

# Asymmetric Synthesis with *N*-Heterocyclic Carbenes. Application to the Copper-Catalyzed Conjugate Addition

Alexandre Alexakis,<sup>a,\*</sup> Caroline L. Winn,<sup>a</sup> Frederic Guillen,<sup>a</sup> Julien Pytkowicz,<sup>b</sup> Sylvain Roland,<sup>b,\*</sup> Pierre Mangeney<sup>b</sup>

<sup>a</sup> Université de Genève, Département de Chimie Organique, 30, quai Ernest-Ansermet, 1211 Genève 4, Switzerland  
Fax: (+41)-22-3287396, e-mail: alexandre.alexakis@chiorg.unige.ch

<sup>b</sup> Laboratoire de chimie des Organoéléments, UMR 7611, Université P. et M. Curie, 4 place Jussieu, 75252 Paris cedex 05, France  
Fax: (+33)-1-44277567, e-mail: sroland@moka.ccr.jussieu.fr

Received: September 11, 2002; Accepted: November 5, 2002

Supporting Information for this article is available on the WWW under <http://asc.wiley-vch.de> or from the author.

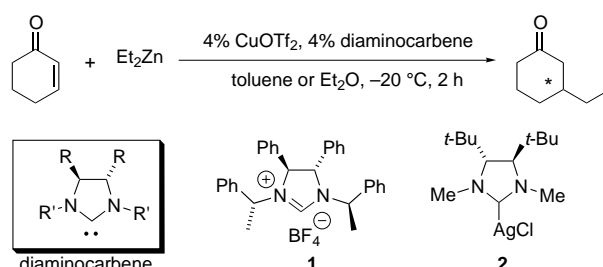
**Abstract:** Chiral *N*-heterocyclic carbenes are good ligands for the copper-catalyzed conjugate addition of dialkylzinc reagents to various Michael acceptors. With as little as 4% of chiral ligand, the enantioselectivity may reach 93% on cycloheptenone.

**Keywords:** asymmetry; conjugate addition; copper; dialkylzinc; *N*-heterocyclic carbenes; Michael acceptors

Diaminocarbenes, and particularly, *N*-heterocyclic carbenes (NHC) are a growing class of ligands for transition metals.<sup>[1]</sup> Their interest lies in their electron-donating ability, and they most often replace advantageously an electron-rich phosphine.<sup>[2]</sup> Many complexes of NHC with transition metals are well characterized.<sup>[1–3]</sup> Such complexes have been used as catalysts for several synthetic transformations.<sup>[2,4]</sup> Despite this booming interest, there are still few applications in asymmetric synthesis.<sup>[5]</sup> Moreover, only three articles mention enantioselectivities reaching 90%.<sup>[5d–f]</sup> We report herein that chiral NHC's efficiently promote the copper-catalyzed conjugate addition of dialkylzinc reagents to a variety of Michael acceptors, with enantioselectivities up to 93%, among the best reported for such ligands.

In a recent communication, Woodward<sup>[6]</sup> showed that Arduengo-type carbenes<sup>[7]</sup> strongly accelerated this reaction, a behavior strikingly similar to trivalent phosphorus ligands. Soon after, chiral diaminocarbene precursors, **1** and **2**, were disclosed by Alexakis<sup>[8]</sup> and Roland<sup>[9]</sup> for this reaction, with enantioselectivities ranging from 23% (with **2**)<sup>[9]</sup> to 50% (for **1**)<sup>[8]</sup> (Scheme 1).

These results were obtained under the usual experimental conditions for this reaction (2–4% Cu(OTf)<sub>2</sub>,



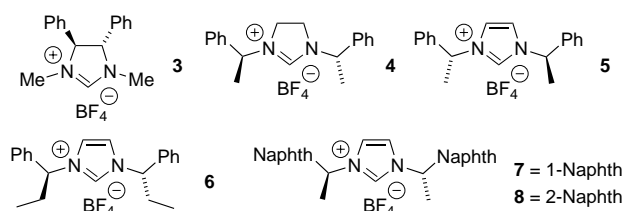
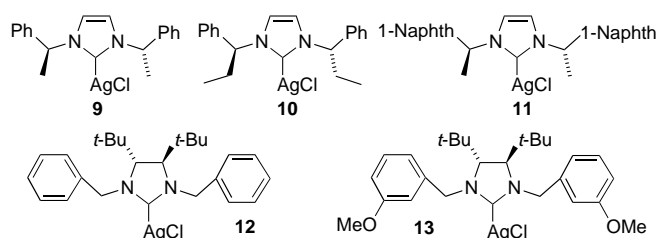
**Scheme 1.**

2–4% ligand, toluene with **2** or Et<sub>2</sub>O with **1**).<sup>[10]</sup> Imidazolinium salt **1** is first treated with *n*-BuLi to generate the carbene, then complexed with the Cu salt, whereas ligand **2**, which is already a carbene, is just transmetalated to the Cu complex. Since these reports, we have found that other experimental conditions were more appropriate (Cu carboxylates, Et<sub>2</sub>O) for the conjugate addition with phosphorus ligands.<sup>[11]</sup> We expected that these new conditions, together with new diaminocarbenes, could afford much better enantioselectivities.

Imidazolinium salt **1** has two chiralities, the endocyclic one and the exocyclic one. Imidazolinium salt precursors **3** and **4** (Scheme 2), with only one type of chirality, were found to be less efficient for the conjugate addition to cyclohexenone (Table 1, entries 2 and 3). The saturated carbenes **1–4** were believed to be more nucleophilic,<sup>[1,2]</sup> and the distortion from planarity of the imidazoline ring was thought to be responsible for the enantioselection. We were therefore very surprised to find that imidazolinium salt **5**, lacking both of the above properties, gave the best enantioselectivity of the series (entry 4). Application of new experimental conditions (Et<sub>2</sub>O, –78 °C, CuOAc<sub>2</sub> or CuTC = copper thiophene-carboxylate),<sup>[11]</sup> led to an increase in ee to 54% (entries 5 and 6). In most cases, these two Cu salts behaved very similarly with 2–5% difference in ee.

**Table 1.** Conjugate addition to cyclohex-2-enone with various chiral imidazolium salts.

Entry	Ligand	Cu salt	Solvent	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	<b>1</b>	CuOTf <sub>2</sub>	toluene	−20	2	92	22 ( <i>S</i> )
2	<b>3</b>	CuOTf <sub>2</sub>	toluene	−20	2	99	4 ( <i>S</i> )
3	<b>4</b>	CuOTf <sub>2</sub>	toluene	−20	2	97	13 ( <i>S</i> )
4	<b>5</b>	CuOTf <sub>2</sub>	toluene	−20	2	60	39 ( <i>R</i> )
5	<b>5</b>	CuOAc <sub>2</sub>	Et <sub>2</sub> O	−78	16	75	54 ( <i>R</i> )
6	<b>5</b>	CuTC	Et <sub>2</sub> O	−78	16	88	52 ( <i>R</i> )
7	<b>6</b>	CuOAc <sub>2</sub>	Et <sub>2</sub> O	−78	16	51	54 ( <i>S</i> )
8	<b>7</b>	CuTC	Et <sub>2</sub> O	−78	16	76	38 ( <i>S</i> )
9	<b>8</b>	CuTC	Et <sub>2</sub> O	−78	16	81	51 ( <i>S</i> )

**Scheme 2.****Scheme 3.**

Such a degree of enantioselectivity is rather astonishing for a flat molecule with only external chirality. The carbene derived from **5** has been coordinated with other metals, particularly with Rh, where it gave a similar level of enantioselectivity in hydrosilylation reactions.<sup>[5a]</sup>

The basic skeleton of **5** could be slightly modified by changing the exocyclic amino group. Thus, the analogous imidazolium salt precursors **6–8** were easily prepared<sup>[12]</sup> and tested. The results are rather similar to ligand **5**, with ligand **7** (with the 1-naphthyl group) being the worst. Improvements had to be found elsewhere.

Although the silver carbene **2** gave a rather low enantioselectivity,<sup>[9]</sup> there were some advantages in using this type of ligand. They are stable, ready to use and not hygroscopic. Therefore, we prepared,<sup>[13]</sup> and tested, the silver carbenes of some of the above imidazolium salts, complexes **9**, **10** and **11** (Scheme 3). In addition, we also prepared some analogues of silver carbene **2**, with benzylic groups on the nitrogen, carbenes **12** and **13** (Scheme 3).<sup>[13]</sup>

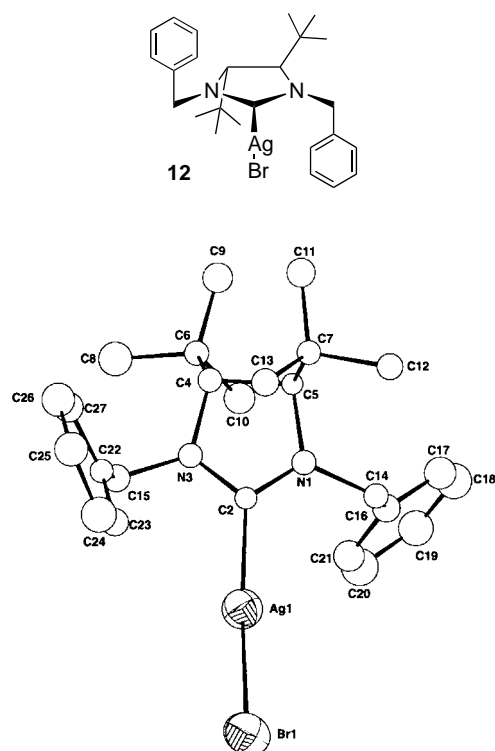
As shown in Table 2, the silver carbenes **9**, **10** and **11** all gave improved enantioselectivity for cyclohexenone (entries 1, 2 and 3). The ee obtained with **9** (62%), exceeds that obtained with the carbene precursor **5** (54% ee), a result which may be ascribed to an incomplete conversion of **5** to the carbene. These results were obtained with the new experimental conditions.<sup>[11]</sup>

To check the net effect of these conditions, we tested ligand **2** under both conditions; the ee was improved from 23 to 30% (entries 4 and 5). The best results of this series were obtained with the new silver carbenes **12** and **13**. The ee reached 69% with the sterically hindered ligand **13** (entry 7). The X-ray structure of **12** is shown below.<sup>[14]</sup> The stereochemical information arises from the orientation of the benzyl groups, one being up and the other one being down.

The efficiency of these new *N*-heterocyclic carbenes compares well with the asymmetric inductions they provide in other metal-catalyzed reactions.<sup>[5]</sup> Having found some good chiral NHC, and in order to generalize

**Table 2.** Conjugate addition to cyclohex-2-enone with various chiral silver carbenes.

Entry	Ligand	Cu salt	Solvent	Temp. [°C]	Time [h]	Yield [%]	ee [%]
1	<b>9</b>	CuTC	Et <sub>2</sub> O	−78	16	99	62 ( <i>S</i> )
2	<b>10</b>	CuOAc <sub>2</sub>	Et <sub>2</sub> O	−78	16	92	55 ( <i>S</i> )
3	<b>11</b>	CuOAc <sub>2</sub>	Et <sub>2</sub> O	−78	16	87	59 ( <i>S</i> )
4	<b>2</b>	CuOTf <sub>2</sub>	toluene	0	0.25	98	23 ( <i>S</i> )
5	<b>2</b>	CuTC	Et <sub>2</sub> O	−78	16	99	30 ( <i>S</i> )
6	<b>12</b>	CuTC	Et <sub>2</sub> O	−78	16	100	58 ( <i>S</i> )
7	<b>13</b>	CuTC	Et <sub>2</sub> O	−78	16	99	69 ( <i>S</i> )



Scheme 4.

the reaction, we screened several other Michael acceptors, under identical experimental conditions. Cyclic and acyclic enones were tested, as well as a nitroalkene.<sup>[15]</sup> The results are shown in Table 3.

From the tested substrates, cyclohept-2-enone is by far the most favorable one (entries 1, 6, 8, 10 and 11). It allows us to reach up to 93% enantioselectivity with ligand **11** (entry 8). This is a remarkably high value for such a relatively simple NHC and it shows that there is a lot of potential for improvement in this type of ligand. All the other silver carbenes also gave high ees, the lowest being 76%. Acyclic enones (entries 2, 3 and 4) were rather disappointing, both in terms of the yield and the enantioselectivity. Perhaps, other structurally differ-

ent NHC could be more efficient for this class of enones. Finally, nitrostyrene, an excellent Michael acceptor, also gave high ees, ranging from 55 to 75%.

In conclusion, we have confirmed that chiral *N*-heterocyclic carbenes are very promising ligands for asymmetric synthesis. Their use in the copper-catalyzed conjugate addition of dialkylzinc reagents allowed us to get among the highest enantioselectivities (up to 93%) for this type of ligands. It should be pointed out that the synthesis of these chiral NHC is very easy and that they are less sensitive and much cheaper than phosphorus-based ligands. Other copper-catalyzed reactions are currently being studied and the results will be reported in due time.

## Experimental Section

### Typical Procedure for Conjugate Addition using Imidazolinium Salt in Et<sub>2</sub>O at –78 °C

A dry Schlenk tube was charged with Cu(OTf)<sub>2</sub> (0.04 mmol) and imidazolinium salt (0.04 mmol), and Et<sub>2</sub>O (3 mL) was added. The resulting solution was cooled to –78 °C, at which time *n*-BuLi (0.05 mmol as a 2 M solution in hexanes) was added. After stirring for 30 minutes at low temperature, the reaction mixture was warmed up to room temperature and stirred for a further 15 minutes to ensure complete deprotonation. After this time, the solution was cooled back to –20 °C and diethylzinc was added (1.5 mmol as a 1 M solution in hexane). The mixture was stirred for 15 minutes before cooling to –78 °C and adding the substrate (1 mmol, either neat if cyclohexenone, or as a solution in toluene). After stirring at –78 °C for 16 hours, the reaction was quenched at low temperature by the addition of HCl (2 mL of a 1 M aqueous solution). The resulting mixture was stirred until clear and enantiomeric excesses could be measured directly using chiral GC (capillary column–Lipodex E, 0.2 μm, 50 m, 0.25 mm). The organic phases could be isolated, dried over MgSO<sub>4</sub> and the solvent concentrated under vacuum to yield the crude product, which could be purified by flash column chromatography to provide the pure product.

**Table 3.** Conjugate addition to other Michael acceptors with various chiral silver carbenes.

Entry	Ligand	Substrate	Cu salt	Yield [%]	ee [%]
1	<b>9</b>	Cyclohept-2-enone	CuOAc <sub>2</sub>	99	88 ( <i>R</i> )
2	<b>9</b>	5-Methyl-hex-3-en-2-one	CuTC	44	49
3	<b>9</b>	Benzalacetone	CuTC	60	42 ( <i>S</i> )
4	<b>9</b>	Non-3-en-2-one	CuTC	67	42 ( <i>S</i> )
5	<b>9</b>	Nitrostyrene	CuOAc <sub>2</sub>	100	75 ( <i>R</i> )
6	<b>10</b>	Cyclohept-2-enone	CuOAc <sub>2</sub>	97	76 ( <i>S</i> )
7	<b>10</b>	Nitrostyrene	CuOAc <sub>2</sub>	98	55 ( <i>S</i> )
8	<b>11</b>	Cyclohept-2-enone	CuOAc <sub>2</sub>	95	93 ( <i>S</i> )
9	<b>11</b>	Nitrostyrene	CuTC	98	69 ( <i>S</i> )
10	<b>12</b>	Cyclohept-2-enone	CuTC	99	76 ( <i>S</i> )
11	<b>13</b>	Cyclohept-2-enone	CuTC	100	88 ( <i>S</i> )

### Typical Procedure for Conjugate Addition using Silver Carbene in Et<sub>2</sub>O at –78 °C

A dry Schlenk tube was charged with copper salt (0.04 mmol) and silver carbene (0.04 mmol) and Et<sub>2</sub>O (3 mL) was added. After stirring for 15 minutes at room temperature, the solution was cooled to –20 °C and diethylzinc was added (1.5 mmol as a 1 M solution in hexane). The mixture was stirred for 15 minutes, then the reaction mixture was cooled to –78 °C for addition of the substrate (1 mmol, either neat if cyclohexenone, or as a solution in toluene). After stirring at –78 °C for 16 hours, the reaction was quenched at low temperature by the addition of HCl (2 mL of a 1 M aqueous solution) and treated as above.

Additional details are provided in the Supporting Information.

### Acknowledgements

The authors thank the Centre National de la Recherche Scientifique, the Swiss National Research Foundation No. 20-61891.00 and COST action D12/0022/99 for financial support.

### References and Notes

- [1] a) D. J. Cardin, B. Cetinkaya, M. F. Lappert, *Chem. Rev.* **1972**, 72, 545; b) W. A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2162; c) T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem.* **2000**, 600, 12; d) D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, 100, 39; e) L. Jafarpour, S. P. Nolan, *Adv. Organomet. Chem.* **2001**, 46, 181.
- [2] W. A. Herrmann, *Angew. Chem. Int. Ed. Engl.* **2002**, 41, 1291 and references cited therein.
- [3] For some Cu complexes see: a) P. L. Arnold, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.* **2001**, 2340; b) A. A. D. Tulloch, A. A. Danopoulos, S. Kleinhez, M. E. Light, M. B. Hursthouse, G. Eastham, *Organometallics* **2001**, 20, 2027 and references cited therein. For Ag complexes see: H. M. J. Wang, I. J. B. Lin, *Organometallics* **1998**, 17, 972 and references cited therein.
- [4] For selected references see: a) C. A. Hillier, G. A. Grasa, M. S. Viciu, H. M. Lee, C. Yang, S. P. Nolan, *J. Organomet. Chem.* **2002**, 653, 69; b) V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr, W. A. Herrmann, *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 1602; c) B. Gradel, E. Brenner, R. Schneider, Y. Fort, *Tetrahedron Lett.* **2001**, 42, 5689; d) D. S. McGuinness, K. J. Cavell, *Organometallics* **2000**, 19, 741; e) T. Weskamp, F. J. Kohl, W. Hieringer, D. Gleich, W. A. Herrmann, *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 2416; f) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, 34, 18; g) H. M. Lee, D. C. Smith Jr., Z. He, E. D. Stevens, C. S. Yi, S. P. Nolan, *Organometallics* **2001**, 20, 794; h) E. Peris, J. A. Loch, J. Mata, R. H. Crabtree, *Chem. Commun.* **2001**, 201.
- [5] a) W. A. Herrmann, L. J. Goossen, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2805; b) D. Enders, H. Gielen, *J. Organomet. Chem.* **2001**, 617-618, 70 and references cited therein; c) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, 66, 3402; d) T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, 3, 3225; e) M. T. Powell, D.-R. Hou, M. C. Perry, X. Cui, K. Burgess, *J. Am. Chem. Soc.* **2001**, 123, 8878; f) D. S. Clyne, J. Jin, E. Genest, J. C. Galluci, T. V. RajanBabu, *Org. Lett.* **2000**, 2, 1125; g) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, 124, 4954.
- [6] P. K. Fraser, S. Woodward, *Tetrahedron Lett.* **2001**, 42, 2747.
- [7] a) A. J. Arduengo III, R. L. Harlow, M. A. Kline, *J. Am. Chem. Soc.* **1991**, 113, 361; b) A. J. Arduengo III, *Acc. Chem. Res.* **1999**, 32, 913.
- [8] F. Guillen, C. L. Winn, A. Alexakis, *Tetrahedron Asymmetry* **2001**, 12, 2083.
- [9] J. Pytkowicz, S. Roland, P. Mangeney, *Tetrahedron Asymmetry* **2001**, 12, 2087.
- [10] a) A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron Asymmetry* **1993**, 4, 2427; b) A. H. M. De Vries, A. Meetsma, B. L. Feringa, *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2374; c) A. Alexakis, J. Vastra, P. Mangeney, *Tetrahedron Lett.* **1997**, 38, 7745; d) B. L. Feringa, *Acc. Chem. Res.* **2000**, 33, 346.
- [11] A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.*, **2002**, 124, 5262.
- [12] Imidazolium salts **6–8** were prepared in a similar way to **5**, according to: W. A. Herrmann, M. Elison, J. Fischer, C. Kocher, G. R. J. Artus, *Chem. Eur. J.* **1996**, 2, 777.
- [13] Silver carbenes **9–13** were prepared in a similar way to **2**, according to: J. Pytkowicz, S. Roland, P. Mangeney, *J. Organomet. Chem.* **2001**, 631, 157.
- [14] The X-ray data have been disclosed in ref.<sup>[13]</sup>
- [15] For a review on the copper-catalyzed asymmetric conjugate addition, with a list of all tested substrates, see: A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221; for other reviews on the same topic: a) M. P. Sibi, S. Man- yem, *Tetrahedron* **2000**, 56, 8033; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171.