J|A|C|S COMMUNICATIONS

Published on Web 01/05/2010

Highly Enantioselective Intramolecular Copper Catalyzed C−H Insertion Reactions of α-Diazosulfones

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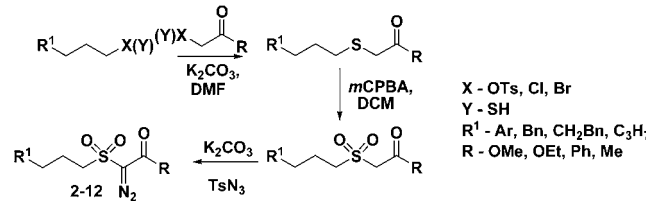
Synthetically powerful C−H insertion processes with α-diazocarbonyl compounds have attracted considerable attention;[1−5] while early studies employing copper catalysts led to low yields and selectivities, introduction of rhodium acetate in the 1980s resulted in very efficient C−H insertions especially in intramolecular processes leading to cyclopentanones.[6] Significant progress has been reported in enantioselective C−H insertion employing rhodium catalysts[1,2,4,5,7] since the first report of a rhodium prolinate catalyst leading to 12% ee, the sole example of asymmetric C−H insertion employing α-diazosulfones.[8] Application of asymmetric copper catalysts to this transformation has been very limited to date, in contrast to cyclopropanation for example,[3,4] and has resulted in modest enantioselectivities (up to 60% ee in intramolecular C−H insertion with one report of 88% ee in the intermolecular version).[7,9−13]

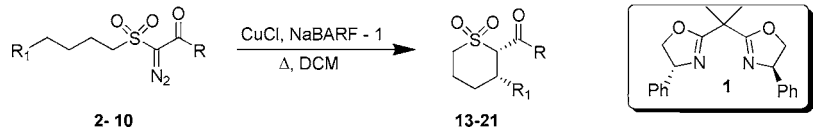
Herein we report that use of copper *bis*-oxazoline catalysts for C−H insertion processes with α-diazosulfones **2**−**12** (synthesis in Scheme 1) leads to enantioenriched cyclic sulfones with up to 98% ee as summarized in Tables 1, 2, and 3. These insertions lead to either thiopyrans or sulfolanes primarily depending on the substrate structure, although the nature of the catalyst and reaction conditions employed also influence the outcome. Formation of six-membered cyclic sulfones in the C−H insertion processes was unexpected, as C−H insertion reactions usually display a strong preference for five-membered ring formation. Interestingly recent reports describe both 5- and 6-membered ring formation in rhodium catalyzed cyclization of α-diazosulfonyl esters and related systems.[14]

Scheme 1



On treatment of the α-diazosulfones **2**−**10** with CuCl-NaBARF-**1**, the *cis*-thiopyrans **13**−**21** were isolated in moderate yields but excellent enantioselectivities (85−98% ee, Table 1), while the α-diazosulfones **11** and **12** led to the *trans*-sulfolanes **22**−**23** in moderate yields and enantiopurities (40−60% ee, Table 2). While the ^{1}H NMR spectra of the crude products were complex, following chromatography the C−H insertion product was isolated as a single compound in each case, i.e. either the *cis*-thiopyran or the *trans*-sulfolane. In some cases (**15**, **18**, **19**, and **22**) minor amounts of isomeric products were also isolated following chromatography in typically <10% yield. Thus, formation of the 6-membered ring is preferred, but when this option is not possible (in **11** and **12**) then insertion is forced to proceed to give the 5-membered ring. The impact of the catalyst in the C−H insertion processes was explored; representatative data with α-diazosulfones **2** and **11** are summarized in Table 3. Use of copper(II) triflate led to inefficient reactions with low yields of thiopyrans **13**−**21** or sulfolanes **22**−**23** even

Table 1. Asymmetric Copper Catalyzed C−H Insertion To Provide Thiopyrans[a]



Entry	α-Diazosulfone	Thiopyran	R	R^1	Time (h)	Yield[b] (%)	% ee[c]
1	**2**	**13**	OMe	Ph	5	47	98
2	**3**	**14**	OMe	4-tolyl	5	64	96
3	**4**	**15**	OMe	4-anisole	22	56	91
4	**5**	**16**	OMe	4-nitrophenyl	2.5	−	−
5	**6**	**17**	OMe	benzyl	7	42	96
6	**7**	**18**	OMe	ethyl	16	68	97
7	**8**	**19**	OBn	octyl	22	66	90
8	**8**	**19**	OBn	octyl	10 min[d]	21	∼70
9	**9**	**20**	Me	Ph	22	30	85
10	**10**	**21**	Ph	Ph	6	49	97

[a] General procedure: 5 mol % CuCl, 6 mol % NaBARF (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), 6 mol % chiral ligand, and diazosulfone (200 mg) in DCM (10 mL) at reflux. [b] *cis*-Thiopyran after chromatography. [c] Determined using Chiralpak AS-H. [d] Microwave reaction, sealed vessel DCM at 80 °C.

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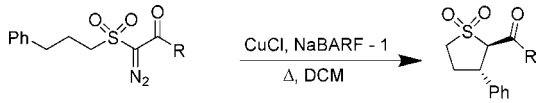
 10.1021/ja909713a

after extended reaction times (15−20 h) in refluxing DCM. Interestingly rhodium acetate catalyzed reaction of α-diazosulfone **12** only proceeded in refluxing toluene with no insertion evident after 24 h in refluxing DCM; evidently the copper catalysts are more effective for C−H insertion with these substrates. Use of $Cu(CH_3CN)_4PF_6$ with the chiral *bis*-oxazoline ligand **1** in refluxing DCM with the α-diazosulfones **2** and **11** resulted in much faster reactions albeit with modest yields. However, the enantioselectivities obtained (94% ee with **13** and 54% ee with **22**) were very promising indeed. Recent results show enhanced enantioselectivity in the presence of NaBARF for copper(I) mediated O−H, N−H, and Si−H insertions[15] and the intramolecular Buchner reaction.[16] Thus, cyclizations of α-diazosulfones **2** and **11** were conducted using copper(I) chloride, NaBARF, and the *bis*-oxazoline ligand **1**. In each case the reaction time was longer than that required with $Cu(CH_3CN)_4PF_6$, but critically increased yields and enantioselectivities were achieved (Table 3) with the thiopyran **13** isolated in 98% ee, representing the highest enantioselectivity achieved to date in a copper mediated C−H insertion process.

Table 2. Asymmetric Copper Catalyzed C−H Insertion To Provide Sulfolanes[a]



11, 12 **22, 23**

α-Diazosulfone	Sulfolane	R	Time (h)	Yield[b] (%)	% ee[c]
11	**22**	OEt	5	57	60
12	**23**	Me	3	40	40

[a] General procedure: 5 mol % CuCl, 6 mol % NaBARF, 6 mol % chiral ligand, and diazosulfone (200 mg) in DCM (10 mL) at reflux. [b] *trans*-Sulfolane after chromatography. [c] Determined using Chiralpak AS-H.

Cyclization of each of the α-diazosulfones **2**−**12** using the CuCl-NaBARF-**1** catalyst system was typically complete in 3−7 h. While, in general, C−H insertion into benzylic C−H bonds displayed shorter reaction times than those leading to the benzyl, ethyl, and octyl thiopyrans **17**, **18**, and **19**, the overall yield was comparable for **17** and higher in the case of the ethyl and octyl derivatives **18** and **19**. Comparison of entries 1−4 (Table 1) highlights a significant electronic effect on the reaction efficiency with no insertion evident in the most electron-deficient 4-nitrophenyl substrate **5** but no detectable effect on the enantioselection (entries 1−3, Table 1). In an attempt to improve the insertion efficiency, slow addition of the α-diazosulfone **2** to preformed CuCl-NaBARF-**1** catalyst in refluxing DCM over 1 h was undertaken and led to a significant decrease in yield but had no effect on the enantiocontrol. Furthermore, use of a microwave reactor with α-diazosulfone **8** showed a large decrease in both insertion efficiency and enantioselection (entry 8 in Table 1).

Comparison of the results obtained with the different substrates shows a number of interesting trends; in both the thiopyran and sulfolane formation, use of the ester and ketone substrates leads to essentially the same outcome in terms of enantiocontrol, although the methyl ketone shows a slight decrease (entry 9, Table 1). Thus, variation of the substituent on the carbene has little impact on the enantioselection. While alteration of the nature of the C−H bond undergoing insertion from benzylic (**13**−**16**, **20**, **21**) to unactivated (**17**−**19**) had a notable impact on the reaction time, the enantioselection was essentially unaffected by this alteration in the electronic properties at the site of reaction. Decreased enantioselection was detected in the minor *trans*-isomers of **15** and **19** (11 and 15% ee respectively) isolated in <10% yield. Clearly the key features affecting the degree of enantioselection in the transition states leading to 5- or 6-membered ring formation differ significantly, presumably due to conformational and/or steric effects.

Table 3. Influence of Catalyst in the C−H Insertions

α-Diazo sulfone	Product	Catalyst	Time (h)	Yield[a] (%)	% ee[b]
2	**13**	CuCl, NaBARF-**1**	5	47	98
		$Cu(CH_3CN)_4PF_6$-**1**	2	19	94
		$Cu(SO_3CF_3)_2$	20	29	−
11	**22**	CuCl, NaBARF-**1**	5	57	60
		$Cu(CH_3CN)_4PF_6$-**1**	1.5	29	54
		$Cu(SO_3CF_3)_2$	15	33[c]	−

[a] *cis*-Thiopyran or *trans*-sulfolane after chromatography. [b] Determined using Chiralpak AS-H. [c] Sample not analytically pure.

The relative and absolute stereochemistry of the cyclic sulfones were confirmed crystallographically on **13**, **21**, and **22** and supported by NOE studies. In each case the 3*S* enantiomer is formed when CuCl-NaBARF-**1** is employed. The stereochemistry of the other products is assigned by analogy.

Acknowledgment. We would like to thank Janssen Pharmaceutical and IRCSET for funding for this work.

Supporting Information Available: Experimental procedures, characterizations, chiral HPLC analysis, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *66*, 6577–6605. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (c) Davies, H. M. L.; Hedley, S. *J. Chem. Soc. Rev.* **2007**, *36*, 1109–1119. (d) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2004**, 3773–3788. (e) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, 98–104.
(2) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.
(3) (a) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (b) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007–9011. (c) Honma, M.; Takeda, H.; Takano, M.; Nakada, M. *Synlett* **2009**, 1695–1712.
(4) Doyle, M. P.; McKervey, M. A.; Ye. T. *Modern catalytic methods for organic synthesis with diazo compounds, from cyclopropanes to ylides*; John Wiley and Sons Inc.: 1998.
(5) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160.
(6) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196–199.
(7) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903.
(8) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. J. *Chem. Soc., Chem. Commun.* **1990**, 361–362.
(9) (a) Doyle, M. P.; Hu, W. *J. Org. Chem.* **2000**, *65*, 8839–8847. (b) Doyle, M. P.; Phillips, I. M. *Tetrahedron Lett.* **2001**, *42*, 3155–3158.
(10) Ye, T.; Garcia, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373–1379.
(11) Lim, H.; Sulikowski, G. A. *J. Org. Chem.* **1995**, *60*, 2326–2327.
(12) (a) Muller, P.; Bolea, C. *Helv. Chim. Acta* **2002**, *85*, 483–494. (b) Muller, P.; Bolea, C. *Molecules* **2001**, *6*, 258–266.
(13) Fraile, J. M.; Garcá, J. I.; Mayoral, J. A.; Roldán, M. *Org. Lett.* **2007**, *9*, 731–733.
(14) (a) Jungong, C. S.; John, J. P.; Novikov, A. V. *Tetrahedron Lett.* **2009**, *50*, 1954–1957. (b) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. J. *Am. Chem. Soc.* **2004**, *126*, 15378–15379. (c) Espino, C. G.; When, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (d) John, J. P.; Novikov, A. V. *Org. Lett.* **2007**, *9*, 61–63. (e) Wolckenhauer, S. A.; Devlin, A. S.; Du Bois, J. *Org. Lett.* **2007**, *9*, 4363–4366. (f) Hrytsak, M.; Etkin, N.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 5679–5682. (g) Babu, S. D.; Hrytsak, M. D.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071–1076.
(15) (a) Chen, C.; Zhu, S.; Liu, B.; Wang, L.; Zhou, Q. *J. Am. Chem. Soc.* **2007**, *129*, 12616–12617. (b) Zhu, S.; Chen, C.; Cai, Y.; Zhou, Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 932–934. (c) Zhang, Y.; Zhu, S.; Wang, L.; Zhou, Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 8496–8498. (d) Liu, B.; Zhu, S.; Zhang, W.; Chen, C.; Zhou, Q. *J. Am. Chem. Soc.* **2007**, *129*, 5834–5835.
(16) O'Neill, S.; O'Keeffe, S.; Harrington, F.; Maguire, A. R. *Synlett* **2009**, 2312–2314.

JA909713A