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Palladium catalysed 3-component cascade synthesis of bis(2-arylallyl) tertiary amines from aryl iodides, allene and primary amines

Xinjie Gai,[a] Ronald Grigg,*[a] Simon Collard[b] and Jayne E. Muir[b]

[a] *Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds, UK LS2 9JT. E-mail: R. Grigg@chem.leeds.ac.uk; Fax: (+44) 113-233 6501; Tel: (+44) 113 233 6501*

[b] *Johnson Matthey, Precious Metal Division, Royston, Herts, UK SG8 5HE*

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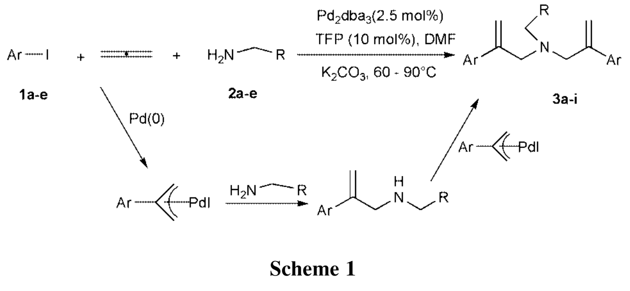
A 3-component cascade synthesis of bis(2-arylallyl) tertiary amines from aryl iodide, allene and primary aliphatic amines is described; chiral amines give analogous products with no detectable racemisation; mixtures of two different aryl iodides can be utilised to give the mixed tertiary amines as the sole, or major, product; the reaction is sensitive to stereoelectronic effects which lead to mono(2-arylallyl) secondary amines.

π-Allylpalladium species react with both carbon- and heteroatom-centred nucleophiles with formation of carbon–carbon or carbon–heteroatom bonds and catalytic versions of these processes have been widely utilized in organic synthesis.[1] Heteroatom nucleophiles, including RCO_2H,[2] H_2O,[3] ROH[4] and amines[5] (primary and secondary), have proved particularly valuable in complex molecule synthesis. The reaction of nitrogen nucleophiles with π-allylpalladium(II) species are amongst the most widely used in organic synthesis. The efficiency of intermolecular amination and its tolerance of a wide range of functional groups has encouraged extensive applications including the synthesis of carbocyclic nucleoside analogues.[6] Aryl, acyl and hydropalladation of allenes are additional versatile routes to π-allylpalladium species which have been imaginatively exploited in harness with nucleophilic attack.[7–9]

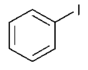
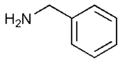
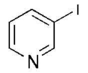
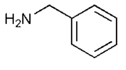
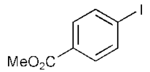
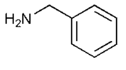
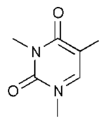
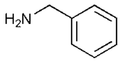
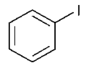
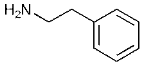
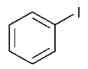
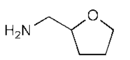
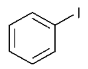
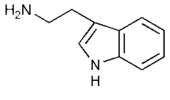
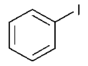
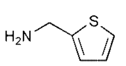
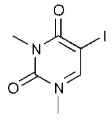
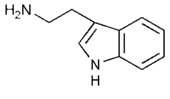
Most reported cases of reactions with amines involve one π-allylpalladium species reacting with a primary or secondary amine to form a secondary amine or tertiary amine respectively. The sequential transfer of two allyl groups from Pd(II) to a primary amine to form a tertiary amine in a one pot reaction has not, to our knowledge, been reported. Herein we report the first cases where primary amines react with π-allylpalladium(II) species, generated from allene, to form tertiary amines. The three component reaction can be carried out under mild conditions in the presence of a palladium catalyst in good yield (Scheme 1) (Table 1) and involves formation of two carbon–carbon bonds and two carbon–nitrogen bonds. The palladium(0) catalyst Pd_2dba_3 (2.5 mol%) in combination with tris(2-furyl)phosphine (TFP) together with allene gas (1 bar) proved effective at 60–90 ° C over 1–2 d.[10]

A range of aryl/heteroaryl iodides and primary amines were evaluated and good yields were obtained in all cases (Table 1). The reaction also works well for vinyl iodides (Table 1, entries 4 and 9) and for a range of primary aliphatic amines. Reaction of primary aliphatic amines with 1 : 1 mixtures of two different aryl iodides gives the desired mixed product as the major or, in some cases, the sole product. Two typical examples are provided by reaction of (−)-myrtanylamine **4** with 1 mol eq. of 4-methoxyiodobenzene and 4-(*N,N*-diethylaminocarbonyl)iodobenzene which affords **5** (56%) as the sole product whilst amine **6** reacts with 4-methoxycarbonyliodobenzene and 3,5-di-



Scheme 1

Table 1 3-Component cascade synthesis of symmetrical bis(2-arylallyl) tertiary amines (**3a–i**)[a]

Entry	Ar-I	Amine	Temp/°C[b]; Time/d	Product	Yield[c] (%)
1	 **1a**	 **2a**	85; 2	**3a**	82
2	 **1b**	 **2a**	60; 2	**3b**	82
3	 **1c**	 **2a**	90; 1	**3c**	70
4	 **1d**	 **2a**	90; 2	**3d**	80
5	 **1a**	 **2b**	90; 1.5	**3e**	78
6	 **1a**	 **2c**	80; 2	**3f**	70
7	 **1a**	 **2d**	80; 1	**3g**	62
8	 **1a**	 **2e**	85; 2	**3h**	72
9	 **1d**	 **2d**	80; 2	**3i**	71

[a] All reactions were run in DMF at 60–90 °C over 1–2 days in the presence of 2.5 mol% Pd_2dba_3, 10 mol% $(2\text{-furyl})_3P$, allene (1 bar) and K_2CO_3(4 mol eq.) in a Schlenk tube. [b] Oil bath temperature. [c] Isolated yield.

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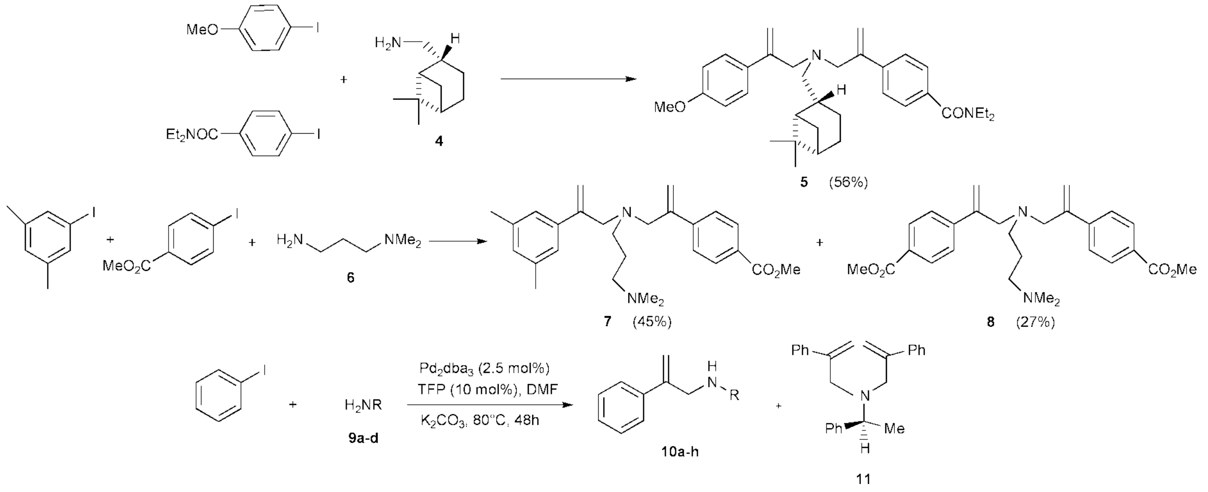
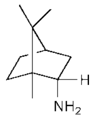
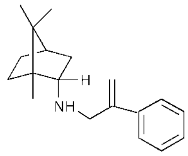
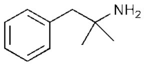
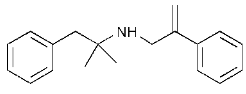
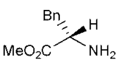
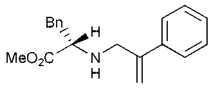
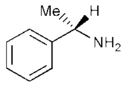
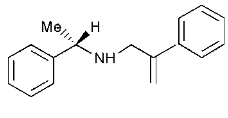
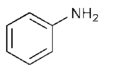
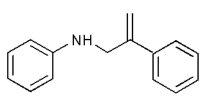
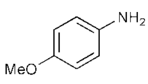
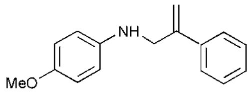
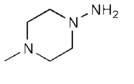
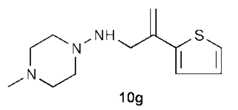
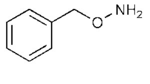
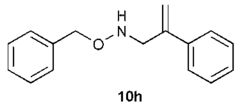


Scheme 2

Table 2 3-Component cascade synthesis of 2-arylallyl secondary amines (**5a–h**)[a]

Entry	Amine	Product	Yield(%)
1	 **9a** (·)	 **10a**	92
2	 **9b**	 **10b**	88
3	 **9c** (*S*) -	 **10c**	72
4	 **9d** (*S*)	 **10d**	73[b]
5	 **9e**	 **10e**	73
6	 **9f**	 **10f**	95
7	 **9g**	 **10g**	48[c]
8	 **9h**	 **10h**	83

[a] All reactions were run in DMF at 80 °C for 48 h. Catalyst and additive as for Table 1. Iodobenzene was the aryl iodide unless otherwise noted. [b] In addition the tertiary amine **6** was obtained. [c] 2-Iodothiophene replaced iodobenzene.

methylbenzene to afford a mixture of **7** and **8**. Clearly there is scope for considerable optimisation in these cases.

The reaction is also sensitive to stereoelectronic factors as demonstrated by Scheme 2 and Table 2.

The monoallylated α-branched primary amines **10a–d** (Table 2, entries 1–4) fail to undergo a second allylation due to substantial steric hindrance. The primary amines **9e–h** (Table 2) are orders of magnitude less basic [11] and nucleophilic than **2a–d** and are also sterically more hindered. These two factors conspire to prevent the second allylation under the specified conditions.

The secondary and tertiary amine products of these cascades are unusual derivatives of the bioactive β-aryl/heteroaryl-(ethyl)amine pharmacophore. Bis(2-arylallyl) tertiary amines have also found applications as additives in copolymer latexes[12] and in endoperoxide[13] chemistry.

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Notes and references

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10 General procedure: a mixture of aryl iodide (2.2–2.5 mol eq.), amine (1 mmol), Pd_2dba_3 (24 mg, 0.025 mmol), TFP (25 mg, 0.10 mmol) and K_2CO_3 (556 mg, 4 mmol) was stirred in DMF (10 ml) and heated at 80–90 °C for 1–2 days in a Schlenk tube under allene (1 bar). On completion of the reaction, the tube was cooled, vented, H_2O (30 ml) was added and the mixture was extracted with ether (3 × 20 ml). The combined organic layer was dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash chromatography.

11 The following pK_a values were calculated with ACD/p*K*a v4.56 using the ACD/I-Lab service: **9e** (4.61), **9f** (5.21), **9g** (7.35) and **9h** (4.63).

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