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Additive effects in palladium–indium mediated Barbier type allylations

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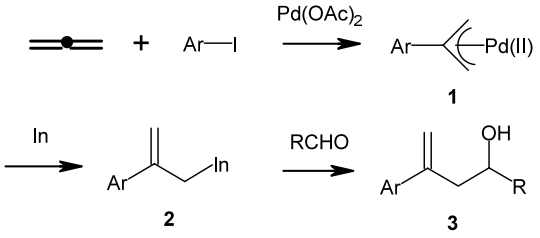
Abstract—The effect of adding 1 equiv. of an amine or 0.2 equiv. of CuI to a Pd/In bimetallic cascade reaction is described. In the class 1 cascade reaction of aldehydes, aryl iodides and allene, generating homoallylic alcohols, the reaction time is reduced from 16 to 2 h and is accompanied by an impressive increase in yield.

The synthesis of homoallylic alcohols via allylation of carbonyl compounds is a valuable and well studied synthetic transformation.[1] We recently reported a Pd/In three component allylation cascade of aryl iodides, aldehydes and allene which has 4 broad synthetic variants and yields homoallylic alcohols (Scheme 1).[2,3] A key step in this reaction is transmetalation of the electrophilic π-allylpalladium species with indium to give a nucleophilic allylindium species which subsequently adds to the carbonyl compound. Related umpolung processes have been reported by others.[4,5] Yields of homoallylic alcohols from the Scheme 1 process are frequently modest. We now report that the addition of 1 equiv. of piperidine to the Pd/In cascade reaction of iodobenzene, benzaldehyde and allene gas (Scheme 1, Ar = R = Ph (**3a**)) dramatically increased the yield from



Scheme 1.

43 to 83% whilst reducing the reaction time from 16 h to 2 h. Encouraged by this observation, a series of amine additives were examined and the results are summarised in Table 1. For strict comparison purposes a standard protocol was adopted: iodobenzene (1.5 mmol), benzaldehyde (1 mmol), amine/amide (1 mmol, 1 equiv.), In (1.5 mmol), $Pd(OAc)_2$ (10 mol%) and tri-(2-furyl)phosphine (TFP) (20 mol%) and allene gas (~1 bar) were reacted in DMF at 80°C for 2 h (Schlenk tube) (Scheme 1). Under these conditions the reaction fails to occur in the absence of an additive (Table 1, entry 1).

It is mechanistically informative to note, that in the presence of secondary amine additives, aldehyde capture by the allylindium species **2** occurs preferentially over amine capture **1**→**4** (Scheme 2) by the π-allylpalladium(II) species except when 2 equiv. of piperidine or piperazine are used (Table 1, entries 3 and 5) and that capture of the allylindium species **2** by the aldiminium ion **5**→**6** is not observed.[6]

The increase in yield exhibited by each of the additives shows no correlation with pK_a values. Piperidine, pyrrolidone and pyridine (Table 1, entries 2, 9 and 15) exhibit a wide range of pK_a values yet all dramatically increase the yield.

All the cyclic amines effect an improvement in yield. Acyclic amines have little or no effect (Table 1, entries 11–14); except for (*S*)-1-phenylethylamine (Table 1,

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Table 1.

Entry	Amine additive	Yield (%[a]), %[b]	pK_a[c]
Cyclic six-membered amines			
1	None	(<10), 0	–
2	Piperidine	(95), 83	11.24
3	Piperidine, 2 equiv.	(48), 28[d]	11.24
4	2,2,6,6-Tetramethylpiperidine	(<7), 0	11.49
5	Piperazine	(100), 28, 34[d]	9.90
6	Morpholine	(96), 70	8.97
Cyclic five-membered amines/amides			
7	Pyrrolidine	(100), 47	11.26
8	3-Hydroxypyrrolidine	(100), 69	10.28
9	Pyrrolidinone	(100), 78	16.62
10	Methyl (*S*)-(+)-pyrrolidinone carboxylate	(100), 88	14.65
Acyclic amines			
11	Triethylamine	(10), 0	10.62
12	Diethylamine	(25), 0	10.76
13	Diisopropylamine	(0), 0	10.76
14	1,1,3,3-Tetramethyl guanidine	(0), 0	15.20
Aromatic additives			
15	Pyridine	(80), 74	5.23
16	DMAP	(55), 41	9.52
17	Phenol	(17), 0	9.86
Chiral amines			
18	(*S*)-2-Methoxymethylpyrrolidine	(95), 85	10.55
19	(*S*)-Prolinamide	(90), 80	9.45
20	(*S*)-1-Phenylethylamine	(80), 70	9.75

[a] Conversion calculated from the NMR of the crude product.
[b] Isolated yields of **3a** after column chromatography unless otherwise stated.
[c] pK_a calculated using ACD pK_a predictor.
[d] Amine captured product.

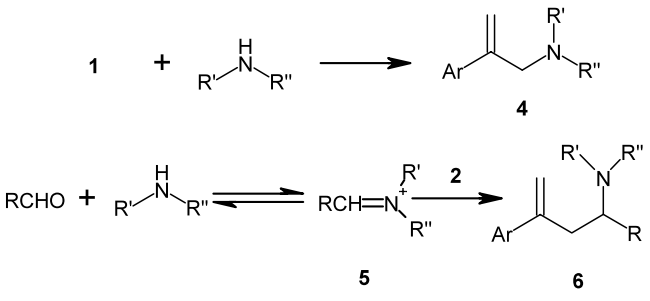
entry 20) suggesting steric effects are important. This is reinforced by the use of 2,2,6,6-tetramethylpiperidine (Table 1, entry 4), where only trace amounts of product were observed. Pyridine and to a lesser extent DMAP (Table 1, entries 15 and 16) both show increased conversions, again illustrating that pK_a is not the important issue. Interestingly certain cyclic amides promote the reaction (Table 1, entries 9 and 10), although with methyl (*S*)-(+)-pyrrolidinone-5-carboxylate as the additive no chirality was induced in the final product (chiral HPLC). (*S*)-2-Methoxymethylpyrrolidine, (*S*)-prolinamide and (*S*)-1-phenylethylamine gave 85, 80 and 70% yields of the racemic homoallylic alcohol, respectively (Table 1, entries 18, 19 and 20).

The generality of the amine additive effect was demonstrated for a variety of aldehydes and aryl iodides using piperidine as the additive (Table 2). A substantial improvement in yield was noted in all cases.

One possible role for the amine is to aid solvation of the indium powder, increasing the concentration of indium in solution, accelerating the rate of transmetalation. To test this hypothesis, two standard Barbier reactions[7] were performed (Scheme 3), one with 1 equiv. of piperidine, one without. The NMR of the crude products indicate that after 1 h reaction time, a higher conversion of aldehyde to product is obtained in the presence of piperidine. Thus the ratio of **7**:**9** is 1:1.5 with piperidine and 5:1 in its absence.

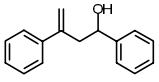
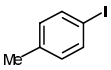
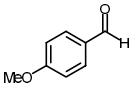
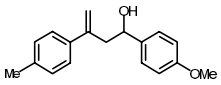
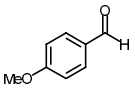
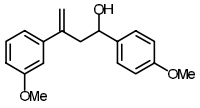
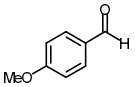
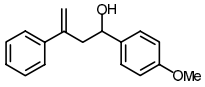
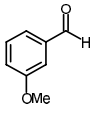
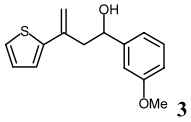
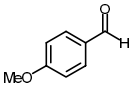
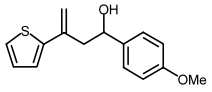
A second role for the amine additives is to protect the catalytically active Pd species. The failure of the amines to compete effectively with In for the π-allylpalladium(II) species and the absence of the iminium ion derived product **6** provides clear evidence of substantial rate differences between the three potentially competing processes.

Cu(I) salts have been used to improve yields in the Stille coupling reaction.[8] Farina and Liebeskind[9,10] describe the 'copper effect' as a complex ligand dependent phenomena, in which the concentration of the phosphine ligand in solution is diminished via complexation to Cu(I). The effect of CuI in the Pd/In Barbier reaction of benzaldehyde iodobenzene and allene was examined. Addition of 1 equiv. of CuI resulted in a yield of 50% (Table 3, entry 1). When both 1 equiv. of

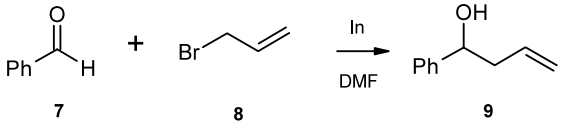


Scheme 2.

Table 2.

Entry	ArI	Aldehyde	Product: Yield %[a] (%)[b]
1			 **3a**: 83 (43)
2			 **3b**: 80 (40)
3			 **3c**: 89 (60)
4			 **3d**: 84 (64)
5			 **3e**: 73 (-)
6			 **3f**: 94 (66)

[a] Isolated yield with 1 eq. piperidine, 2 h reaction time, [b] Isolated yield with no added piperidine, 16 h reaction time.



Scheme 3.

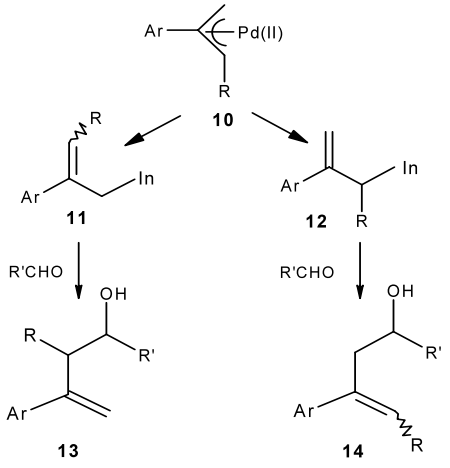
piperidine and 1 equiv. of CuI were used the yield decreases, due to complexation of CuI to the piperidine (Table 3, entry 2). Blank experiments demonstrated that no reaction was observed in the absence of either $Pd(OAc)_2$ or In (Table 3, entries 3 and 4). Employing 0.1 equiv. of CuI as the additive gave a 64% yield (Table 3, entry 5). Using equimolar portions of TFP and CuI showed the greatest rate acceleration and yield, 88% (Table 3, entry 6). CuBr and CuCl did not promote the reaction as well as CuI (Table 3, entries 7 and 8). Copper bronze displays the same reaction pattern as CuI (Table 3, entries 9 and 10).

Substituted allenes were incorporated into the cascade (Scheme 4), initially the cascade was attempted with 1

Table 3. Copper additives in Pd/In cascade reaction of benzaldehyde, iodobenzene and allene[a]

Entry	In (equiv.)	Piperidine (equiv.)	Additive (equiv.)	Yield (%)
1	1.5	–	CuI (1.0)	50
2	1.5	1	CuI (1.0)	37
3	–	–	CuI (1.0)	0
4[b]	1.5	–	CuI (1.0)	0
5	1.5	–	CuI (0.1)	64
6	1.5	–	CuI (0.2)	88
7	1.5	–	CuBr (0.1)	18
8	1.5	–	CuCl (0.1)	19
9	1.5	–	Cu bronze (1.0)	53
10	1.5	–	Cu bronze (0.2)	69

[a] Standard protocol adopted.
[b] No $Pd(OAc)_2$ was added to this reaction.



Scheme 4.

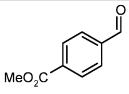
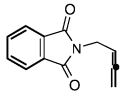
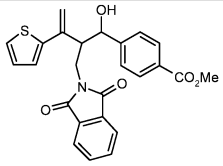
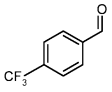
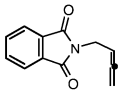
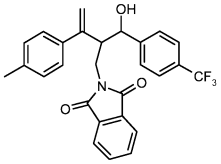
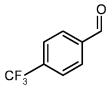
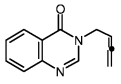
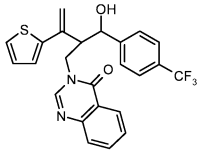
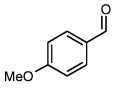
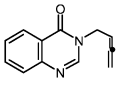
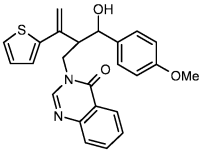
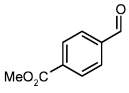
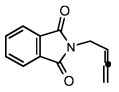
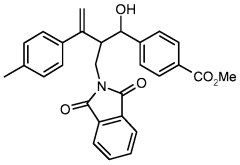
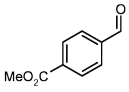
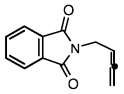
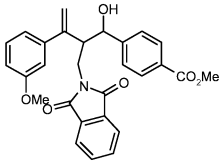
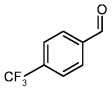
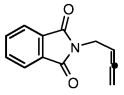
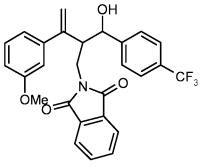
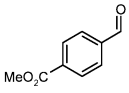
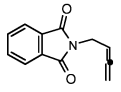
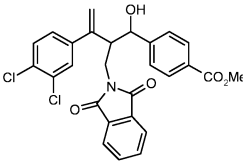
equiv. of piperidine as the additive, the reaction time for these cascades were generally 24–48 h, and showed moderate yields (Table 4, entries 2 and 4), 0.1 equiv. of CuI also resulted in moderate yields (Table 4, entries 1 and 3).

However with 0.2 equiv. of CuI the reaction proceeded cleanly, leading to easier isolation and improved yields (Table 4, entries 5–8). There are two possible products from the transmetalation of **10** with In via a Zimmerman–Traxler transition state, only the product **13** derived from **11** is observed. Further studies of the effects of additives on Pd/In cascades are underway.

Acknowledgements

We thank the University of Leeds, GSK and the EPSRC for support.

Table 4.

Entry	ArI	Aldehyde	Allene	Additive (equiv.)	Product	Product no.	Yield (%)	d.r [a]
1				CuI (0.1)		**13a**	50	29 : 71
2				Piperidine (1.0)		**13b**	55	47 : 53
3				CuI (0.1)		**13c**	50	25 : 75
4				Piperidine (1.0)		**13d**	53	38 : 62
5				CuI (0.2)		**13e**	77	43 : 57
6				CuI (0.2)		**13f**	66	33 : 67
7				CuI (0.2)		**13g**	78	45 : 55
8				CuI (0.2)		**13h**	70	40 : 60

[a] Diastereoisomeric ratio determined from the NMR of the crude product, assignment of *syn*/*anti* stereochemistry is currently under investigation b. Standard experimental protocol was adopted with reaction time of 24 h for entries 2 and 4 and 48 h for entries 1,3, 5-8. Only 1 eq. of indium is required for entries 5-8.

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