Comparative evaluation of enantiocontrol for intramolecular cyclopropanation of diazoacetates with chiral Cu^{I}, Rh^{II} and Ru^{II} catalysts

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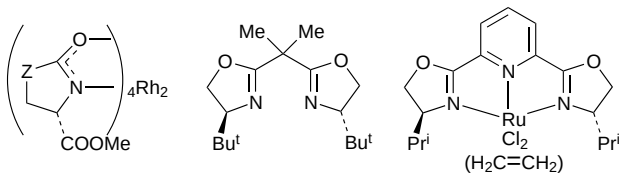
Enantioselectivity for intramolecular cyclopropanation of allylic diazoacetates shows complementarity in comparisons of chiral Cu^{I}, Rh^{II} and Ru^{II} catalysts.

A broad selection of chiral catalysts for enantioselective cyclopropanation with diazoacetates has been described.[1] The vast majority fall into two structural classes: (i) those, including the appropriately substituted semicorrin[2] and bis-oxazoline[3] complexes of copper(i) and (pybox)$RuCl_2$(ethene),[4] whose chiral ligands are C_2-symmetric and (ii) chiral dirhodium(ii) carboxamidates whose ligand arrange- ment in these octahedral complexes places two distinguishing ester attachments *cis* to each other.[5] The success of chiral dirhodium(ii) carboxamidates, especially dirhodium(ii) tetrakis[methyl 2-oxopyrrolidine-5(*R* or *S*)-carboxylates], Rh_2(5*R*-MEPY)$_4$ and Rh_2(5*S*-MEPY)$_4$ **1a**,[6] for highly enantio-selective intramolecular cyclopropanation of allylic diazoacetates has been described but, surprisingly, these same synthetically useful transformations have not been examined using copper(i) with C_2-symmetric ligands nor comprehensively with chiral (pybox)RuCl_2(ethene). We now present our preliminary results which demonstrate complementarity in enantiocontrol between these diverse catalysts.

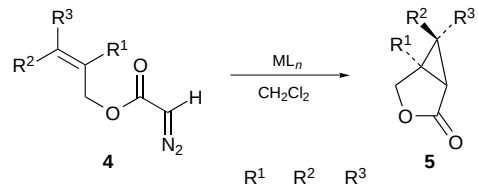
Treatment of a selection of allylic diazoacetates (Scheme 1) with 1.0 mol% Cu(OTf)/**2**[7] in CH_2Cl_2 resulted in the expected cyclopropanation products **5** in moderate to relatively low isolated yields and with often variable enantiomeric excesses (ee). Dramatic improvements in isolated yields without a corresponding change in enantioselectivity were achieved with the use of Cu(MeCN)$_4$PF$_6$/**2** (Table 1). The air stability and handling ease of Cu(MeCN)$_4$PF$_6$[8] render this copper(i) reagent superior to the universally employed[9] Cu(OTf) for catalytic cyclopropanation reactions. Comparative yields and enantiomeric excesses for Rh_2(5*S*-MEPY)$_4$ catalysed reactions (0.1–1.0 mol% **1a**)[5] and for **3** (3–5 mol%) are also given in Table 1. Surprisingly, the absolute configurations of cyclopropane products **5c** and **5d** from catalysis by CuPF$_6$/**2** are opposite to those formed with **3**.

Enantioselectivity in copper(i)/**2** catalysed reactions is higher with allylic diazoacetates that have 2-alkyl (**4e,f**)[10] substituents, and these are the substituents that give the lowest enantioselectivities in Rh_2(5*S*-MEPY)$_4$-catalysed reactions. With the (pybox)$RuCl_2$(ethene) catalyst **3**, these diazo substrates did not undergo intramolecular cyclopropanation under a variety of reaction conditions; carbene dimers were the only isolated products. However, use of Rh_2(4*S*-MPPIM)$_4$ **1b** instead of Rh_2(5*S*-MEPY)$_4$ causes an enormous enhancement in enantiocontrol for **5e** and **5f** as well as for intramolecular cyclopropanation of *trans*-2-hexen-1-yl diazoacetate (**4c**).[11] The preference for higher enantiocontrol with *trans*- disubstituted alkenes **4c** for **3** relative to *cis*-disubstituted systems **4d** with **1a** contrasts with the low % ee values observed for catalysis by CuPF$_6$/**2** of



1a Z = CH_2
b Z = $NCOCH_2CH_2Ph$

2 **3**



4 **5**

	R^1	R^2	R^3
a	H	H	H
b	H	Me	Me
c	H	H	Pr
d	H	Pr	H
e	Me	H	H
f	Bu	H	H

Scheme 1

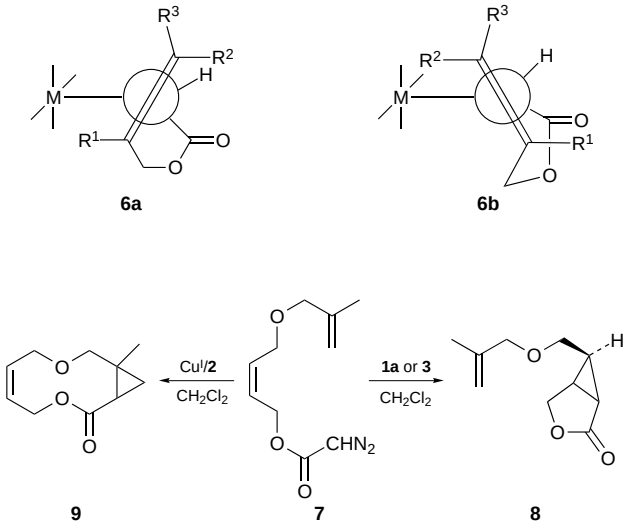
Table 1 Comparative yields and enantioselectivities of Cu^{I}, Rh^{II} and Ru^{II} catalysed intramolecular cyclopropanation reactions of **4a–f**

Cyclo-propane **5**	Cu(MeCN)$_4$PF$_6$/**2**		Rh_2(5*S*-MEPY)$_4$ **1a**		Rh_2(4*S*-MPPIM)$_4$ **1b**		(pybox)$RuCl_2$(ethene) **3**	
	Yield (%)	ee (%)[a]	Yield (%)	ee (%)[a]	Yield (%)	ee (%)[a]	Yield (%)	ee (%)[a]
a	61	20 (1*R*,5*S*)	75	95 (1*R*,5*S*)	—	—	—	—
b	80	13 (1*R*,5*S*)	89	95 (1*S*,5*R*)	—	—	91	76 (1*R*,5*S*)
c	74	29 (1*S*,5*R*)	93	95 (1*R*,5*S*)	83	95 (1*R*,5*S*)	68	78 (1*R*,5*S*)
d	82	37 (1*S*,5*S*)	88	94 (1*R*,5*S*)	—	—	54	21 (1*R*,5*S*)
e[b]	58	87 (1*S*,5*R*)	72	7 (1*R*,5*S*)	75	89 (1*S*,5*R*)	0	—
f[c]	73	82 (1*S*,5*R*)	72	35 (1*S*,5*R*)	82	93 (1*S*,5*R*)	0	—

[a] Configurational assignment in parentheses (ref. 5). [b] Absolute configuration determined from the X-ray structure of 1-(1-naphthyl)-ethylamide derivative (L. E. Overman, private communication). [c] Configuration assigned by analogy with **5e** and order of elution on a 30 m Chiraldex G-TA column.

either **4c** or **4d**. Thus each of these catalytic systems has unique capabilities for enantio- selection, independent of whether their ligands are C_2-symmetric (**2** and **3**) or if they have a *cis*-array of chiral attachments (**1**). However, as is evident from these data, chiral dirhodium(ii) carboxamidates are the catalysts of choice for these intramolecular cyclopropanation reactions.

The selectivities for allylic cyclopropanation observed with catalysts **1**–**3** are consistent with the alkene approach trajectories that are depicted by the Newman projections of **6a,b**. In these representations the ligated metal (M) orients the carbon–carbon double bond to a frontside approach to the carbene centre; the backside approach produces the enantiomeric forms. For **6a**, which models selectivity with $Rh_2(MEPY)_4$ catalysts, interaction of R^1 with the catalyst face is most pronounced and, appropriate to the high enantiocontrol observed with *cis*-disubstituted allylic diazoacetates, R^2 is oriented away from the catalyst (**6b**). High enantiocontrol observed in cyclopropanation reactions of allylic diazoacetates having R^3 or R^1 groups (*e.g.* with Cu^I/**2** or **3**) is consistent with **6b**. However, the absence of cyclopropane products from **4e,f** with **3** suggests that conformation **6a** is required for these substrates, whereas **6b** is operative for **4b–d**. That catalysis by **3** and $CuPF_6$/**2** forms **5c** and **5d** which have opposite configura- tions demands a more subtle explanation than has heretofore been accorded these reactions.



Scheme 2

Another comparative measure of selectivity in intramolecular cyclopropanation reactions is regioselection, particularly with **7** which is designed to undergo either γ-lactone formation or macrocyclization (Scheme 2). With $CuPF_6$/**2** macrocycle formation was the predominant intramolecular process (**9**: 87% ee, 43% yield; **8**: 41% ee, 19% yield),[12] whereas only **8** was produced by catalysis with either **1a** (96% ee, 84% yield) or **3** (17% ee, 45% yield). The formation of **8** catalysed by **1a**, $CuPF_6$/**2** and **3** occurred with % ee values and enantiomer configurations that are similar to and predictable from results for **5d** in Table 1.

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References

1 M. P. Doyle, in *Comprehensive Organometallic Chemistry II*, ed. L. S. Hegedus, Pergamon Press, New York, 1995, vol. 12, ch. 5; M. P. Doyle, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH Publishers, New York, 1993, ch. 3.
2 A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 39.
3 R. E. Lowenthal and S. Masamune, *Tetrahedron Lett.*, 1991, **32**, 7373; D. A. Evans, K. A. Woerpel and M. J. Scott, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 430; D. Müller, G. Umbricht, D. Weber and A. Pfaltz, *Helv. Chim. Acta*, 1991, **74**, 232.
4 H. Nishiyama, Y. Itoh, Y. Sugaware, H. Matsumoto, K. Aoki and K. Itoh, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1247; S.-B. Park, K. Murata, H. Matsumoto and H. Nishiyama, *Tetrahedron: Asymmetry*, 1995, **6**, 2487.
5 M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q.-L. Zhou and S. F. Martin, *J. Am. Chem. Soc.*, 1995, **117**, 5763.
6 M. P. Doyle, W. R. Winchester, J. A. A. Hoorn, V. Lynch, S. H. Simonsen and R. Ghosh, *J. Am. Chem. Soc.*, 1993, **115**, 9968.
7 D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726.
8 G. J. Kubas, *Inorg. Synth.*, 1979, **19**, 90.
9 T. G. Grant, M. C. Noe and E. J. Corey, *Tetrahedron Lett.*, 1995, **36**, 8745.
10 L. E. Overman was the first to report that high enantiocontrol was achieved in Cu(OTf)/**2** catalysed reactions of **4e**: 209th National Meeting of the American Chemical Society, Anaheim, California, April 2–6, 1995; ORGN-172.
11 M. P. Doyle, Q.-L. Zhou, A. B. Dyatkin and D. A. Ruppar, *Tetrahedron Lett.*, 1995, **36**, 7579.
12 M. P. Doyle, C. S. Peterson and D. L. Parker, Jr., *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1334.

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