Catalytic Amide-Directed Palladadesilylation–Alkenylation

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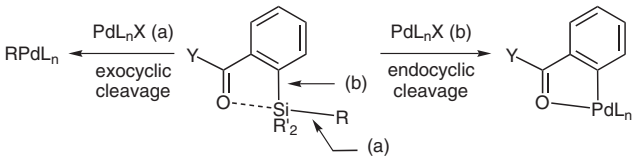
Abstract: Palladium(II) complexes catalyse the amide-directed displacement of an aryl–Si group and its replacement by an electrophilic alkene at ambient temperature, analogous to an oxidative Heck reaction. A palladacyclic intermediate is involved, and the reaction enables substitution to occur specifically in the electron-poor ring of benzanilides. The procedure described provides a formal link between directed lithiation and the Heck reaction.

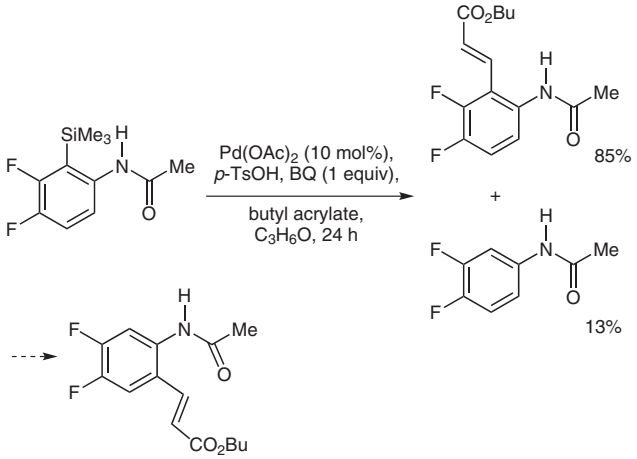
Key words: palladium, oxidative Heck reaction, palladacycle, benzanilides, regiocontrol

The use of arylsilanes as the nucleophilic component in palladium coupling reactions is well-established through the pioneering work of Hiyama[1] and Denmark.[2] In these cases the C–Si bond is activated by external fluoride ion or by a silanol; alternatively an alkoxide group can bind to silicon,[3] so that activation of the transferred group occurs exocyclic to the dative-bonded ring. In a similar vein we have demonstrated the exocyclic activation of Si–Me groups by a neighbouring urea or amide group, enabling catalytic intermolecular methyl transfer from silicon to an electrophilic alkene.[4] It was observed that an alternative course of reaction occurred in some cases leading to endocyclic aryl–methyl coupling, but with only modest efficiency. The present paper describes development of an effective endocyclic coupling through intermediate palladacycle formation from silane precursors (Scheme 1).[5]



Scheme 1 Contrasting pathways for directed C–Si activation leading to distinct palladium intermediates in catalysis.

Many aryl C–H activation reactions are effected by anilide directing groups, as was first observed stoichiometrically by Horino[6] and then catalytically by DeVries and coworkers.[7,8] There have been several subsequent developments based on this theme.[9,10] The reaction is likely to involve an intermediate palladacycle formed by electrophilic substitution directed by the anilide carbonyl group.[11] The anilide ring (σ^p 0.00, σ_m 0.21) is more electron rich than the carboxamide ring (σ^p 0.36, σ_m 0.35),[12] and for this reason the directed Heck reaction of benzanilide occurs in the ring adjacent to nitrogen (six-membered palladacycle) rather than that adjacent to the carbonyl group (five-membered palladacycle), since the more electron-rich site is favoured. Palladacycles formed by CH activation *ortho* to an arene-bound carbonyl group are less common,[13] as would be expected on electronic grounds, since an electrophilic attack is disfavoured at that position. The *ortho*-carbonyl position is the preferred site for lithiation of benzanilide **1** and its relatives, however.[14] Coupled to the fact that C–Si is intrinsically more reactive to electrophilic substitution than C–H,[15] we wondered whether this offered the possibility of an alternative regioisomeric product in the benzanilide case. There are early examples of stoichiometric Pd activation of an aryl–Si bond.[16] In our own work (Scheme 2), palladadesilylation has been used to control the regiochemistry of palladacycle formation and enabled a demonstration of catalytic turnover through an anilide directing group, albeit accompanied by competing protodesilylation resulting in formation of the alternative regioisomer.[4,17]



Scheme 2 A prior example of alkenylation via palladadesilylation[17]

This encouraged further efforts to use the known silane **2a** (ref. 14) as the reactant in catalytic alkenylation, thus directing the new bond into the less reactive ring of benzanilide. The outcome of the first reaction attempted was partially successful, and a 49% yield of the desired product **3** was obtained (Table 1, entry 1). Formation of the desired product was accompanied by protodesilylation, which ultimately led to CH alkenylation of the anilide ring. A systematic effort was made to optimize the C–C bond-forming process as indicated in Table 1, avoiding acid as far as possible.[18] After considerable trial and error,

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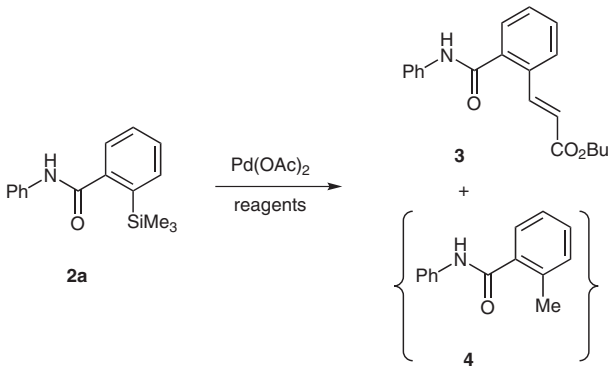
with the more informative experiments collated in Table 1, a moderately high-yielding procedure was discovered. For some of the test reactions methyl transfer to the arene or alkene, the latter giving (*E*)-butyl crotonate, were significant side reactions.[4] The optimum conditions involved the use of the weaker acid $PhPO_3H_2$, although this occurred at an impractically slow rate.

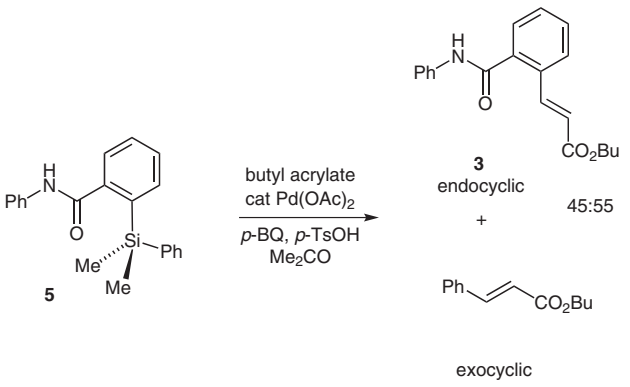
Table 1 Preliminary Reactions with Silane **2a**



Entry[a]	Oxidant	Solvent	Temp (°C)	Time (h)	Results
1[b]	*p*-BQ	Me_2CO	20	24	**3** 49%; see text
2[c]	$Cu(OAc)_2$	DMF	90	3	**3** 2%, **1a** 33%
3[b]	*p*-BQ	$CDCl_3$	20	1	**1a** only; fast
4	*p*-BQ	$AcOH/C_7H_8$	20	60	very slow, **3** + **4**
5	*p*-BQ	AcOH	70	2	**3** 55%, **4** 30%
6[d]	*p*-BQ	Me_2CO	20	50	**3** 80%

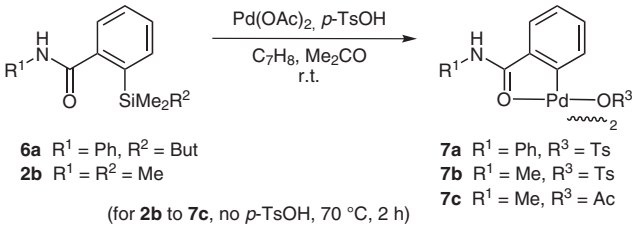
[a] $Pd(OAc)_2$ (5 mol%) used unless otherwise stated, *p*-BQ is *p*-benzoquinone.
[b] PTSA (1 equiv).
[c] No reaction in THF.
[d] $Pd(OAc)_2$ (10 mol%), $PhPO_3H_2$ (1 equiv) added, faster but with more side reactions at 50 °C, but very slow with $PhCO_2H$ as acid.

Two structural variants were prepared. Firstly, the $PhMe_2Si$ analogue **5** provided a convenient test of exo- vs. endocyclic C–Si activation. In acetone [5 mol% $Pd(OAc)_2$, *p*-BQ, PTSA] the two processes occurred at comparable rates yielding product **3** and (*E*)-$PhCH{=}CHCO_2Bu$ in a 45:55 ratio (Scheme 3). Many other products were formed in AcOH, including those derived by Me transfer.



Scheme 3 Dual pathway in the alkenylation of **5**

At this point it was surmised that avoidance of direct C=O–silyl bonding would direct Pd attack to the *ipso*-carbon and suppress the side reactions. The bulkier TBDMS derivative **6a** was prepared and reacted with butyl acrylate under $Pd(OAc)_2$ catalysis with added PTSA and oxidant. Clean formation of product **3** was observed, now without competing protodesilylation. The X-ray structure of silane **6a** shows an absence of C=O….Si contact,[19] consistent with the endocyclic activation observed. Intermediacy of isolable palladacycles **7a**,**b** was demonstrated in stoichiometric reactions starting from silylbenzanilide **6a** or silylacetanilide **2b**[4] (Scheme 4). At 70 °C in the absence of strong acid, the palladacyclic acetate **7c** was formed.



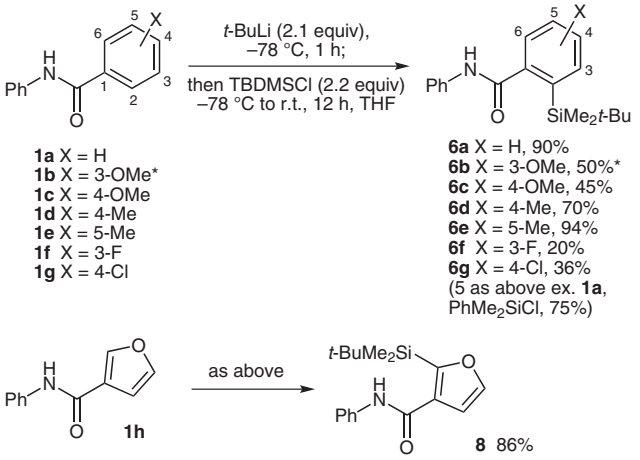
Scheme 4 Five-membered palladacycle formation from silylamides

These initial results encouraged the synthesis of a range of TBDMS-substituted benzanilides substituted in the amide ring. For the 3-F analogue **1f**, only one product was isolated derived from the substituent-flanked ArLi isomer and in low yield.

The same alkenylation methodology that had been used for the formation of alkene **3** from the parent TBDMS derivative **6a** was applied to the preparation of a range of ring-substituted variants of compound **6a** (Scheme 5). The reaction worked smoothly for the range of benzanilides tested. For entry 3 (**9c** as product, Table 2), competing desilylation was observed with 5 mol% $Pd(OAc)_2$, and hence 10 mol% of catalyst was employed. The higher catalyst ratio was also used for the slower examples of entries 6–8 leading to **9f**,**g**, and **10**.

Only in the case of entry 3 was arene methylation observed as a side reaction. In the general case, neither the reactant nor the product is susceptible to cyclopalladation and ensuing reaction in the *ortho*-anilide ring. This suggests that steric pressure from a 2-substituent adjacent to the carbonyl group inhibits formation of the six-membered palladacyclic intermediate. In the X-ray structure of compound **6a** described above, the silane-bearing ring is twisted out of the plane of the amide by 55° and 72°, respectively, in two independent molecules.[20,21] In accord with acetanilide CH activation experiments,[10b] the electron-poor 4-Cl analogue **6g** reacts slowly (entry 7). The electron-rich furylsilane **8** was only sluggishly reactive, however, perhaps because a five-membered ring palladacycle fused to a five-membered aromatic ring is more strained.

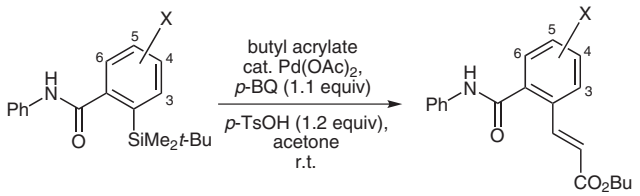
Catalytic palladadesilylation as described here requires a directing group, and efficient reaction is limited at this stage to silanes with a neighbouring carboxamido group. Thus 2-(trimethylsilyl)benzofuran is inert to our standard



Scheme 5 Synthesis of TBDMS derivatives of benzanilides

reaction conditions, albeit electron rich. Success depends critically on the role of the TBDMS group, whose steric bulk inhibits competing reactions requiring direct silyl activation. In turn, this encourages the formation of silyl-stabilized intermediates related to cationic intermediate **11** (Figure 1), with the amide associated with Pd rather than Si. An interesting feature of this chemistry is the absence of competition from the 'conventional' pathway involving substitution in the anilide ring.

Table 2 Alkenylation of TBDMS-Benzanilides



Entry	Product[a]	Time (h)	Yield (%, conversion)
1	**3** X = H	24	77 (90)
2[c]	**9b** X = 3-OMe	36	72 (90)
3[b]	**9c** X = 4-OMe	24	52
4	**9d** X = 4-Me	24	73 (90)
5	**9e** X = 5-Me	20	77 (90)
6[c]	**9f** X = 3-F	36	(50)
7[c]	**9g** X = 4-Cl	24	46 (60)
8[c]	**10** (ex. **8**)	36	(20)

[a] Substitution in **9** matches that in **6**; $Pd(OAc)_2$ (5 mol%) unless otherwise stated.
[b] 20% arene methylation, cf. **4**.
[c] $Pd(OAc)_2$ (10 mol%).

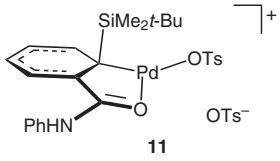


Figure 1 Proposed reactive intermediate in palladadesilylation

The chemistry described here provides access to novel palladacyclic intermediates under mild and readily accessible conditions via displacement of an aromatic silyl group, and has potential in catalysis beyond the oxidative Heck reactions described here.[22] The principles involved ought not to be limited to anilides. At present it is less effective for electron-rich aromatic systems where protodesilylation pathways compete more effectively.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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