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COMMUNICATIONS

Published on Web 02/19/2003

Asymmetric Catalysis on the Intramolecular Cyclopropanation of α-Diazo-β-keto Sulfones

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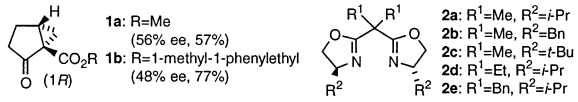
Received December 1, 2002; E-mail: mnakada@waseda.jp

Since the pioneering work of Nozaki et al.,[1] asymmetric catalysis on cyclopropanations has been studied,[2] and some excellent enantioselectivities have been reported for the catalytic asymmetric intramolecular cyclopropanation of α-diazo ketones, α-diazo acetates, and α-diazo acetamidates.[2,3]

However, only modest enantioselectivities have been found for α-diazo-β-keto esters, even with all of their versatile utilities.[2,4] For example, the derivative of 2-oxobicyclo[3.1.0]hexane **1a** was obtained from the corresponding α-diazo-β-keto ester with 56% ee, and the more-bulky ester **1b** was obtained with 48% ee.[5] We surmised that such low selectivity might be attributed to the small steric difference between the keto group and the ester group in the substrates.

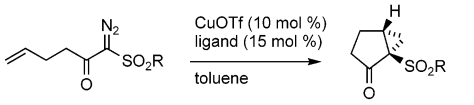


Hence, we started to investigate asymmetric catalysis on the intramolecular cyclopropanation of α-diazo-β-keto sulfones because (1) the sulfonyl group is apparently sterically different from the keto group, implying that good enantioselectivity would emerge, (2) the sulfonyl group would be a better surrogate for the ester group because of its utility, and (3) α-diazo-β-keto sulfones are easily prepared and stable, fulfilling the requirements for the synthesis of natural products.

Surprisingly, only one example has been reported for asymmetric catalysis on the intramolecular cyclopropanation of α-diazo-β-keto sulfones.[6] Therefore, first we carried out the reaction of substrate **3a** using the easily accessible ligand **2a**.[7a] The intramolecular cyclopropanation of **3a** with the in situ prepared asymmetric catalyst of $(CuOTf)_2C_6H_6$ and ligand **2a** afforded **4a** (65% ee, 91% yield; entry 1). We then examined the reactions of **3a** with other ligands **2b**,[7b] **2c**,[7a] **2d**,[7c] and a new ligand **2e**. As shown in Table 1, the enantioselectivity increased to 75% ee (entry 2) in the reaction of **3a** with ligand **2b**, and ligands **2d** and **2e** showed comparable results of 72 and 73% ee, respectively.[8] Interestingly, the reaction with ligand **2c** was slow and resulted in the worst selectivity.

Because **4a** was obtained with better enantioselectivity as compared to **1a**, we were confident that the utility of sulfones is rational as discussed above. Hence, we next examined the reaction of a more bulky sulfone, mesityl sulfone **3b**. The reaction of **3b** with **2a** did not proceed at ambient temperature, but proceeded smoothly at 50 °C to afford **4b** at 83% ee. Although a somewhat reduced enantioselectivity (72% ee) was observed in the reaction with ligand **2b** (Table 1), the enantioselectivities were increased markedly to 90% ee with **2d**, and to 93% ee with **2e**; thus, the combination of the mesityl sulfone and the ligands was found to be crucial. We

Table 1. Intramolecular Cyclopropanations of Sulfones **3a** and **3b**



entry	product	ligand	ee (%)[a,b]	yield (%)[c]	temp (°C)	time (h)
1	**4a**	**2a**	65 (1*R*)	91	rt	2
2	**4a**	**2b**	75 (1*R*)	67	rt	2
3	**4a**	**2c**	32 (1*R*)	61	50	5.5
4	**4a**	**2d**	72 (1*R*)	67	rt	5.5
5	**4a**	**2e**	73 (1*R*)	61	rt	2
6	**4b**	**2a**	83 (1*R*)	93	50	1.5
7	**4b**	**2b**	72 (1*R*)	78	rt, 50[d]	2, 2[d]
8	**4b**	**2c**	31 (1*R*)	48	50, 70[d]	2, 3[d]
9	**4b**	**2d**	90 (1*R*)	89	rt, 50[d]	2, 2[d]
10	**4b**	**2e**	93 (1*R*)	87	rt, 50[d]	2, 2.5[d]

[a] ee determined by HPLC. For HPLC conditions, see Supporting Information. [b] Absolute configuration determined by X-ray crystallographic analysis or the comparison of optical rotation. [c] Isolated yields. [d] Reaction was carried out at the indicated temperatures for the indicated times, respectively.

were gratified by these promising results (Table 1), and therefore we began to investigate the reactions of other mesityl sulfones.

As summarized in Table 2, high enantioselectivities were obtained for all substrates.[8] It should be noted that **2e** was a most effective ligand on all substrates, and the reversal of enantioselection was found in the reactions of **3e** (entry 9−12).

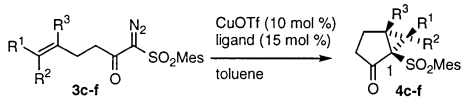
We have also applied this protocol to substrates that will afford tricyclic compounds. That is, the 2, 5-cyclohexadiene derivatives **5a**, **5b**, **7a**, and **7b** were prepared and subjected to this catalytic asymmetric reaction.

The results in Table 3 clearly show that the tricyclic products **6b**, **8a**, and **8b** were constructed with high enantioselectivities (entry 4−7). Reactions of **5a** and **5b**, forming tricyclo[4.3.0.0]nonene derivatives (entry 1−4), showed the same trend in enantioselection as summarized in Tables 1 and 2. That is, the highest ee was again recorded by the combination of mesityl sulfone **5b** with ligand **2e** (entry 4). To form tricyclo[4.4.0.0]decene derivatives with high enantioselectivity, however, use of the less bulky phenyl sulfone **7a** and ligand **2a** was sufficient (entries 5, 7), and ligand **2e** resulted in a low yield (entries 6, 8). These results suggest that the combination of the sulfone and the ligand is important, and therefore this combination should be examined in each case to achieve high enantioselectivity. Interestingly, the reversal of enantioselection was again observed in the reactions of **6a** and **6b** (entries 1−4).

As all of the products in this study were crystalline, the absolute structures have been determined successfully by X-ray crystallographic analysis. Although further investigations are required to deduce the mechanistic details, the outcome of the enantioselective

10.1021/ja029534l CCC: $25.00

Table 2. Intramolecular Cyclopropanation of Mesityl Sulfones **3c−f**



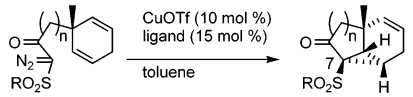
3c: R^1=H, R^2=H, R^3=Me
3d: R^1=H, R^2=H, R^3=Br
3e: R^1=Me, R^2=Me, R^3=H
3f: R^1=H, R^2=H, R^3=CH_2OTr

4c: R^1=H, R^2=H, R^3=Me
4d: R^1=H, R^2=H, R^3=Br
4e: R^1=Me, R^2=Me, R^3=H
4f: R^1=H, R^2=H, R^3=CH_2OTr

entry	product	ligand	ee (%)[a,b]	yield (%)[c]	temp (°C)	time (h)
1	**4c**	**2a**	81 (1*R*)	96	50	1
2	**4c**	**2b**	69 (1*R*)	98	rt, 50[d]	2, 2.5[d]
3	**4c**	**2d**	87 (1*R*)	94	rt, 50[d]	2, 1.5[d]
4	**4c**	**2e**	98 (1*R*)	90	50	2
5	**4d**	**2a**	92 (1*S*)	68	50	1
6	**4d**	**2b**	56 (1*S*)	44	50	1.5
7	**4d**	**2d**	95 (1*S*)	43	50	1.5
8	**4d**	**2e**	98 (1*S*)	63	50	2.5
9	**4e**	**2a**	74 (1*R*)[e,f]	74	50	1.5
10	**4e**	**2b**	71 (1*R*)[e,f]	77	50	0.5
11	**4e**	**2d**	76 (1*R*)[e,f]	54	50	2
12	**4e**	**2e**	92 (1*R*)[e,f]	84	rt	5
13	**4f**	**2a**	78 (1*R*)	91	rt, 50, 70[d]	1.5, 12, 10[d]
14	**4f**	**2b**	73 (1*R*)	96	50, 70[d]	10, 20[d]
15	**4f**	**2d**	84 (1*R*)	75	rt, 50, 70[d]	3.5, 13, 5[d]
16	**4f**	**2e**	91 (1*R*)	98	rt, 50, 70[d]	3.5, 13, 7[d]

[a−d] See the footnotes to Table 1. [e] The absolute structure is the opposite of the depicted structure above. [f] CuOTf (20 mol %) and ligand (30 mol %) were used because the reaction was sluggish.

Table 3. Enantioselective Formation of the Tricyclic Compounds



5a: n=1, R=Ph; **5b**: n=1, R=Mes
7a: n=2, R=Ph; **7b**: n=2, R=Mes

6a: n=1, R=Ph; **6b**: n=1, R=Mes
8a: n=2, R=Ph; **8b**: n=2, R=Mes

entry	product	ligand	ee (%)[a,b]	yield (%)[c]	temp (°C)	time (h)
1	**6a**	**2a**	33 (7*S*)[e]	quant.	rt	0.5
2	**6a**	**2e**	66 (7*S*)[e]	81	rt	5
3	**6b**	**2a**	79 (7*S*)[e]	76	rt, 50[d]	2, 20[d]
4	**6b**	**2e**	93 (7*S*)[e]	61	rt, 50[d]	1, 27[d]
5	**8a**	**2a**	92 (7*R*)	78	rt	3.5
6	**8a**	**2e**	90 (7*R*)	37	rt, 50[d]	1, 2[d]
7	**8b**	**2a**	97 (7*R*)	69	rt	27
8	**8b**	**2e**	87 (7*R*)	7	rt, 50[d]	1, 29[d]

[a−e] See the footnotes to Table 1.

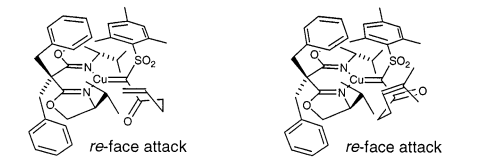


Figure 1. Proposed models A and B.

reactions would be well explained by the proposed models A and B (Figure 1).[9]

The cyclopropanation reactions are thought to occur preferentially at the *re*-face (defined by the Cu═C−C arrangement) of the chiral catalyst-carbene complexes, because steric hindrance will be encountered during cyclopropanation reactions at the *si*-face. That is, if the olefin approaches from the *si*-face, the resultant pyramidal conformation of the carbene C atom in the transition state[9] means that the aryl sulfonyl group will interact unfavorably with the isopropyl group and also with the benzyl group of the ligand, with steric repulsion. As a result, the *si*-face will be sterically hindered during the cyclopropanation reactions. By contrast, the reaction at the *re*-face would be preferred because the unfavorable interactions with the aryl sulfonyl group would be negligible in the transition states arising from models A and B. Thus, the aryl sulfonyl group has a crucial role in the enantioselection. The high enantioselectivities obtained for the mesityl sulfones are also well explained by the increased unfavorable interactions with the mesityl group.

The reversal of enantioselection for **3e**, **5a**, and **5b** would be rationalized by model B because the steric strain with the substrates would disfavor model A. The depicted orientation of the alkene with respect to the *re*-face of the complex well explains the (1*R*, 5*R*) configuration for **4e**, and the (1*S*, 5*R*, 6*R*, 7*S*) configuration for **6a** and **6b**.

For **7a** and **7b**, model A would operate. As the steric strain with the substrate is so large in this case, the use of a less bulky phenyl sulfone might be sufficient for high enantioselectivity.

In summary, highly enantioselective asymmetric catalysis on the intramolecular cyclopropanation of α-diazo-*β*-keto sulfones has been developed. The products possess great potential for natural product synthesis because (1) a variety of chemistries of cyclopropane, ketone, and sulfone are available, and (2) the products are highly crystalline, facilitating the production of enantiomerically pure synthetic intermediates.

Acknowledgment. We thank Messrs Kenji Namoto and Koichi Yonezawa for early experiments, and Dr. M. Shiro of Rigaku for assistance with X-ray crystallography. This work was financially supported in part by 21COE "Practical Nano-Chemistry".

Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). An X-ray crystallographic file is available in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The same reaction condition of entry 1 in Table 1 was used. See Supporting Information for the details.
(6) The highest ee observed for **4a** was ca. 12% ee: Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361−362.
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(8) Solvents other than toluene afforded diminished enantioselectivities.
(9) Models A and B are depicted on the basis of Pfaltz's model[10] and the recent theoretical analysis.[11]
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JA029534L