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TETRAHEDRON: *ASYMMETRY*

Enantioselective copper-catalyzed conjugate addition using chiral diaminocarbene ligands

Frédéric Guillen, Caroline L. Winn and Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, 30, quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

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Abstract—Chiral diaminocarbene ligands, generated by in-situ deprotonation of the corresponding chiral imidazolinium salts, are shown to be efficient ligands in the asymmetric copper-catalyzed 1,4-conjugate addition of diethylzinc to enones, allowing enantiomeric excesses of up to 51% to be achieved.

Stabilized carbenes, such as diaminocarbenes, are highly σ-donating and low π-accepting species, showing coordination properties similar to those of basic phosphorus-based ligands.[1] Their coordination chemistry has been studied since the early 70's: diaminocarbene–transition metal complexes were prepared from tetraaminoolefins, which can be considered as the dimeric form of the diaminocarbene,[2] or via in situ generation of the carbene.[3]

The discovery of stable diaminocarbenes by Arduengo[4] in 1991 has increased interest in the use of diaminocarbene ligands in organonometallic catalysis, especially in palladium catalyzed coupling reactions[5] and ruthenium catalyzed olefin ring closing metathesis.[6] However, only a few examples of asymmetric catalysis using diaminocarbene-based metal complexes have been reported.[7]

Interestingly, few diaminocarbene–copper complexes have been synthesized[8] and their catalytic properties were not investigated. Very recently, Woodward et al. demonstrated the ability of carbene **1** to accelerate the copper-catalyzed addition of diethylzinc to cyclohexenone.[9] Herein, we describe the first use of chiral diaminocarbenes as ligands in the copper(I)-catalyzed 1,4-conjugate addition of diethylzinc to enones.

Among the various methods allowing the formation of diaminocarbenes, deprotonation of imidazolium salts occupies a prominent place. The direct synthesis of imidazolium halide salts from the primary amine and glyoxal,[10] or of imidazolinium salts from the corresponding diamine,[11] gives ready access to various saturated or unsaturated carbenes via simple deprotonation of the salt[12] or thermal decomposition of the alkoxyaminal derivative.[13]

In order to investigate the influence of several parameters such as the steric bulk of the nitrogen substituents, the presence of a chiral backbone, of chiral substituents on the nitrogen atoms and the ring size, the synthesis of the novel imidazolinium salts **2**–**6** (Fig. 1) was effected by a reported procedure[11] in good yields, from the readily available chiral diamines (Scheme 1). Although the presence of a bulky alkyl or aryl substituent on each nitrogen is necessary to stabilize the free diaminocarbene (especially the saturated imidazolinyl-2-ylidenes),[14]

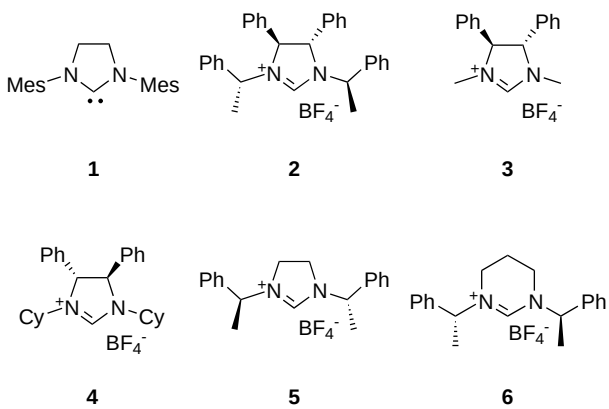

Figure 1.

* Corresponding author. Tel.: +41 (0)22 702 65 22; fax: +41 (0)22 328 73 96; e-mail: alexandre.alexakis@chiorg.unige.ch

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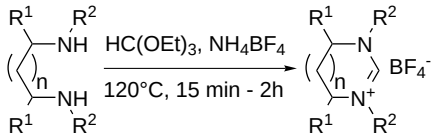
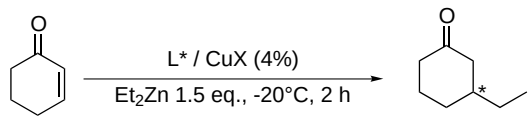


2: 95 % **3**: 88 %
4: 96 % **5**: 80 %
6: 79 %

Scheme 1. Synthesis of imidazolinium tetrafluoroborates **2**–**6**.

it was thought that in situ trapping of the carbene derived from **3** should give access to the corresponding copper complex.

Determination of the optimum experimental conditions was conducted using the salt **2**, bearing chiral substituents on the nitrogen in addition to the chiral backbone, and the reactive cyclohexenone (Scheme 2). Addition of 1 equiv. of previously deprotonated **2** to a suspension of copper(II) triflate in dry degassed toluene, followed by diethylzinc and the cyclohexenone afforded, after 14 h at −20°C, the expected ethylcyclohexanone in quantitative yield with a modest e.e. of



Scheme 2. Conjugate addition of diethylzinc on cyclohexenone.

14% (Table 1, entry 1). The use of 2 equiv. of the ligand, which usually improves the selectivity when using phosphorus-based ligands, induced a dramatic decrease of the reactivity, the addition product being obtained in 15% yield (Table 1, entry 2).

In situ generation of the diaminocarbene gave enhanced enantioselectivity when compared to the use of the pre-formed diaminocarbene (Table 1, entry 3). For this reason, along with the simplified experimental procedure, in situ carbene preparation was used throughout the rest of this study.

In order to ascertain the formation of the diaminocarbene–copper complex, several control experiments were carried out. No enantioselectivity was observed in the addition of diethylzinc to cyclohexenone when no deprotonating agent was added to the $Cu(OTf)_2$/**2** mixture (Scheme 3, equation 1); this experiment also showed that diethylzinc alone is not basic enough to deprotonate the imidazolinium salt **2**, confirming the need for an added base. Alternatively, the use of diamine **7** as ligand for copper afforded a reduced conversion and e.e. as compared to the diaminocarbene–copper system (Scheme 3, equation 2). These two experiments, along with the results in Table 1, clearly indicate that a diaminocarbene–copper complex is involved in the catalytic cycle.

Different copper(I) or copper(II) salts can be used as precursors of the active copper(I) catalyst (Table 1, entries 4–6). However, only copper(II) triflate-based catalysts lead to high conversions and e.e.s above 10%.

Table 1. Conjugate addition of diethylzinc to cyclohexenone

Entry	Imidazolinium salt	Copper salt	Solvent	Duration	Yield (%)[a]	E.e. (%)[b]
1[d]	**2** (4%)	$Cu(OTf)_2$ (4%)	Toluene	14 h	>99	14 (*S*)
2[d]	**2** (8%)	$Cu(OTf)_2$ (4%)	Toluene	14 h	15	20 (*S*)
3	**2** (4%)	$Cu(OTf)_2$ (4%)	Toluene	2 h	92	22 (*S*)
4	**2** (4%)	CuCN (4%)	Toluene	2 h	93	0
5	**2** (4%)	$CuBF_4.CH_3CN$ (4%)	Toluene	2 h	63	11(*S*)
6	**2** (4%)	$CuPF_6.CH_3CN$ (4%)	Toluene	2 h	26	11 (*S*)
7[c]	**2** (4%)	$Cu(OTf)_2$ (4%)	CH_2Cl_2	2 h	90	27 (*S*)
8	**2** (4%)	$Cu(OTf)_2$ (4%)	THF	2 h	24	3 (*S*)
9	**2** (4%)	$Cu(OTf)_2$ (4%)	Ether	15 min	97	19 (*S*)
10	**3** (4%)	$Cu(OTf)_2$ (4%)	Toluene	2 h	>99	4 (*S*)
11	**4** (4%)	$Cu(OTf)_2$ (4%)	Toluene	2 h	97	7 (*R*)
12	**5** (4%)	$Cu(OTf)_2$ (4%)	Toluene	2 h	>99	13 (*S*)
13	**6** (4%)	$Cu(OTf)_2$ (4%)	Toluene	2 h	>99	13 (*R*)

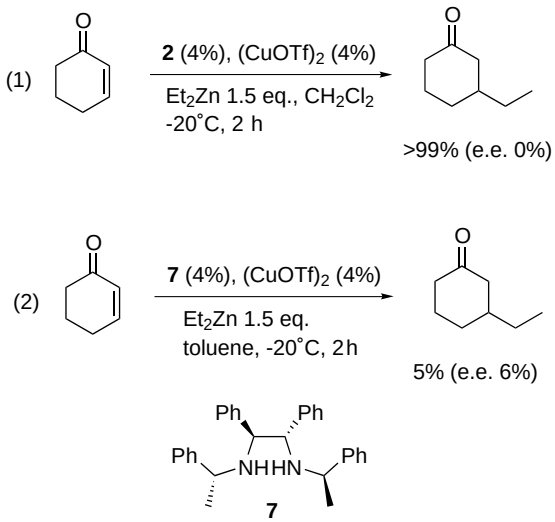
Representative procedures: (i) *Pre-formed ligand*: A solution of *n*-BuLi (1.6 M solution in hexane, 150 μL, 0.24 mmol) was slowly added at −78°C to a suspension of salt **2** (104 mg, 0.2 mmol) in dry, degassed toluene (5 mL) under argon and the reaction mixture allowed to warm to room temperature. A 1 mL aliquot of the resulting cloudy yellow solution was then added to a suspension of copper(II) triflate (14 mg, 39 μmol) in toluene (2 mL) at −20°C. After 30 min, diethylzinc (15% solution in hexane, 1.7 mL, 1.5 mmol) and cyclohex-2-enenone (98 μL, 1.0 mmol) were added at this temperature. After stirring the mixture for 2 h, the reaction mixture was hydrolyzed with aqueous 2 M HCl solution (2 mL), extracted with ether and filtered through a short plug of silica gel. (ii) *In situ ligand formation*: A solution of *n*-BuLi (1.6 M solution in hexane, 31 μL, 50 μmol) was added to a suspension of salt **2** (21 mg, 40 μmol), copper(II) triflate (14 mg, 39 μmol) and cyclododecane (50 mg, internal standard) in the appropriate dried, degassed solvent (3 mL) at −78°C. The temperature was then allowed to rise slowly to −20°C, then diethylzinc (15% solution in hexane, 1.7 mL, 1.5 mmol) and cyclohex-2-enenone (98 μL, 1.0 mmol) were added at this temperature.

[a] Determined by GC/MS.

[b] Determined by chiral GC (Lipodex E).

[c] Deprotonation was conducted in 1 ml of toluene, then, after addition of the diethylzinc solution, 3 ml of CH_2Cl_2 was added.

[d] Pre-formed ligand.



Scheme 3. Control experiments.

The use of dichloromethane as co-solvent leads to an increased product e.e. (Table 1, entry 7). However, the need for a solvent compatible with *n*-BuLi for the deprotonation step prohibits the use of dichloromethane alone. Whereas THF, as expected for a Lewis basic solvent, displays the lowest enantioselectivity and activity (Table 1, entry 8), an increase in activity was observed in ether without significant loss of selectivity (Table 1, entry 9: the reaction rate is one order of magnitude higher than in toluene). Lowering the temperature to −50°C did not improve the enantioselectivity of the reaction, whilst at −78°C the reaction becomes sluggish although there was an increase in enantioselectivity to 50% when the reaction was allowed to run for 16 h (Table 2, entry 3).

Table 2. Influence of the reaction temperature in ether

Entry	Temperature	Yield (%)[a]	E.e. (%)[b]
1[c]	−20°C	>99	19
2[c]	−50°C	97	20
3[d]	−78°C	91	50

Experimental procedure as in Table 1, the addition of diethylzinc is carried out at −20°C and the reaction mixture cooled down to the appropriate temperature before addition of the cyclohexenone.
[a] See Table 1.
[b] See Table 1.
[c] Yields and e.e. after 2 h.
[d] Yields and e.e. after 16 h.

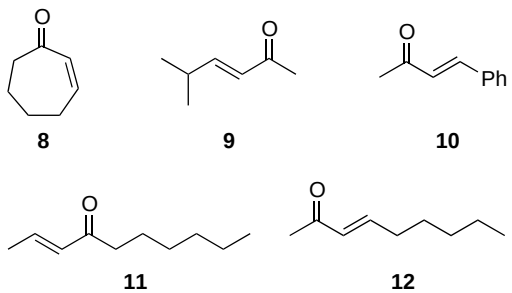


Figure 2.

A study of the influence of the ligand structure was conducted using the standard conditions (Table 1, entry 10–13). Compounds **3**–**4**, lacking a chiral nitrogen substituent, afforded the lowest e.e. Table 1, entry 10–11). The presence of the chiral 1-phenylethyl substituent on the nitrogen increased the e.e., with no influence of the ring size (Table 1, entry 12–13). The imidazolinium salt **2**, possessing a chiral backbone *and* chiral nitrogen substituents, gave the best e.e. values.

In order to ascertain the scope of the catalytic system, several enones, covering a wide range of structural features (Fig. 2), were submitted to the two sets of conditions determined previously (i.e. imidazolium salt **2**, copper(II) triflate in either toluene/dichloromethane at −20°C for 16 h, or in Et_2O at −78°C for 16 h).

The results are presented in Table 3. Both reactivity and selectivity depend heavily on the substrate structure. At −78°C, every substrate that was tested exhibited lower reactivity than the cyclohexenone. In the case of the cycloheptenone **8** (entry 1) and the decenone **11** (entry 7), this lowered reactivity toward the diethylzinc addition induced a large increase in the reaction of the intermediate zinc enolate with the starting enone, whereas steric hindrance appears to prohibit this reaction for 5-methyl-3-hexen-2-one **9** (entry 3). Only 3-nonen-2-one **12** reached 20% e.e., with a 75% yield (entry 9). At −78°C however, there was no evidence for the formation of a double addition product and although the 1,4 addition reaction did not occur for every substrate (entries 4 and 6 show results for 5-methyl-3-hexen-2-one **9** and benzylacetone **10**, respectively), it was possible to achieve an e.e. of 51% using decen-4-one **11** as a substrate in excellent yield (entry 8). This was a vast improvement on the result obtained using the original conditions. Both cycloheptanone **8** and 3-nonen-2-one **12** also gave better yields and enantioselectivities at low temperature than could be achieved using toluene/dichloromethane at −20°C.

Table 3. 1,4 Addition of diethylzinc on various enones

Entry	Substrate	Yield (%)[a]	E.e (%)[b]	Enolate addition (%)
1[c]	8	55	9 (−)	28
2[d]	8	66	12 (−)	0
3[c]	9	23	10	0
4[d]	9	0	–	0
5[c]	10	27	11 (+)	8
6[d]	10	0	–	0
7[c]	11	40	1 (+)	42
8[d]	11	99	51 (+)	0
9[c]	12	75	20 (*R*)	9
10[d]	12	99	26 (*R*)	0

[a] See Table 1.
[b] See Table 1.
[c] Toluene/DCM, −20°C, 16 h.
[d] Et_2O, −78°C, 16 h.

The optimisation of the diaminocarbene ligand structure as well as the study of the diaminocarbene–copper catalyzed conjugate addition of organozinc reagents on various Michael acceptors is currently underway. In the accompanying paper, Mangeney et al. disclose their results from enantioselective conjugate addition reactions using a catalytic silver(I) diaminocarbenes–$Cu(OTf)_2$ system.[15]

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