 **1c**	 **2c**	80	5	82
3[b]	 **1h**	 **2h**	115	8	89
4[b]	 **1i**	 **2i**	115	8	93
5[b]	 **1j**	 **2j**	115	2	92
6[c]	 **1k**	 **2k**	125	4	65
7[c]	 **1l**	 **2l**	125	4	60
8[b]	 **1m**	 **2m**	80	5	75
9[b]	 **1n**	 **2n**	115	8	89
10[b]	 **1o**	 **2c**	140	17	4[d]

[a] Determined by HPLC.
[b] Pd/C D5 (4 mol%), PPh_3 (0.16 equiv), Zn dust (0.4 equiv), Br_2 (0.2 equiv), $Zn(CN)_2$ (0.6 equiv).
[c] Pd/C D5 (8 mol%), PPh_3 (0.32 equiv), Zn dust (1.2 equiv), Br_2 (0.4 equiv), $Zn(CN)_2$ (0.5 equiv).
[d] Conversion (%).

present in Pd/C. To account for the consistency of the concentration of Pd in the solution phase, re-deposition of Pd to the solid surface of Pd/C should take place during the reaction,[17] proving that the Pd/C does not just serve as a reservoir for Pd. The use of heterogeneous Pd/C carrying suitable charcoal matrix is, therefore, crucial for attaining satisfactory progression of the cyanation.

A possible reaction pathway of the present cyanation is described in Scheme 4. In Pd/C, Pd metal is attached to the charcoal matrix through coordination with various functional groups (carboxyl group etc.) present on the solid support.[18] Based on the mechanism of Pd-catalyzed cross coupling reaction, demonstrated by Amatore and coworkers,[19] the Pd^{II}-activated charcoal complex (Pd^{II}/C) would rapidly coordinate with PPh_3 to form tetrasubstituted Pd^{II} complex **5**. Reduction of **5** with Zn dust in the presence of $ZnBr_2$ gives trisubstituted Pd^0 complex **6**. The Pd^0 complex **6**, thus obtained, is activated through coordination of the carbonyl oxygen with Zn^+Br cation to form reactive Pd^0 species, which is, closer to coordinatively unsaturated $Pd^0(PPh_3)_2$.[19] While, in the Amatore's system,[19] this type of

Table 4. Comparison of the cyanation of **1a** to **2a** employing Pd/C with those catalyzed by homogeneous catalysts



Entry	Pd catalyst (mol%)	Additive (equiv)	Temp (°C)	Period (h)	Conv. (%)[a]	Assay yield (%)	**2a**:**4**
1	Pd/C D5 (4)	PPh_3 (0.16), Zn (0.6), Br_2 (0.2)	115	4	100	91	98:2
2	$Pd(OAc)_2$ (5)	PPh_3 (0.2), Zn (0.56)	150	2	82	—[b]	75:25
3	$Pd(OAc)_2$ (4)	PPh_3 (0.16), Zn (0.6), Br_2 (0.2)	115	3	100	87	98:2
4	$Pd(OAc)_2$ (1.2)	PPh_3 (0.16), Zn (0.6), Br_2 (0.2)	115	4	44	—[b]	74:26
5	Pd/C D5 (1.2)	PPh_3 (0.16), Zn (0.6), Br_2 (0.2)	115	4	33	—[b]	91:9

[a] Determined by HPLC.
[b] Not determined.

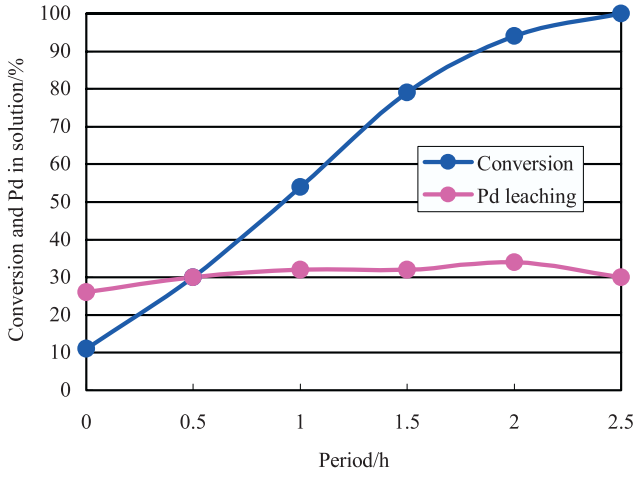
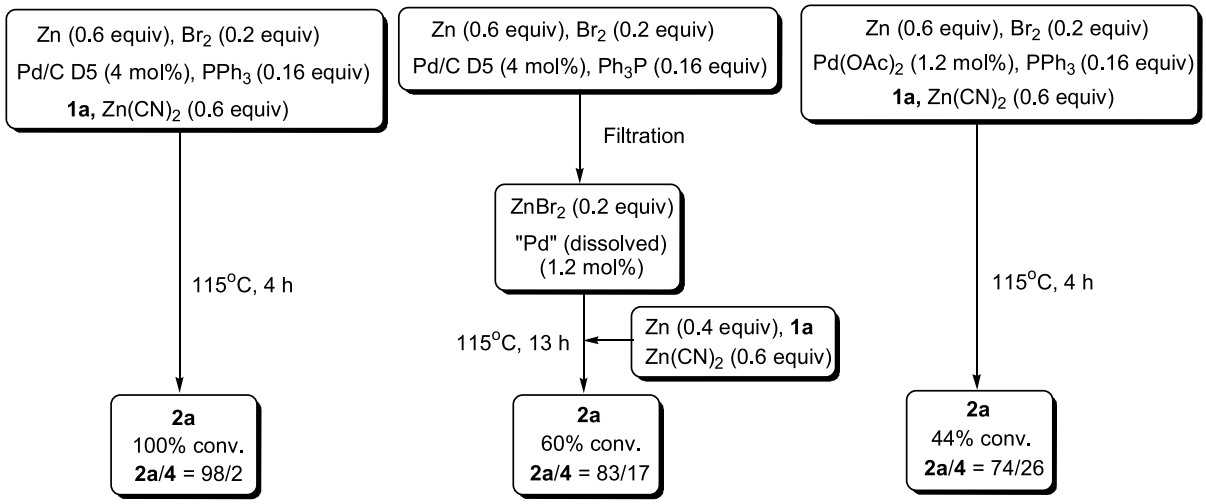
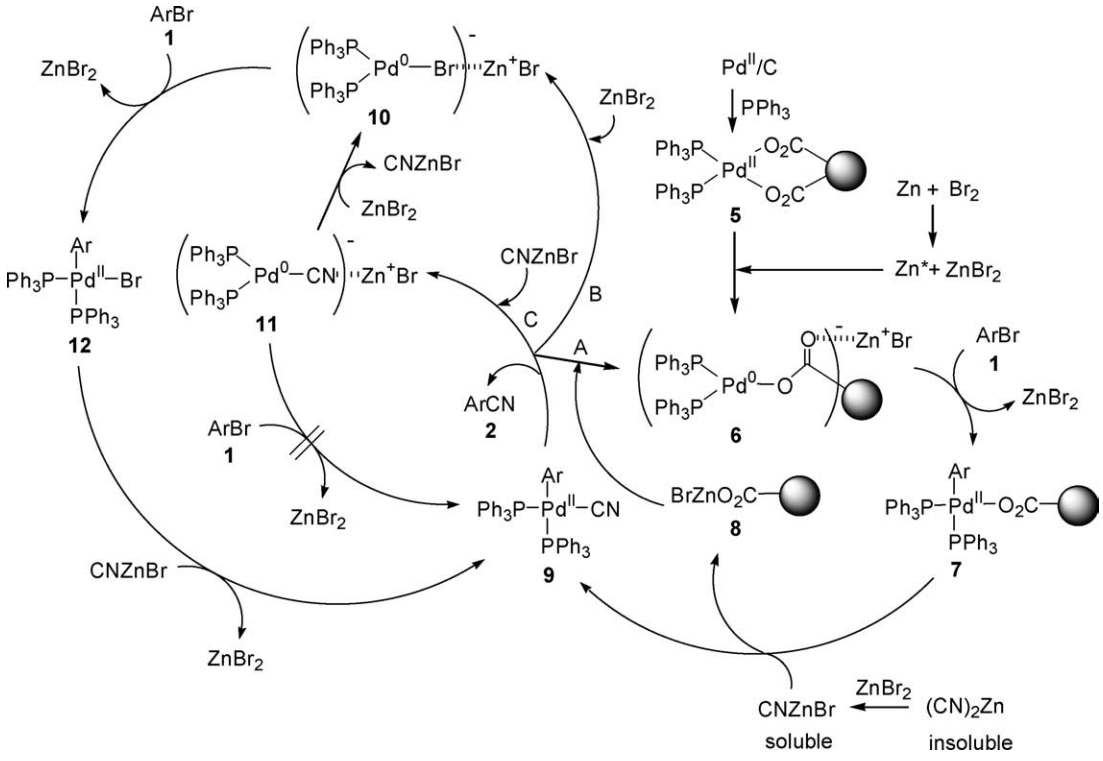


Figure 2. Pd leaching in the cyanation of aryl bromide **1b** to aryl nitrile **2b**. The Pd leaching was determined by XRF analysis of the filtered solution. The conversion was determined by HPLC. The reaction was conducted by the use of Pd/C D5 (4 mol%), Zn (0.4 equiv), Br_2 (0.2 equiv) and PPh_3 (0.16 equiv) at 80 °C in DMA.

intermediate has been generated by reduction at electrode, the present reaction, that employs Zn dust as the reductant, is much easier to be conducted on a large-scale preparation. Oxidative addition of aryl bromide **1** to **6** is accelerated as well by liberating $ZnBr_2$ of good leaving group activity to form *cis*-tetrasubstituted Pd^{II} complex **7**. The preference of $ZnBr_2$ over ZnI_2 or $ZnCl_2$, shown in Table 2, might be a consequence of higher Lewis acidity of $ZnBr_2$ ($ZnBr_2 > ZnI_2 > ZnCl_2$),[20] that acts as a balance to the modest leaving group ability of $ZnBr_2$ ($ZnI_2 > ZnBr_2 > ZnCl_2$). Cyanation of **7** with CNZnBr, that might be generated by the reaction of $Zn(CN)_2$ with $ZnBr_2$, would subsequently take place to give *cis*-cyanated Pd^{II} complex **9**. In this stage, the complex **9** dissolves into the solution phase, with zinc bromide salt of activated charcoal **8** left in the mixture. After reductive elimination of aryl nitrile **2** from **9**, three pathways (path A, B and C), shown in Scheme 4, are possible. In path A, the reduced Pd^0 complex $[Pd^0(PPh_3)_2]$, generated from **9**, coordinates back to **8** to regenerate three coordinated Pd^0 complex **6**. In path B, the reaction with $ZnBr_2$ affords trisubstituted Pd^0 complex **10**, which is, activated by coordination of Br^- ligand with Zn^+Br. Following the reaction with aryl bromide **1** and subsequently with



Scheme 3. Comparison of the cyanation of **1a** employing Pd/C D5 with those employing $Pd(OAc)_2$ or dissolved Pd species from Pd/C D5.



Scheme 4. A possible reaction pathway for the cyanation of aryl bromides **1** to aryl nitriles **2** employing $Zn(CN)_2$ in the presence of Pd/C, Zn dust and $ZnBr_2$.

CNZnBr, the complex **10** is converted to the cyanated Pd^{II} complex **9** that, upon reductive elimination, would provide aryl nitrile **2** (**10**→**12**→**9**→**2**). Path C is an undesirable pathway, which leads to trisubstituted cyanated Pd^0 complex **11**, that is, unable to participate in the oxidative addition with aryl bromide **1**.[3j] However, through the reaction of **11** with $ZnBr_2$, the active Pd species **10** would be produced. As a consequence, the crucial roles of $ZnBr_2$ in the present reaction might be as follows: (1) initial generation of **6** from **5**, (2) trap of the fragile Pd^0 species $[Pd^0(PPh_3)_2]$, generated from **9**, as a form of **10** (**9**→**10** through path B), (3) conversion of the inactivated cyanated Pd^0 species **11** to **10** (**11**→**10** through path C), and (4) possible activation of $Zn(CN)_2$ to CNZnBr.

The elevated formation of reduction byproduct **4**, from **1a** by employing homogeneous $Pd(OAc)_2$ in the absence of $ZnBr_2$ (Table 4, entry 2), reflects the significance of the use of heterogeneous Pd/C in combine with $ZnBr_2$ to generate monomeric Pd^0 species such as **6**. The competing reaction, that is, reduction of **1a** to **4**, takes place with Pd on the metal surface of Pd^0 black. Without $ZnBr_2$ or the solid support for Pd, the Pd^0 species tends to cluster and eventually precipitates to Pd^0 black that effects the reduction of **1a** to **4**. Although precise estimation of the contribution of each pathway (path A, B and C) is not obtained, some extent of cyanation may proceed through path A, because not all the Pd was dissolved into the solution phase (Fig. 2). The role of the solid support is, as mentioned above, to anchor Pd metal on the solid support in a highly dispersed manner to allow the generation of the monomeric Pd phosphine complexes such as **6** and **7** without agglomerating to Pd black, at least in the initial stage of the reaction.

The issue of high catalyst loading needs to be addressed, especially when it comes to a stage of production. Because the catalyst loading of 4 mol%, employed in the present protocol, is relatively high, efficient recovery of Pd should be achieved for attaining the cost-effective process. The recovery of Pd was carried out in the reaction of **1a** to **2a** by initial oxidation of PPh_3 that coordinates Pd and dissolves Pd into the solution.[21] After air bubbling of the reaction mixture at 60 °C, Pd was recovered in 97% yield through simple filtration followed by usual recovery process involving combustion.

3. Conclusions

As described above, a practical cyanation of aryl bromides employing heterogeneous Pd/C was worked out by the use of inexpensive Zn dust, $ZnBr_2$ (in situ generated from Zn dust and Br_2) and PPh_3. The use of heterogeneous Pd/C not only allows the facile recovery of the catalyst but also contributes to promote and maintain the catalytic cycle. The present reaction produces a lot of Zn waste. However, Zn waste is relatively innocuous[22] by-product, compared with heavy metals such as Cu[3a] or Sn,[3g] found in the previous cyanation protocols. The feasibility of the present process was undoubtedly confirmed at pilot-plant scale (60 kg scale) synthesis of 4-morpholinocarbonyl-2-hydroxybenzonitrile (**2a**). The present process is featured by many advantages such as ease of operation, versatility of the substrates, less Pd contamination into the product, high recovery of Pd, use of inexpensive phosphine ligand (PPh_3), and additives (Zn dust and $ZnBr_2$), and high reproducibility, which would

permit to fuel a lot of expansion as one of the efficient approaches to multifunctional aryl nitriles.

4. Experimental

4.1. General methods

Melting points were measured using Büchi melting point apparatus (B-540) and are uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a Bruker Avance 400 spectrometer using tetramethylsilane as the internal standard. Mass spectra were obtained on a Hitachi M-2000A double-focusing mass spectrometer and on a Finnigan MAT LC-Q. Elemental analyses were measured on a Perkin-Elmer 2400II microanalyzer. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in ethanol-heat or they were visualized by UV light where feasible. Zinc cyanide (purity: 98%, caution: highly toxic[23]) was purchased from Sigma-Aldrich Fine Chemicals. Zinc dust was purchased from Hakusui Tech (Pb content: less than 50 ppm). All solvents and reagents were used as received. Pd/C D1, D2, D3, D5, and D6 were purchased from Degussa Japan Co., Ltd. They have properties listed in Table 5.

4.1.1. Synthesis of 3-cyano-4-hydroxymorpholinobenzamide (2a) through Rosenmund-von Braum reaction of 3-bromo-4-hydroxymorpholinobenzamide (1a). A reaction vessel was charged with **1a** (3 g, 11.2 mmol) and $Cu(CN)_2$ (1.4 g, 16.8 mmol) and DMA (15 mL). The vessel was then briefly evacuated and backfilled with N_2 three times. The mixture was stirred under reflux (165 °C) for 4 h. After the reaction was finished, the suspension was cooled down to 80 °C, and then added concd HCl (3.5 mL). After air bubbling of the mixture for 1 h at the same temperature, the solvent was evaporated. The residue was crystallized by adding AcOEt (10 mL), c.-HCl (1.7 mL) and H_2O (18 mL), and the crystals formed were collected by filtration to give **2a** (1.59 g, 61%) as colorless crystals. Mp 238–240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) $\delta=11.58$ (s, 1H), 7.70 (d, $J=2.0$ Hz, 1H), 7.57 (dd, $J=2.0$, 8.8 Hz, 1H), 7.07 (d, $J=8.8$ Hz, 1H), 3.59 (br, 4H), 3.48 (br, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=167.3$ (s), 161.1 (s), 134.0 (d), 132.5 (d), 126.6 (s), 116.3 (s), 116.0 (d), 98.6 (s), 65.9 (2t); IR (ATR) $\nu_{max}=2229$, 1578 cm^{-1}; MS (APCI) m/z 233 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{12}N_2O_3$; C, 62.06; H, 5.21; N, 12.06; found: C, 61.63; H, 5.2; N, 11.81.

4.2. General procedure for the cyanation of aryl bromides employing Pd/C

A reaction vessel was charged with zinc dust (0.8 mmol, 52 mg) and DMA (5.7 mL). The vessel was then briefly evacuated and backfilled with N_2 five times. Then, Br_2 (20 μL, 0.4 mmol) was dropwise added at 25 °C and the mixture was stirred at 25 °C for 0.5 h. To the mixture were successively added $Zn(CN)_2$ (114 mg, 1.2 mmol), PPh_3 (85 mg, 0.32 mmol), Pd/C D5 (Pd: 5 wt%, 170 mg, 0.08 mmol) and aryl bromide (2 mmol) at 25 °C. The vessel was briefly evacuated and backfilled with N_2 five times. The mixture was stirred at 80–125 °C for 3–15 h. After completion of the reaction, the suspension was cooled down to room temperature, diluted with AcOEt (15 mL) and filtered. The filtrate was concentrated, and the residue was purified by silica gel column chromatography or recrystallization to provide the desired product. When recovery of the catalyst was needed, the reaction mixture, obtained after the reaction, was subjected to air bubbling at 60–65 °C for 1 h, and then the mixture was cooled to 25 °C. The mixture was diluted with AcOEt (15 mL) and filtered through paper filter that was pre-coated with activated charcoal. The solids obtained were allowed to recovery process involving combustion to recover Pd in 97% yield based on the initially added Pd.

4.2.1. Methyl 4-cyanobenzoate (2b).[24] The crude material was purified by silica gel column chromatography (AcOEt/hexane=3:97–15:85) to afford **2b** (97%) as colorless crystals. Mp 68–69 °C, (lit.[24]: 67–68 °C); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=8.12$–8.09 (m, 2H), 8.03–8.00 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=165.0$, 133.4 (2s), 132.7, 129.7 (2d), 118.0, 115.4 (2s), 52.7 (q); IR (ATR) $\nu_{max}=3676$, 2988, 2229, 1717 cm^{-1}; MS (70 eV, EI) m/z 161 $[M]^+$; elemental analysis calcd (%) for $C_9H_7NO_2$; C, 67.08; H, 4.38; N, 8.69; found: C, 67.02; H, 4.34; N, 8.61.

4.2.2. 2-Hydroxy-5-morpholinocarbonylbenzonitrile (2a). The crude material was crystallized from acetone–H_2O to afford **2c** (91%) as colorless crystals. The chemical properties of the product were identical with those of **2a** obtained by Rosenmund-von Braum reaction (Section 4.1.1).

Table 5. Properties of the Pd/C catalysts

Catalyst[a]	Pd distribution	Impregnation depth (nm)	Reduction degree (%)[b]	Pd dispersion (%)[c]	Water content (wt%)[c]
Pd/C D1	eggshell	50–150	0–25	28	3.2
Pd/C D2	eggshell	50–150	25–99	27	4.2
Pd/C D3	uniform	—[d]	0–25	36	1–1.5
Pd/C D4	uniform	—[d]	25–99	36	1.8
Pd/C D5	thickshell	200–500	0–25	35	1–1.5
Pd/C D6	thickshell	200–500	25–99	26	3.0

[a] Purchased from Degussa Japan Co., Ltd Catalysts Division.[8]
[b] Detected by temperature programmed reduction (TPR) measurement.
[c] Pd dispersion is calculated with CO chemisorption.
[d] Not determined.

4.2.3. 4-Acetylbenzonitrile (2c).[24] The crude material was purified by silica gel column chromatography (AcOEt/hexane=10:90–15:85) to afford **2c** (82%) as colorless crystals. Mp 57–58 °C, (lit.[24]: 57–60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.05 (ddd, J=1.6, 3.2, 4.8 Hz, 2H), 7.78 (ddd, J=1.2, 3.2, 4.8 Hz, 2H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=196.5, 139.9 (2s), 132.5, 128.7 (2d), 117.9, 116.4 (2s), 26.8 (q); IR (ATR) ν_{max}=2229, 1684 cm^{-1}; MS (70 eV, EI) m/z 145 $[M]^+$; elemental analysis calcd (%) for C_9H_7NO; C, 74.56; H, 4.86; N, 9.65. Found: C, 74.56; H, 4.69; N, 9.56.

4.2.4. 4-Trifluoromethylbenzonitrile (2d).[3g] The crude material was purified by silica gel column chromatography (hexane/MTBE=8:1) to afford **2d** (91%) as colorless crystals. Mp 35 °C; IR (ATR) ν_{max}=2237, 1314 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.84–7.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=134.6 (q), 132.8 (d), 126.3 (q), 123.2 (q), 117.5 (s), 116.2 (s); MS (70 eV, EI) m/z 171 $[M]^+$.

4.2.5. 4-Chlorobenzonitrile (2e).[25] The crude material was purified by silica gel column chromatography (AcOEt/hexane=5:95–25:75) to afford **2e** (58%) as colorless crystals. Mp 90 °C (lit.[25]: 90.5–91.5 °C); IR (ATR) ν_{max}=2226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.62–7.60 (m, 2H), 7.48–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=139.6 (s), 133.3 (d), 130.0 (d), 118.0 (s), 110.8 (s); MS (70 eV, EI) m/z 137 $[M]^+$.

4.2.6. 4-Methoxybenzonitrile (2h).[26] The crude material was purified by silica gel column chromatography (AcOEt/hexane=5:95–20:80) to afford **2h** (89%) as colorless crystals. Mp 59–60 °C, (lit.[26]: 59 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.60–7.57 (m, 2H), 6.97–6.94 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=162.9 (s), 134.0 (d), 119.2 (s), 114.8 (d), 104.0 (s), 55.6 (q); IR (ATR) ν_{max}=2217, 1604 cm^{-1}; MS (70 eV, EI) m/z 133 $[M]^+$; elemental analysis calcd (%) for C_8H_7NO; C, 72.17; H, 5.30; N, 10.52; found: C, 72.31; H, 5.25; N, 10.52.

4.2.7. 2-*N*,*N*-Dimethylaminobenzonitrile (2i).[27] The crude material was purified by silica gel column chromatography (hexane to AcOEt/hexane=15:85) to afford **2i** (93%) as pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51–7.49 (m, 1H), 7.43–7.38 (m, 1H), 6.90–6.88 (m, 1H), 6.86–6.82 (m, 1H), 3.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=155.3 (s), 135.0, 133.5 (2d), 119.7 (s), 119.1, 116.7 (2d), 101.3 (s), 43.0 (q); IR (ATR) ν_{max}=2214, 1597 cm^{-1}; MS (70 eV, EI) m/z 145 $[M]^+$.

4.2.8. Naphthalene-1-carbonitrile (2j).[28] The crude material was purified by silica gel column chromatography (hexane to AcOEt/hexane=8:92) to afford **2j** (92%) as pale yellow crystals. Mp 36–38 °C (lit.[28]: 37–38 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.25 (d, J=8.4 Hz, 1H), 8.09 (d, J=8.2 Hz, 1H), 7.93 (d, J=8.2 Hz, 1H), 7.92 (dd, J=1.0, 7.2 Hz, 1H), 7.70 (ddd, J=1.3, 7.2, 8.2 Hz, 1H), 7.63 (ddd, J=1.0, 6.9, 7.2 Hz, 1H), 7.53 (dd, J=7.2, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=133.2 (d), 132.9 (s), 132.6 (d), 132.3 (s), 128.6, 128.5, 127.5, 125.1, 124.9 (5d), 117.8, 110.1 (2s); IR (ATR) ν_{max}=2219 cm^{-1}; MS (70 eV, EI) m/z 153 $[M]^+$; elemental analysis calcd (%) for $C_{11}H_7N$; C, 86.25; H, 4.61; N, 9.16. Found: C, 85.98; H, 4.39; N, 9.16.

4.2.9. 4-Aminobenzonitrile (2k).[29] The crude material was purified by silica gel column chromatography (AcOEt/hexane=20:80–4:55) to afford **2k** (65%) as red crystals. Mp 85–86 °C (lit.[29]: 84–85 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.40 (ddd, J=2.4, 4.4, 4.8 Hz, 2H), 6.65 (ddd, J=2.4, 4.4, 4.8 Hz, 2H), 4.21 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=150.5 (s), 133.8 (d), 120.2 (s), 114.4 (d), 100.1 (s); IR (ATR) ν_{max}=3477, 3369, 2212, 1622, 1600 cm^{-1}; MS (APCI) m/z 119 $[M+H]^+$.

4.2.10. 2-Hydroxybenzonitrile (2l).[30] The crude material was purified by silica gel column chromatography (AcOEt/hexane=2:1) to afford **2l** (60%) as colorless crystals. Mp 91–92 °C (lit.[30]: 97–98 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51–7.44 (m, 2H), 7.03–6.95 (m, 2H), 5.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=158.8 (s), 134.8, 132.9, 120.9, 116.7 (4d), 116.5, 99.4 (2s); IR (ATR) ν_{max}=3232, 2231, 1630 cm^{-1}; MS (70 eV, EI) m/z 119 $[M]^+$.

4.2.11. 3-Cyanopyridine (2m).[28] The crude material was purified by silica gel column chromatography (AcOEt/hexane=2:1) to afford **2m** (75%) as colorless crystals. Mp 50–51 °C (lit.[28]: 52 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.91 (d, J=1.6 Hz, 1H), 8.84 (dd, J=1.6, 4.8 Hz, 1H), 7.99 (ddd, J=2.0, 4.0, 6.0 Hz, 1H), 7.48–7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=153.0, 152.5, 139.3, 123.7 (4d), 116.5, 110.2 (2s); IR (ATR) ν_{max}=3062, 2230, 1587, 1564 cm^{-1}; MS (APCI) m/z=105 $[(M+H)^+]$.

4.2.12. Benzo[*b*]thiophene-3-carbonitrile (2n).[31] The crude material was purified by silica gel column chromatography (AcOEt/hexane=2:98–4:96) to afford **2n** (89%) as colorless crystals. Mp 73–74 °C (lit.[31]: 70–71 °C); IR (ATR) ν_{max}=3108, 2222 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.11 (s, 1H), 7.98 (d, J=7.7 Hz, 1H), 7.90 (d, J=8.2 Hz, 1H), 7.55–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=128.5 (s), 137.5 (d), 137.3 (s), 126.2, 126.0, 122.8, 122.5 (4d), 114.3 (s), 107.1 (s); MS (70 eV, EI) m/z 159 $[M]^+$; elemental analysis calcd (%) for C_9H_5NS; C, 67.9; H, 3.17; N, 8.8. Found: C, 67.73; H, 3.08; N, 8.77.

Acknowledgements

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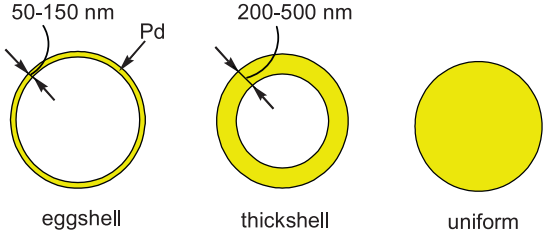

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