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Modular ligands in asymmetric synthesis. Copper-mediated cyclopropanation

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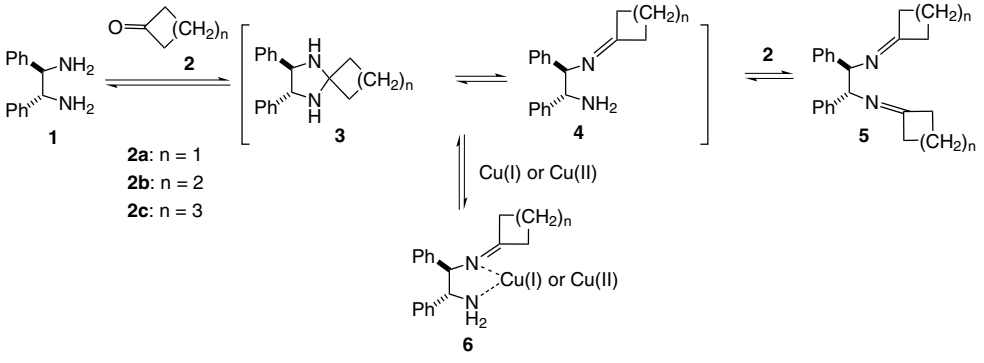
Abstract—The chiral imidazoline/copper catalyst system efficiently mediates asymmetric intermolecular cyclopropanations. Complexes derived from (*R*,*R*)- or (*S*,*S*)-1,1-diphenylethylenediamine, cyclic ketones, and Cu(I) or Cu(II) triflates were compared. The reaction between (−)-menthyl diazoacetate and 1,1-diphenylethylene affords cyclopropane carboxylates in up to 80% yield and with up to 78% de.

The concept of a modular system, which allows quick access to a great diversity of ligands from simple components, continues to attract considerable interest. Recently, we developed an efficient system, which catalyzes asymmetric Diels–Alder reactions between Danishefsky's diene and a variety of dienophiles.[1] The catalyst preparation is based on the condensation of 1,2-diamines of type **1** with cycloalkanones **2**, which affords imidazolidines **3** in equilibrium with the open form **4** (Scheme 1). The corresponding bis-imine **5** and the starting diamine **1** are also present in the reaction mixture.[2] We anticipated that metals such as Cu(I) or Cu(II) could shift this equilibrium toward the metallacyclic form **6** through the formation of a bidentate complex (Scheme 1).

A remarkable advantage of this system is the great number of ligand structures which can be generated without multi-step syntheses. Although there is no precedent for the use of this type of ligand in enantiocatalytic reactions, literature analogies suggest that these complexes may be active in a number of reactions.[3] In continuation of earlier work done on imidazolidine-based chiral catalyst systems, asymmetric cyclopropanation was examined (Scheme 2).[4] The addition of (−)-menthyl diazoacetate **8** to 1,1-diphenylethylene **7** was



Scheme 1.

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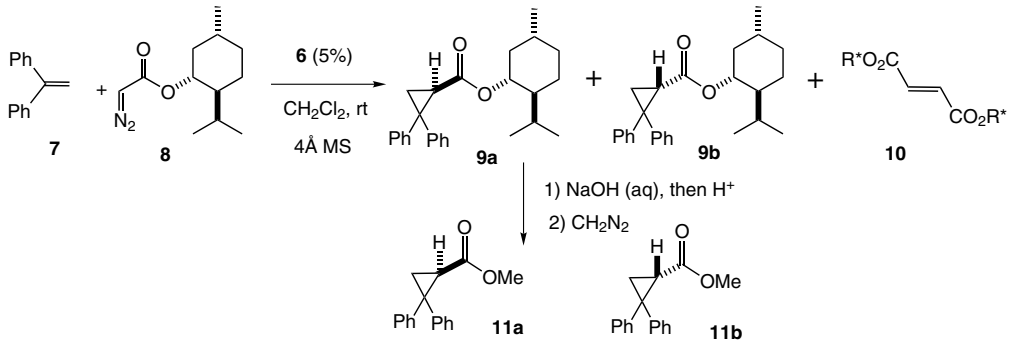

Scheme 2.

selected as the model reaction.[5] Both Cu(I) and Cu(II) complexes were examined as catalysts.

Complexes derived from Cu(I) were tested first. The effect of the ligand structure, particularly the influence of the ketone component and the ligand/metal stoichiometry, on the diastereoselectivity was examined. Accordingly, ligands **3a**–**c**, derived from (*R*,*R*)-diphenylethylenediamine (**1**), cyclobutanone (**2a**), cyclopentanone (**2b**), or cyclohexanone (**2c**), and $(CuOTf)_2{\cdot}C_6H_6$, leading to **6a**–**c** were tested. A solution of (−)-menthyl diazoacetate in dichloromethane was added by syringe pump to a mixture of 1,1-diphenylethylene and catalyst (5%) in dichloromethane (Scheme 2).[6] The reaction afforded the desired cyclopropane carboxylate **9** as a mixture of inseparable diastereoisomers (Table 1), whose ratio was established either by GC–MS or by ^1H NMR. It is worth noting that variable amounts (15–22%) of dimenthyl fumarate **10** were also obtained from dimerization of the diazoester. These results are summarized in Table 1. The absolute configuration of the newly formed stereocenter was determined after saponification of the cyclopropylcarboxylate esters **9**, followed by esterification and comparison with the optical rotation of the (*R*)-carboxycyclopropane derivative **11a**.[7] Independently, the absolute configuration of the major isomer **9a** was ascertained by GC comparison with a sample of known configuration prepared according to Nishiyama's procedure.[8,9]

Catalysts derived from (1*R*,2*R*)-diphenylethylenediamine mediated the formation of the (*R*)-cyclopropylcarboxylate ester **9a** as the major product independently of the nature of the ketone used to prepare the catalyst. As depicted in Table 1, the best results were obtained when the cyclopentanone-derived catalyst **6b** was used (entry 3 vs entries 1 and 7). Although the Diels–Alder and Mukaiyama-aldol reactions worked best with catalyst **6c** in a 1:1 ratio of ligand–copper salt,[1] the asymmetric cyclopropanation reaction gave better yields and selectivity in the presence of catalyst **6b** in a 2:1 ratio of ligand–copper salt (entries 2–4). The selectivity of the reaction was not further ameliorated by increasing the ligand–copper salt ratio above 2. In fact, the high ligand–copper ratio decreased the yield of the cyclopropanation reaction (entry 4).

The match/mismatch effect of the chiral ester with the asymmetric catalyst was also studied (entry 5).[10] When the ligand derived from (1*S*,2*S*)-diphenylethylenediamine and cyclopentanone was used in the presence of (−)-menthyl diazoacetate, the diastereomer **9b** was obtained as the major isomer although with a slight erosion in the diastereoselectivity (de = 50% vs 62%; Table 1, entries 3 and 5). This fact demonstrates that the stereochemistry of the cyclopropanation of **7** using chiral diazoacetate **8** is not substrate but ligand controlled.

The preparation of the catalyst also affects the selectivity of the reaction. In particular, the time of complexation of the catalyst ('aging') markedly affected the reaction. Better selectivity was observed when the catalyst was used after 3 days of complexation compared to the one used after the usual 1 day preparation (entries 3 and 6).

Complexes derived from Cu(II) were tested likewise (Table 2). Catalysts were prepared from (1*S*,2*S*)-diphenylethylenediamine, cyclopentanone, and $Cu(OTf)_2$, and reactions were run according to the same procedure used for the Cu(I) complexes.[11] Although both Cu(I)

Table 1

Entry	**1**[11]	**2**	Ligand:Cu(I) (**cat.**)	Time of complexation (days)	**9a+9b** Yield (%)	**9a**:**9b** (Dr)
1	(*R*,*R*)-**1**	**2a**	2:1 (**6a**)	1	31	(77:23)
2	(*R*,*R*)-**1**	**2b**	1:1 (**6b**)	1	64	(79:21)
3	(*R*,*R*)-**1**	**2b**	2:1 (**6b**)	1	84	(81:19)
4	(*R*,*R*)-**1**	**2b**	6:1 (**6b**)	1	39	(81:19)
5	(*S*,*S*)-**1**	**2b**	2:1 (**6b**)	1	67	(25:75)
6	(*R*,*R*)-**1**	**2b**	2:1 (**6b**)	3	68	(89:11)
7	(*R*,*R*)-**1**	**2c**	2:1 (**6c**)	1	50	(75:25)

Table 2

Entry	2	Ligand:Cu(II)[12] (cat.)	T_c[a] (%)	9a+9b Yield (%)	9a:9b (Dr)
1	**2b**	1:1 (**6b**)	50	18	(79:21)
2	**2b**	2:1 (**6b**)	50	25	(85:15)
3	**2a**	2:1 (**6a**)	45	14	(77:23)
4	**2c**	2:1 (**6c**)	90	45	(75:25)

[a] T_c = conversion.

Table 3

Entry	Ligand **3a** ee (%)	T_c[a] (%)	**9a+9b** Yield (%)	**9a:9b** (Dr)
1	50.0	99	81	(59:41)
2	71.0	95	65	(66:34)
3	85.0	99	64	(75:25)
4	99.9	99	84	(81:19)

[a] T_c = conversion.

and Cu(II) derived salts showed similar trends in stereoselectivity, Cu(II) complexes were less reactive and afforded lower conversions.

The relationship between the optical purity of the catalyst and the diastereomeric ratio of the products was probed (Table 3). In this study, complexes derived from Cu(II) triflate and ligand **3a**, which came from (1*R*,2*R*)- or (1*S*,2*S*)-diphenylethylenediamine and cyclopentanone, were mixed and used in the desired ratio. As in the previous experiments, the stoichiometry of the complex was set to a 2:1 ratio of ligand–Cu(II) salt and the catalyst was allowed to stand for 1 day in order to ensure complexation. The analysis of the data shows a clear negative nonlinear effect (NLE). These data may be explained either by the formation of aggregates or by the participation of two or more ligands in the active complex.[13]

In summary, complexes derived from chiral imidazolidines and copper(I) or copper(II) triflates were shown to mediate asymmetric cyclopropanation reactions. By using 1,1-diphenylethylene and (−)-menthyl diazoacetate, the reaction afforded the corresponding cyclopropane carboxylates in good yield and diastereoselectivity. Although the diastereoselectivity trends of the cyclopropanation were similar in both cases, higher yields were observed when Cu(I) complexes were used. This work forms the basis for the use of imidazoline-based systems in diazoester-mediated cyclopropanations.

References and notes

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5. Chiral ligands were made by mixing the carbonyl compound **2a–c** with the (*R*,*R*)- or (*S*,*S*)-1,2-diphenylethylenediamine. Catalysts were prepared by mixing equimolar amounts of $Cu(OTf)_2$ or $(CuOTf)_2{\cdot}C_6H_6$, respectively, with chiral ligands **3a–c** in dichloromethane, and allowing the mixture to stand for at least 1 day. The complexes were blue-green to purple.
6. The selectivity of the reaction depends marginally on the temperature in the range of 0–40 °C. The transformation was, however, highly sensitive to lower temperatures. At −20 °C and below, the cyclopropanation reaction was inhibited.
7. (a) $[\alpha]_D^{20}$ −78.6 (*c* 0.21, acetone); (b) Walborsky, H. M.; Hornyák, F. M. *J. Am. Chem. Soc.* **1955**, *77*, 6026; (c) Altmann, L. J. *J. Am. Chem. Soc.* **1969**, *91*, 5163.
8. GLC–MS were performed with a HP 6890 GC apparatus equipped with a 12 m × 0.20 mm dimethylpolysiloxane capillary column, linked to a HP 5973 EIMS. The mixure showed two signals: 11.77 min (**9b**) and 11.81 min (**9a**), respectively.
9. Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247.
10. Catalyst was prepared from (*S*,*S*)-1,2-diphenylethylenediamine and cyclopentanone under standard conditions.
11. Catalysts were prepared from imidazolidines **3a–c** and $(CuOTf)_2{\cdot}C_6H_6$, and were used after 24 h of mixing.
12. Catalysts were prepared from imidazolidines **3a–c** and $Cu(OTf)_2$, and were used after 24 h of mixing.
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