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Cyclopropanation versus carbon–hydrogen insertion. The influences of substrate and catalyst on selectivity

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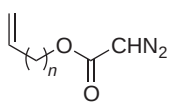
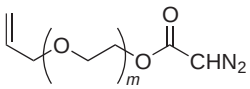
Abstract—Reactions of diazoacetates with varying linkages from the diazo-carbon to a vinyl group, catalyzed by chiral copper(I) and rhodium(II) compounds, were examined for selectivity in their intramolecular reactions. Bis-oxazoline-ligated copper(I) has advantages for cyclopropanation that form medium-to-large rings. Dirhodium(II) carboxamidates have advantages for small-ring-fused cyclopropane compounds and for carbon–hydrogen insertion. © 2001 Elsevier Science Ltd. All rights reserved.

Methods to achieve high selectivity in catalytic metal carbene transformations are being developed, and their underlying principles are being revealed.[1–5] Only a few years ago there was a paucity of examples for effective catalytic intramolecular cyclopropanation that could provide ring sizes beyond six.[6,7] Competition with intramolecular C–H insertion limited applications to either cyclopropanation or insertion that were synthetically useful.[8,9] Furthermore, the overlay of stereoselectivity on this competition in chemoselection has presented a challenge of considerable magnitude. We wish to report results that identify those factors responsible for these forms of selectivity and the catalysts that are most effective for each transformation.

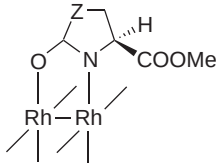
Diazoacetates **1**–**7** were subjected to diazo decomposition with catalysts **8**–**13** for the purpose of examining trends in enantioselectivity and to determine the extent of competition between cyclopropanation and



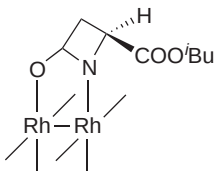
1 : $n = 1$
2 : $n = 2$
3 : $n = 3$
4 : $n = 4$
5 : $n = 8$



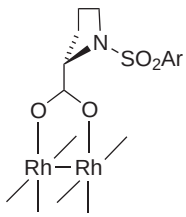
6 : $m = 1$
7 : $m = 2$



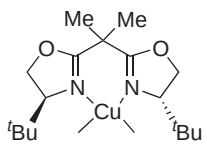
8 : Z = CH_2, Rh_2(5*S*-MEPY)$_4$
9 : Z = O, Rh_2(4*S*-MEOX)$_4$
10: Z = $COCH_2CH_2Ph$, Rh_2(4*S*-MPPIM)$_4$



11: Rh_2(4*S*-IBAZ)$_4$



12: Ar = R-^{t}BuC$_6$H$_4$, Rh_2(5*S*-TBPRO)$_4$



13: Cu(box)PF_6

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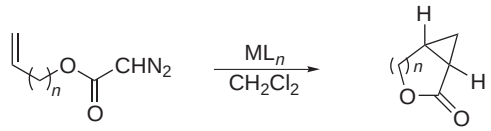
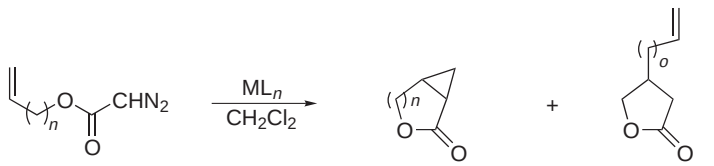
C–H insertion. With **1** and **2** the only product formed in characterizable amounts with the use of any of the catalysts was intramolecular cyclopropanation (Eq. (1)).[10,11] Beginning with **3** and extending through **5**, insertion became competitive with cyclopropanation (Eq. (2)), and this competition also occurred with **6** and **7** (Eq. (3)). Product yields were in the range 50–95% with all diazo compounds and catalysts, except **3** and **4**; with these latter diazoacetate esters, dimer formation and O–H insertion were in competition, sometimes resulting in yields for cyclopropanation plus C–H insertion products that were less than 50%. Lower yields in these cases are understandable in light of the presumed higher energy for cyclopropanation.

Table 1 reports % ee values for cyclopropane products as a function of catalyst and ring size. For **18** and **23** diastereomeric *cis* and *trans* cyclopropane products were formed, and their % ee values are given. Note that % ee values decrease with increasing ring size for dirhodium(II) carboxamidate catalysts **8**–**11** but increase with increasing ring size for the chiral bis-oxazoline ligated copper(I) catalyst **13**; a plot of % ee versus ring size for catalysts **8** and **13** (Fig. 1) shows this effect clearly, and a mechanistic rationale for this divergence has been presented.[12,13] The results obtained with $Rh_2(TBPRO)_4$ show that, as previously reported by Davies,[14] this catalyst does not exhibit high selectivity with diazoacetates.



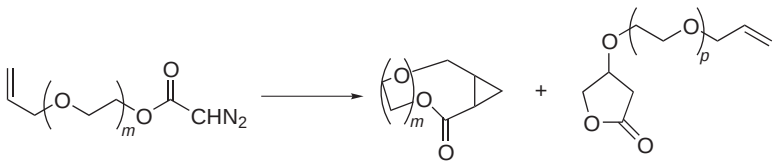
1 : $n = 1$ **14** : $n = 1$
2 : $n = 2$ **15** : $n = 2$

(1)



3 : $n = 3$ **16** : $n = 3$ **19** : $o = 1$
4 : $n = 4$ **17** : $n = 4$ **20** : $o = 2$
5 : $n = 8$ **18** : $n = 8$ **21** : $o = 6$

(2)



6 : $m = 1$ **22** : $m = 1$ **24** : $p = 0$
7 : $m = 2$ **23** : $m = 2$ **25** : $p = 1$

(3)

Table 1. Enantioselectivities as a function of catalyst and ring size[a]

Catalyst	% ee[b,c]								
	14(5)[10]	**15**(6)	**16**(7)	**17**(8)	**22**(8)[12]	**23*Z***(11)[12]	**23*E***(11)[12]	**18*Z***(12)	**18*E***(12)
Rh_2(5*S*-MEPY)$_4$ (**8**)	95	82	52	66	n.a.	53	65	46	42
Rh_2(4*S*-MEOX)$_4$ (**9**)	94	83	47	52	n.a.	48	67	37	30
Rh_2(4*S*-MPPIM)$_4$ (**10**)	87[13]	76	26	40	n.d.	n.d.	n.d.	24	23
Rh_2(4*S*-IBAZ)$_4$ (**11**)	80	72	47	44	49	56	64	70	71
Rh_2(5*S*-TBPRO)$_4$ (**12**)	n.d.	4	8	24	28	11	12	4	4
Cu(box)PF$_6$ (**13**)	20	42	52	76	71	79	85	81	83

[a] Reactions performed in refluxing dichloromethane with 1.0 mol% of catalyst with 1.0 mmol of diazo ester.
[b] The ring size is given in parenthesis. Enantiomeric excesses were obtained by GC on chiral Chiraldex columns.
[c] n.a., not available; n.d., not determined.

Table 2. Chemoselectivity and diastereoselectivity in catalytic reactions of **3**–**7**[a]

Catalyst	Chemoselectivity					Diastereoselectivity	
	16:**19**	**17**:**20**	**22**:**24**[12]	**23**:**25**[12]	**18**:**21**	**23** (*Z*:*E*)[12]	**18** (*Z*:*E*)
$Rh_2(OAc)_4$	>99:<1	84:16	82:18	96:4	68:32	87:13	69:31
$Rh_2(5S\text{-MEPY})_4$ (**8**)	42:58	14:86	<1:>99	5:95	4:96	88:12	75:25
$Rh_2(4S\text{-MEOX})_4$ (**9**)	19:81	9:91	<1:>99	1:99	1:99	88:12	76:24
$Rh_2(4S\text{-MPPIM})_4$ (**10**)	47:53	13:87	n.d.	n.d.	2:98	n.d.	77:28
$Rh_2(4S\text{-IBAZ})_4$ (**11**)	92:8	50:50	5:95	42:58	18:82	88:12	67:33
$Rh_2(5S\text{-TBPRO})_4$ (**12**)	>99:<1	82:18	95:5	98:2	79:21	87:13	71:29
Cu(box)PF_6 (**13**)	>99:<1	>99:<1	[b]	100:0	86:14	86:14	59:41

[a] Ratios were obtained by GC (SBP-5 column).
[b] The major product was that from intramolecular oxonium ylide formation followed by [2,3]-sigmatropic rearrangement.

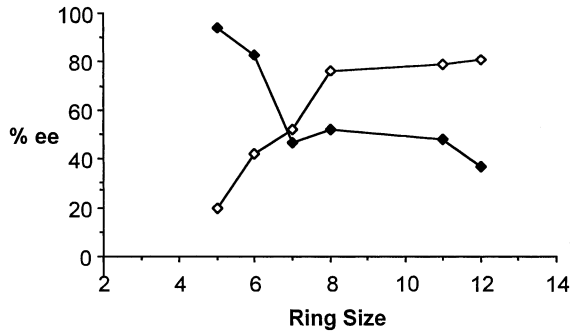


Figure 1. % Ee as a function of ring size for Cu(box)PF_6 (◇) and $Rh_2(4S\text{-MEOX})_4$ (◆).

Table 2 provides complementary information to the enantioselectivity data of Table 1: chemoselectivity (cyclopropanation versus C–H insertion) and diastereoselectivity for cyclopropanation of **5** and **7**. There is an obvious preference for C–H insertion exhibited by chiral dirhodium(II) carboxylates **8**–**11** relative to dirhodium(II) carboxamidates, and Cu(box)PF_6 (**13**) shows virtually no tendency to undergo C–H insertion. Insertion at a C–H bond adjacent to oxygen is preferred in this series of diazo ester decompositions (compare **22**:**24** with **17**:**20**), and this is consistent with prior observations,[15] but the influence is greater with **8**–**11** than with $Rh_2(OAc)_4$ or **12**. Diastereoselectivity is relatively invariant with the catalyst employed.

Table 3 provides % ee values for the products of C–H insertion. Here dirhodium(II) carboxamidates **8**–**10** are clearly superior to all others. Since they also show high preference for C–H insertion over cyclopropanation reactions that form medium-to-large rings, they are the catalysts of choice. In fact, $Rh_2(4S\text{-MPPIM})_4$ has been shown in earlier studies to be superior to all others examined by achieving the highest level of enantiocontrol.[16] Enantiomers of **21** could not be resolved by chromatographic methods.

Table 3. Enantioselectivity for products from C–H insertion

Catalyst	% ee			
	19	**20**	**24**[12]	**25**[12]
$Rh_2(5S\text{-MEPY})_4$ (**8**)	93	95	91	92
$Rh_2(4S\text{-MEOX})_4$ (**9**)	98	97	96	92
$Rh_2(4S\text{-MPPIM})_4$ (**10**)	98	>97	–	–
$Rh_2(4S\text{-IBAZ})_4$ (**11**)	–	50	91	90
$Rh_2(5S\text{-TBPRO})_4$ (**12**)	–	10	19	14
Cu(box)PF_6 (**13**)	–	74	27	–

The data now available portray unique advantages for chiral dirhodium(II) carboxamidates and for Cu(box)PF_6 that are complementary. Efforts to examine the relative advantages of some of the newer catalysts[17–19] should now be undertaken.

Acknowledgements

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