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Enantio- and diastereoselective palladium catalysed arylative and vinylative allene carbocyclisation cascades†

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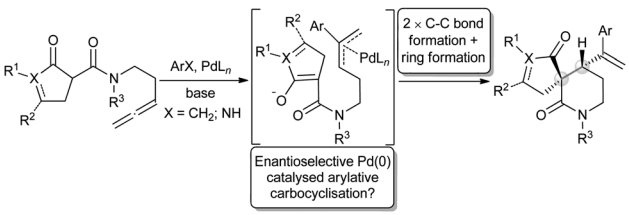
The enantioselective synthesis of heavily decorated spirolactams has been accomplished *via* an arylative or vinylative allene carbocyclisation cascade. Mediated by silver phosphate, a range of allene-linked pro-nucleophiles and aryl or vinyl iodides were reacted in the presence of catalytic $Pd(OAc)_2$ and chiral bis-(oxazoline) ligands to afford the spirolactam products in good yields and high enantio- and diastereoselectivities.

Cascade reaction processes, whereby simple starting materials combine in a series of carbon–carbon or carbon–heteroatom bond forming events, provide a resource efficient way of generating complex, three dimensional molecular structures.[1] When bond formation is enabled by the action of a catalyst, the nature and structure of any ligating groups, as well as other parameters, can govern the relative and absolute configuration of the desired product.[2] In this vein, we recently described an efficient cascade process to access biologically relevant azaspirocyclic structures[3] *via* a palladium catalysed diastereoselective arylative carbocyclisation of pro-nucleophile-linked allenes[4] with aryl halides. With its many points of diversity and breadth in scope, this cascade reaction was useful for library generation.[5] However, in the absence of any chiral controller the azaspirocyclic products were obtained as racemic mixtures. As part of a broader program of work in our group targeting polycyclic alkaloid natural products[6] we recognised that an enantioselective variant of this complexity building reaction was highly desirable (Scheme 1). To date there have been only a handful of reports on the catalytic enantioselective coupling reactions of allenes with organic halides to afford enantioenriched cyclic products.[7–9] Inspired by these findings, herein we wish to describe our preliminary results leading to the first enantioselective palladium catalysed arylative allene carbocyclisation cascade.



Scheme 1 Proposed Pd(0) catalysed enantioselective arylative allene carbocyclisation cascade.

The readily prepared allene-linked ketoamide **1a** was selected as a representative pro-nucleophile for our preliminary asymmetric carbocyclisation studies with methyl 4-iodobenzoate as the aryl halide coupling partner (Table 1). Our previously reported conditions were used to test substrate reactivity and generate the racemic product.[5] Thus, reacting **1a** and methyl 4-iodobenzoate with $Pd_2(dba)_3$ (5 mol%), dppe (10 mol%) and K_2CO_3 (2 equiv.) in DMSO at 70 °C for 8 hours, afforded spirolactam **2a** in 14 : 1 dr and 65% yield. Initial attempts to induce asymmetry used similar conditions, but in place of $Pd_2(dba)_3$ and the achiral bisphosphine ligand dppe, $Pd(OAc)_2$ and the (*S*)-phenylalanine-derived (*S*,*S*)-bis(oxazoline) ligand **3f** (Fig. 1) were used instead.[10] Under these conditions, product **2a** was obtained in 65% yield with 18 : 1 dr, but unfortunately no enantiocontrol was observed (Table 1, entry 1). It has previously been demonstrated that in the presence of silver salts significantly enhanced levels of asymmetric induction can be achieved in ligand-controlled catalytic asymmetric coupling reactions of allenes with aryl or vinyl iodides.[8,9,11] Accordingly, the reaction conditions were modified to include a basic silver salt. Thus, K_2CO_3 was replaced with Ag_3PO_4 (0.5 equiv.) and pleasingly significantly enhanced levels of enantioselectivity were witnessed; **2a** was obtained in 77% yield with 27 : 1 dr and 59% ee (Table 1, entry 2). Variation of the solvent had a pronounced effect on the enantioselectivity. Less polar solvent

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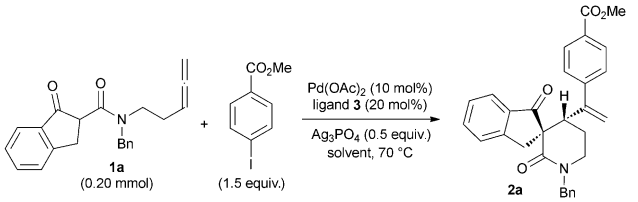
† Electronic supplementary information (ESI) available: Synthetic procedures, experimental data, ^{1}H NMR spectra, ^{13}C NMR spectra, HPLC traces and VCD data are available. See DOI: 10.1039/c3cc42079e

Table 1 Optimisation studies using allene-linked indanone ketoamide **1a** and methyl 4-iodobenzoate



Entry	Solvent	Ligand	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1[d]	DMSO	**3f**	16	65	18 : 1	0
2	DMSO	**3f**	10	77	27 : 1	59
3	DMSO	**3a**	36	60	22 : 1	7
4	DMSO	**3b**	12	82	18 : 1	21
5	DMSO	**3c**	24	50	18 : 1	39
6	DMSO	**3d**	12	58	20 : 1	59
7	DMSO	**3e**	12	40	8 : 1	25
8	DMSO	**3g**	12	45	33 : 1	67
9	DMSO	**3h**	16	57	16 : 1	0
10	NMP	**3g**	24	77	17 : 1	66
11	MeCN	**3g**	48	78	27 : 1	80
12	1,4-Dioxane	**3g**	24	70	5 : 1	80
13	PhMe	**3g**	24	82	4 : 1	80
14	DCE	**3g**	16	70	>99 : 1	80
15	DCE	**3i**	36	84	>99 : 1	85

[a] Combined yield of two diastereomers after purification. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis. Enantiomeric excess of major diastereomer reported. [d] K_2CO_3 (0.5 equiv.) used as base.

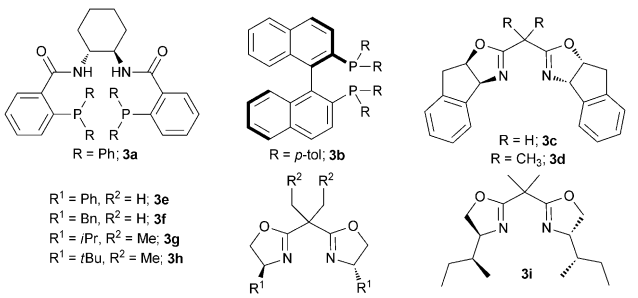
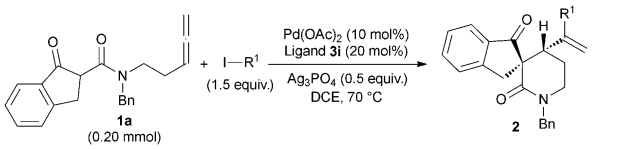


Fig. 1 Chiral ligands screened during optimisation studies.

systems were found to be essential for achieving high levels of enantiocontrol, with 1,2-dichloroethane giving a single diastereomeric product in 70% yield and 80% ee (Table 1, entry 14). With a significant level of enantioinduction already achieved the final variable examined was the chiral ligand itself. A variety of chiral ligands were purchased or prepared (Fig. 1) and then examined in the optimisation study. With regard to the ligand structure, it was observed that ligands forming six-membered rings when coordinated to the Pd metal centre resulted in products with higher enantioenrichment compared to the ligands that form larger ring systems. The best enantioselectivities were obtained using the bis(oxazoline) ligands, particularly ligand **3i** which afforded a single diastereomer of **2a** in 85% ee and 84% yield (Table 1, entry 15). Interestingly, overly bulky ligands such as **3h**, imparted no enantiocontrol in the reaction. Overall, the optimal conditions were **1a** (1.0 equiv.), aryl iodide (1.5 equiv.), Ag_3PO_4 (0.5 equiv.), $Pd(OAc)_2$ (10 mol%) and **3i** (20 mol%) in DCE at 70 °C.

Table 2 Scope of the carbocyclisation of indanone ketoamide **1a** with aryl iodides and vinyl iodides

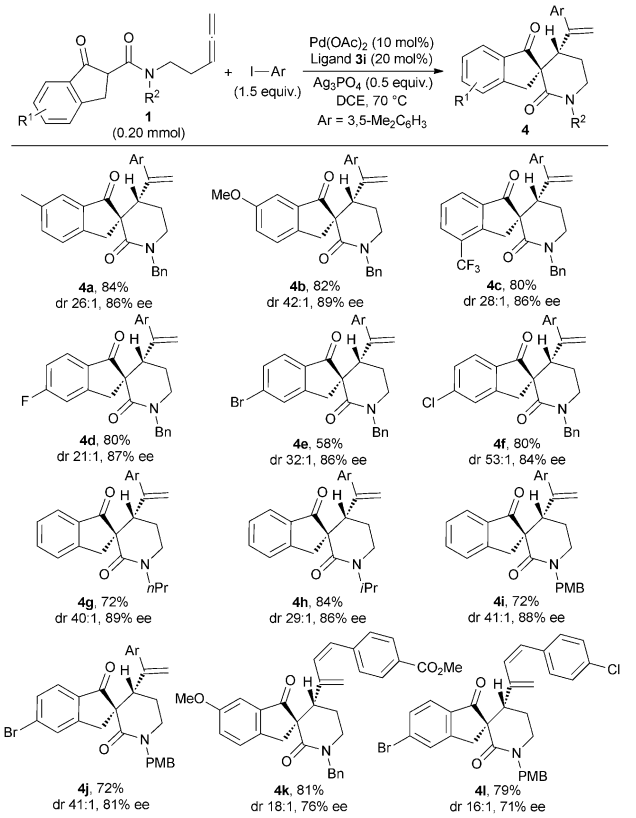


Entry	R^1 (aryl or vinyl)	2	Time (h)	Yield[a] (%)	dr[b]	ee[c] (%)
1	Ph	**2b**	96	82	45 : 1	87
2	*p*-$MeOC_6H_4$	**2c**	48	85	56 : 1	87
3	3,5-$Me_2C_6H_3$	**2d**	60	76	39 : 1	89
4	*m*-$MeO_2CC_6H_4$	**2e**	48	86	41 : 1	86
5	*p*-BrC_6H_4	**2f**	84	79	25 : 1	86
6	*p*-ClC_6H_4	**2g**	72	84	33 : 1	87
7	*m*-$NO_2C_6H_4$	**2h**	40	77	35 : 1	86
8	2-Thienyl	**2i**	72	70	40 : 1	75
9	*trans*-PhCH=CH	**2j**	36	61	21 : 1	53
10	*cis*-PhCH=CH	**2k**	72	72	23 : 1	77
11	*cis*-*p*-$MeOC_6H_4CH$=CH	**2l**	72	67	20 : 1	65
12	*cis*-*p*-ClC_6H_4CH=CH	**2m**	96	78	18 : 1	76
13	*cis*-*m*-$NO_2C_6H_4CH$=CH	**2n**	36	77	16 : 1	73
14	*cis*-*p*-$MeO_2CC_6H_4CH$=CH	**2o**	36	68	17 : 1	82
15	*cis*-2-FurylCH=CH	**2p**	96	70	19 : 1	71
16	*cis*-2-ThienylCH=CH	**2q**	64	65	18 : 1	75

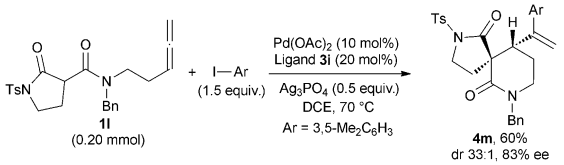
[a] Isolated yield of major diastereomer after purification. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis.

Using substrate **1a**, the scope of the allene carbocyclisation cascade with respect to the aryl or vinyl iodide was investigated (Table 2). Gratifyingly, a range of electron-rich and electron-poor aryl iodides bearing substituents in the *meta*- and *para*-positions easily tolerated the reaction, with good yields (76–86%) and enantioselectivities (86–89%) being obtained in all cases (Table 2, entries 1–7). A variety of vinyl iodide substrates were also found to be compatible with the cascade reaction. It was observed that the *cis*-isomer of styryl iodide (77% ee; Table 2, entry 10) provided much higher enantiomeric excess compared to the corresponding *trans*-isomer (53% ee; Table 2, entry 9). Therefore *cis*-vinyl iodides were used to further explore the scope of this methodology, with the corresponding products being obtained in good yields with good diastereo- and enantioselectivities (Table 2, entries 10–16). Pleasingly, no *cis–trans* isomerisation was observed when using vinyl iodides, demonstrating that both the products and starting materials are configurationally stable under the reaction conditions.

Additionally, extension of this carbocyclisation cascade methodology to structurally modified allene-linked indanone-derived pro-nucleophiles was readily achieved (Scheme 2). With 3,5-dimethyl iodobenzene, a range of pro-nucleophiles with electron-donating or withdrawing substituents on the aromatic ring of the indanone moiety, showed good compatibility with the cascade reaction. Yields were good to excellent with diastereoselectivities ranging from 21 : 1 to 53 : 1, whilst enantioselectivities ranged from 84–89% ee (**4a–4f**, Scheme 2). Variation of the nitrogen atom substituent to linear and branched alkyl chains did not significantly affect the reactivity or selectivity of the carbocyclisation (**4g–4j**, Scheme 2). The vinylative carbocyclisation with *Z*-configured styryl iodides also



Scheme 2 Scope of the carbocyclisation of various pro-nucleophiles with 3,5-dimethyl iodobenzene and vinyl iodides.



Scheme 3 Carbocyclisation of pro-nucleophile **1l** with 3,5-dimethyl iodobenzene.

successfully afforded the desired spirolactam products in high yields (**4k** and **4l**, Scheme 2).

Finally, *N*-tosylated γ-lactam derived pro-nucleophile **1l**, a substrate less reactive than indanone-derived systems, underwent cyclisation with 3,5-dimethyl iodobenzene to afford spiropiperidin-2-one **4m** in good yield with 83% ee (Scheme 3).

In the absence of a suitably crystalline spirocyclic product or derivative for single crystal X-ray diffraction, the relative configuration of spirolactams **2** and **4** were assigned by analogy to our previous study[5] and by NOESY analysis of compound **4b** (see ESI†). The absolute configuration was determined by comparison of the measured and computed vibrational circular dichroism (VCD) spectra.[12] Using this method, the absolute configuration of **4b** was assigned as (2*R*,4′*S*) with 99% confidence.

In summary, we have developed a mild and efficient palladium catalysed enantio- and diastereoselective cyclisation cascade methodology for the synthesis of a range of stereodefined arylated or vinylated spirolactam compounds. Being operationally simple and tolerating multiple points of diversity this reaction should find use in complex natural product synthesis as well as compound library production. Work to expand and apply these findings is currently underway.

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