

Conjugate Reduction of α,β -Unsaturated Carbonyl Compounds Catalyzed by a Copper Carbene Complex

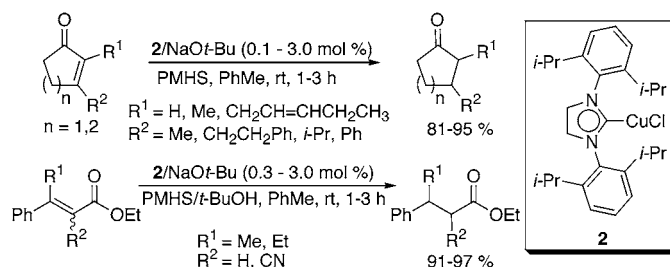
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ABSTRACT



An N-heterocyclic carbene copper chloride (NHC–CuCl) complex (**2**) has been prepared and used to catalyze the conjugate reduction of α,β -unsaturated carbonyl compounds. The combination of catalytic amounts of **2** and NaOt-Bu with poly(methylhydrosiloxane) (PMHS) as the stoichiometric reductant generates an active catalyst for the 1,4-reduction of tri- and tetrasubstituted α,β -unsaturated esters and cyclic enones. The active catalytic species can also be generated in situ from 1,3-bis(2,6-di-isopropylphenyl)-imidazolium chloride (**1**) CuCl₂·2H₂O in the presence of NaOt-Bu and PMHS.

N-Heterocyclic carbenes (NHCs) have emerged as a new class of ligand for homogeneous catalysis in the past decade.¹ Being strong σ -donors but very poor π -acceptors,² NHCs exhibit bonding similar to that of bulky phosphines.³

In the course of studying the reaction chemistry between transition metal complexes and carbon dioxide, one of us (J.P.S.) decided to prepare complex **2**. Arduengo reported the first NHC–copper complex derived from imidazolium salt and copper triflate.^{4,5} Such copper complexes have been shown to catalyze conjugate additions of diethylzinc to enones. Modest to excellent enantioselectivities were ob-

tained using chiral versions of carbene ligands for these transformations.⁶

We have recently described the asymmetric conjugate reductions of α,β -unsaturated esters and cyclic ketones catalyzed by a chelating phosphine in combination with CuCl.⁷ With **2** in hand, we felt it natural to investigate the

(5) For recent structural studies of N-heterocyclic carbene copper complexes, see: (a) Tulloch, A. A. D.; Danopoulos, A. A.; Kleinhenz, S.; Light, M. E.; Hursthouse, M. B.; Eastham, G. *Organometallics* **2001**, *20*, 2027. (b) Arnold, P. L.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2001**, 2340.

(6) (a) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083. (b) Pytkowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087. (c) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345.

(7) (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (b) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (c) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129. (d) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (e) Buchwald, S. L.; Appella, D. H.; Moritani, Y.; Shintani, R.; Jurkauskas, V. U.S. Patent 6 465 664, 2002. (f) Hughes, G.; Kimura, M.; Buchwald, S. L. Submitted for publication.

(1) For reviews, see: (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

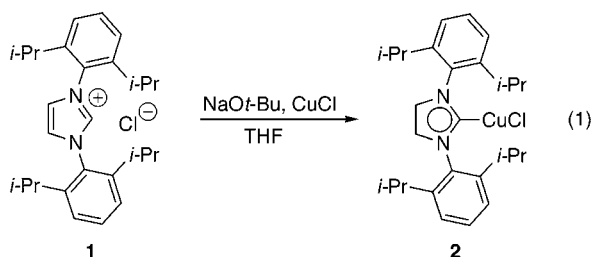
(2) (a) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913. (b) Tafipolsky, M.; Sherer, W.; Öfele, K.; Artus, G.; Pedersen, B.; Herrmann, W. A.; McGrady, G. S. *J. Am. Chem. Soc.* **2002**, *124*, 5865.

(3) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370.

(4) Arduengo, A. J., III; Dias, H. V. R.; Calabrese, J. C.; Davidson, F. *Organometallics* **1993**, *12*, 3405.

use of **2** in copper-catalyzed conjugate reductions of α,β -unsaturated carbonyl compounds.⁸ We report here use of **2** for the conjugate reduction of α,β -unsaturated carbonyl compounds.

We chose 1,3-bis(2,6-di-*i*-propylphenyl)-imidazolium chloride (**1**)⁹ for the preparation of the copper adduct. The air- and moisture-stable NHC–copper(I) complex **2** was readily prepared by deprotonation of **1** with NaO*t*-Bu in the presence of CuCl (eq 1).¹⁰



The initial study of conjugate reductions using **2** and NaO*t*-Bu in the presence of poly(methylhydrosiloxane) (PMHS) as a stoichiometric reductant showed that **2** is an effective catalyst even when used at high substrate/catalyst ratio (Tables 1 and 2). Notably, the reaction is not limited to the

Table 1. Catalytic Conjugate Reduction of a Cyclic Enone

entry	silane	solvent	2 , mol %	time, h	yield, ^a %
1	PMHS	toluene	0.1	1	88
2	Ph ₂ SiH ₂	toluene	0.1	1	87
3	PMHS	THF	0.1	1	86
4	Ph ₂ SiH ₂	THF	0.1	1	88
5	PMHS	toluene	0.05	6	86

^a Isolated yield. All reactions reached full conversion as determined by GC.

use of PMHS; no change in reaction time or yield was observed with diphenylsilane as the stoichiometric reducing

(8) Conjugate reductions using Cu-phosphine complexes: (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (c) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573. (d) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901. (e) Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580. Conjugate reductions using Cu with no ligand: (f) Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887.

(9) Available from Strem Chemicals, Inc.

(10) Procedure for the preparation of **2**. An oven-dried 25 mL Schlenk flask was charged with 0.900 g (2.12 mmol) of 1,3-bis(2,6-di-*i*-propylphenyl)imidazolium chloride, 0.210 g (2.12 mmol) of CuCl, 0.204 g (2.12 mmol) of NaO*t*-Bu, and 10.6 mL of dry THF. The resulting mixture was stirred for 4 h at room temperature. The reaction mixture was filtered over Celite, and the solvent was removed in vacuo. The product was dried under vacuum. NHC–CuCl (**1**) was obtained (0.774 g, 1.59 mmol, 75% yield) as a gray powder.

Table 2. Catalytic Conjugate Reduction of an α,β -Unsaturated Ester

entry	<i>t</i> -BuOH, equiv	2 , mol %	time, h	conversion, ^a %	yield, %
1		1.0	20	65	
2	3	0.1	20	80	
3	4	0.1	20	100	89
4	4	0.3	1	100	91

^a Conversions were determined by GC.

agent (Table 1, entries 1 and 2). Similarly, conjugate reductions catalyzed by **2** can be performed in both toluene and tetrahydrofuran; no change in reactivity was observed (Table 1, entries 1 and 3). It is noteworthy that cyclic enone can undergo conjugate reduction with as little as 0.05 mol % **2**, although a longer reaction time is required (Table 1, entry 5).

We next investigated the use of **2** for the conjugate reduction of α,β -unsaturated esters. Using 1 mol % **2**, the reduction of ethyl *trans*- β -methylcinnamate (**3**) was incomplete even after 20 h. We previously have found that the inclusion of an alcohol in the conjugate reduction of unsaturated esters, lactones, and lactams leads to an increased rate of reduction.^{7f} Here, too, a rate enhancement for the conjugate reduction of α,β -unsaturated esters was observed in the presence of a bulky alcohol (Table 2, entries 1 and 2).¹¹ In the presence of *t*-BuOH (4 equiv), conjugate reduction of **3** can be accomplished in 1 h with only 0.3 mol % **2** (Table 2, entry 4).

Encouraged by these results, we investigated the scope of conjugate reductions catalyzed by **2**. Several α,β -unsaturated carbonyl compounds were tested to determine the catalyst's tolerance to steric hindrance at the β -carbon, number of substituents at the double bond, and different functional groups (Table 3). As shown in Table 3, 0.1 mol % **2** was sufficient to effect 1,4-reductions of trisubstituted cyclic enones regardless of the size of substituent at β -carbon (entries 4–7). It is important to note that similar reductions catalyzed by (bis-phosphine)CuH complex require much larger amounts of catalyst and longer reaction times.^{8b} As mentioned earlier, addition of a stoichiometric amount of *tert*-butyl alcohol was necessary to reduce trisubstituted α,β -unsaturated esters effectively with 0.3 mol % catalyst (entries 1 and 2).

The conjugate reduction of a tetrasubstituted double bond represents a great challenge. Using **2**, the efficient 1,4-reduction of tetrasubstituted double bonds can be accomplished (Table 3, entries 3 and 8–10). Substrates containing a cyano group (entry 3) or an isolated double bond

(11) Addition of *t*-BuOH had an adverse effect on the rate of conjugate reduction of 3-phenethylcyclopentenone.

Table 3. N-Heterocyclic Carbene Copper Complex (2)-Catalyzed Conjugate Reductions of α,β -Unsaturated Carbonyl Compounds¹²

entry	starting material	product	2, mol %	time, h	yield, ^a %
1 ^b			0.3	1	91
2 ^b			0.3	1	97
3 ^c			2	4	93 ^d
4 ^e			0.1	1	88
5 ^e			0.1	3	95
6 ^e			0.1	1	81
7 ^e			0.1	1	93
8 ^f			1	1	85 ^g
9 ^f			1	1	90 ^h
10 ^f			3	3	94 ⁱ

^a Full conversions as determined by GC. Isolated yield of >95% purity as determined by GC and ¹H NMR. ^b Used 4 equiv of PMHS and 4 equiv of *t*-BuOH. ^c Used 12 equiv of PMHS and 12 equiv of *t*-BuOH. ^d Dr = 1.5:1 as determined by ¹H NMR. ^e Used 1.6 equiv of PMHS. ^f Used 3 equiv of PMHS. ^g Dr = 4:1 as determined by GC. ^h Dr = 4:1 as determined by GC. ⁱ Dr = 5:1 as determined by GC.

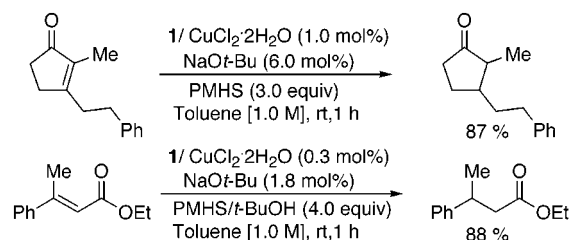
(entry 8) were successfully reduced; in each instance, reduction products were obtained with the functional group intact.

It is also possible to generate the NHC–copper catalyst in situ¹³ by mixing imidazolium salt **1**, air- and moisture-

(12) A typical experimental procedure for the conjugate reduction of 3-phenethyl cyclopentenone (Table 3, entry 4) is as follows: An oven-dried round-bottom flask under argon was charged with 3.0 mg (5.91×10^{-3} mmol) of **2**, 1.0 mg (5.9×10^{-3} mmol) of NaOt-Bu, and 1.0 mL of dry toluene. The resulting mixture was stirred for 10 min at room temperature, and then 0.2 mL (3.3 mmol) of PMHS was added. The resulting yellow/orange mixture was stirred for 5 min. Then, 2.0 mL of toluene followed by 0.37 mL (6.1 mmol) of PMHS were added. A solution of 3-phenethylcyclopentenone (5.9 mmol) in toluene (2.9 mL) was added via

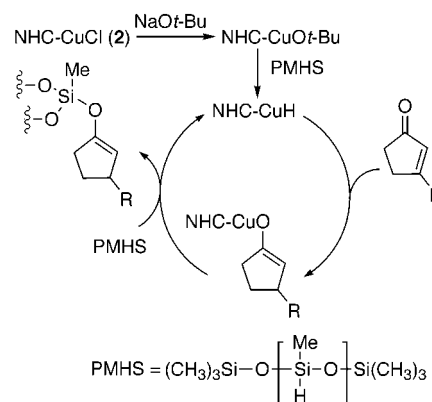
stable CuCl₂·2H₂O, and NaOt-Bu in toluene followed by the addition of PMHS. When used in conjugate reduction reactions, the in situ-generated catalyst exhibited efficiency identical to that found for **2** (Scheme 1).^{14,15}

Scheme 1



We propose that an N-heterocyclic carbene copper hydride (NHC–CuH) is the active catalyst in the catalytic cycle of the reaction.⁷ We postulate that upon combination of **2** and NaOt-Bu, formation of NHC–CuOt-Bu occurs.¹⁶ Presumably, addition of PMHS results in a σ -bond metathesis between NHC–CuOt-Bu and siloxane,¹⁷ generating NHC–CuH (Scheme 2). Conjugate reduction then takes place,

Scheme 2



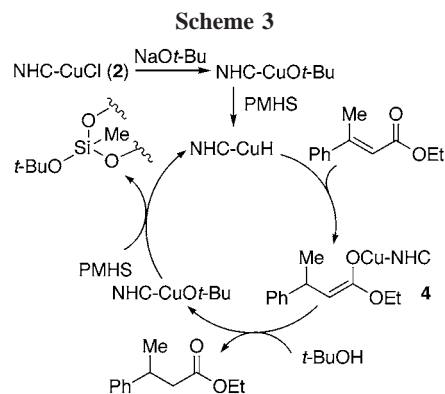
resulting in formation of a copper enolate intermediate¹⁸ that in turn undergoes σ -bond metathesis with PMHS to produce silyl enol ether in the case of cyclic enone.¹⁹ Since addition of *t*-BuOH results in a rate enhancement for the reductions of α,β -unsaturated esters, this suggests that the intermediate

cannula, and the reaction was stirred at room temperature for 1 h. At this point, H₂O (5.0 mL) was added; then, the layers were separated, and the aqueous layer was back-extracted (three times) with Et₂O (100 mL). The organic extracts were combined and washed with brine, dried with MgSO₄, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/ethyl acetate 10:1) afforded 0.98 g (5.20 mmol, 88% yield) of 3-phenethylcyclopentanone (Table 3, entry 4) as a colorless oil.

(13) For selected examples of in situ-generated N-heterocyclic carbene-transition metal catalysts, see: (a) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (c) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510. (d) Sémeril, D.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2002**, *344*, 585 and references therein.

(14) See Supporting Information for a detailed procedure.

copper ketene acetal **4** undergoes rapid protonation by *t*-BuOH to afford the saturated ester, regenerating NHC–CuO*t*-Bu. The latter then undergoes σ -bond metathesis with PMHS to regenerate the active catalyst NHC–CuH (Scheme 3).²⁰



In conclusion, the method we report here represents the most active catalytic system for the conjugate reductions of

(15) Conjugate reduction catalyst can also be generated in situ by mixing 1,3-bis(2,6-di-*isopropylphenyl*)-4,5-dihydro-imidazolium tetrafluoroborate (available from a Strem Chemicals, Inc.), $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, and KOt-Bu in THF/toluene in the presence of PMHS, although much higher amounts of catalyst (2–5 mol %) were needed to effectively reduce trisubstituted α,β -unsaturated carbonyl compounds.

(16) For the formation of a phosphine–Cu alkoxide complex, see: Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, 29, 3749.

α,β -unsaturated carbonyl compounds. While displaying great reactivity, a high level of functional group tolerance is also seen. The combination of catalytic amounts of **2** and NaOt-Bu , with PMHS or a silane as a stoichiometric reductant, generates NHC–CuH that efficiently catalyzes 1,4-reductions of tri- and tetrasubstituted α,β -unsaturated esters and cyclic enones. Additionally, NHC–CuH can be generated in situ from commercially available 1,3-bis(2,6-di-*isopropylphenyl*)imidazolium salt **1**, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, NaOt-Bu , and PMHS. Our current efforts are focused on determining the scope and mechanism of this catalyst system and the investigation of new chiral N-heterocyclic carbene ligands to effect this transformation in an enantioselective manner.

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Supporting Information Available: Preparation and characterization of all substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL034560P

(17) Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, 128, 1267.

(18) For the formation of copper enolate intermediates in bis-phosphine–copper-catalyzed aldol reactions, see: Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, 37, 3124.

(19) For evidence of silyl enol ether formation in analogous (bis-phosphine)CuH-catalyzed conjugate reductions, see refs 7b–d.

(20) Similar rate enhancement using a bulky alcohol is observed in the (bis-phosphine)CuH-catalyzed conjugate reduction of α,β -unsaturated esters; see, ref 7f.