Asymmetric Conjugate Addition to Cyclic Enone Catalyzed by Cu-NHC Complexes with C_2 Symmetry

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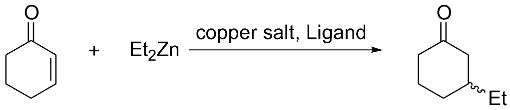
A series of chiral, C_2 symmetric tridentate *N*-heterocyclic carbene precursors, containing two *N*-functionalized hydroxyl or alkoxyl groups, were synthesized. They were applied to catalyze the asymmetric conjugate addition of diethylzinc to cyclohex-2-enone and cyclopent-2-enone. Enantioselectivity of corresponding reactions can be accomplished with up to 76% *ee*, and 65% *ee*, respectively. Flip of major enantiomer was observed when different bases or copper sources were utilized.

Keywords asymmetric catalysis, copper-NHC, imidazolinium salt, C_2 symmetry, Michael addition

Introduction

Asymmetric reactions catalyzed by chiral *N*-heterocyclic carbene (NHC)-metal complexes have attracted broad attention in recent years.[1] NHC has displayed strong σ-donor capacity, and its corresponding complexes with transition metals have been used as efficient catalysts in asymmetric olefin metathesis,[2] conjugate addition,[3] cross-coupling reaction,[4] hydrosilylation,[5] and hydrogenation.[6] In phosphorous ligand-participating enantioselective reactions, bidentate phosphorus ligands, especially those with C_2 symmetry, were generally furnished with higher *ee*'s and they were superior to monodentate phosphines. It was also found in asymmetric reactions that those bidentate NHCs derived from chelating imidazolium or imidazolinium salts afforded better enantioselectivity when compared with monodentate NHC ligands.[7] For instance, imidazolinium salts **1** was successfully prepared by Hoveyda's group,[8,9] and later it was applied to olefin metathesis and allylic alkylation affording high enantioselectivities (up to 98% *ee*). Cu-NHC complex, derived from biphenyl **2**, demonstrated good selectivities in catalytic asymmetric conjugate additions, *i.e.* asymmetric Michael addition, of alkylzinc, arylzinc or alkyl aluminum reagents to the *β*-substituted cyclic enones.[10] Cu-NHC complex, derived from imidazolium salt **3** by Arnold,[11] was used in the reaction of cyclohex-2-enone with diethylzinc furnishing 3-ethylcyclohexanone [Eq. (1)] with *ee* up to 51%. Recently, Mauduit and coworkers[12] have reported that in the copper-catalyzed Eq. (1), NHC precursors **4**—**6** and their analogues resulted in high enantioselectivity with up to 87% *ee*. Furthermore, Katsuki[13] has reported that 97% *ee* was achieved when chiral imidazolinium salt **7**-Cu(II) was used in the conjugate addition of dialkyl zinc to acyclic enones. However, very poor enantioselectivity (3% *ee*) was observed in the case of using cyclohex-2-enone.



(1)

Even though C_2 symmetry in the catalyst and ligand is well recognized as an important structural element in the catalytic enantioselective reactions, there were only a few reports to date regarding asymmetric reactions using chiral multidentate NHC with C_2 symmetry.[14] Recently, Wilhelm *et al.*[15] prepared C_2-symmetric imidazolinium salts **8**, and related analogues containing two hydroxyl groups, and employed their NHCs as ligand in the diethylzinc addition to aldehydes resulting in up to 80% *ee*. The NHC precursor **9** also demonstrated good enantioselectivity (80% *ee*) in the asymmetric conjugate addition of Grignard reagents to 3-alkylcyclohex-2-enone.[16] Structures of imidazol(in)ium salts **1**—**9** are listed in Figure 1. We envisioned that **8** might have potential in the transition metal-catalyzed asymmetric transformation based on its symmetrical dihydroxyl imidazolinium structural features. To this end we are reporting that high enantioselectivity was obtained in the Eq. (1) when utilizing **10**, oxygen atom tethered tridentate imidazolinium salts with C_2-symmetry.

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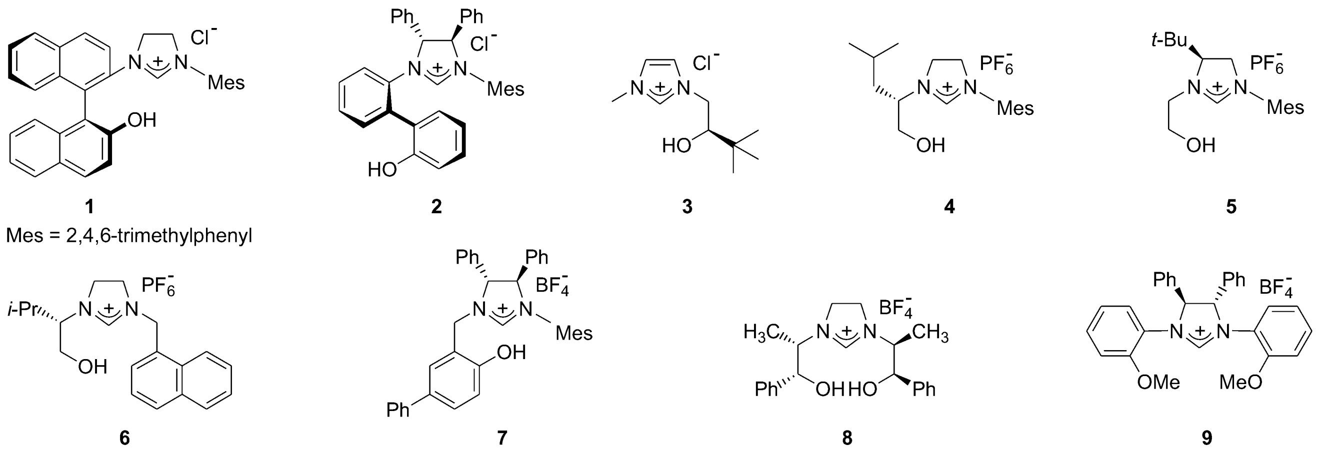


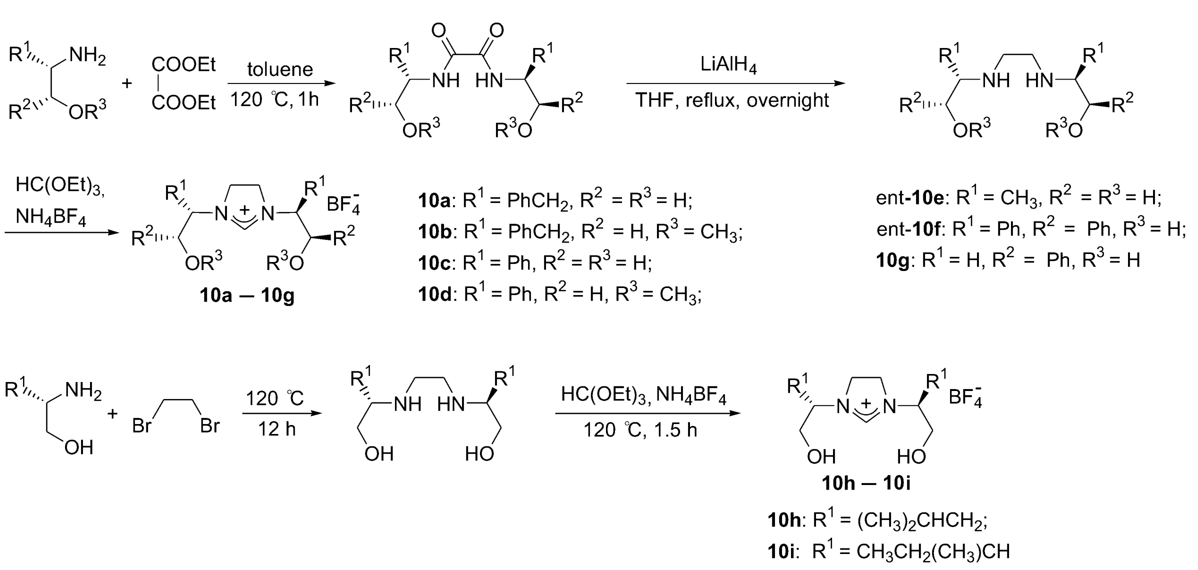
Figure 1 Typical NHC precursors containing oxygen atom(s) on the N-side chain.

Results and discussion

Chiral imidazolinium salts **10a**—**10i** were readily prepared in two to three steps from commercially available enantiopure *β*-amino alcohols (Scheme 1). This protocol is very straightforward compared to the preparation of **4** by Mauduit,[12] which needed five steps from related amino alcohol.

With these NHC ligands precursors in hand, we set to explore their potential application to the Eq. (1). Catalysts were prepared *in situ* by adding base to the mixture of copper salt and imidazolinium salts **10a**—**10i**. The resulting catalysts were directly used for next step of catalytic Eq. (1) without further purification. Reaction conditions were optimized with the imidazolinium salts **10a**. First, **10a**-Cu(OTf)$_2$ and *n*-BuLi were used to prepare corresponding catalyst under different temperatures. Initially, ether was used as the solvent according to the literature result.[12a] Here (*R*) isomer of the conjugate adduct was observed as the major enantiomer and this result is in agreement with Mauduit's report using monohydroxyl imidazolinium salt **4**.[12a] As it can be seen from Table 1, both the conversion of cyclohex-2-enone and the *ee* of the 3-ethylcyclohexanone were greatly influenced by reaction temperatures employed for the catalyst preparation as well as alkylation reaction. The best result was obtained when deprotonation of imidazolinium salt **10a** was carried out at 0—5 ℃, followed by the Eq. (1) at −30 ℃. The reaction was furnished in 98% yield with 71% *ee* (Entry 5). Lowering the deprotonation temperature (−30 ℃) led to significant decrease of conversion. Accordingly, reaction conditions in Entry 5 were used for the further investigation.

Scheme 1 Synthetic routes of imidazolinium salts **10a**—**10i**



10a: R^1 = $PhCH_2$, R^2 = R^3 = H;
10b: R^1 = $PhCH_2$, R^2 = H, R^3 = CH_3;
10c: R^1 = Ph, R^2 = R^3 = H;
10d: R^1 = Ph, R^2 = H, R^3 = CH_3;
ent-**10e**: R^1 = CH_3, R^2 = R^3 = H;
ent-**10f**: R^1 = Ph, R^2 = Ph, R^3 = H;
10g: R^1 = H, R^2 = Ph, R^3 = H
10h: R^1 = $(CH_3)_2CHCH_2$;
10i: R^1 = $CH_3CH_2(CH_3)CH$

Table 1 Influence of the temperature on Eq. (1) with **10a**^{a}

Entry	T_1/℃	T_2/℃	Conv.^{b}/%	ee^c/%
1	r.t.	r.t.	99	51 (*R*)
2	0	r.t.	98	58 (*R*)
3	−5—0	r.t.	98	57 (*R*)
4	−5—0	−20	99	62 (*R*)
5	−5—0	−30	99	71 (*R*)
6	−5—0	−40	90	65 (*R*)
7	−10—−5	−30	90	58 (*R*)
8	−30	−30	10	—

^{a} Reaction conditions: cyclohex-2-enone 0.5 mmol, diethylzinc 0.75 mmol, 3 mol% NHC ligand, 4 mol% $Cu(OTf)_2$, 18 mol% *n*-BuLi, ether, 2 h. *n*-BuLi and diethylzinc were added at T_1, and cyclohex-2-enone was added and reaction was performed at T_2. ^{b} Determined by GC analysis. ^{c} Determined by chiral GC analysis, major isomer is indicated in parenthesis.

Next, solvent and base effects were also investigated (Table 2). Less favorable yield and/or *ee* were observed in dichloromethane or THF (Entries 1 and 2). Toluene improved the *ee* to 66% (Entry 3), however it was still lower than that obtained in ether (Entry 4). With ether as the solvent, switching the base to KHMDS resulted in the best *ee* (76%). However overall low *ee*'s were observed with *t*-BuOK, DBU or K_2CO_3 as the base (Entries 6—8).

Table 2 Effect of the solvent and base with NHC ligand **10a** in Eq. (1)^a

Entry	Base	Solvent	Conv./%	*ee*/%
1	*n*-BuLi	CH_2Cl_2	50	38 (*R*)
2	*n*-BuLi	THF	99	38 (*R*)
3	*n*-BuLi	Toluene	85	66 (*R*)
4	*n*-BuLi	Et_2O	99	71 (*R*)
5	KHMDS	Et_2O	99	76 (*R*)
6	*t*-BuOK	Et_2O	84	60 (*R*)
7	DBU	Et_2O	92	20 (*R*)
8	K_2CO_3	Et_2O	60	0

^{a} Reaction conditions are the same as those of Entry 5 in Table 1 unless noted.

Various copper salts were also examined, and related results are summarized in Table 3. $Cu(OTf)_2$ gave satisfied results in terms of yield and *ee*. $Cu(acac)_2$ also afforded high yield but with lower *ee*. Both $CuCl_2$ and CuBr gave reasonable *ee*, but the other copper salts were inferior (Entries 2, 5, 7).

Table 3 Scan of copper salts for Eq. (1) with NHC ligand derived from **10a**^{a}

Entry	CuX	Conv./%	*ee*/%
1	$Cu(OTf)_2$	99	71 (*R*)
2	CuCl	90	24 (*R*)
3	$CuCl_2$	98	58 (*R*)
4	CuBr	99	63 (*R*)
5	CuI	99	37 (*R*)
6	$Cu(acac)_2$	99	64 (*R*)
7	$Cu(OAc)_2$•H_2O	95	26 (*R*)

^{a} Reaction conditions are the same as those of Entry 5 in Table 1 unless noted.

Further optimization of the reaction conditions was carried out and related results are summarized in Table 4. When initially using 2 mol% ligand **10a**, 4 mol% $Cu(OTf)_2$ and 12 mol% *n*-BuLi, the reaction conversion and selectivity were lower (Entry 1) and this can be improved by adding more ligand (Entry 2). However, large excess ligand led to decreased *ee* (Entry 3). Lowing the ratio of *n*-BuLi to **10a** resulted in low enone conversion and *ee* of the product (Entry 4). Reducing amount of pre-catalyst led to almost identical *ee* though with decreased yield. Replacement of *n*-BuLi with KHMDS gave the highest *ee* with 3 mol% **10a**, 4 mol% $Cu(OTf)_2$ and 18 mol% base (Entry 5). Further increasing the amount of base, either *n*-BuLi or KHMDS, reduced enantioselectivity (Entries 6—10).

Table 4 Optimization of the ratio of ligand, CuX and the base with **10a** in Eq. (1)^a

Entry	Base	**10a**	$Cu(OTf)_2$	Base	Conv./%	*ee*/%
1	*n*-BuLi	2	4	12	75	16 (*R*)
2	*n*-BuLi	3	4	18	99	71 (*R*)
3	*n*-BuLi	6	4	36	99	54 (*R*)
4	*n*-BuLi	3	4	12	75	60 (*R*)
5	KHMDS	3	4	18	95	76 (*R*)
6	*n*-BuLi	3	4	24	99	68 (*R*)
7	KHMDS	3	4	24	99	44 (*R*)
8	*n*-BuLi	3	4	30	99	60 (*R*)
9	KHMDS	3	4	30	99	34 (*R*)
10	*n*-BuLi	4	4	24	99	64 (*R*)

^{a} Reaction conditions are the same as those of Entry 5 in Table 1 unless noted.

Based on aforementioned discussion, optimal conditions were applied to the Eq. (1), and the results are listed in Table 5 with different imidazolinium salts **10b**—**10i**. Compared to Mauduit's results using monohydroxyl based ligand **4**, lower *ee*'s were obtained with using bi-hydroxyl ligand **10a** — **10i**.[12a] However, these pre-ligands are still attractive due to their preparation easiness. When the hydroxyl group in **10a** was replaced by methoxyl group, both conversion and *ee* value were decreased (Entry 3 vs. Entry 1). A similar phenomenon was observed in the case of **10c** and **10d** (Entry 6 vs. Entry 4). Neutral oxygen has inferior coordinative ability compared to anionic oxygen atom derived from hydroxyl and a strong base. Therefore, it can be concluded that strong coordinative oxygen atom in a NHC moiety which served as a di- or multidentate chelating ligand, led to higher enantioselectivity. It was also found that the reactivity and selectivity of Eq. (1) can be affected by the steric effect of *N*-substituents as well as the location of chiral center along the side chain. Increasing the steric hindrance of branch *β*-carbon atom relative to N atom reduced the enantioselectivity significantly even though the chiral centers were closer to metal atom (Entries 8, 9). It is noteworthy that replacement of *n*-BuLi with KHMDS resulted in stereochemistry flip of the major product from (*R*) to (*S*) in the presence of ligand **10c** only (Entry 5). Previously, Katsuki[13] has reported that different bases (*t*-BuONa, *n*-BuLi) induced reversed enantioselectivity in asymmetric conjugate addition of acyclic enones. Sakaguchi[7] also reported that replacing $Cu(OTf)_2$ with $Cu(acac)_2$ led to different major enantiomers in copper-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones, in which the same chiral NHC ligand was employed. Additionally, it was found that the results of Eq. (1) were sensitive to the addition order of the reactants and the base. Higher *ee*'s were obtained if adding base to the mixture of copper salt and **10a**—**10i** followed by cyclohex-2-enone, whereas poor enantioselectivities (*ca*. 2% *ee*) were observed if deprotonation of imidazolinium salts were carried out prior to the addition of a Cu source, even though in this case high yield (99%) can be obtained. Among the imidazolinium salts **10a**—**10i** studied, **10a** is the most efficient one.

Table 5 Evaluation of the NHC ligands derived from **10a**—**10i** in Eq. (1)[a]

Entry	L	Base	Conv./%	*ee*/%
1	**10a**	*n*-BuLi	99	71 (*R*)
2	**10a**	KHMDS	95	76 (*R*)
3	**10b**	*n*-BuLi	85	22 (*R*)
4	**10c**	*n*-BuLi	90	51 (*R*)
5	**10c**	KHMDS	98	40 (*S*)
6	**10d**	*n*-BuLi	85	36 (*R*)
7	**10e**	*n*-BuLi	90	50 (*S*)
8	**10f**	*n*-BuLi	80	28 (*S*)
9	**10g**	*n*-BuLi	94	10 (*S*)
10	**10h**	*n*-BuLi	95	48 (*R*)
11	**10i**	*n*-BuLi	93	50 (*R*)

[a] Reaction conditions are the same as those of Entry 5 in Table 1 unless noted.

Ligands derived from **10a**—**10d** were also tested in conjugate addition of diethylzinc to cyclopentene-2-one. With a combination of **10a** (or **10c** or **10d**)-$Cu(OTf)_2$-*n*-BuLi, low *ee* in favor of (*R*)-isomer, was obtained. In the presence of **10a**, (*S*)-isomer was obtained as the major enantiomer under either a combination of $Cu(acac)_2$-*n*-BuLi or $Cu(OTf)_2$-KHMDS, and 65% *ee* was obtained in the later case. A similar result was observed for **10c**, as the enantioselectivity was reversed with KHMDS as the base yielding (*S*)-isomer as the preferred product. We speculated that major product chirality flip might be due to different catalytic species involved as a result of altering bases. Related reaction results are summarized in Table 6.

Table 6 Conjugate addition of Et_2Zn to cyclopent-2-enone promoted by Cu(II)-base-**10**[a]

Entry	L	CuX	Base	Conv.[a]/%	*ee*[b]/%
1	**10a**	$Cu(OTf)_2$	*n*-BuLi	95	14 (*R*)
2	**10a**	$Cu(acac)_2$	*n*-BuLi	94	7 (*S*)
3	**10a**	$Cu(OTf)_2$	KHMDS	96	65 (*S*)
4	**10c**	$Cu(OTf)_2$	*n*-BuLi	64	9 (*R*)
5	**10c**	$Cu(OTf)_2$	KHMDS	91	42 (*S*)
6	**10d**	$Cu(OTf)_2$	*n*-BuLi	63	9 (*R*)

[a] Reaction conditions are the same as those of Entry 5 in Table 1 except that 2-cyclopent-2-enone was used as the substrate and reaction was carried out at −30 ℃. [b] Determined by chiral GC.

Conclusion

In conclusion, imidazolinium salts **10a**—**10i** of C_2 symmetry with two ancillary oxygen atoms on the *N,N'*-side chains were readily prepared from corresponding enantiopure amino alcohols. Deprotonation of these salts in the presence of copper salts led to Cu-NHC complexes. The resulting Cu-NHCs are efficient in catalyzing enantioselective conjugate addition to cyclohex-2-enone and cyclopent-2-enone. Adduct of conjugate addition was obtained with up to 76% *ee* and 99% yield for cyclohex-2-enone, and up to 65% *ee* for the 5-membered ring substrate. Enantioselectivity flip of the major isomer was observed in some examples when the base or copper sources were changed.

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