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ENANTIOSELECTIVELY CATALYZED INTRAMOLECULAR CYCLOPROPANATIONS OF UNSATURATED DIAZO CARBONYL COMPOUNDS

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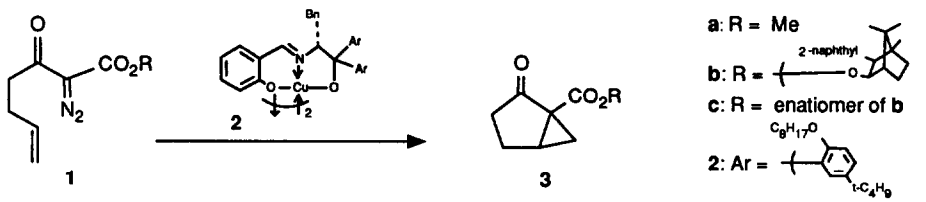
Abstract: *A series of unsaturated α-diazo carbonyl compounds underwent enantioselective intramolecular cyclopropanation (ee = 4-77%) when treated with an enantiomerically pure chiral copper catalyst. The nature of the diazo substrate was critical: α-diazo ketones gave the best enantioselectivities whereas α-diazo β-keto ester systems showed diminished enantioselectivities.*

The ubiquitous occurrence of cyclopentanoid rings in natural products[1] creates an ongoing need for better enantioselective syntheses of substituted cyclopentane ring systems. During the course of studies directed towards the synthesis of diterpene natural products, there was a need for a variety of optically active cyclopentane subunits with the general structures shown in Scheme I. Although a variety of

Scheme I

bicyclo[3.1.0]hexane compounds have previously been prepared in optically active form by resolution of racemic precursors[2] and by the application of a diastereoselective Simmons-Smith reaction,[3] a method for the direct synthesis of enantiomerically pure cyclopentane units would be of high utility. There are very few examples of intramolecular carbene-olefin cyclopropanations in the presence of chiral catalysts[4] and in only one case was a significant ee reported.[4a] Towards this end intramolecular cyclopropanation has been studied using an enantiomerically pure chiral copper catalyst which is known to produce high levels of optical activity in intermolecular olefin cyclopropanations with α-diazoacetates.[5] The generality and efficiency of this catalyst system in intramolecular systems has been investigated by examining the effects of carbonyl positioning about the carbene center in a variety of unsaturated α-diazo carbonyl compounds.

The present study was initiated by examining the reaction of **1a**[6] in the presence of the chiral copper catalyst **2** (absolute configuration is as shown).[5] Although the chemical yield of **3a**[6c] was 75%, very little chiral



induction was observed (Table I, entry 1). Attempts to induce double diastereoselection by using each antipode of a chiral auxiliary [7] (**1b, 1c**) with the R configuration of **2** gave very modest results as well (Table I, entries 3 and 6).[8] The use of DIBAH to activate the catalyst did not work well with this system.[9] Similar low enantioselectivities were observed when unsaturated α-diazo β-keto carbonyl and α-diazo β-keto sulfone compounds were treated with chiral cobalt[10] or chiral rhodium[4e] catalysts. Only one example of an

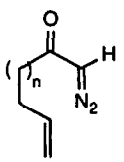
enantioselectively catalyzed intermolecular olefin cyclopropanation involving an α-diazo β-diketone system has been reported (ee = >90 %) using a 3-trifluoroacetylcamphor derived copper catalyst.[11] In the present study this catalyst provided a high chemical yield of **3a** as a racemic mixture (Table 1, entry 2).

Table I: β-Keto ester cyclopropanations.

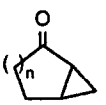
	diazo compound	product	yield(%)	ee(%)	reaction conditions
1	**1a**	**3a**	75	10[a]	15 mol% **2**, refluxing benzene, 24 h
2	**1a**	**3a**	89	0[a]	15 mol% camphor cat.,[b] refluxing benzene, 24 h
3	**1b**	**3b**	90	13[c]	10 mol% **2**, refluxing toluene, 2 h
4	**1c**	**3c**	95	0[c]	10 mol% $Cu(AcAc)_2$, refluxing toluene
5	**1c**	**3c**	98	4[c]	10 mol% $Cu(TBS)_2$, refluxing toluene, 30 min[d]
6	**1c**	**3c**	95	9[c]	10 mol% **2**, refluxing toluene, 2 h

[a]ee based on de determined by ^1H NMR of (-)-menthol esters, ref. 2a. [b]Ref. 11. [c]ee based on de determined by ^1H NMR. [d]Ref. 8.

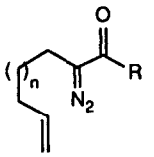
Diazo ketones **4**[12] and **5**[13] were obtained from the corresponding acid chlorides[14] by treatment with excess diazomethane.[15] Although β-keto esters undergo facile diazo transfer,[6b] direct diazo transfer to the corresponding ester enolates of **6** and **7** with mesyl azide did not work. However, initial formylation[6d] of the esters (LDA, EtO_2CH, -78 °C, THF) followed by treatment with mesyl azide gave reasonable yields (50-70%) of



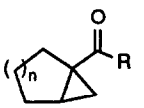
4: n=1
5: n=2



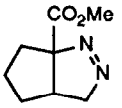
10: n=1
11: n=2



6: n=1, R=OMe
7: n=2, R=OMe
8: n=2, R=H



12: n=1, R=OMe
13: n=2, R=OMe
14: n=2, R=Me



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6[16] and **7**.[16] Diazo ester **6** was thermally unstable (half-life of 1 h at 25 °C), giving the [2+3] pyrazoline cycloadduct **9**.[4d,17] Diazo aldehyde **8** was unstable and could only be prepared in low yield from the corresponding β-aminoacrolein intermediate.[18]

Table II: Mono-carbonyl cyclopropanations.

	diazo cmpd	product	yield(%)	$[\alpha]_D^{25}$ (c, $CHCl_3$)	ee(%)	reaction conditions
1	**4**	**10** (1R,5S)	54	+11.8 ° (4.4)	77[a]	3 mol% **2**, 0.75 mol% DIBAH, benzene, RT, 1 h
2	**4**	**10** (1R,5S)	40	+6.7 ° (0.76)	44[a]	3 mol% **2**, refluxing benzene, 1.5 h
3	**5**	**11** (1S,6R)	63	-4.6 ° (4.9)	29[b]	3 mol% **2**, 0.75 mol% DIBAH, benzene, 5 °C, 2h
4	**5**	**11** (1S,6R)	38	-5.3 ° (2.3)	34[b]	3 mol% **2**, 0.75 mol% DIBAH, CH_2Cl_2, -10 °C
5	**5**	**11** (1S,6R)	72	-3.4 ° (4.0)	22[b]	3 mol% **2**, 0.75 mol% DIBAH, benzene, RT, 1 h
6	**5**	**11** (1S,6R)	55	-0.4 ° (2.3)	2[b]	5 mol% camphor cat.,[c] CH_2Cl_2, 1 h
7	**6**	**12**	26		0[d]	25 mol% **2**, 7.5 mol% DIBAH, benzene, RT, 12 h
8	**7**	**13**	47	-17.5 ° (1.9)	25[e]	25 mol% **2**, 1.25 mol% DIBAH, benzene, RT, 3 h

[a]Personal communication, Mash, E.A., 1989. [b]Rotations compared with that of an optically pure sample, see Mash, E.A.; Nelson, K.A. Tetrahedron 1987, 43, 679-92. [c]See ref. 11. [d]ee based on $Eu(Tfc)_3$ ^1H NMR. [e]ee determined by optical rotation of known analog **14**, see text.

The cyclopropanation reactions of **4-8** (Table II) were carried out in benzene at room temperature in the presence of 0.015-0.125 equivalents of **2** which had been activated[5,9] with 0.007-0.03 equivalents (based on amount of diazo compound) of DIBAH prior to addition of the diazo species (see Table II). A variety of solvents were examined (THF, CH_2Cl_2, pentane, CH_3NO_2, benzene, toluene) and benzene gave the best overall results. Lowering the reaction temperature gave a slight improvement in enantioselectivity accompanied by a slight decrease in yield (entries 3-5, Table II). The best optical induction observed (ee = 77%) was in the cyclopropanation of **4**. It is interesting to note that use of a chiral semicorrinato cobalt catalyst gave better

enantioselectivity for the [4.1.0] product **11** (ee = 80%), as compared to the [3.1.0] product **10** (ee = 60%).[4a]

Due to the poisoning of catalyst **2** by pyrazoline **9**,[19] the cyclopropanation of **6** required more catalyst and **12**[20] could only be obtained in low yield as a racemic mixture (Table II, entry 7). Diazo ester **7** underwent cyclopropanation to give a moderate yield of **13**.[21] Nucleophilic ester cleavage of **13** (LiI/NaCN in DMF at 120-130 °C) followed by MeLi addition gave the known methyl ketone **14** (ee = 25%).[3b] Diazo aldehyde **8** gave a complex mixture of products which contained only traces of cyclopropanated material upon treatment with activated **2** in benzene at 25 °C.

The mechanistic details of copper catalyzed cyclopropanation are not yet fully understood.[4d,20,22] An empirical method for predicting the absolute stereochemistry of **2** catalyzed intermolecular cyclopropanation products has been developed which is based on a proposed metallacyclobutane intermediate.[5] Direct application of this method to the intramolecular cyclopropanation of **4** predicts the opposite major enantiomer from that observed experimentally, whereas with **5**, this method correctly predicts the observed major enantiomer. Due to geometric constraints, only *cis*-cyclopropane products are formed in the intramolecular examples described above. In the intermolecular examples using catalyst **2**, the *cis*-cyclopropanes generally gave lower enantioselectivities than the corresponding *trans*-isomers. The factors responsible for diminishing the enantioselectivity of the intermolecular *cis*-products may also be operating in the intramolecular reactions. An alternative mechanistic possibility proposed by Doyle[22] is difficult to apply to the intramolecular examples due to ambiguities in the steric and electronic nature of the interactions between **2** and the diazo carbonyl substrates.

This is the first reported study in which the chirally catalyzed cyclopropanations of a variety of α-diazo carbonyl compounds have been compared. The chiral catalyst employed was not found to be generally effective in intramolecular systems. Although unsaturated α-diazo ketones show moderate to good enantioselectivity, α-diazo β-keto esters show very little selectivity. The interactions responsible for the diminished selectivity in these intramolecular systems appears to involve both steric and electronic factors. Diazo ketone **5** and diazo ester **7** are electronically similar and sterically quite distinct, yet **11** and **13** are obtained with comparable enantiomeric excesses. Comparison of **4** and **6** is difficult due to the formation of **9**. The carbene generated from a α-diazo β-keto ester is more stable[23] and should interact less strongly with a metal catalyst. Both **1** and **8** are sterically similar, but **13** is obtained with an ee of 25% while **3** is obtained with an ee of only 10-13%. In addition, α-diazo β-keto ester **1** has been shown to display little or no enantioselectivity with any of the currently known chiral cyclopropanation catalysts. Based on the current findings, the substrate-catalyst relationship of **2** appears to be highly specific and extrapolation of the results of existing methods of enantioselectively catalyzed cyclopropanations to new systems should be made with due caution.

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12) Diazoketone **4**: Christensen, B.G.; Cama, L.D.; Guthikonda, R.N. *J. Am. Chem. Soc.* **1974**, *96*, 7584-5.

13) Diazoketone **5**: IR (neat film) 2100, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.75 (m, 1 H), 5.2 (s br, 1 H), 4.9 (m, 2 H), 2.31 (s br, 2 H), 2.1 (q, *J*=7 Hz, 2 H), 1.7 (m 5 peaks, *J*=7 Hz, 2 H).

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20) **12**: IR 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.65 (s, 3 H), 2.1 (ddd, *J*=8.3, 11.7, 11.7 Hz, 1 H), 1.85 (dd, *J*=8, 12.8 Hz, 1 H), 1.6-1.8 (m, 4 H), 1.3 (dd, *J*=4.5, 8.1 Hz, 1 H), 1.2-1.3 (m, 1 H), 0.82 (dd, *J*=4.8, 4.8 Hz, 1 H) ppm ; ^{13}C NMR (100.6 MHz) δ 175.47, 51.48, 31.66, 29.45, 27.17, 26.65, 20.94, 15.9 ppm.

21) **13**: IR 1725 cm^{-1}; ^1H NMR ($CDCl_3$,500 MHz) δ 3.6 (s, 3 H), 2.46 (m, 1 H), 1.86 (m, 1 H), 1.6 (m, 3 H), 1.3 (dd, *J*=3.9, 9.7 Hz, 1 H), 1.2 (m, 4 H), 0.6 (dd, *J*=3.9, 6.8 Hz, 1 H) ppm; ^{13}C NMR (125 MHz) δ 176.58, 51.65, 24.09, 23.0, 22.06, 21.64, 20.98, 20.63, 20.23 ppm.

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