Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 667

www.rsc.org/obc

COMMUNICATION

Asymmetric copper-catalysed intramolecular C–H insertion reactions of α-diazo-β-keto sulfones†

Catherine N. Slattery[a] and Anita R. Maguire*[b]

Received 21st October 2010, Accepted 15th November 2010
DOI: 10.1039/c0ob00914h

Asymmetric copper-catalysed intramolecular C–H insertion reactions of a series of α-diazo-β-keto sulfones are reported. Enantioselectivities of up to 82% ee were achieved in moderate to good yield. These results represent the highest level of enantiocontrol achieved to date for a copper-catalysed cyclopentanone synthesis *via* C–H insertion.

C–H insertion reactions of α-diazocarbonyl compounds have long attracted attention in organic synthesis owing to their potential in synthesizing chemically complex structures *via* C–C bond formation.[1–3] While initial studies exploring C–H insertion processes employed copper catalysts, rhodium(II) complexes have dominated this field since their introduction in the early 1980s.[4] Highly enantioselective diazo decompositions are possible in the presence of chiral rhodium(II) catalysts, of which rhodium(II) carboxylates and carboxamidates have found particular success. In contrast, the application of asymmetric copper catalysts in C–H insertion reactions has not been widely exploited in recent times. Limited reports exist, however, the level of enantiocontrol achieved has been generally moderate, up to a maximum of 60% ee[5] for intramolecular C–H insertion and 88% ee[6] for the intermolecular reaction.

Recently, we demonstrated that the copper complex of chiral bis(oxazoline) ligand **1** is a highly efficient catalyst for asymmetric intramolecular C–H insertions of α-diazosulfones.[7] In this previous study, cyclic sulfones were prepared in up to 98% ee, representing the highest enantioselectivity recorded to date for a copper-catalysed C–H insertion reaction. As part of our continuing investigations into the employment of chiral copper complexes in diazocarbonyl chemistry, we report herein our investigations on the enantioselective C–H insertion reactions of α-diazo-β-keto sulfones to yield α-sulfonyl cyclopentanones.

Five α-diazo-β-keto sulfones **5–9** were chosen as substrates for this study permitting examination of the steric and electronic effects of the group adjacent to the C–H insertion site. The diazo compounds were synthesized from the corresponding esters following standard procedures.[8–11]

C–H insertion reactions of the α-diazo-β-keto sulfones were conducted in refluxing CH_2Cl_2 with a copper catalyst generated *in situ* from 5 mol% CuCl and 6 mol% ligand. Four chiral bis(oxazoline) ligands **1–4** (Fig. 1) were examined for their ability to induce enantioselectivity in the insertion reactions. Exclusive *trans*-cyclopentanone formation was recorded in each of the reactions conducted, however, in some cases, minor amounts of byproducts were also observed.

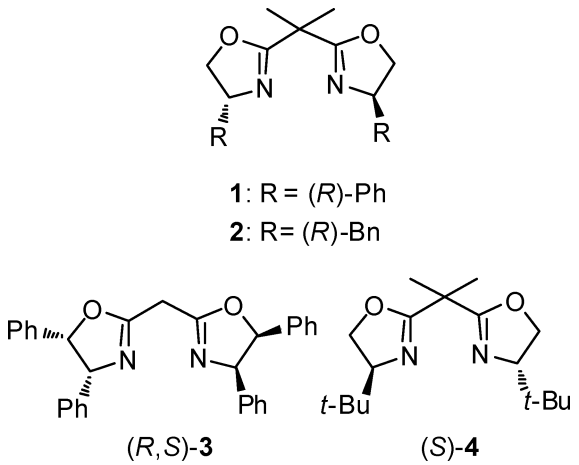


Fig. 1 Bis(oxazoline) ligands.

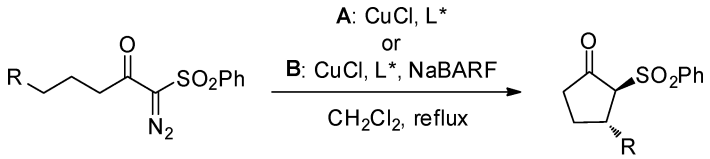
Each of the copper complexes of ligands **1–4** catalysed the desired reaction, generating the cyclopentanone products **10–14** in moderate yield, with long reaction times typically required (Table 1, conditions A). The level of enantiocontrol achieved for these initial reactions was poor, ranging from 0 to 33% ee. The use of NaBARF, {BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} which functions as a non-coordinating counterion, has previously been demonstrated by us and other research groups to enhance the enantioselectivity of diazo decomposition reactions.[12–15] With these reports in mind, 6 mol% NaBARF was added to the catalytic mixture consisting of CuCl and bis(oxazoline) ligand, with the objective that the addition of this borate counterion would provide a similar beneficial effect on enantiocontrol.

This was indeed found to be true; for each of the diazo substrates examined a significant increase in asymmetric induction was

[a]*Department of Chemistry and Analytical and Biological Chemistry Research Facility, University College Cork, Ireland*
[b]*Department of Chemistry, School of Pharmacy and Analytical and Biological Chemistry Research Facility, University College Cork, Ireland. E-mail: a.maguire@ucc.ie; Fax: +353-(0)21-4274097; Tel: +353-21-4902125*

† Electronic supplementary information (ESI) available: General Procedures, characterisation data of the cyclopentanone products **10–14** and chiral HPLC analysis See DOI: 10.1039/c0ob00914h

Table 1 Copper-catalysed C–H insertion reactions



5-9 **10-14**

Entry	α-Diazo-β-keto sulfone	*R*	Cyclopentanone	L*	Time/h		Yield[a] (%)		% ee[b,c] (%)	
					A	B	A	B	A	B
1	**5**	Me	**10**	(*R*)-**1**	22	27	72	94	0	30 (2*S*,3*R*)
2	**5**	Me	**10**	(*R*)-**2**	40	3	71	62	0	58 (2*S*,3*R*)
3	**5**	Me	**10**	(*R*,*S*)-**3**	—	21	—	75	—	0
4	**5**	Me	**10**	(*S*)-**4**	—	22	—	73	—	14 (2*R*,3*S*)
5	**6**	Et	**11**	(*R*)-**1**	24	6	42	97	0	29 (2*S*,3*R*)
6	**6**	Et	**11**	(*R*)-**2**	—	15	—	70	—	62 (2*S*,3*R*)
7	**6**	Et	**11**	(*R*,*S*)-**3**	—	21	—	76	—	11 (2*S*,3*R*)
8	**6**	Et	**11**	(*S*)-**4**	—	**15**	—	73	—	28 (2*R*,3*S*)
9	**7**	*i*-Pr	**12**	(*R*)-**1**	21	4	68	54	0	37 (2*S*,3*S*)
10	**7**	*i*-Pr	**12**	(*R*)-**2**	—	16	—	95	—	60 (2*S*,3*S*)
11	**7**	*i*-Pr	**12**	(*R*,*S*)-**3**	21	21	54	43	0	14 (2*S*,3*S*)
12	**7**	*i*-Pr	**12**	(*S*)-**4**	—	24	—	55	—	42(2*R*,3*R*)
13	**8**	Ph	**13**	(*R*)-**1**	26	4	42	68	0	49 (2*S*,3*S*)
14	**8**	Ph	**13**	(*R*)-**2**	24	19	40	62	8 (2*S*,3*S*)	82 (2*S*,3*S*)
15	**8**	Ph	**13**	(*R*,*S*)-**3**	42	22	47	82	33 (2*S*,3*S*)	58 (2*S*,3*S*)
16	**8**	Ph	**13**	(*S*)-**4**	—	19	—	55	—	64 (2*R*,3*R*)
17	**9**	Bn	**14**	(*R*)-**1**	24	21	42	57	5 (2*S*,3*S*)	28 (2*S*,3*S*)
18	**9**	Bn	**14**	(*R*)-**2**	—	6	—	54	—	57 (2*S*,3*S*)
19	**9**	Bn	**14**	(*R*,*S*)-**3**	—	21	—	46	—	0
20	**9**	Bn	**14**	(*S*)-**4**	—	8	—	62	—	33 (2*R*,3*R*)

[a] Isolated after flash chromatography. [b] Determined by chiral HPLC (see ESI† for details). [c] Stereochemical assignments are in agreement with previously reported data.[16]

observed for C–H insertion in the presence of NaBARF (Table 1, conditions B). Ligand **2** was found to be the most enantioselective, providing cyclopentanone **13** in 62% yield and 82% ee (Table 1, entry 14).

To the best of our knowledge, this result represents the highest level of asymmetric induction reported to date for cyclopentanone synthesis *via* copper-catalysed C–H insertion, and parallels results obtained with chiral rhodium(II) carboxylates for the decomposition of α-diazo-β-keto esters, although in this earlier work very sterically demanding ester substituents were required to achieve high levels of enantioselection.[17,18]

As summarized in Fig. 2, a number of interesting trends can be seen in terms of the enantioselectivity of the copper complexes derived from each of the bis(oxazoline) ligands. With the Ph-substituted ligand **1**, relatively consistent enantiocontrol is observed across the series of α-diazo-β-keto sulfones, typically around 30% ee, with enhanced enantioselectivity (49% ee) for insertion into the benzylic C–H bond. The Bn-substituted ligand **2** gives consistently good asymmetric induction in the region of 60% ee, independent of the nature of the R group at the insertion site. As was observed for ligand **1**, the enantioselectivity achieved with ligand **2** is increased (82% ee) in the formation of **13**.

In contrast, ligand **3**, which features a diphenyl substitution pattern, was found to proceed with modest enantiocontrol (58% ee) for only one substrate (**13**); for each of the other diazo

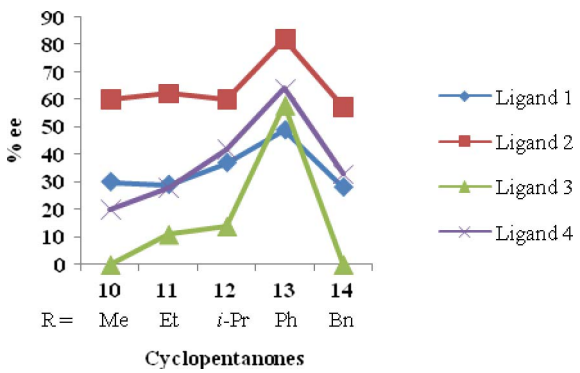


Fig. 2 Trends in enantioselectivity for ligands **1–4**.

sulfones, very little enantioselection was observed. With the *t*-Bu-substituted ligand **4**, a steady increase in enantiocontrol is noted on increasing the size of the R group adjacent to the C–H insertion site, indicating an important steric effect with this ligand. As before, the best results for bis(oxazoline) **4** were achieved in the synthesis of cyclopentanone **13**.

Comparison of the results obtained with ligands **1** and **3** is particularly interesting. With substrates **5**, **6**, **7** and **9**, the enantiocontrol using ligand **3** is much less than that achieved using ligand **1**. Thus, the conformational impact of the additional

Ph substituent and the alteration to an unsubstituted methylene bridge in ligand **3** appears to orient the ligand in a less favorable position in terms of asymmetric induction than can be achieved with the more conformationally mobile ligand **1**. The only exception to this pattern is with substrate **8**, where 58% ee was achieved using ligand **3**.

In an attempt to improve the enantioselectivity of the decomposition of **8**, the reaction conditions were carefully optimized using ligands **2** and **3** and NaBARF. A range of copper salts were examined, including $CuCl_2$, $Cu(MeCN)_4PF_6$ and $Cu(OTf)_2$, however no additional positive effect was detected. A change of reaction solvent to toluene was found to result in a decrease in overall enantiocontrol.

The experiments summarized in Table 1 involve pre-generation of the catalytic species for 1.5 h prior to addition of the diazo sulfone. A number of experiments were conducted where the diazo compound and catalytic mixture were added directly to the reaction flask prior to heating to reflux with significant detrimental effect on the enantioselectivity, but without a noticeable effect on reaction efficiency. Interestingly, this is in direct contrast to our earlier reports on C–H insertion to form cyclic sulfones,[7] where preformed catalysts were not necessary to achieve the excellent enantiopurities observed.

In conclusion, we have demonstrated that the use of copper bis(oxazoline) catalysts, in the presence of the non-coordinating counterion NaBARF, for C–H insertion reactions with α-diazo-β-keto sulfones leads to enantioenriched cyclopentanones with up to 82% ee. The results achieved in this study represent, to the best of our knowledge, the highest enantioselectivity realised to date in a copper-mediated C–H insertion cyclopentanone synthesis. Further investigation is underway to explore substrate, catalyst, ligand and counterion effects, with a view to determining the mechanism for asymmetric induction and expanding the scope of this powerful enantioselective C–H insertion process.

Acknowledgements

Financial support from the Irish Research Council for Science, Engineering and Technology, and Eli Lilly is gratefully acknowledged.

Notes and References

1 C. N. Slattery, A. Ford and A. R. Maguire, *Tetrahedron*, 2010, **66**, 6681–6705.
2 H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861–2904.
3 M. P. Doyle, R. Duffy, M. Ratnikov and L. Zhou, *Chem. Rev.*, 2010, **110**, 704–724.
4 A. Demonceau, A. F. Noels, A. J. Hubert and P. Teyssié, *J. Chem. Soc., Chem. Commun.*, 1981, 688–689.
5 P. Müller and C. Bolea, *Molecules*, 2001, **6**, 258–266.
6 J. M. Fraile, J. I. Garcia, J. A. Mayoral and M. Roldan, *Org. Lett.*, 2007, **9**, 731–733.
7 C. J. Flynn, C. J. Elcoate, S. E. Lawrence and A. R. Maguire, *J. Am. Chem. Soc.*, 2010, **132**, 1184–1185.
8 M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano and M. Nakada, *J. Am. Chem. Soc.*, 2003, **125**, 2860–2861.
9 A. M. P. Koskinen and L. Munoz, *J. Chem. Soc., Chem. Commun.*, 1990, 652–653.
10 M. Kennedy, M. A. McKervey, A. R. Maguire and G. H. P. Roos, *J. Chem. Soc., Chem. Commun.*, 1990, 361–362.
11 A. R. Maguire and L. L. Kelleher, *Tetrahedron Lett.*, 1997, **38**, 7459–7462.
12 S. O'Neill, S. O'Keeffe, F. Harrington and A. R. Maguire, *Synlett*, 2009, 2312–2314.
13 S.-F. Zhu, C. Chen, Y. Cai and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2008, **47**, 932–934.
14 C. Chen, S.-F. Zhu, B. Liu, L.-X. Wang and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2007, **129**, 12616–12617.
15 B. Liu, S.-F. Zhu, W. Zhang, C. Chen and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2007, **129**, 5834–5835.
16 A. R. Maguire, L. L. Kelleher and G. J. Ferguson, *J. Mol. Catal. B: Enzym.*, 1996, **1**, 115–126.
17 S.-i. Hashimoto, N. Watanabe, T. Sato, M. Shiro and S. Ikegami, *Tetrahedron Lett.*, 1993, **34**, 5109–5112.
18 S.-i. Hashimoto, N. Watanabe and S. Ikegami, *Synlett*, 1994, 353–355.