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Synthesis of α-iminoimidates by palladium catalysed double isonitrile insertion

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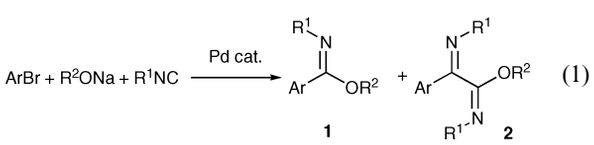
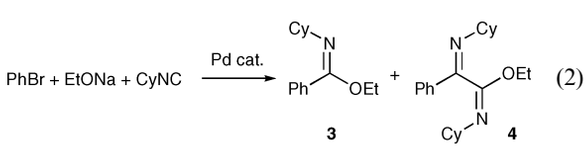
Palladium catalysed selective double insertion of isonitriles into aryl bromides with trapping by sodium alkoxides provides an efficient 4-component synthesis of unusual α-iminoimidates.

We recently reported the palladium catalysed synthesis of amidines, imidates, and thioimidates from aryl halides, isonitriles, and amines, alcohols, and thiols respectively.[1,2] In the case of the formation of imidates **1** from aliphatic alcohols and electron rich aryl bromides, yields under our initial conditions were poor and the problem was traced to the formation of substantial amounts of the product **2** of bis-insertion of the isonitrile [eqn. (1)]. Selective mono-insertion was obtained by slow addition of the isonitrile, but we now report optimisation to afford the α-iminoimidates **2**.



Palladium-catalysed double carbonylation reactions are well-established for the synthesis of α-keto-esters and -amides.[3] To our knowledge, metal catalysed double isonitrile insertion is not known. The stoichiometric double and triple insertion of isonitriles into palladium–carbon bonds is known[4,5] as well as palladium catalysed isonitrile polymerisation.[6] Although α-iminoimidates are virtually unknown,[7] 1,2-diimines have found applications as ligands.[8] A recent route is the palladium catalysed reductive dimerisation of imidoyl chlorides.[9]

We first noted formation of α-iminoimidates in a system consisting of bromobenzene (1 eq.), cyclohexylisonitrile (1.5 eq.), NaOEt (5 eq., as 2 M soln, in EtOH), palladium dichloride (5 mol%), 1,1′-bis(diphenylphosphinyl)ferrocene (dppf) (10 mol%) in toluene at 98 °C which gave around a 1 : 1.3 ratio of mono- : bis-inserted products **3** and **4** [eqn. (2)]. Use of iodobenzene gave the same ratio of **3** : **4**, but in a slow and low yielding reaction. A range of alternative ligands were investigated [1,3-bis(diphenylphosphinyl)propane (dppp), 1,2-bis(diphenylphosphinyl)ethane (dppe), P(*o*-Tol)$_3$, PPh$_3$, PPh$_2$Me, P(Furyl)$_3$, P(Cy)$_3$ and P(^{t}Bu)$_3$] but had little effect on the bis : mono ratio (1.3–2). For PPh$_3$ the ratio was 2.8, but conversion was poor, and for P(*o*-tol)$_3$ it was 1.1 and a very fast reaction was noticed. The bidentate ligands dppe and dppp gave poor conversions, with extensive formation of unidentified side products.



The influence of the quantity of isonitrile was next studied, and as expected increased amounts gave a much higher ratio of **4** : **3** (Table 1, entries 1–6). With 5 equiv of cyclohexylisocyanide with respect to bromobenzene greater than 90% selectivity for the bis-insertion product **4** is obtained (entry 6) with only trace amounts (detected by electrospray MS) of tris-inserted product. It is significant that even at very low isonitrile concentrations substantial amounts of the bis-inserted product **4** are formed (Table 1, entry 2). The reaction was also found to be faster at lower isonitrile concentrations, possibly due to partial deactivation of the palladium catalyst by the isonitrile at higher concentrations.† Lower temperatures strongly favoured formation of the bis-inserted product **4** (Table 1 entries 1, 7–9), but at the expense of long reaction times and poorer yields.

We then turned our attention to the effect of the amount of sodium ethoxide used. We changed to dioxane as solvent, preliminary experiments demonstrating that it gave similar **3** : **4** ratios as toluene and had the advantage that mixtures remained homogeneous. Using a constant amount of ethanol, to reduce solvent effects, we varied the amount of sodium ethoxide and found that lower concentrations strongly favoured the formation of the bis-inserted product **4** (Table 2 entries 1–4). For preparative reactions when variation in the alkoxide component is required it would be more convenient to use a base separate from the alcohol component of the α-iminoimidate. Use of Cs_2CO_2 and K_2CO_3 gave poor conversions, but NaO^{t}Bu worked well. To determine the optimum amount of alcohol we carried out a series of experiments in which the amount of ethanol was varied and were interested to find a dramatic effect on the ratio of **3** : **4** (Table 2, entries 5–8). Use of solid NaO^{t}Bu to further reduce the amount of hydroxylic solvent present, with 5 equivalents of ethanol to avoid formation of products from ^{t}BuO$^-$ addition, gave optimum conditions for both yield, and selectivity for formation of the α-iminoimidate **4** (Table 2 entry 9). We also examined how the ethoxide metal counterion affected the **3** : **4** ratio. LiO^{t}Bu gave a very slow and messy reaction, but NaO^{t}Bu, KO^{t}Bu and CsO^{t}Bu gave good yields of the desired products, and with a dramatic preference for *mono*-insertion of isonitrile as the metal ion gets larger (*i.e.* as the ethoxide anion gets more nucleophilic) (Table 2 entries 10–12). A related observation was that addition of 15-crown-5 (2 equiv) to reactions using NaOEt under the conditions of Table 1 entry 1 increased the ratio of **4** : **3** from 1.3 : 1 to 4.7 : 1.

The above experiments, and others, lead to conditions optimised for the formation of bis-inserted products: 1.2 eq. NaO^{t}Bu, 5 eq. R^{2}OH, 3 eq. R^{1}NC in dioxane at 98 °C. Under these conditions, a range of α-iminoimidates **5** were obtained in high yield (Table 3). Generally less than 5% of the mono-inserted product was formed. The successful double insertion using electron poor aromatic systems is notable since under our original conditions for imidate formation,[2] double insertion was not observed. No double insertion was observed using phenol as the nucleophile, a result which may be related to

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Table 1 Effect of [CyNC] and temperature on formation of **3** and **4**[a]

Entry	CyNC/mmol	Temp/°C	Time/h	**3**/%[b]	**4**/%[b]	**4** : **3**
1	0.6	98	2	36.7	47.8	1.30
2	0.1	98	2	10.0	5.2	0.52
3	0.2	98	2	15.3	10.1	0.66
4	0.4	98	2	21.8	26.7	1.22
5	0.8	98	2	7.0	33.1	4.73
6	2.0	98	2	5.2	60.8	11.69
7	0.6	50	60	0.7	4.0	5.71
8	0.6	70	60	6.6	38.0	5.76
9	0.6	90	12	20.0	40.3	2.02

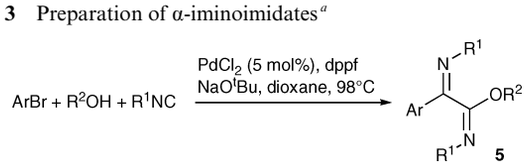
[a] 0.4 mmol PhBr, 0.02 mmol $PdCl_2$, 0.04 mmol dppf, 2 mmol EtONa in 1 mL EtOH, 3 mL toluene. [b] Yields by GC *vs* tridecane as internal standard.

Table 2 Effect of base and [ethanol] on formation of **3** and **4**[a]

Entry	ROM/mmol	EtOH	Time/h	**3**/%[b]	**4**/%[b]	**4** : **3**
1	0.12 NaOEt[c]	0.44 mL	15	2.0	27.8	13.9
2	0.24 NaOEt[c]	0.38 mL	15	2.9	41.0	14.1
3	0.48 NaOEt[c]	0.26 mL	15	6.1	48.5	7.9
4	1.0 NaOEt[c]	0	15	13.4	49.4	3.7
5	0.24 NaO^{t}Bu[d]	10 mmol	15	10.9	43.9	4.0
6	0.24 NaO^{t}Bu[d]	1 mmol	15	7.9	53.3	6.7
7	0.24 NaO^{t}Bu[d]	0.5 mmol	15	1.8	62.0	34.4
8	0.24 NaO^{t}Bu[d]	0.25 mmol	15	0.7	56.4	80.6
9	0.24 NaO^{t}Bu	1 mmol	15	5.3	92.3	17.4
10[e]	0.24 NaO^{t}Bu	1 mmol	4	5.3	51.0	9.6
11[e]	0.24 KO^{t}Bu	1 mmol	4	57.0	25.3	0.44
12[e]	0.24 CsO^{t}Bu	1 mmol	4	65.3	10.2	0.16

[a] 0.2 mmol PhBr, 0.6 mmol CyNC, 0.01 mmol $PdCl_2$, 0.02 mmol dppf, 2 mL dioxane, 98 °C. [b] By GC *vs.* tridecane as internal standard. [c] As a 2 M soln. in EtOH. [d] As a 1M solution in ^{t}BuOH. [e] 0.3 mmol CyNC used.

Table 3 Preparation of α-iminoimidates[a]



Entry	Ar	R^1	R^2	**5**	Yield (%)[b]
1	Ph	Cy	Et	**a**	79
2	Ph	Bu	Et	**b**	70
3	Ph	Cy	^{i}Pr	**c**	88
4	*p*-$MeOC_6H_4$	Cy	Et	**d**	72
5	*p*-$MeOC_6H_4$	Bu	Et	**e**	74
6	*p*-$MeOC_6H_4$	Cy	^{i}Pr	**f**	71
7	*p*-NCC_6H_4	Cy	Et	**g**	73

[a] ArBr (1 equiv), ^{t}BuONa (1.2 equiv), R^2OH (5 equiv), R^1NC (3 equiv), $PdCl_2$ (0.05 eqiv), dppf (0.1 equiv), dioxane, 98 °C, 4h. [b] Isolated yield of distilled product.

the reported failure of palladium catalysed bis-carbonylations when aniline was the nucleophile.[3]

A crystal structure of **5c** was obtained confirming the 1*E*,2*Z* stereochemistry indicated and showing a 90° dihedral angle for the N=CC=N group.‡ The stereochemistry of the products probably tells us little about the mechanism of the reaction since *E*/*Z* isomerisation of the C=N bonds is likely to occur under the reaction conditions.[10] The observed 1*E*,2*Z* isomer of **5** formed is probably the thermodynamically most stable of the 4 possibilities.§

The work described above was aimed at optimisation, rather than mechanistic study, but the strong effects on the ratio of mono- to bis-inserted products formed of both the concentration of isonitrile and the ethoxide concentration and nucleophilicity, suggest a direct competition between the two at the point where the catalytic cycles diverge. The catalytic cycle shown in Fig. 1 is one possibility. Insertion of isonitrile into the Pd–iminoacyl bond preceding alkoxide attack in formation of the α-iminoimidate is one of many possible variations.

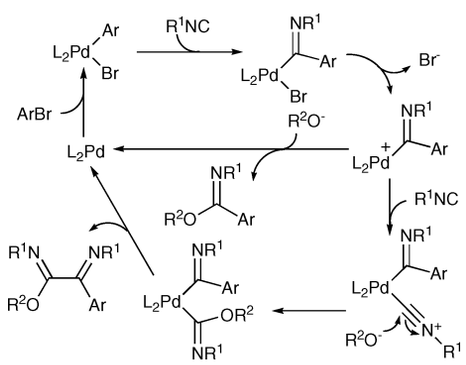


Fig. 1 Possible catalytic cycles.

Overall we have described an efficient palladium catalysed 4-component synthesis of α-iminoimidates.

Acknowledgements

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Notes and references

† Tris-insertion of isonitrile may give a very stable chelated palladium complex—ref 5.

‡ Crystal data for **5c**: $C_{23}H_{34}N_2O$, $M_r = 354.52$, monoclinic, space group $P2_1$, $a = 9.1902(5)$, $b = 14.4440(7)$, $c = 15.8727(10)$ Å, $\beta = 94.398(2)°$, $U = 2100.8(2)$ Å^3, $Z = 4$, μ(Mo-Kα) = 0.068 mm^{-1}, $T = 120(2)$ K, 6538 independent reflections ($R_{int} = 0.0447$), final $R1 = 0.0753$, $wR2 = 0.1018$ for all data. CCDC reference number 232994. See http://www.rsc.org/suppdata/ob/b4/b408673m/ for crystallographic data in .cif or other electronic format.

§ DFT calculations using B3LYP method and 6.31G* basis set gave the relative energies of (1*E*,2*Z*)-, (1*E*,2*E*)-, (1*Z*,2*Z*)-, and (1*Z*,2*E*)-PhC(=N^{i}Pr)C(=N^{i}Pr)OEt as 0, 17.6, 19.6, and 31.8 kJ mol^{-1} respectively.

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