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Co(II)–salen-catalyzed asymmetric intramolecular cyclopropanation

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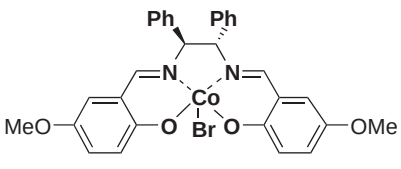
Abstract—Optically active Co(II)–salen complexes (**5** and **7**) were found to catalyze highly enantioselective intramolecular cyclopropanation of 2-alkenyl α-diazoacetates in the presence of *N*-methylimidazole under high substrate concentration.

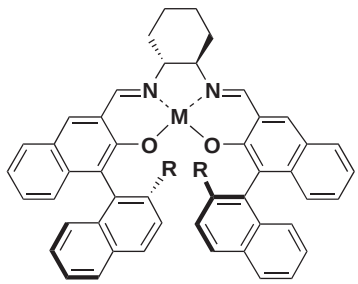
Intramolecular cyclopropanation is a useful methodology for the construction of [*n*,1,0]bicyclic structures that appear in various natural products as their subunits, and much effort has been directed to its asymmetrization.[1] Thus far, Cu[bis(oxazoline)s],[2] Cu(azasemicorrin),[2a] Cu(diamine),[3] Ru(Pybox),[4] Rh(MEPY) and its related complexes,[5] Rh_2(*S*-DOSP)$_2$,[6] have been successfully applied to asymmetric intramolecular cyclopropanation and high enantioselectivities have been achieved.[1] However, enantioselectivities obtained are dependent on the substrates used to a considerable extent,[7] and development of a new catalyst for asymmetric cyclopropanation has been strongly desired.

We have demonstrated that (salen)cobalt and (salen)ruthenium complexes (**1**, **3**, and **2**) serve as catalysts for intermolecular cyclopropanation and that both high *trans*-[8] and *cis*-selectivities[9] together with excellent enantioselectivity can be obtained by choosing a suitable metal center and appropriate tuning of the salen ligand. Furthermore, we recently found that complex **2** and its modified complexes **4** and **6** served as catalysts for intramolecular cyclopropanation of *trans*-cinnamyl α-diazoacetates under photo-irradiated conditions and good enantioselectivities were obtained with **4** and **6** as catalysts.[10] We also examined (salen)cobalt complex **3** as the catalyst under the same conditions (substrate concentration = 0.01 M, THF solution) without photoirradiation, but the desired reaction was not observed (Scheme 1).

However, we found that complex **3** also promoted intramolecular cyclopropanation of *trans*-cinnamyl α-diazoacetates at much higher substrate concentration



1



2: M= Ru(NO)Cl, R= Ph
3: M= Co, R= Ph
4: M= Ru(NO)Cl, R= Me
5: M= Co, R= Me
6: M= Ru(NO)Cl, R= H
7: M= Co, R= H

Keywords: chiral (salen)cobalt(II) complex; asymmetric intramolecular cyclopropanation; 2-alkenyl α-diazoacetates.
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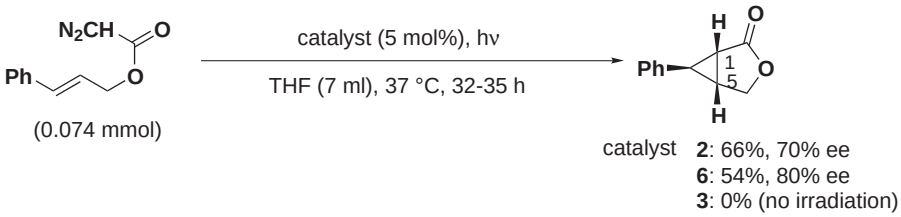
PII: S0040-4039(01)00218-0

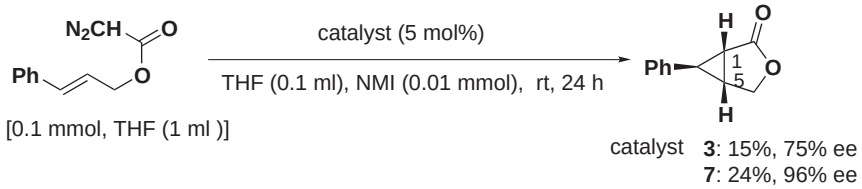


Scheme 1.

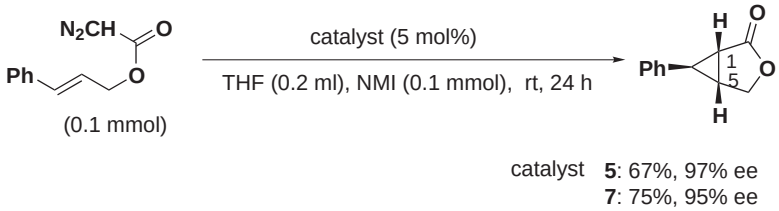
(0.1 M, THF solution) in the presence of *N*-methyl imidazole,[11,12] though the reaction rate was still slow. In this reaction, the diazoacetate was slowly added to the reaction medium to avoid its dimerization, which was a major side reaction when ruthenium complexes **2**, **4**, and **6** were used as the catalysts, but no dimerization was detected in this reaction.[13] The reaction was next examined with complex **7** as the catalyst under otherwise the same conditions and much better enantioselectivity was found to be achieved, though the chemical yield was modest. Dimerization of the substrate was also not observed (Scheme 2).

Thus, we examined Co complexes (**5** and **7**) as the catalysts in the cyclopropanation of *trans*-cinnamyl α-diazoacetate in the presence of 1 equivalent of *N*-methylimidazole without using high-dilution technique, yielding excellent enantioselectivity as well as acceptable chemical yields (Scheme 3). Although **5** showed slightly better enantioselectivity than **7**, **7** exhibited somewhat higher catalytic activity than **5**.[14]

The configuration of the product could be explained by the model proposed for the Ru-catalyzed intramolecular cyclopropanation (Fig. 1),[10] in which the carbonyl oxygen of the intermediate carbenoid has been assumed to be positioned *anti* to the cobalt ion[15] and the olefinic unit to approach along the Co–N bond with an orientation perpendicular to the Co–C bond, rotating clockwise to give the major enantiomer.[9d] This transition state model suggests that *E*-allyl α-diazoacetates ($R^1 = R^3 = H$, $R^2 \neq H$) are the best substrates for this reaction. The presence of *Z*-substituent R^1 may cause some steric repulsion upon the rotation of the olefinic unit, espe-



Scheme 2.



Scheme 3.

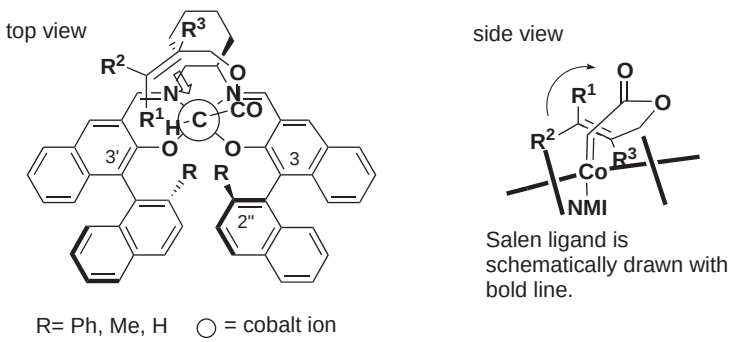
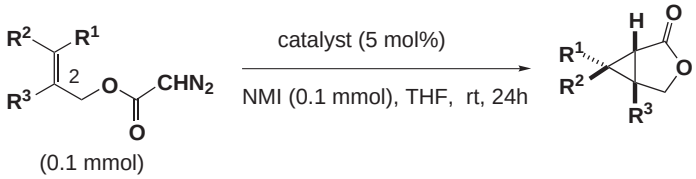


Figure 1.

Table 1. Asymmetric intramolecular cyclopropanation using Co(II)–salen complexes (**5** and **7**) as catalysts



Entry	Catalyst	R^1	R^2	R^3	Yield (%)	% ee
1	**5**	H	*p*-ClC_6H_4	H	72	98[a]
2	**7**	H	*p*-ClC_6H_4	H	88	96[a]
3	**5**	H	*p*-$MeOC_6H_4$	H	70	98[a]
4	**7**	H	*p*-$MeOC_6H_4$	H	93	96[a]
5	**5**	H	*p*-BrC_6H_4	H	70	97[b]
6	**7**	H	*p*-BrC_6H_4	H	52	96[b]
7	**5**	H	Ph–C≡C	H	32	93[c]
8	**7**	H	Ph–C≡C	H	24	84[c]
9	**7**	H	$PhCH_2CH_2$	H	10	91[d]
10[e]	**7**	H	$PhCH_2CH_2$	H	48	82[d]
11[f]	**7**	H	$PhCH_2CH_2$	H	81	79[d]
12[f]	**5**	H	$PhCH_2CH_2$	H	18	73[d]
13[e]	**7**	H	$(CH_3)_2CH$	H	34	75[g]
14	**5**	Me	Ph	H	70	90[h]
15	**7**	Me	Ph	H	47	91[h]
16	**7**	Ph	Ph	H	23	79[i]
17[e]	**7**	Ph	Ph	H	65	74[i]
18	**5**	Ph	Ph	H	35	81[i]
19	**5**	Ph	H	H	16	74[a]
20	**7**	Ph	H	H	24	68[a]
21[f]	**7**	H	Ph	Me	12	38[d]

[a] Enantiomeric excess was determined by HPLC analysis using chiral column (Daicel Chiralpak AD, hexane:isopropanol = 15:1).
[b] Enantiomeric excess was determined by HPLC analysis using chiral column (Daicel Chiralpak ADx2, hexane:isopropanol = 15:1).
[c] Enantiomeric excess was determined by HPLC analysis using chiral column (Daicel Chiralpak AD, hexane:isopropanol = 20:1).
[d] Enantiomeric excess was determined by GLC analysis using Chiral β-DEX column operated at 160°C.
[e] Reaction was carried out at 35°C in the presence of 0.2 mmol of *N*-methylimidazole.
[f] Reaction was carried out at 45°C in the presence of 0.2 mmol of *N*-methylimidazole.
[g] Enantiomeric excess was determined by GLC analysis using Chiral β-DEX column operated at 120°C.
[h] Enantiomeric excess was determined by HPLC analysis using chiral column (Daicel Chiralcel OB-H hexane:isopropanol = 15:1).
[i] Enantiomeric excess was determined by HPLC analysis using chiral column (Daicel Chiralpak AD, hexane:isopropanol = 9:1).

cially when R^1 is sterically bulky, and depress enantioselectivity to some extent. On the other hand, the presence of substituent R^3 is considered to destabilize the transition state strongly and to depress enantioselectivity.

In accord with the transition state model, high enantioselectivity was also achieved in the reactions of other *E*-aryl-substituted substrates with complex **5** or **7** as the catalyst (Table 1, entries 1–6). However, *E*-alkynyl- and alkyl-substituted substrates were less reactive and their reactions showed slightly diminished enantioselectivity (entries 7–13). Chemical yield was improved as reaction temperature was raised, but enantioselectivity was reduced to some extent (entries 9–11). These results suggest that *E*-aryl substituents attractively interact with the salen ligands. As anticipated from the model, enantioselectivity was reduced by introduction of the *Z*-substituent, reflecting its bulkiness: the reaction of β-methylcinnamyl α-diazoacetate with **5** showed high enantioselectivity of 90% ee that was slightly less than the selectivity observed in the reaction of cinnamyl α-diazoacetate itself (entry 14), while the reaction of β-phenylcinnamyl α-diazoacetate showed enantioselectivity of 81% ee. On the other hand, the reaction of *cis*-cinnamyl α-diazoacetate was slow and less selective (68% ee, entry 20), supporting the above hypothesis that the *E*-aryl substituent has an advantageous effect on enantioselectivity. A substrate bearing a substituent ($R_3 \neq H$) showed poor reactivity and enantioselectivity was poor, as the model anticipated (entry 21).

In summary, we were able to demonstrate that Co(II)–salen complexes served as good catalysts for intramolecular asymmetric cyclopropanation reactions of 2-alkenyl α-diazoacetates under high substrate concentration.

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12. Enantioselectivity of intermolecular cyclopropanation catalyzed by complex **3** was also improved by the addition of *N*-methylimidazole (Ref. 9c).
13. In intermolecular cyclopropanation using **3** as the catalyst, no dimerization has been detected.
14. Typical experimental procedure was exemplified with the reaction of (*E*)-cinnamyl α-diazoacetate using **7** as the catalyst: (*E*)-3-Cinnamyl α-diazoacetate (0.1 mmol, 20.2 mg) was placed in a Schlenk tube and the tube was purged with nitrogen. To the tube were added a 0.5 M THF solution (0.2 ml) of *N*-methylimidazole and Co(II)–salen complex (5 mol%, 3.6 mg) successively. The reaction mixture was stirred for 24 h at room temperature (25°C) and the solvent was removed in vacuo. The crude residue was chromatographed on silica gel using hexane and ethyl acetate as eluent to give bicyclic lactone (13 mg) in 75% yield. The ee of the product was determined by GLC analysis using CHIRAL β-DEX column operated at 160°C.
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