

Catalytic processes for the functionalisation and desymmetrisation of malononitrile derivatives

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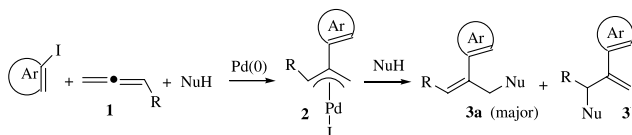
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Abstract—Palladium catalysed 3-component cascades are described involving aryl/heteroaryl iodides, allene and benzyl malononitrile. Catalytic monohydration and monoamination of malononitriles to the corresponding monoamides and monoamidines are also described together with several examples of mono-oxazoline formation.

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1. Introduction

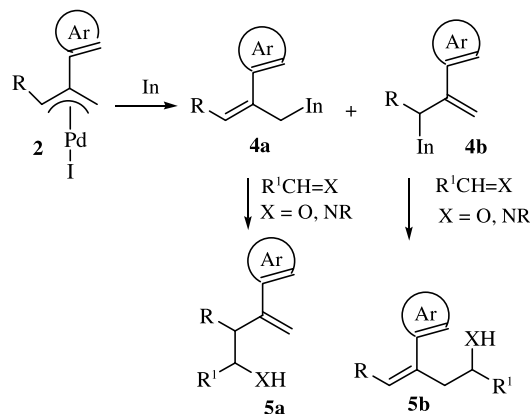
π -Allylpalladium (II) complexes are important intermediates in a plethora of catalytic reactions including allylic substitutions,¹ allylic oxidation² and 1,4-oxidation of conjugated dienes.³ These reactions all involve nucleophilic attack of carbon or heteroatom nucleophiles on the π -allyl moiety. Heteroatom nucleophiles, including RCO_2H ,⁴ H_2O ,⁵ ROH ⁶ and amines⁷ (primary and secondary), have proved particularly valuable in complex molecule synthesis. Carbon nucleophiles include malonates,⁸ malononitriles,⁹ and ketones.¹⁰ We and others have been involved in generating π -allylpalladium (II) intermediates via aryl/heteroaryl iodides and allenes in the presence of palladium(0)^{11–15} (Scheme 1).



Scheme 1.

In the Pd(0) catalysed reactions of allene **1** with aryl/heteroaryl iodides, carbopalladation of allene with ArPdI

takes place to give π -allylpalladium (II) intermediate **2**, which reacts with nucleophiles mainly or exclusively at the less substituted terminus to give **3a/3b** (Scheme 1). Acyl and hydropalladation of allenes are additional versatile routes to π -allylpalladium species, which have been imaginatively exploited in harness with nucleophilic attack.^{16–18} We have also demonstrated how the normal electrophilic reactivity of π -allylpalladium **2** generated from aryl/heteroaryl iodides and allenes can be reversed by reductive transmetalation with indium powder. The resultant umpolung allylindium species **4a/4b** subsequently add to electrophilic $\text{C}=\text{X}$ ($\text{X}=\text{O}$, NR) derivatives affording homoallylic alcohols/amines **5a/5b** (Scheme 2).¹⁹



Scheme 2.

Keywords: 3-Component cascade; Palladium catalysis; Hydration; Amidines; Oxazolines.

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
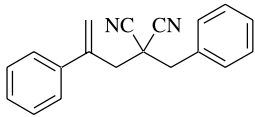
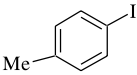
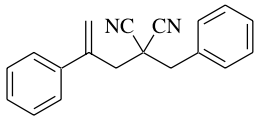
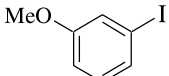
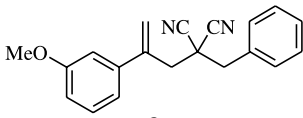
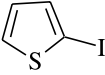
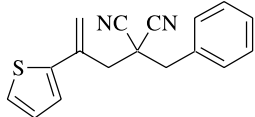
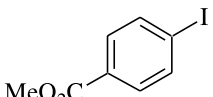
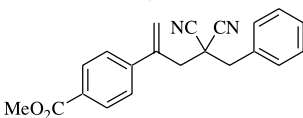
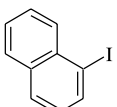
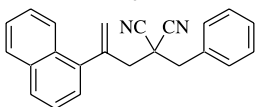

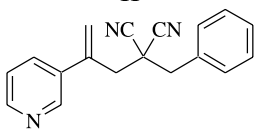
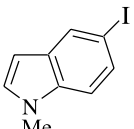
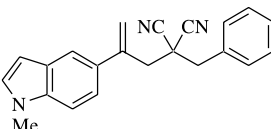
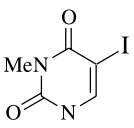
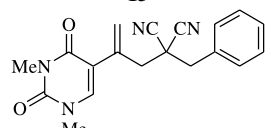
In this paper, we report the palladium catalysed 3-component cascade synthesis of 2-benzyl aryl/heteroaryl allyl malononitriles utilising benzyl malononitrile as the pronucleophile (Scheme 1) and the subsequent selective desymmetrisation of malononitrile derivatives by catalytic monohydration, and monoamination.

1.1. 3-Component cascades

Iodobenzene (1.5 mmol) reacted with allene (1 bar), benzyl malononitrile (1 mmol), Pd(OAc)₂ (5 mol%),

triphenylphosphine (10 mol%) and Cs₂CO₃ (2 mol equiv) in THF (10 ml) at 90 °C for 14 h to afford **6** in 85% yield (Table 1, entry 1). Electron rich, electron poor, and neutral aryl iodides were successfully employed in the cascade process affording **6–11** in 60–73% yield (Table 1, entries 2–6). However, 3-iodopyridine, 1-methyl-5-iodoindole and 5-iodo-1,3-dimethyluracil resulted in moderate yields of **12–14** (Table 1, entries 7–9). We further optimized reaction conditions using 3-iodopyridine as the model compound. Decreasing the reaction temperature to 70 °C afforded **12** in 67% yield whilst changing the base to K₂CO₃ afforded a

Table 1. Palladium catalysed 3-component cascades^a

Entry	Ar-I	Product	Yield (%) ^b	
			Cs ₂ CO ₃	K ₂ CO ₃
1			85	87
2			73	78
3			66	80
4			66	80
5			66	83
6			60	75
7			44	80 ^c
8			59	70 ^c
9			40	85 ^c

^a All the reactions were carried out in THF at 100 °C for 14 h in a Schlenk tube using Pd(OAc)₂ (10 mol%), PPh₃ (20 mol%), base (2 mol equiv), allene (1 bar), aryl iodide (1.5 mmol) and benzyl malononitrile (1 mmol).

^b Isolated yield.

^c 70 °C, 14 h.

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