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Stereoselective Spirolactam Synthesis via Palladium Catalyzed Arylative Allene Carbocyclization Cascades

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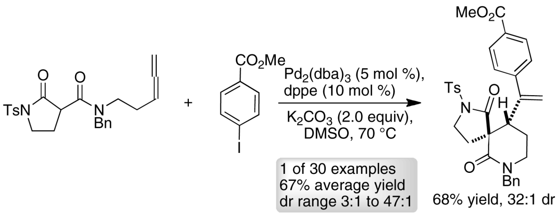
ABSTRACT



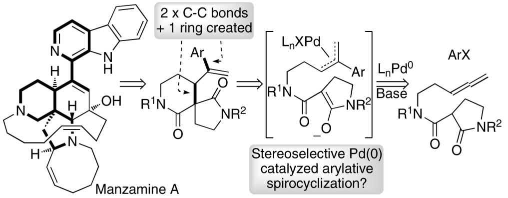
1 of 30 examples
67% average yield
dr range 3:1 to 47:1

68% yield, 32:1 dr

A diastereoselective arylative carbocyclization of pro-nucleophile-linked allenes with aryl and heteroaryl halides to provide spirocyclic lactam products with moderate to high diastereoselectivities and good yields under Pd(0) catalysis is reported. Being operationally simple and tolerant of multiple points of diversity, this complexity building reaction cascade, in which two new carbon−carbon bonds and one new heterocyclic ring are created, should be of high value in both complex natural product synthesis as well as compound library synthesis.

The aza-spirocyclic motif is found in many biologically active natural compounds ranging from the structurally simple to the architecturally complex, including Manzamine A,[1] which exhibits a broad range of interesting biological properties. Highly innovative and increasingly efficient ways of accessing these structures have been developed over the past decade. In this vein, we wished to extend our research in the field of transition metal catalyzed carbocyclizations of alkynes[2] to appropriately substituted allenes to provide direct access to arylated spirolactam products of high synthetic value (Scheme 1).

Scheme 1. Concept and Context of the Palladium(0) Catalyzed Allene Carbocyclization Cascade with Aryl Halides



Stereoselective Pd(0) catalyzed arylative spirocyclization?

Allenes are a reactive class of compounds able to undergo a diverse range of chemical transformations (most notably under palladium catalysis), making them useful starting materials and intermediates for organic synthesis.[3] Hydrofunctionalization of allene under heating (275 °C) was

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[1] For a review of the isolation of this and related compounds, see: (a) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201. For syntheses, see: (b) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425. (c) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (d) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (e) Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10233.

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[3] For reviews, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (c) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; WILEY-VCH Verlag GmbH & Co.: Weinheim, 2004. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

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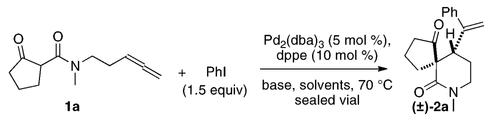
reported by Bertrand.[4] Recently, the transition metal-catalyzed hydrofunctionalization of allenes with carbon and heteroatom nucleophiles has been investigated. For example, Pd(II), Ag(I), Au(III) and Cu(I) complexes can catalyze the hydrofunctionalization of allenes with C-,[5] N-,[6] O-[7] and S-[8] nucleophiles. Relevant to this work, the groups of Ma[9] and Oh[10] have reported the regioselective Pd(0)-catalyzed coupling cyclization reaction of 2-(2′,3′-allenyl)malonates with organic halides leading to either cyclopropyl or cyclopentene derivatives. Furthermore Pd-catalyzed coupling reactions of allenic carboxylic acids,[11] or allenols,[12] or amino allenes[13] or carbon nucleophiles[14] with organic halides can lead to the production of arylated heterocyclic motifs. As part of an ongoing program of research targeting polycyclic alkaloid natural products, we were interested in the possibility of developing an efficient and diastereoselective palladium-catalyzed arylative carbocyclization of allene-tethered pronucleophiles with organic halides. Such a reaction, with its many points of diversity, would be useful in library generation and natural product synthesis alike. Herein we report our findings.

Allene-linked ketoamide **1a** was selected for our preliminary cyclization studies. A coarse screen of Pd(0) catalysts, ligands, bases and solvents in the presence of 1.5 equiv of iodobenzene was rapidly met with some success; spirolactam **2a** was isolated in 31% yield from a 3:2 mixture of product diastereomers (56% combined yield) when $Pd_2(dba)_3$ (5 mol %), dppe (10 mol %) and K_2CO_3 (2.0 equiv) in tetrahydrofuran at 70 °C (sealed vial) were employed (Table 1, entry 1). Further studies showed that the reaction diastereoselectivity was dependent on the solvent polarity and could be improved to 17:1 using DMSO (Table 1, entries 1−3, 5−9). When methanol was employed as solvent, only substrate decomposition was witnessed (Table 1, entry 4). A screen of typical inorganic bases showed that K_2CO_3, Cs_2CO_3 and K_3PO_4 were all productive, affording the desired product with high diastereoselectivities and in moderate to good yields (Table 1, entries 8−10). However, use of NaO^{t}Bu resulted in the decomposition of the starting material (Table 1, entry 11). Thus it was established that $Pd_2(dba)_3$ (5 mol %), dppe (10 mol %), iodobenzene (1.5 equiv) and K_2CO_3 (2.0 equiv) in DMSO at 70 °C were the optimal reaction conditions (Table 1, entry 9).

Table 1. Optimization Studies on Test Substrate **1a**



entry	solvent	base	time/h	convn/%[b]	yield/%[c]	dr[d]
1	THF	K_2CO_3	24	100	31	3:2
2	DCE	K_2CO_3	48	100	33	3:2
3	DME	K_2CO_3	20	100	33	6:5
4	CH_3OH	K_2CO_3	16	–[a]	–	–
5	TBME	K_2CO_3	50	100	32	3:2
6	CH_3CN	K_2CO_3	20	100	60	10:1
7	DMF	K_2CO_3	19	100	58	14:1
8	DMF	Cs_2CO_3	16	100	32	9:1
9	**DMSO**	$\mathbf{K_2CO_3}$	**16**	**100**	**58**	**17:1**
10	DMSO	K_3PO_4	17	100	50	15:1
11	DMSO	NaO^{t}Bu	17	-[a]	-	-

[a] Decomposed. [b] From crude ^{1}H NMR; [c] Isolated yields of major diastereomer; [d] dr determined from crude ^{1}H NMR before separation.

With optimal conditions established for **1a**, the scope of the diastereoselective arylative allene carbocyclization cascade with respect to the (hetero)aromatic halide and the *N*-substituent of **1** was investigated. Electron-rich and electron-deficient (hetero)aromatic iodides were investigated, as were 1-bromonaphthalene, 2-bromonaphthalene and 2-bromopyridine (Table 2). With **1a**, reaction yields were good to excellent and selectivities ranged from 13:1 to 22:1 (Table 2, entries 1−6). Variation to the spectator nitrogen substituent was not only tolerated but in general led to notable improvements in the reaction diastereoselectivity; when *N*-benzyl substrate was reacted with various aryl and heteroaryl halides, the observed diastereoselectivities ranged from 25:1 to 47:1 (Table 2, entries 7−10). Altogether 5 different *N*-substituents and 12 different (hetero)aryl halides (iodides and bromides) were successfully employed in the reaction.

Additionally, extension of this cyclization methodology to homologous and structurally modified allene-linked pronucleophilic substrates was also achieved and provided access to a range of spirocyclic scaffolds. Following the optimized procedure, either iodobenzene or methyl 4-io-

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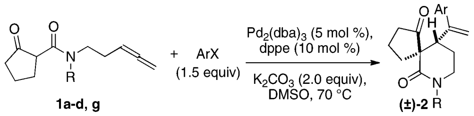
Table 2. Scope of the Palladium(0) Catalyzed Arylative Carbocyclization Cascade with Aromatic and Heteroaromatic Halides

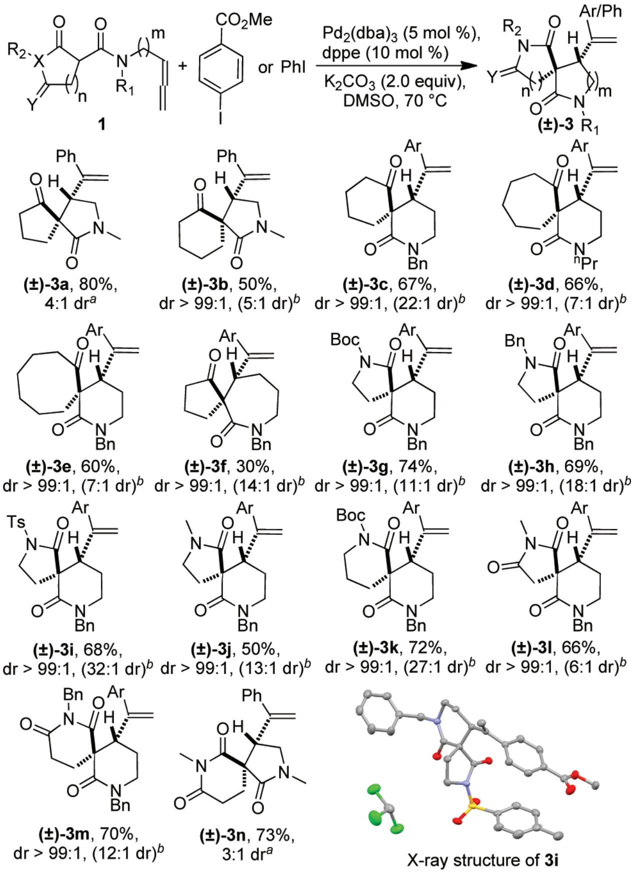


entry	R	1	ArX	time/h	2	yield/%[a]	dr[b]
1	Me	**a**	*p*-MeOC$_6$H$_4$I	12	**b**	79	18:1
2	Me	**a**	3,5-MeC$_6$H$_3$I	12	**c**	66	15:1
3	Me	**a**	*p*-MeO$_2$C$_7$H$_4$I	10	**d**	83	22:1
4	Me	**a**	*m*-MeO$_2$C$_7$H$_4$I	10	**e**	86	13:1
5	Me	**a**	2-bromonaphthalene	16	**f**	61	15:1
6	Me	**a**	*p*-BrC$_6$H$_4$I	45	**g**	61	15:1
7	Bn	**b**	*p*-N(CH$_3$)$_2$C$_6$H$_4$I	20	**h**	50	33:1
8	Bn	**b**	2-iodothiophene	16	**i**	77	25:1
9	Bn	**b**	*m*-NO$_2$C$_6$H$_4$I	12	**j**	74	30:1
10	Bn	**b**	*p*-MeO$_2$C$_7$H$_4$I	16	**k**	67	47:1
11	Pr	**c**	1-bromonaphthalene	24	**l**	65	16:1
12	Pr	**c**	*p*-MeO$_2$C$_7$H$_4$I	10	**m**	70	19:1
13	Allyl	**g**	*p*-MeO$_2$C$_7$H$_4$I	14	**n**	66	30:1
14	Et	**d**	*p*-MeO$_2$C$_7$H$_4$I	12	**o**	75	36:1
15	Et	**d**	2-bromopyridine	20	**p**	53	12:1

[a] Isolated yield of single major diastereoisomer. [b] dr in crude product.

dobenzoate was employed as the haloarene and the results are shown in Figure 1. In the formation of spiropiperidin-2-ones, good reactivity was observed with substrates possessing six-, seven- and eight-membered ring cyclic ketones (for 5-membered rings see Table 2) and diastereoselectivities ranged from 7:1 to 22:1 (Figure 1, **3c**−**3e**). Spiropyrrolidin-2-one products were also accessible in good to excellent yield albeit with moderate diastereoselectivity (Figure 1, **3a**, **3b**, **3n**). A single example of attempted spiroazapan-2-one production was met with partial success; product **3f** was isolated in 30% yield and 14:1 dr. A range of differentially *N*-substituted γ- and δ-lactam derived allene-linked pro-nucleophilic substrates underwent cyclization with methyl 4-iodobenzoate to give spiropiperidin-2-one products in moderate to good yields and good to excellent diastereoselectivity (Figure 1, **3g**−**3k**). Similarly *N*-protected succinimide or glutarimide substrates had good reactivity and afforded spiropyrrolidin-2-one and spiropiperidin-2-one products in good yield and with moderate to good diastereoselectivities (Figure 1, **3l**−**3n**).

The relative stereochemistries of all the major diastereomeric products of **2** and **3** were assigned by analogy to that of **3i**, which was determined by single crystal X-ray diffraction[15] (Figure 1).



(±)-3a, 80%, 4:1 dr[a]
(±)-3b, 50%, dr > 99:1, (5:1 dr)[b]
(±)-3c, 67%, dr > 99:1, (22:1 dr)[b]
(±)-3d, 66%, dr > 99:1, (7:1 dr)[b]
(±)-3e, 60%, dr > 99:1, (7:1 dr)[b]
(±)-3f, 30%, dr > 99:1, (14:1 dr)[b]
(±)-3g, 74%, dr > 99:1, (11:1 dr)[b]
(±)-3h, 69%, dr > 99:1, (18:1 dr)[b]
(±)-3i, 68%, dr > 99:1, (32:1 dr)[b]
(±)-3j, 50%, dr > 99:1, (13:1 dr)[b]
(±)-3k, 72%, dr > 99:1, (27:1 dr)[b]
(±)-3l, 66%, dr > 99:1, (6:1 dr)[b]
(±)-3m, 70%, dr > 99:1, (12:1 dr)[b]
(±)-3n, 73%, 3:1 dr[a]
X-ray structure of 3i

Figure 1. Scope of the arylative allene carbocyclization cascade. [a]Inseparable. [b]dr in crude product.

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(15) X-ray Data were collected at low temperature [Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr.* **1986**, *19*, 105–107] using an Enraf-Nonius KCCD diffractometer [Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode Methods Enzymol*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: New York, 1997; p 276]. The crystal structure of **3i** was solved using SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli., M. *J. Appl. Crystallogr.* **1994**, *27*, 435] and refined using the CRYSTALS software suite [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487] as per the Supporting Information (CIF file). Crystallographic data (excluding structure factors) for **3i** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 784231), and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

In conclusion, we have developed a mild, efficient, and diastereoselective cyclization methodology for the synthesis of a range of stereodefined arylated spirolactam compounds. Altogether 15 different spirocyclic structures have been accessed using this new methodology. Being operationally simple and tolerating multiple points of diversity, this reaction should be of use in complex natural product synthesis as well as compound library synthesis. Work to expand and apply these findings is ongoing and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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