Bimetallic catalytic synthesis of annelated benzazepines†

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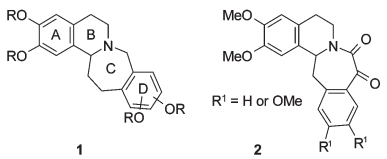
A novel short synthetic route to annelated benzazepines, using additive enhanced palladium–indium catalytic 3-component cascade methodology is described.

Homoprotoberberines (**1**)[1] are a group of alkaloids which exhibit anti-malarial and anti-bacterial properties[2] whilst homoprotoberberine (**2**) has been found to be potent against human breast carcinoma cells.[3] Current synthetic routes to homoprotoberberines are invariably multi-step procedures with low overall yields.[1–4]



We have developed powerful catalytic palladium–indium three-component cascade methodology involving reductive transmetallation of a π-allylpalladium(II) species, generated from allenes and aryl iodides, with indium and subsequent addition of the umpolung allylindium species to an electrophilic component (aldehydes, ketones, imines). Four synthetic variants of this process, depending upon whether the palladium-catalysed and indium-mediated steps are *inter*- or *intra*-molecular, have been identified.[5–8] Transmetallation of allenylpalladium(II)[9] and conventionally generated π-allylpalladium(II) species by indium salts has also been reported by others.[10–12] The addition of an allylindium reagent to 1-acylpyridinium salts has also been reported.[13]

We have recently reported the beneficial effect of additives on 3-component cascade processes. Thus piperidine (1 mol eq.) or copper(I) iodide (0.2 mol eq.) were both found to decrease the reaction time from 18 h to 2 h while increasing the yield significantly.[14,15]

In this communication we report our preliminary results using iminium ions derived from a range of nitrogen heterocycles as the electrophilic component of both class 2 and class 1 processes. The former products bear a close structural relationship to the homoprotoberberines (**1**).

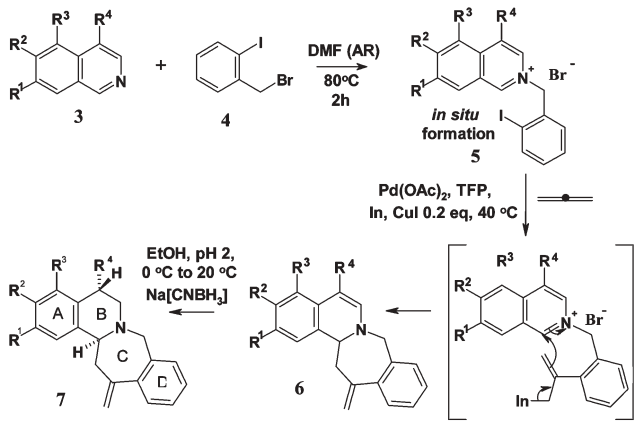
Annelation of benzazepines to isoquinolines proceeds *via* generation of iminium ion (**5**) *in situ* from isoquinoline (**3**) and 2-iodobenzyl bromide (**4**). Subsequent addition of allene, palladium(II) acetate, indium powder and additives initiates a class 2 Pd/In 3-component cascade reaction to generate enamines (**6**) (Scheme 1) *via* regioselective 7-*endo*-trig cyclisation. Reduction of (**6**) with sodium cyanoborohydride gives benzazepines (**7**). A range of substituted benzazepines (**7a–7h**) have been prepared with a variety of substituents in the A and B rings (Table 1), using copper(I) iodide (20 mol %) as the additive. The use of piperidine (1 mol eq.) proved ineffective in this case. Various catalytic systems and temperatures were evaluated with $Pd(OAc)_2$ (10 mol %), trifuryl phosphine (TFP) (20 mol %), In (1.5 mol eq.) and Cu(I)I (20 mol %) in *N*,*N*-dimethylformamide (10 ml/mmol) at 40 °C for 20 h, proving the most effective of those surveyed.

Compounds **7f–7h** were obtained as single stereoisomers. Stereochemistry was assigned from n.O.e. data together with an X-ray crystal structure of **7g** (Fig. 1). The 7-membered ring C adopts a chair-like conformation whilst ring B assumes a half chair conformation. The *N*-lone pair adopts a pseudo equatorial position on the same side of the molecule as the axial 14a-H, resulting in a *cis* ring B/C junction. Substitution can also be introduced into ring D as exemplified by utilising 3,4-methylenedioxy- and 3,4-dimethoxy-2-iodobenzyl bromides (**4a** and **4b**)[16] (Table 2).

Annelation of benzazepines to *N*-protected β-carbolines **8a** and **8b**, (Table 3), occurs in an analogous manner. Currently the yields of **9a** and **9b** are lower than when isoquinoline is used as the parent heterocycle, possibly due to the steric encumbrance arising from *N*-Me and *N*-Ts groups.

Pyridines (**11a–d**) can be utilised as annelation partners and give rise to **13a–d** in good yield (Table 4). Compounds **13a–d** were obtained as single regioisomers. An X-ray structure of **13d** (Fig. 2) indicates that the 7- and 6-membered rings adopt chair like and half chair conformations, with the *N*-lone pair and 12a-H *cis*.

Class 1 reactions involving iminium ions (**15**) generated *in situ* from isoquinoline (**3**) and the appropriate benzyl bromide (**14**), aryl iodide and allene afford 1,2-dihydroisoquinolines (**16**) which upon sodium cyanoborohydride reduction give 1,2,3,4-tetrahydroisoquinolines (**17**) (Scheme 2) (Table 5). Compounds related to **17a** and **b** inhibit platelet aggregation.[17]



Scheme 1

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b5/b503213j/

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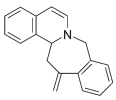
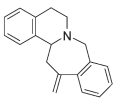
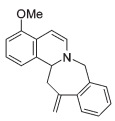
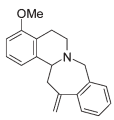
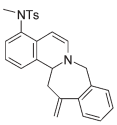
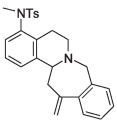
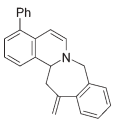
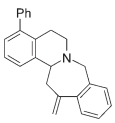
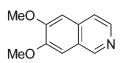
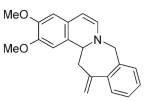
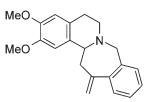
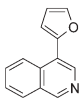
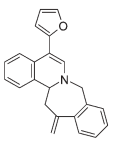
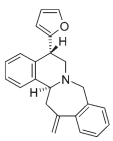
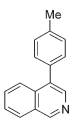
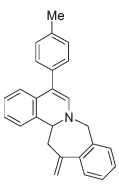
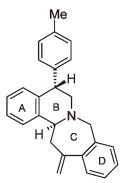
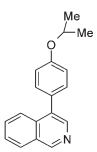
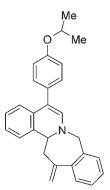
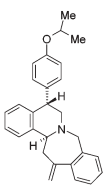
Table 1 Benzazepines (**7**) derived from substituted isoquinolines (**3**)[a]

Entry	Isoquinoline **3**	Enamine **6** (%)[b]	Benzazepine **7** (%)[c]
1			
	3a	**6a** (70)	**7a** (58)
2			
	3b	**6b** (80)	**7b** (94)
3			
	3c	**6c** (52)	**7c** (84)
4			
	3d	**6d** (70)	**7d** (85)
5			
	3e	**6e** (49)	**7e** (69)
6			
	3f	**6f** (84)	**7f** (68)
7			
	3g	**6g** (63)	**7g** (66)
8			
	3h	**6h** (75)	**7h** (73)

[a] Standard reaction procedure: isoquinoline (**3**) (1 mmol), 2-iodobenzyl bromide (**4**) (1 mmol), $Pd(OAc)_2$ (10 mol %), TFP (20 mol %), indium (1.5 mol eq.), CuI (20 mol %), DMF (AR, 10 ml/mmol), 40 °C, 20 h. [b] Yield calculated using an internal standard of MeOH 1 mmol/2 ml $CDCl_3$. [c] Isolated yield for the reduction of (**6**) to (**7**).

Further work on these and related palladium–indium cascades is currently underway.‡

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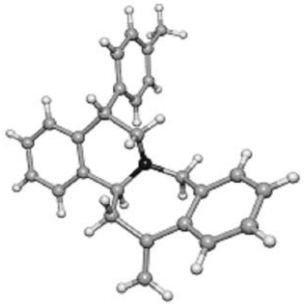
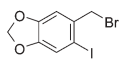
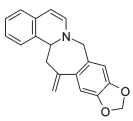
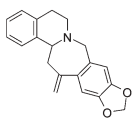
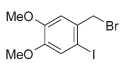
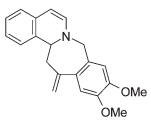
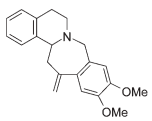
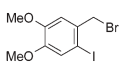
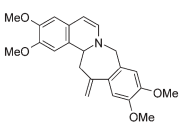
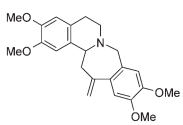


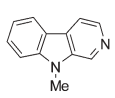
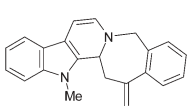
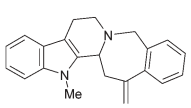
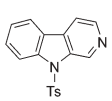
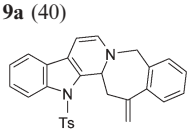
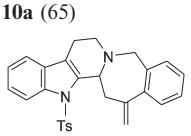
Fig. 1 X-Ray crystal structure of **7g**.

Table 2 Incorporation of substituted 2-iodobenzyl bromides (**4**)

Entry	Aryl iodide **4**	Enamine **6** (%)[a]	Benzazepines **7** (%)[b]
1			
	4a	**6i** (80)	**7i** (75)
2			
	4b	**6j** (50)	**7j** (74)
3			
	4b	**6k** (81)	**7k** (78)

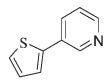
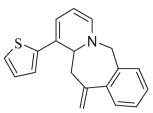
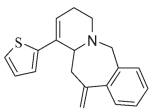
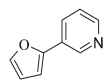
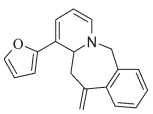
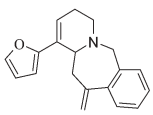
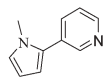
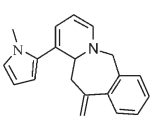
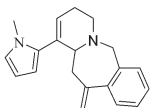
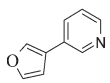
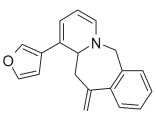
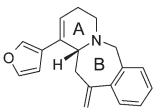
[a] Yield calculated using an internal standard of MeOH 1 mmol/2 ml $CDCl_3$. [b] Isolated yield for the reduction of (**6**) to (**7**).

Table 3 β-Carboline derived annelated benzazepines

Entry	β-Carboline **8**	Enamine **9** (%)[a]	Benzazepines **10** (%)[b]
1			
	8a	**9a** (40)	**10a** (65)
2			
	8b	**9b** (30)	**10b** (64)

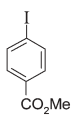
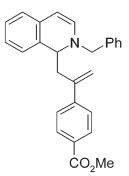
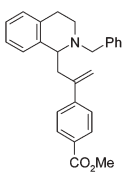
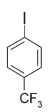
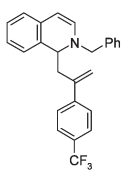
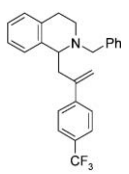
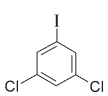
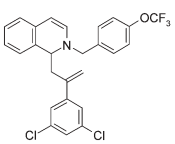
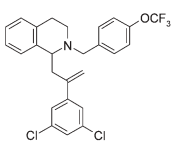
[a] Yield calculated using an internal standard of MeOH 1 mmol/2 ml $CDCl_3$. [b] Isolated yield for the reduction of (**9**) to (**10**).

Table 4 Pyridine (**11a–d**) derived annelated benzazepines (**13a–d**)

Entry	Pyridine **11**	Enamine **12** (%)[a,b]	Benzazepine **13** (%)[c]
1			
	11a	**12a** (60)	**13a** (60)
2			
	11b	**12b** (75)	**13b** (63)
3			
	11c	**12c** (82)	**13c** (61)
4			
	11d	**12d** (64)	**13d** (72)

[a] Yield calculated using an internal standard of MeOH 1 mmol/2 ml $CDCl_3$. [b] Thiophene (2 mol eq.) used as an additional additive. [c] Isolated yield for the reduction of (**12**) to (**13**).

Table 5 Class 1 inter–inter 1,2,3,4-tetrahydroisoquinoline (**17**)

Entry	Aryl iodide	1,2-Dihydroisoquinoline **16** (%)[a]	1,2,3,4-Tetrahydroisoquinoline **17** (%)[b]
1			
		16a (49)	**17a** (36)
2			
		16b (71)	**17b** (47)
3			
		16c (70)	**17c** (48)

[a] Yield calculated using an internal standard of MeOH 1 mmol/2 ml $CDCl_3$ [b] Isolated yield for the reduction of (**16**) to (**17**)

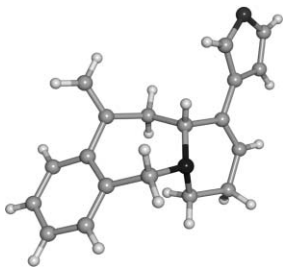
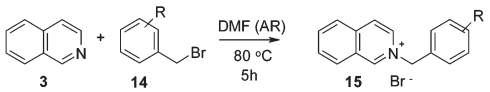


Fig. 2 X-Ray crystal structure of **13d**.



Scheme 2

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Notes and references

‡ Crystallographic data: **7g** ($C_{26}H_{25}N$), M = 351.47, orthorhombic, a = 10.3740(2), b = 19.2830(7), c = 9.7330(3) Å, V = 1947.01(10) Å^3, T = 150(2) K, space group $Pna2_1$, Z = 4, μ = 0.069 mm^{-1}, R_1 = 0.0395, wR_2 = 0.1031 for 10989 reflections, CCDC 266425. **13d** ($C_{19}H_{19}NO$), M = 277.35, monoclinic, a = 10.0020(3), b = 13.1350(4), c = 10.9480(4) Å, V = 1436.56(8) Å^3, T = 150(2) K, space group $P2_1/c$, Z = 4, μ = 0.079 mm^{-1}, R_1 = 0.0419, wR_2 = 0.1166 for 12805 reflections, CCDC 266424. See http://www.rsc.org/suppdata/cc/b5/b503213j/ for crystallographic data in CIF or other electronic format.

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