C_2 Symmetric Chiral NHC Ligand for Asymmetric Quaternary Carbon Constructing Copper-Catalyzed Conjugate Addition of Grignard Reagents to 3-Substituted Cyclohexenones

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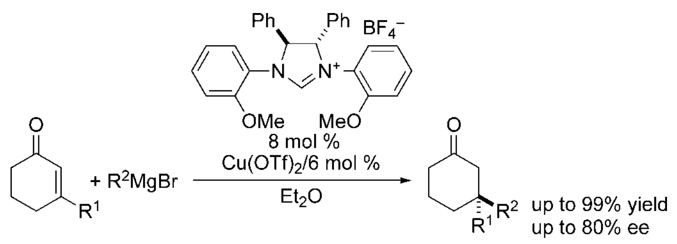

The asymmetric construction of quaternary carbon centers by conjugate addition of Grignard reagents to 3-methyl- and 3-ethylcyclohexenones was realized in a maximum enantioselectivity of 80% by using a C_2 symmetric chiral *N*-heterocyclic carbene (NHC)-copper catalyst, generated from (4*S*,5*S*)-1,3-bis(2-methoxyphenyl)-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate and copper(II) triflate. The stereostructures of the NHC-Au complexes were analyzed by X-ray crystallography, which rationalized the good stereocontrolling ability of *N*-aryl NHCs.

Introduction

We have been engaged in the development of chiral ligand-metal-catalyzed[1] or mediated asymmetric reactions. In the asymmetric conjugate addition reaction,[2] C_2 symmetric chiral diether **1**[3] for lithiated nucleophiles and chiral phosphines **2**[4] for the copper- and rhodium-catalyzed reactions have been developed as representative examples of our successes (Figure 1). A phosphorus ligand **3** (Mes = 2,4,6-trimethylphenyl) also has been developed with limited success for the copper-catalyzed conjugate addition of organozinc reagents to cycloalkenones.[5] Since the C_2 symmetry is one of the central motifs for the design of efficient chiral ligands,[6] we explored the carbene version of **3**: replacement of its phosphorus moiety with a carbene leads to C_2 symmetric *N*-heterocyclic carbene (NHC) **4**.[7,8] By the

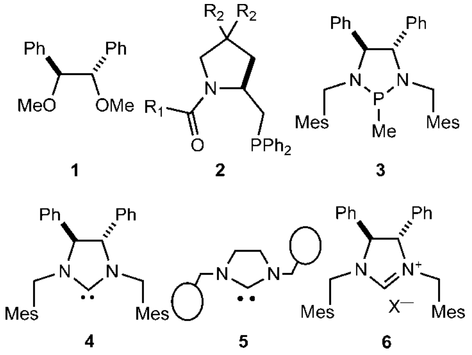

FIGURE 1. Chiral ligands and NHC precursor.

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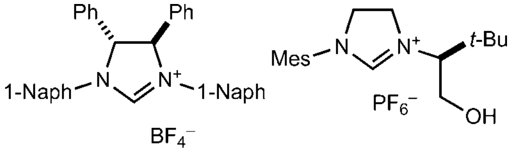


7 **8**

FIGURE 2. Successful NHC precursors **7** and **8**.

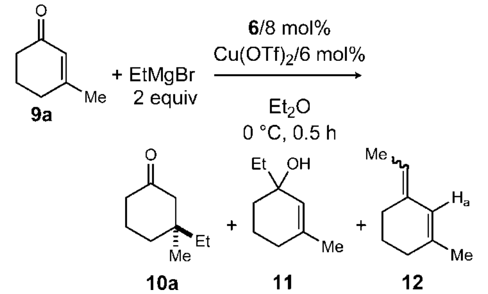
conformational fixation of *N*-substituent, an asymmetric space would be created around the carbene moiety of **5**, and thus the asymmetric space of **4** appears to be more rigid than that of **3** due to lack of a substituent on the carbene. Consequently **4** should afford a more efficient asymmetric induction than **3**. We have also investigated the design and application of C_2 symmetric carbene **4**[9] as an organocatalyst for asymmetric Stetter reaction.[10]

Recent brilliant successes in chiral NHC-copper(I)-catalyzed conjugate addition reactions,[11] especially asymmetric construction of a quaternary carbon,[12] stimulated us to explore the reaction by using C_2 symmetric carbene **4**. In this report, we describe the chiral NHC-copper(I)-catalyzed asymmetric quaternary carbon constructing conjugate addition reaction of Grignard reagents with 3-methyl- and 3-ethylcyclohexenones giving enantioenriched 3,3-disubstituted cyclohexanones.

Results and Discussion

Asymmetric Conjugate Addition of Ethylmagnesium Bromide in the Presence of 6. We followed the reaction procedure reported by Alexakis and Mauduit where an efficient quaternary carbon constructing conjugate addition reaction of Grignard reagents has been realized by using chiral NHC precursors **7** and **8** (Figure 2).[12b] The reaction of 2 equiv of ethylmagnesium bromide with 3-methylcyclohexenone (**9a**) in the presence of 8 mol % of **6a** (X = BF_4) and 6 mol % of copper(II) triflate in diethyl ether at 0 °C for 0.5 h gave a 42:58 mixture of desired **10a** and diene **12** derived from 1,2-adduct **11** (Table 1, entry 3). The absolute configuration of **10a** was assigned to be *S* based on the specific rotation.[13] The enantioselectivity (21% ee) of **10a** was determined by a chiral gas chromatography (Gamma Dex 225, 90 °C, helium gas flow of 4 mL/min, rt: 17.7 min (*R*), 20.2 min (*S*)). The production of **12** was ascribable to almost complete dehydration of **11** by 10% hydrochloric acid treatment of the reaction mixture. The catalysis by an NHC-copper complex was apparent from the reactions that gave no conjugate addition product **10a** in the absence of both or a copper source (entries 1 and 2). The counteranion species, tetrafluoroborate (**6a**), chloride (**6b**), and hexafluorophosphate (**6c**), were not a critical factor in determining 1,4- versus 1,2-addition ratio and also percent ee (entries 3−6). Molar concentration of **6** was not decisive (entries 4 vs 5).

TABLE 1. The 6-Cu(OTf)$_2$-Mediated Asymmetric Conjugate Ethylation



entry	6	X	Cu(OTf)$_2$, mol %	M,[a] mol/L	**10a**:**12**[b]	yield of **10a**, %	ee, %
1	none		0		1:99	trace	nd
2	**6a**	BF_4	0	0.012	1:99	trace	nd
3	**6a**	BF_4	6	0.012	42:58	34	21
4	**6b**	Cl	6	0.008	45:55	45	20
5	**6b**	Cl	6	0.024	55:45	52	19
6	**6c**	PF_6	6	0.012	41:59	34	21

[a] Molar concentration of **6**. [b] The molar ratio determined by ^{1}H NMR (the triplet Me of **10a**:singlet H$_a$ of **12**).

Asymmetric Reaction by Using Variously Modified NHC. A range of *N*-variant precursors of NHC **6** and **27-38** were readily prepared starting from chiral 1,2-diamino-1,2-diphenylethane (**13**) by standard imidazolium forming procedure of *N*-alkylation **14-19** and *N*-arylation products **20-26** as shown in Scheme 1.[14]

It became apparent from our investigation that NHCs bearing RCH_2 or R_2CH *N*-substituents **6** and **29−31** gave poor yields of **10a** (20−51%) (Table 2, entries 1 and 4−6). Exceptions are NHCs **27** and **28** bearing a coordinatable heteroatom group, F and MeO, at the ortho position of a phenyl ring that gave good yields (81% and 70%) (entries 2 and 3), while ee was not satisfactory (24% and 35% ee).

On the contrary, the NHCs bearing an aryl group directly attached to the amino nitrogen, **32−38**, exerted relatively satisfactorily higher efficiency in chemical yield and ee (entries 7−13). It is surprising to find that even unsubstituted phenyl group **32** exerted a better activation behavior to give **10a** with 64% ee in 60% yield. The ratio of 1,4-addition versus 1,2-addition was improved up to 80:20 (entry 7). Both ortho 2,6-dimethyl and diethyl substitutions on a phenyl ring, **33** and **34**, exerted profound effect on yield to give **10a** in 93% and 62% yields, respectively, although ee values, 64% and 59%, were not affected much (entries 8 and 9).

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SCHEME 1. Synthesis of Various NHC Precursors 6 and 27−38 from 13

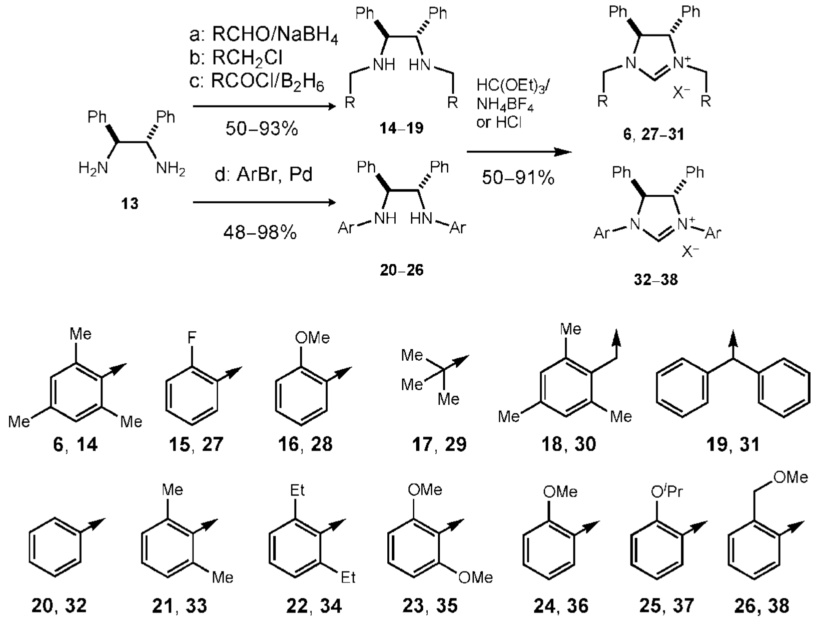
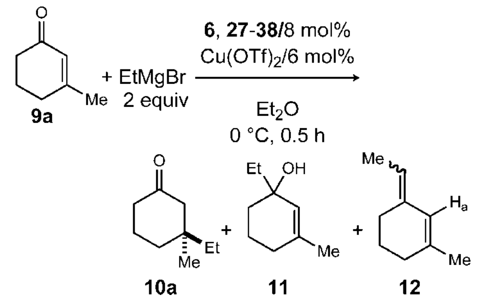


TABLE 2. The 6 and 27−38-Copper-Catalyzed Asymmetric Conjugate Ethylation



entry	**6**, **27**−**38**	X	**10a**:**11** (**10a**:**12**)[a]	yield, %	ee, %	*R*/*S*
1[b]	**6a**	BF_4	(42:58)	34	21	*S*
2	**27**	Cl	(81:19)	81	24	*S*
3	**28**	Cl	(74:26)	70	35	*S*
4	**29**	BF_4	(30:70)	20	10	*R*
5	**30**	BF_4	(59:41)	51	29	*R*
6	**31**	BF_4	29:71	27	8	*S*
7	**32**	BF_4	80:20	64	60	*S*
8	**33**	BF_4	95:5	93	64	*S*
9	**34**	BF_4	64:36	62	59	*S*
10	**35**	BF_4	93:7	93	50	*S*
11	**36**	BF_4	96:4	94	71	*S*
12	**37**	BF_4	79:21	74	57	*S*
13	**38**	BF_4	54:46	40	49	*S*
14[c]	**36**	BF_4	>99:1	99	77	*S*
15[d]	**36**	BF_4	98:2	98	80	*S*

[a] The reaction was quenched with 10% HCl in entries 1−5, while sat. NH_4Cl was used for quenching in entries 6−15 to avoid the formation of **12** from **11**. [b] Table 1, entry 3. [c] Reaction was performed at −40 °C for 0.5 h [d] Reaction was performed at −60 °C for 1.5 h.

Dimethoxy substitution of **35** was also effective to give 93% yield of **10a** with 50% ee (entry 10). Monosubstitution with a methoxy group as in **36** was much more effective to give 94% yield of **10a** with improved enantioselectivity (71% ee), while more bulky isopropoxy-substituted **37** and methoxymethyl-substituted **38** were not effective, 74% yield with 57% ee and 40% yield with 49% ee (entries 11−13). The reactions promoted by **36** at lower temperatures gave **10a** with 77% and 80% ee values in nearly quantitative yields (entries 14 and 15).

The Reaction with Other Grignard Reagents. The reactions of various Grignard reagents (R^2MgBr) with **9a** were also successfully catalyzed by **36**-copper triflate complex to give the products with good ee (74−80%) in high yields (89−99%) (Figure 3, **10b**−**e**), except phenylation product **10f**. 3-Ethylcyclohexenone (**9b**) was also converted to the quaternary carbon-containing product **10g** with good 65% ee by the reaction with isobutylmagnesium bromide. Unfortunately, methylmagnesium bromide was not a good nucleophile to give methylation product *ent*-**10a** with 18% ee. With the exception of **10c** with unknown absolute configuration, nucleophiles attacked from the *Si*-face of cyclohexenones.

The Reaction with Cyclohexenone. The reaction of cyclohexenone **9c** in place of 3-substituted cyclohexenones **9a**,**b** with ethylmagnesium bromide was also successfully catalyzed by

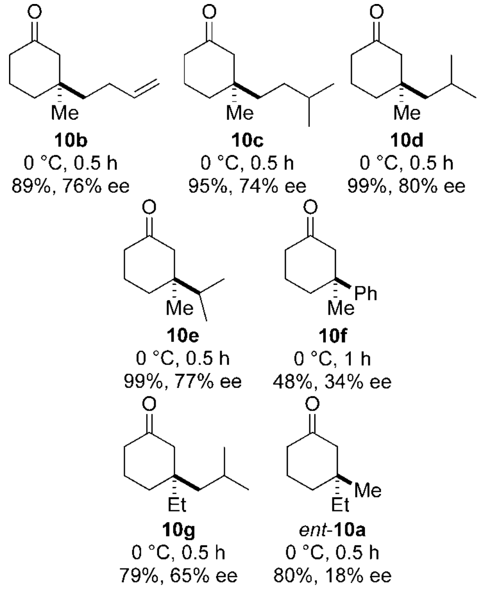
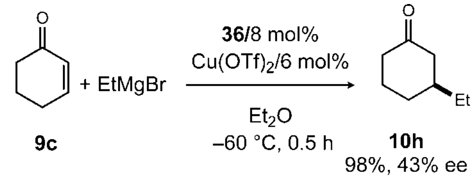


FIGURE 3. The asymmetric reaction products.

SCHEME 2. Asymmetric Conjugate Ethylation of Cyclohexenone



36-copper triflate complex to give (*S*)-**10h**[15] (Scheme 2) with 43% ee in 98% yield. The sense of asymmetric induction is the same as that of **9a** and **9b**, indicating the same type of stereochemical control by the NHC-copper derived from **36**.

The X-ray Crystal Structure Analysis of NHC-Au. The realization of the asymmetric space concept shown as **5** was confirmed by the X-ray crystal structure of NHC-Au complexes. Although copper complexes failed to give crystals suitable for X-ray analysis, gold-NHC complexes gave suitable crystals.[16] As shown in Figure 4, the two mesityl groups of **4**-AuCl are placed down- and up-sides of the 5-membered NHC ring plane, avoiding steric repulsion with the adjacent phenyl groups. However, it is impressive to find that the two mesityl groups are folded like an umbrella blown inside out against the carbene−Au bond, placing both phenyl and mesityl rings parallel. On the other hand, the two 2-methoxyphenyl groups of the **36**-derived carbene-Au complex are stuck out according to the carbene−Au bond, placing the methoxy groups down- and up-sides of the NHC plane and hence creating a more efficient asymmetric environment around the reaction site.

The chiral environment around the gold atom in the **36**-derived carbene-Au complex is surrounded by two 2-methoxyphenyl groups potentially making it much more effective than the **4**-Au complex. Presumably, this is responsible for the higher asymmetric induction by the NHC derived from **36**.

Conclusion

Thirteen C_2 symmetric chiral NHCs derived from 1,2-diamino-1,2-diphenylethane were examined on their abilities in mediating the asymmetric quaternary carbon constructing conjugate addition reaction. Efficient construction of a chiral space around the metallic active site was vital to the realization of high asymmetric induction such as the 80% ee obtained by the use of **36**. The origin of the high stereocontrolling ability of the NHC derived from **36** can be deduced from the X-ray crystal structure analysis of NHC-metal complexes.

Experimental Section

The Asymmetric Conjugate Addition of Ethylmagnesium Bromide to 3-Methylcyclohexenone (9a) (Table 2, entry 15). Under argon atmosphere, to a suspension of copper(II) triflate (43 mg, 6 mol %) and imidazolinium tetrafluoroborate **36** (84 mg, 8 mol %) in diethyl ether (15 mL) was added a 3.0 M diethyl ether solution of ethylmagnesium bromide (0.67 mL, 2.0 mmol) over 3 min at 0 °C and the mixture was stirred at 0 °C for 0.5 h. Then the mixture was cooled to −60 °C and a solution of 3-methylcyclohex-2-enone (**9a**) (0.23 mL, 2.0 mmol) in diethyl ether (10 mL) was added over 10 min. After being stirred for 1.5 h at −60 °C, the reaction was quenched with satd NH_4Cl (15 mL) and 25% NH_3 (15 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. Concentration and column chromatography (hexane/Et_2O = 19/1) gave (*S*)-**10a**[12b] (277 mg, 98%) of $[\alpha]^{20}_D$ −6.57 (*c* 1.10, $CHCl_3$). Chiral GC (Gamma Dex 225, 90 °C, helium gas constant flow of 4 mL/min, Rt = 17.7 min (*R*), 20.2 min (*S*)) indicated 80% ee. The absolute configuration was determined by the specific rotation.[12b]

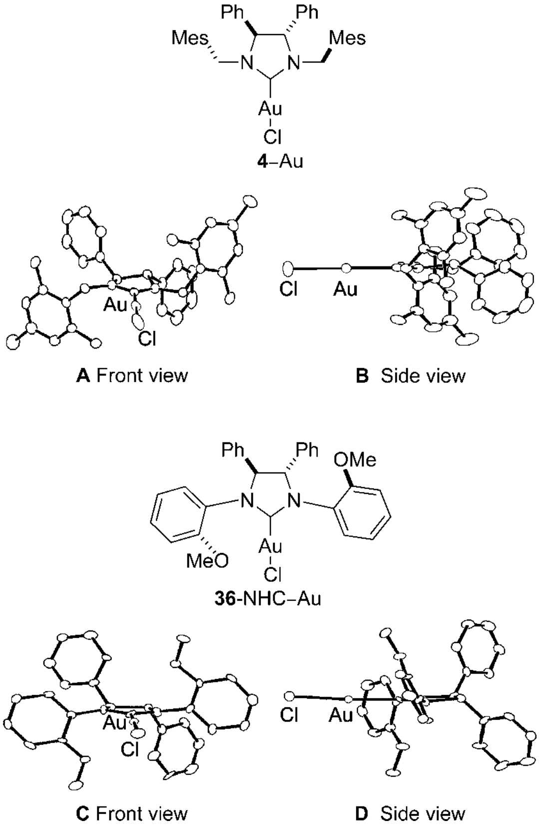


FIGURE 4. The X-ray crystal structure analysis (ORTEP views).

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Supporting Information Available: Synthesis of diamines **14**−**26** and imidazolinium salts **6a**, **6b**, **6c**, and **27**−**38**, ^1H NMR and ^{13}C NMR charts for the products, and the CIF of the gold−carbene complexes **4**-Au and **36**-Au. This material is available free of charge via the Internet at http://pubs.acs.org.

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