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COMMUNICATION

Enantioselective synthesis of spirooxoindoles *via* chiral auxiliary (bicyclic lactam) controlled S_NAr reactions†

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A highly efficient enantioselective S_NAr reaction of chiral acyl bicyclic lactam with substituted-2,4-dinitrobenzenes was developed, affording products containing quarternary stereogenic centers. They are further utilized towards an enantioselective synthesis of spirooxoindoles.

Introduction

The spiropyrrolidinyloxindole skeleton has garnered considerable interest in the area of natural product synthesis and pharmaceutical research owing to their presence in the core of a number of alkaloids, which possess significant biological activity.[1] They are interesting and challenging targets for chemical synthesis. Over the past years, various strategies have been developed for the construction of these interesting moieties.[2] In this communication, we describe an efficient synthesis of spiro-pyrrolidone-3,3′-oxoindole structure in excellent enantioselectivity, in decent yields and with high atom economy under mild reaction conditions *via* regio and asymmetric C-selective S_NAr reactions of α-acylated chiral bicyclic lactams with *o*-nitro aryls, followed by a facile reduction of the nitro group and *in situ* intramolecular amide formation.

The utilitarian chiral bicyclic lactams have provided access to a gamut of natural and unnatural products in high enantiomeric purity.[3] Their synthetic versatility generated a number of enantiomerically pure compounds bearing quarternary carbon centers.[4] Chiral bicyclic lactams of type **I**–**IV** (Fig. 1) have been extensively used as scaffolds in enantioselective synthesis primarily based on the initial alkylation of methylene group adjacent to the amide carbonyl either by treatment of base followed by reaction with an alkyl halide or by thio-Claisen rearrangement of the corresponding thiolactams.[5] To date synthetic methods for the asymmetric arylation of a chiral bicyclic lactam have not been reported. In a bid to develop an asymmetric S_NAr reaction, involving carbon nucleophiles, we employ these bicyclic lactams as chiral auxiliaries.

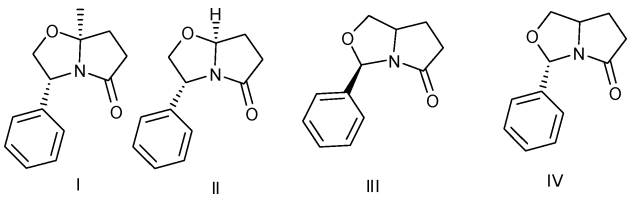

Fig. 1 Various bicyclic lactams.

The nucleophilic aromatic substitution (S_NAr) one of the most fundamental reactions in organic chemistry, mostly utilizes amines and phenols as nucleophiles.[6,7] 1,3-Dicarbonyl compounds are also sporadically utilized as carbon nucleophiles for arylation under mild conditions.[8] In spite of being known for more than a century, there are only few reports in S_NAr of chiral induction on quaternary or tertiary stereocenters formed when carbon nucleophiles are involved, that too for intramolecular reactions and with oxygen nucleophiles.[9] To the best of our knowledge there is only one report of organo catalytic chiral induction in S_NAr reactions involving carbon nucleophiles.[10] Furthermore, there is no report of chiral auxiliary controlled S_NAr reactions have been developed to our knowledge.

Results and discussion

Our journey began with the synthesis of chiral bicyclic lactam **II**, by condensation of succinic anhydride with (*R*)-(−)-phenyl glycinol in the presence of triethyl amine with azeotropic removal of water. The resulting crude was then reduced with $NaBH_4$ in presence of ethanolic HCl. Purification by column chromatography generated a single diastereomer in 72% yield.[11] Treatment of lactam **II** with lithium bis(trimethylsilyl)amide at −78 °C followed by reaction with chloromethylformate generated monoacylated bicyclic lactam **2** as an inseparable 1 : 1 mixture of epimers at the new chiral center at C_7 in 72% yield. The S_NAr reaction of the lactam **2** commercially available 2,4-dinitro-fluorobenzene in THF and with KOH as the base was completed in few hours and in high yields. However, the diastereomeric excess of the product **10** was disappointing (entry 1, Table 1). An initial screening at various temperatures indicated better diastereoselectivity at lower temperature, but with poor conversion (entry 2–6). Finally successful stereoselective S_NAr reaction occurred at 0 °C with NaH

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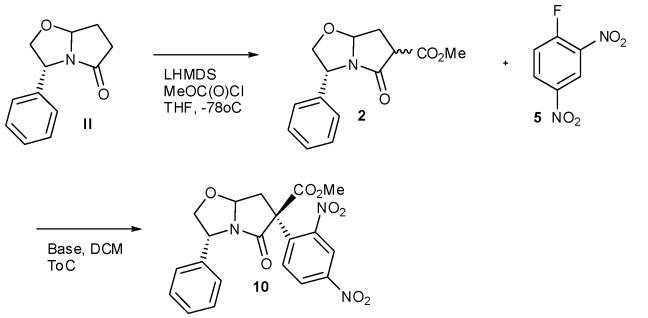
Table 1 Acylation followed by asymmetric C selective arylation of **II**



Entry	Base	T/°C	Time/h	Yield[a] (%)	Diastereomeric ratio (dr)[b]
1	KOH	25	03	87	1 : 1
2		–40	16	54	70 : 30
3		–78	36	28	90 : 10
4	Cs_2CO_3	25	04	90	1 : 1
5		–40	14	50	70 : 30
6		–78	32	24	90 : 10
7	NaH	25	03	92	1 : 1
8		0	06	86	99 : 1

[a] Isolated yield. Entry 2, 3, 5 and 6 the reactions were quenched while the starting material was not completely consumed. [b] dr by HPLC.

as base (entry 8). We were pleased to observe that the extent of diastereomeric excess under these conditions increased to 99 : 1.

In Table 2, the generic aspect of the regioselective and asymmetric S_NAr reaction is demonstrated for variety of aromatic compounds **5–7** with several monoacyl lactams (**1–4**) in decent yield and with up to 99% de. Substituted bicyclic lactam such as **1**, undergo S_NAr reaction smoothly but with moderate diastereoselectivity of 70%. Since the final products are solid and crystalline, the de was enhanced to 99% by recrystallization. The crystals obtained were suitable to determine the absolute configuration by X-ray analysis.[12] The relative configuration is shown in Fig. 2.

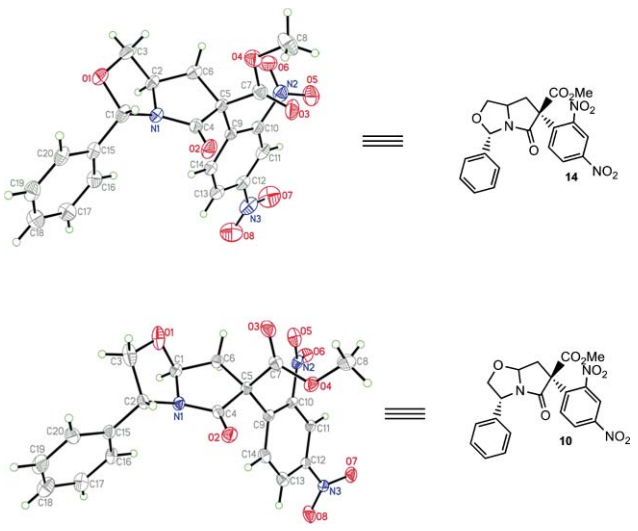
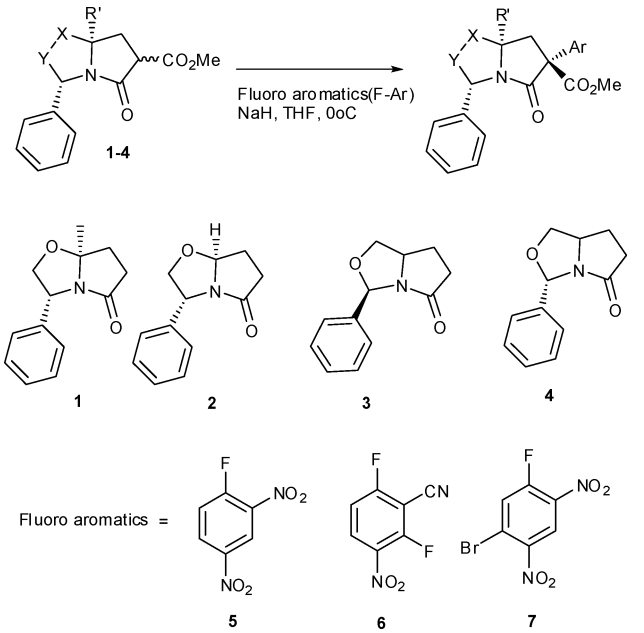


Fig. 2 X-Ray crystal structure of **10** and **14**.

These products are precursors of oxoindoles possessing a chiral quarternary carbon center. This scaffold is present in a variety of natural products. Hence this approach provides an easy route

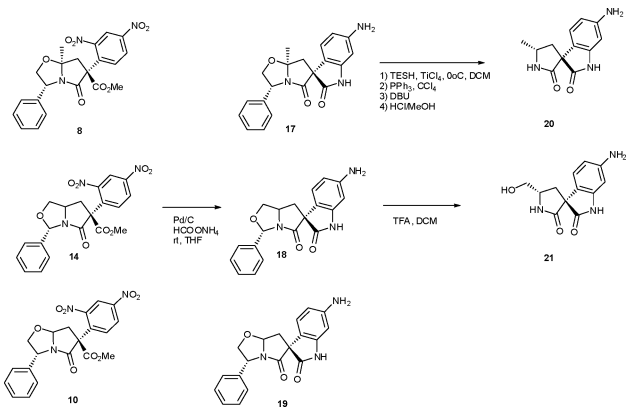
Table 2 Asymmetric C-selective arylation of acylated bicyclic lactam **1–4**



Entry	Acylated lactam	Fluoro aromatics	Product	Yield[a] (%)	Diastereomeric ratio (dr)[b]
1	**1**	**5**	**8**	72	70 : 30
2		**6**	**9**	75	70 : 30
3	**2**	**6**	**11**	58	99 : 1
4		**7**	**12**	75	99 : 1
5	**3**	**5**	**13**	65	99 : 1
6	**4**	**5**	**14**	80	99 : 1
7		**6**	**15**	69	99 : 1
8		**7**	**16**	59	99 : 1

[a] Isolated yield. [b] Diastereomeric ratio determined by HPLC.

toward this class of molecules (Scheme 1). Herein we present relevant examples were **8**, **10** and **14** are converted to protected oxoindoles **17**, **18** and **19** respectively *via* reduction of the ring nitrogen followed by *in situ* amidation. Oxoindole **18** was further treated with TFA to remove the chiral auxiliary and generate the desired spirooxoindole **21**. As for **17**, it was treated with triethyl silane and titanium(IV) chloride at 0 °C followed by an elimination hydrolysis procedure where the alcohol was converted into the corresponding chloride with carbon tetrachloride and triphenyl



Scheme 1 Conversion of arylated bicyclic lactams to spirooxoindoles.

phosphine, subsequent elimination with DBU and treatment of the resulting styrene with HCl in methanol generated the desired spirooxoindole **20**.

Conclusion

In summary, we have developed an extremely novel regioselective and asymmetric C-selective aromatic nucleophilic substitution reaction in rigid systems like bicyclic lactams. A tremendous improvement in enantioselectivity has been achieved by NaH at 0 °C. This methodology has been further applied towards an efficient diastereoselective synthesis of spiro[pyrrolidone-3,3′-oxoindole] bearing a quarternary carbon center in high enantioselectivity, in excellent yields and with high atom economy. Further investigations (theoretical and experimental studies) are in progress to rationalize the mode of arylation and also utilize the scaffold towards the synthesis of various spirooxoindole natural products.

References

1 (*a*) A. Jossang, P. Jossang, H. A. Hadi, T. Sevenet and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527–6530; (*b*) C. B. Cui, H. Kakeya and H. Osada, *J. Antibiot*, 1996, **49**, 832–835; (*c*) C. Pelligrini, M. Weber and H. J. Borschberg, *Helv. Chim. Acta*, 1996, **79**, 151–168; (*d*) R. C. Elderfield and R. E. Gilman, *Phytochemistry*, 1972, **11**, 339–343; (*e*) K. Ghedira, M. Z. Hanrot, B. Richard, G. Massiot, L. L. M. Oliver, T. Sevener and S. H. Goh, *Phytochemistry*, 1988, **27**, 3955–3962; (*f*) S. Sakai, N. Aimi, K. Yamaguchi, H. Ohhira, K. Hori and J. Haginiwa, *Tetrahedron Lett.*, 1975, **16**, 715–718; (*g*) N. Aimi, K. Yamaguchi, S. Sakai, J. Haginiwa and A. Kubo, *Chem. Pharm. Bull*, 1978, **26**, 3444–3449; (*h*) O. Diderberg, J. Lamotte-Brasseur, L. Dupont, H. Campsteyn, M Vermeire and L. Angenot, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1977, **33**, 1796–1801.

2 (*a*) S. T. Hilton, T. C. T. Ho, G. Pjevaljcic and K. Jones, *Org. Lett.*, 2000, **2**(17), 2639–2641; (*b*) X-H. Chen, Q. Wei, S-W. Luo, H Xiao and L-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819–13825; (*c*) E. E. Van Tamelin, J. P. Yardley, M. Miyano and W. B. Hinshaw Jr., *J. Am. Chem. Soc.*, 1969, **91**, 7333–7338; (*d*) A. Pictet and T. Spenglar, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 2030; (*e*) A. Bischler and B. Napiralski, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 1903–1908; (*f*) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, 1962, **84**, 1318–1320; (*g*) K. Somei, K. Noguchi, R. Yamagami, Y. Kawada, K. Yamada and F. Yamada, *Heterocycles*, 2000, **53**, 7–10; (*h*) N. Finch, I. H. C. Hsu, C. W. Gemenden and W. I. Taylor, *J. Am. Chem. Soc.*, 1963, **85**, 1520–1523; (*i*) H. Takayama, K. Masubuchi, M. Kitajima, N. Aimi and S. Sakai, *Tetrahedron*, 1989, **45**, 1327–1336.

3 (*a*) A. A. Meyers and B. A. Lefker, *J. Org. Chem.*, 1986, **51**, 1541–1544; (*b*) A. I. Meyers and B. A. Lefker, *Tetrahedron*, 1987, **43**, 5663–5676; (*c*) A. I. Meyers, R. Hanreich and K. T. Wanner, *J. Am. Chem. Soc.*, 1985, **107**, 7776–7778; (*d*) A. I. Meyers and D. J. Berney, *J. Org. Chem.*, 1989, **54**, 4673–4676; (*e*) A. I. Meyers, J. L. Romine and A. J. Robichaud, *Heterocycles*, 1990, **30**, 339–340; (*f*) A. I. Meyers and M. Sturgess, *Tetlett.*, 1989, **30**, 1741–1744; (*g*) D. Romo, J. L. Romine, W. Midura and A. I. Meyers, *Tetlett.*, 1989, **45**, 4951–4994.

4 (*a*) D. Romo and A. I. Meyers, *Tetrahedron*, 1991, **47**(46), 9503–9569; (*b*) A. I. Meyers and G. P. Brengel, *Chem. Commun.*, 1997, 1–8.

5 (*a*) A. I. Meyers, M. A. Seefeld, B. A. Lefker, J. F. Blake and P. G. Willard, *J. Am. Chem. Soc.*, 1998, **120**, 7429–7438; (*b*) P. Devine and A. I. Meyers, *J. Am. Chem. Soc.*, 1994, **116**, 2633–2634.

6 See *e.g.*: (*a*) M. B. Smith, J. March *Advanced Organic Chemistry*, 5 ed. WILEY-INTERSCIENCE, New York, 2001, pp. 850; (*b*) E. Buncel, J. M. Dust and F Terrier, *Chem. Rev.*, 1995, **95**, 2261–2280.

7 (*a*) R. J. Snow, T. Butz, A. Hammach, S. Kapadia, T. A. Morowick, A. P. Propokowicz, H Takahashi, J. D. Tan, M. A. Tschantz and X. –J. Wang, *Tetrahedron Lett.*, 2002, **43**, 7553–7560.

8 (*a*) N. Selvakumar, B. Yadi Reddy, G. Sunil Kumar and J. Iqbal, *Tetlett*, 2001, **42**, 8395–8398; (*b*) N. J. Lawrence, C. A. Davies and M. Gray, *Org. Lett.*, 2004, **6**, 4957–4960.

9 (*a*) K. C Nicolau, H Li, C. N. C Boddy, J. M. Ramanjulu, T. Y Yue, S. Natarajan, X. J Chu, S. Bräise and F. Rübsam, *Chem.–Eur. J.*, 1999, **5**, 2584–2601; (*b*) T. Lais and J. Zhu, *Tetlett.*, 1999, **40**, 83–86.

10 (*a*) M. Bella, S. Kobbelgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 3670–3671; (*b*) S. Kobbelgaard, M Bella and K. A. Jørgensen, *J. Org. Chem.*, 2006, **71**, 4980–4987.

11 (*a*) L. B. Burgess and A. I. Meyers, *J. Am. Chem. Soc.*, 1991, **113**, 9858–9859; (*b*) M. Penhoat, S. Leleu, G. Dupass, G. Papamicaël, F. Marsais and V. Levacher, *Tetlett*, 2005, **46**, 8385–8389.

12 Please refer experimental section for X-ray analysis data.

