ORGANIC LETTERS

2009
Vol. 11, No. 20
4688−4691

Conformational Effects in Diastereoselective Aryne Diels−Alder Reactions: Synthesis of Benzo-Fused [2.2.1] Heterobicycles

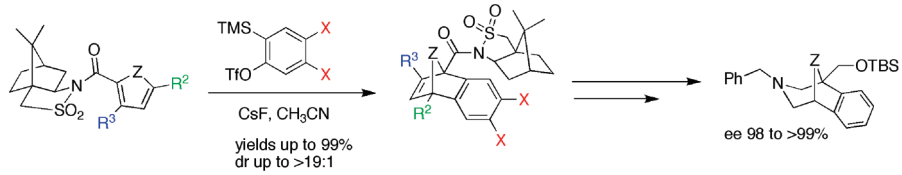
Robert Webster and Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

mlautens@chem.utoronto.ca

Received August 26, 2009

ABSTRACT

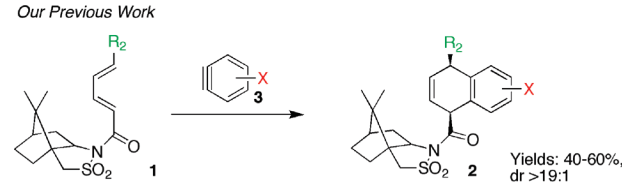


It was found that the diastereoselectivity of the Diels−Alder reaction between arynes and substituted furans is highly sensitive to substitution, which affects the reactive conformation. By varying the location of the groups on the diene partner, it is possible to obtain both excellent chemical yields and high stereoselectivity. This methodology offers rapid and convenient access to enantiomerically pure bicyclic scaffolds which are difficult to prepare by other means.

Arynes have attracted considerable interest from the synthetic community as reactive intermediates;[1] however, asymmetric reactions involving them are exceedingly rare and remain a challenge in the field.[3a] We previously reported the first diastereoselective aryne Diels−Alder (ADA) reaction to yield enantiomerically enriched products with acyclic dienes bearing Oppolzer's sultam as a chiral auxiliary, which gives convenient entry into the biologically privileged 1,4-dihydronaphthalene core (Scheme 1).[3c]

While excellent selectivites were obtained (>19:1), yields were more modest, ranging from 40−60%, presumably due to the acyclic scaffold's thermodynamic preference to occupy the s-trans conformation. During the course of our investigation to prepare enantiomerically enriched unsymmetrical

Scheme 1. ADA Cycloaddition with Acyclic Dienes[3c]



(1) For recent reviews on arynes see: (a) Pelissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Wenk, H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–527. (c) Dyke, A.; Hester, A.; Lloyd-Jones, G. *Synthesis* **2006**, *24*, 4093–4112. (d) Peña, D.; Pérez, D.; Guitián, E. *Heterocycles* **2007**, *74*, 89–100. (e) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215–291.

(2) For aryne trapping with furan, see: (a) Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67*, 348. (b) Gilman, H.; Gorsich, R. *J. Am. Chem. Soc.* **1957**, *79*, 2625–2629. (c) Stiles, M.; Miller, R. *J. Am. Chem. Soc.* **1960**, *82*, 3802. (d) Harrison, H.; Heaney, H.; Lees, P. *Tetrahedron* **1968**, *24*, 2625–2629. (e) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214. (f) Kitamura, T.; Wasai, K.; Todaka, M.; Fujiwara, Y. *Synlett* **1999**, *6*, 731–732.

(3) Only three reports of stereoselective reactions of arynes to yield enantiomerically enriched products have appeared in the literature: (a) Diego, P.; Pérez, D.; Guitián, E. *Chem. Rec.* **2007**, *7*, 326–333. (b) Caeiro, J.; Diego, P.; Cobas, A.; Pérez, D.; Guitián, E. *Adv. Synth. Catal.* **2006**, *348*, 2466–2474. (c) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028–15029.

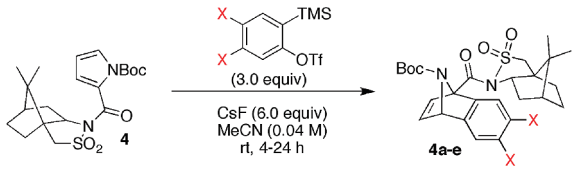
(4) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444–445.

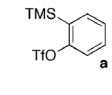
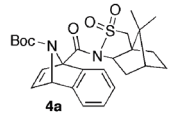
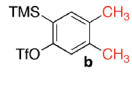
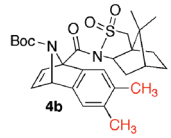
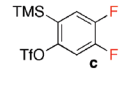
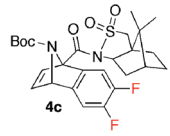
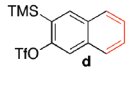
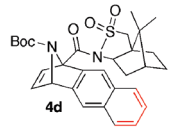
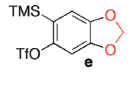
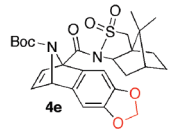
10.1021/ol9019869 CCC: $40.75
Published on Web 09/24/2009

oxabenzonorbornenes to study their behavior in ring-opening chemistry,[4] it was found that the analogous ADA reaction with heterocyclic dienes fixed in the s-cis state gave much improved yields, but a fluctuation of diastereoslectivity was observed depending on the diene substrate. We felt this phenomenon warranted further study.

When chiral pyrroles were treated with the silylaryl triflate aryne precursors pioneered by Kobayashi,[2e] in the presence of CsF and acetonitrile at room temperature, it was discovered that **4** is an excellent substrate which reacts with a variety of arynes in a highly efficient and diastereoselective manner (Table 1). The use of Boc as a protecting group

Table 1. ADA Reaction of *N*-Boc-pyrroles



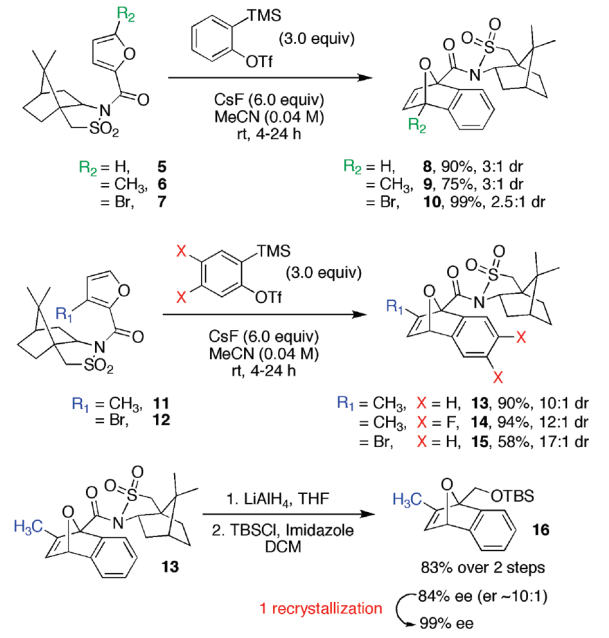
entry	aryne precursor	product	yield (%)	dr[a]
1			96	>19:1
2			92[b]	>19:1
3			99	>19:1'
4			77[b,c]	>19:1
5			74	>19:1

[a] NMR peak broadening due to Boc groups was observed. Products were deprotected using acetyl chloride in methanol, and the dr was assigned from the crude ^{1}H NMR of the corresponding HCl salt. [b] Absolute configuration proven using X-ray analysis of deprotected HCl salt. [c] 4.5 equiv of the aryne precursor was used. [d] Assignment of dr confirmed by ^{19}F NMR.

affords a favorable balance of reactivity, as the *N*-tosylpyrrole was completely unreactive under these conditions and the *N*-methylpyrrole was quickly consumed to yield an intractable mixture of products. Due to line broadening in the ^{1}H NMR spectra of the *N*-Boc-azabicycles **4a**−**e**, it was not possible to unambiguously report a dr without first removing the Boc group. This removal was accomplished by treating the products with acetyl chloride in methanol to cleanly afford the HCl salts which gave adequately resolved ^{1}H NMR spectra. In addition, it was possible to use the ^{19}F NMR of the crude **4c** to confirm the dr was >20:1. Somewhat lower yields were observed for the formation of **4d** and **4e** (Table 1, entries 4 and 5), presumably due to the relatively slow formation of naphthyne and electron-rich arynes, respectively.[5] The absolute configuration of adducts **4b** and **4d** was determined by deprotection followed by X-ray analysis of its HCl salt and shows the same facial selectivity observed for the acyclic dienes.

To our surprise, the ADA reaction of simple furan substrates showed a large decrease in diastereoselectivity (Scheme 2). The absolute configuration of the products **8**

Scheme 2. Steric Buttressing of the Chiral Auxiliary



and **13** were confirmed by single-crystal X-ray analysis. The facial selectivity of the major diastereomer of the furan cycloaddition was observed to be the same as that arising from cycloaddition with the acyclic diene. Presumably, for **5** the oxygen of the furan and the sulfonamide moiety may experience electrostatic repulsion,[6] making the reactive conformer significantly different than in the acyclic scaffold. Various Lewis acid additives (BF_3•Et_2O, $Cu(OTf)_2$, $Zn(OTf)_2$, $Ti(OiPr)_4$) were employed in an attempt to influence the dominant conformation in the transition state, but all proved to have a negative impact on the yield and little effect on the selectivity of the cycloaddition.[7]

Overall, the stereoselectivity proved to be relatively insensitive to temperature, as reactions between benzyne at

(5) Zhijian, L.; Larock, R. *J. Org. Chem.* **2007**, *72*, 4689–4691.

(6) The use of Oppolzer's sultam as a chiral auxiliary in thermal reactions has been thoroughly reviewed: Kim, B.; Curran, D. *Tetrahedron* **1993**, *49*, 293–318.

(7) See the Supporting Information for the data table.

60 °C with **5** and **11** as the diene component gave similar product ratios. We suspected the large excess of cesium cations present might have some effect; however, using alternate methods of benzyne generation in the absence of cesium gave similar results,[8] suggesting that a cesium chelate is not responsible for the changes in selectivity. Furthermore, 1D and 2D ^{1}H NMR spectra of various dienes showed no observable change with the addition of CsF. The use of other chiral auxiliaries led to lower observed selectivity,[7] in accord with our previous report on the reactions of acyclic dienes.[3b]

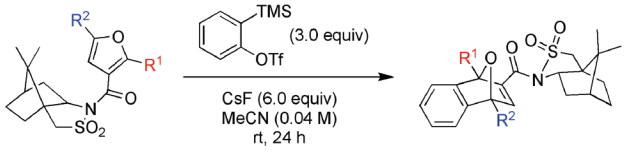
We considered that adding a bulky substituent to the 3-position of the furan ring (Scheme 2) may overcome the presumed electrostatic repulsion and force the π system to adopt a reactive conformation similar to that of the acyclic dienes. Compound **11** with a methyl group substituted at the 3-position of the furan showed a significant increase in diastereoselectivity (10:1) relative to the parent substrate when exposed to the same reaction conditions. Replacement of the methyl with bromine in **12** gives even higher selectivity (17:1).

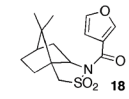
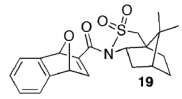
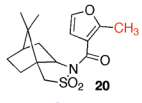
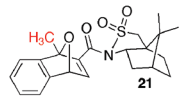
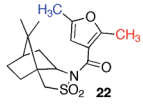
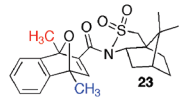
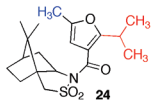
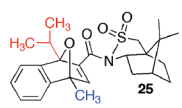
The chiral auxiliary can be easily removed under reductive conditions (Scheme 2). HPLC analysis of **16** showed an er of 92:8 in agreement with the dr of 10:1 estimated from the ^{1}H NMR of **13**. Recrystallization of **16** gave 99% ee material suitable for X-ray analysis. Tethering the chiral auxiliary to the 3-position of the furan shows similar, but less exaggerated, effects on the stereochemical outcome. The absolute configuration of **23** (Table 2) was also identified using X-ray analysis and was shown to arise from the opposite facial selectivity observed for both products **8** and **13**. The methyl group at the 2-position in furan **22** is on the opposite side of the chiral auxiliary relative to the methyl group in **11** and may twist the π system into adopting the opposite rotamer as the major reactive conformation in solution. It remains unclear if the dramatic increase in stereoselectivity in the azabicycle series (Table 1) is due to a similar conformational change in the orientation of the chiral auxiliary or perhaps owing to facial shielding by the Boc group directed by the auxiliary.[9]

The ADA conditions are amenable to gram scale production and upon scale-up require as little as 1.3 equiv of aryne precursor. For example, **8** can be conveniently isolated by dissolution of the crude product in ethyl acetate followed by precipitation using a small amount of pentane, giving a 60% yield of the major diastereomer (98% de) without recourse to chromatography. This constitutes a major improvement compared to typical aryne trappings of this type, which commonly employ a large excess of the furan (often 5−50 equiv).[2]

To demonstrate the utility of these substrates, post cycloaddition transformations were performed (Scheme 3). Following a dihydroxylation/oxidative cleavage/reductive amination protocol[10] it was possible to convert the aza- and oxabenzonorbornenes into orthogonally protected aza- and oxa-bridged

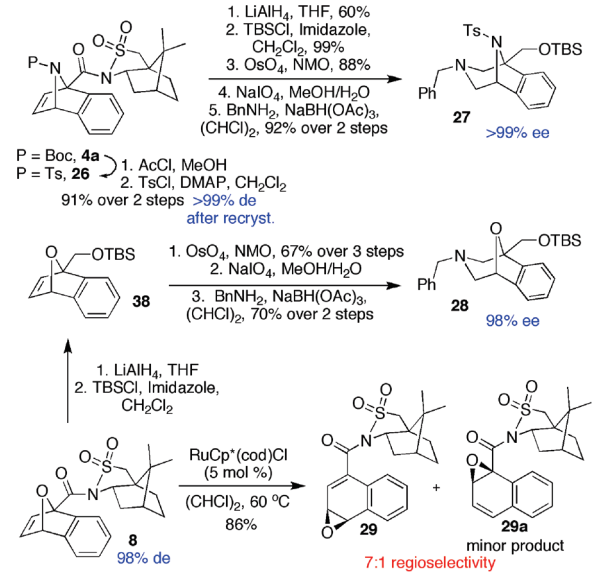
Table 2. Obtaining Opposite Facial Selectivity: Conformational Control with the Auxiliary in the 3-Position



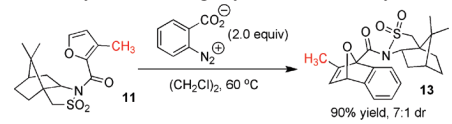
entry	substrate	product	yield (%)	dr[a]
1[c]	 18	 19	30	2.5:1
2	 20	 21	56	5.2:1
3	 22	 23	79[b]	6.6:1
4	 24	 25	84[b]	7.4:1

[a] Ratio assinged from crude ^{1}H NMR by relative peak integration. [b] Absolute configuration proven using X-ray analysis. [c] Absolute configuration of the major diastereomer is unknown.

Scheme 3. Synthesis of Optically Pure Bridged Benzazepine and 1,2-Naphthalene Oxide Scaffolds



(8) Reactions with benzenediazonium carboxylate at elevated temperatures gave similar yields and slightly lower selectivity.



(9) It would be expected that if the Boc group was simply acting as a steric anchor at the 1-position of the pyrrole, the absolute configuration of the azabicyclic products would be the opposite of that observed in the reaction of furan substrate **11** which bears a methyl group on the opposite side of the heterocycle relative to the chiral auxiliary.

(10) Brooks, P.; Caron, S.; Coe, J.; Ng, K.; Singer, R.; Vazquez, E.; Vetelino, M.; Watson, H.; Whritenour, D.; Wirtz, M. *Synthesis* **2004**, *11*, 1755–1758.

benzazepines **27** and **28**, respectively. Although such heterocycles are rare, they show an interesting range of biological activity, and currently no alternative simple methodology exists for their preparation as single enantiomers.[11] When **8** was subjected to Tam's Ru(II)-catalyzed isomerization conditions[12] (Scheme 3), **29** was isolated as a 7:1 mixture of regioisomeric epoxides with opposite selectivity expected based on Tam's original report, possibly due to a directing effect involving Ru chelation by the sultam moiety. X-ray crystallography of **29** confirms the structure, but both regioisomers were found to cocrystallize in an approximately 7:1 ratio.

In summary, a practical synthesis of optically pure [2.2.1] benzo-fused oxa- and azabicyclic alkenes has been developed, and by careful choice of substituents to affect the conformation of the substrates, both high yields and selectivites are obtainable and the absolute configuration at the bridgehead junction can be controlled. These products allow rapid access to enantiomerically pure aza-/oxa-bridged benzazepines and 1,2-naphthalene oxides. Further mechanistic and computational models are currently being investigated to better understand the nature of the stereoselectivity in the cycloaddition.

Acknowledgment. This work is supported by NSERC (Canada), Merck-Frosst (IRC), and the University of Toronto. R.W. thanks Dr. Christian Böing (Univeristy of Toronto) for highly useful discussions and assistance with preliminary parts of this work. We also thank Dr. A. Lough (University of Toronto) for X-ray analysis.

Supporting Information Available: Experimental procedures, characterization data for new compounds, and additional data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9019869

(11) For oxa-benzazepines as c-Met kinase inhibitors, see: Gulzar, A.; Bohnstedt, A.; Breslin, H.; Burke, J.; Curry, M.; Diebold, J.; Dorsey, B.; Dugan, B.; Feng, D.; Gingrich, D.; Guo, T.; Ho, K.; Learn, K.; Lisko, J.; Liu, R.; Mesaros, E.; Milkiewicz, K.; Ott, G.; Parrish, J.; Theroff, J.; Thieu, T.; Tripathy, R.; Underiner, T.; Wagner, J.; Weinberg, L.; Wells, G.; You, M.; Zificsak, C. WO 2008051547, Oct 23, 2007. As ulcer treatments: Wachter, M.; Karanewsky, D. US 4761413, Dec 22, 1986. For aza-benzazepines as histamine H4 receptor ligands: Bell, A.; Lane, C.; Mowbray, C.; Selby, M.; Swain, D.; Williams, N. WO 2007072163, June 28, 2007.

(12) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, *128*, 3514–3515.