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Palladium-catalysed three component synthesis of α,β-unsaturated amidines and imidates

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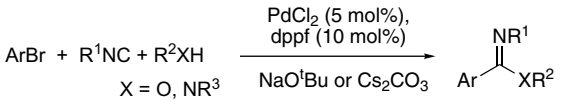
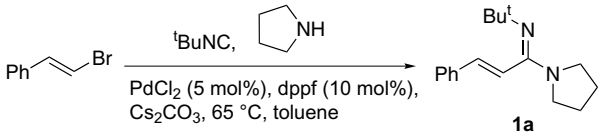
Abstract—Palladium-catalysed three component coupling of an alkenylbromide, isonitrile and an amine or alkoxide/phenoxide affords α,β-unsaturated-amidines and -imidates.

We recently reported the palladium-catalysed three component synthesis of aryl-amidines[1] and -imidates[2] from aryl bromides, isonitriles and amines or alcohols, respectively (Scheme 1). We now report that the reaction also works well with alkenyl bromides to afford α,β-unsaturated-amidines and -imidates. The related palladium catalysed carbonylation of alkenyl bromides to afford esters and amides is known.[3]

We first tried the coupling reaction between β-bromostyrene (>99% *E*),[4] *tert*-butylisonitrile and pyrrolidine using the same conditions developed for coupling of aryl bromides (5 mol% $PdCl_2$, 10 mol% dppf, Cs_2CO_3, toluene).[1] Pleasingly the desired amidine **1a** (Scheme 2) was formed in excellent yield in less than 15 min at 65 °C, a marked contrast to the 2 h at 109 °C needed for the equivalent reaction of bromobenzene. On a preparative scale extraction of the crude product into 2.5% aqueous acetic acid, basification by addition of solid KOH, extraction of the product into diethyl ether and removal of solvent gave the amidine **1a** as a pale yellow crystalline solid in good yield (Table 1, entry 1). Amidine **1a** was formed as a 99:1 mixture of *E*:*Z* alkene stereoisomers. When the commercial 85:15 *E*:*Z* mixture of β-bromostyrene was used product **1a** was formed as a 90:10 alkene *E*:*Z* mixture. Only one isomer about the C=N bond was observed.



Scheme 1.



Scheme 2.

X-ray crystallography of **1a** (Fig. 1)[5] showed that the (*E*)-stereoisomer of the imine had been formed, the same stereochemistry as observed in the formation of aryl amidines (Scheme 1),[6] and probably reflects thermodynamic stability[7,8] rather than the mechanism of formation. The barrier to rotation about the C–N single bond in **1a** was very low—no line broadening was observed in carbon or proton NMR at 213 K.[9]

A variety of primary and secondary amines were tried in the reaction with the results given in Scheme 3 and Table 1. The amidines derived from primary amines (entries 5–7) exist entirely in the tautomeric form **2** as judged from the ^{1}H NMR shifts of the *tert*-butyl groups at (δ_H 1.41–1.43) compared to amidines **1** derived from secondary amines (δ_H 1.23–1.26) in accordance with similar observations on aryl amidines.[10] We have not proven the imine stereochemistry in amidines **2**, but that shown is predicted by calculations.[11]

Keywords: Isonitrile; Multi-component; Amidine; Imidate; Palladium catalysed.
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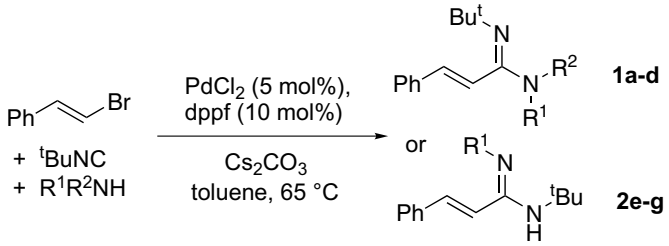


Scheme 3.

Table 1. Formation of 3-phenyl-2-alkenylamidines

Entry	R^1, R^2	Product	Yield (%)[a]	*E*:*Z*[b]
1	–$(CH_2)_4$–	**1a**	77	>99:1 (90:10)[c]
2	Et, Et	**1b**	61	95:5 (91:9)[c]
3	–$(CH_2)_2O(CH_2)_2$–	**1c**	62	>98:1 (93:7)[c]
4	–$(CH_2)_5$–	**1d**	71	>98:1 (90:10)[c]
5	Me, H	**2e**	71	>99:1
6	Cy, H	**2f**	71	>99:1
7	Ph, H	**2g**	25[d]	>97:3

[a] Isolated yield. Reagents and conditions: β-bromostyrene (1.2 mmol), amine (6 mmol), ^{t}BuNC (1.8 mmol), Cs_2CO_3 (1.5 mmol), $PdCl_2$ (0.06 mmol), dppf (0.12 mmol), toluene, 65 °C, 15–30 min.
[b] Alkene stereochemistry from >99% (*E*)-β-bromostyrene.
[c] Alkene stereochemistry from 85:15 mixture of *E*:*Z*-β-bromostyrene.
[d] Required heating at 109 °C for 35 h.

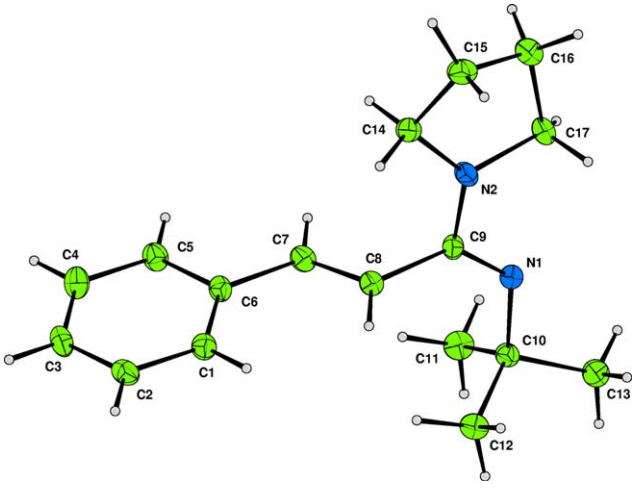
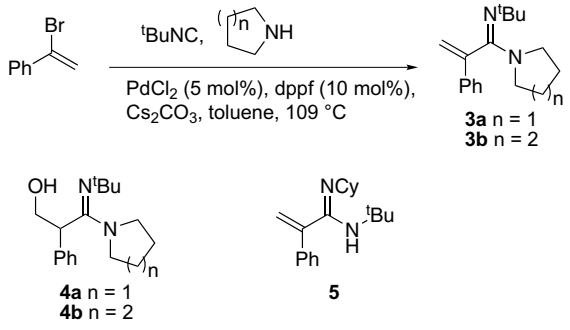


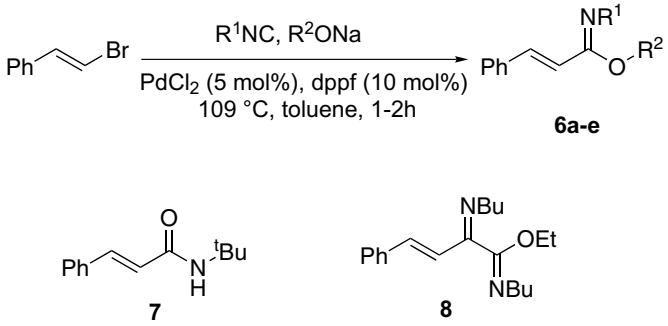
Figure 1. Crystal structure of **1a**. Thermal ellipsoids drawn at the 30% probability level. Selected measurements: C9–N2 = 1.363 Å; C9–N1 = 1.291 Å; C9–C8 = 1.497 Å; C8–C7 = 1.32 Å; N2–C9–N1 = 117.5°; N1–C9–N2–C17 = 179.8°; N1–C9–C8–C7 = 105.6°; C8–C7–C6–C1 = 3.0°.

When aniline was the amine source the reaction was very slow with little conversion to products after 18 h stirring at 65 °C. After 35 h at 109 °C the starting bromide had all reacted, but only a low yield of the amidine **2g** was isolated. Attempts to replace *tert*-butylisonitrile with *n*-butyl-, cyclohexyl- or benzyl-isonitriles in the synthesis of alkenylamidines were unsuccessful.

We next examined the reaction of α-bromostyrene with *tert*-butylisonitrile and pyrrolidine and piperidine and found that 2 h at 109 °C was needed to give good conversion, by GC, to the methylidine amidines **3a** and **3b** (Scheme 4). Surprisingly our standard work-up by extraction into aqueous acetic acid followed by basification with solid KOH and extraction into ether gave substantial conversion into the β-hydroxyamidines **4a** and **4b** (40:60–25:75 **3**:**4** by GC in various experiments). Alcohols **4a** and **4b** could be isolated by column chromatography (5% triethylamine, 10% diethyl ether in petrol as eluent) in 25% and 29% yields, respectively. Amidine **3a** was stable in the acid solution so hydration must be occurring on addition of the base. The addition of water could be avoided by vigorous stirring of the acid solution with diethyl ether during addition of the KOH to give **3a** and **3b** in 71% and 64% isolated yields, respectively. We have not proven the stereochemistry of the imine in **3** and **4**, but it is expected to be (*E*) by comparison with similar systems (Schemes 1 and 2 above), and in accordance with calculations.[11] The reaction between α-bromostyrene, *tert*-butylisonitrile and cyclo-



Scheme 4.



Scheme 5.

Table 2. Formation of 3-phenyl-2-alkenylimidates

Entry	R^1	R^2	Time (h)	Product	Yield (%)[a]
1	^{t}Bu	Et	1.5	**6a**[b]	25
2	^{t}Bu	Ph	0.5	**6b**	60
3	^{n}Bu	Et	1.0	**6c** + **8**	64[c]
4	^{n}Bu	Ph	0.5	**6d**[d]	72
5	Cy	Ph	1.0	**6e**[d]	55

[a] Isolated yield. Reagents and conditions: PhCHCHBr (1 mmol), R^1NC (1.5 mmol), PhONa or EtONa (5 mL of 1 M soln in THF or ethanol, respectively), toluene (20 mL), 109 °C.
[b] 26% of **7** also isolated.
[c] 1:2 ratio **6c** to **8**.
[d] 65:35 mixture of imine stereoisomers.

hexylamine gave the tautomer **5** in 53% yield (Scheme 4) and in this case hydration was not observed. Attempts to replace *tert*-butylisonitrile with *n*-butyl- or cyclohexyl-isonitriles were unsuccessful.

We now turned to the synthesis of imidates. Initial GC optimisation of the palladium-catalysed reaction between β-bromostyrene, *tert*-butylisonitrile and sodium ethoxide to afford **6a** (Scheme 5) showed that 1 h at 109 °C was required for complete reaction. It is interesting that the rate is much slower than amidine formation. In the formation of aryl-amidines and -imidates the latter was somewhat faster.[1,2] The product **6a** proved unstable to both chromatography and distillation, substantial amounts of amide **7** being formed, reducing the isolated yield to 25% (Scheme 5, Table 2, entry 1). *n*-Butylisonitrile also worked well in the reaction, but the main product was the α-iminoimidate **8** resulting from bis-insertion of the isonitrile (Table 2, entry 3)—a similar result to the analogous reaction starting with aryl bromides.[12,13]

Palladium-catalysed reaction of β-bromostyrene and sodium phenoxide with *tert*-butyl-, *n*-butyl- and cyclohexyl-isonitriles afforded the desired imidates **6b**, **6d** and **6e** in good yield (Scheme 5, Table 2 entries 2, 4 and 5). No bis-insertion of isonitrile was observed and the products were more stable to silica than the alkoxy-imidates. Although the β-bromostyrene used for all the above reactions was a 99:1 mixture of (*E*)-:(*Z*)-alkene stereoisomers, none of the (*Z*)-isomer of **6** was observed by GC or NMR. Compounds **6a** and **b** were either single isomers at the imine double bond, or more likely the isomers were rapidly interconverting at room temperature.[7,14] Phenoxyimidates **6d** and **6e** were each a 65:35 mix of imine stereoisomers, whereas **6c** was a single isomer. Theoretical calculations[15] are consistent with these observations. For **6a**, **6b** and **6c** the (*E*)-imine stereoisomer is calculated to be 15, 7 and 20 kJ/mol more stable than the (*Z*). For **6d** and **6e** the energy difference is <3 kJ/mol (favouring the (*Z*)-stereoisomer) consistent with the observed mixture.

Synthesis of imidates using α-bromostyrene was not successful. Even after 18 h at 125 °C (pressure tube) the starting bromide was largely unreacted.

In conclusion, we have shown that α,β-unsaturated amidines and imidates are readily formed in a three component palladium-catalysed reaction.

Acknowledgements

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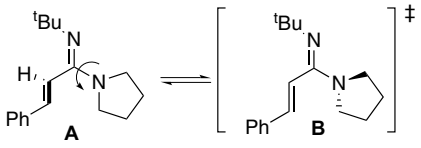

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