ORGANIC LETTERS

2006
Vol. 8, No. 26
6059−6062

A Three-Component Tandem Reductive Aldol Reaction Catalyzed by N-Heterocyclic Carbene–Copper Complexes

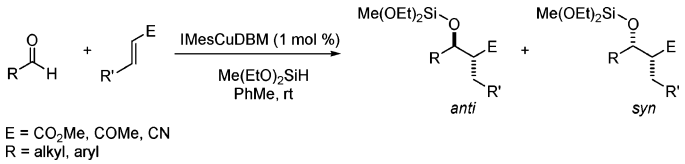
Alexandre Welle,[†] Silvia Díez-González,[‡] Bernard Tinant,[§] Steven P. Nolan,*[,‡] and Olivier Riant*[,†]

Unité de Chimie Organique et Médicinale and Unité de Chimie Structurale et des Mécanismes Réactionnels, Place Louis Pasteur 1, Université catholique de Louvain, 1348 Louvain la Neuve, Belgium, and Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

riant@chim.ucl.ac.be; snolan@iciq.es

Received October 10, 2006

ABSTRACT



An efficient catalytic system for the three-component coupling of electrophilic alkenes, aldehydes, and silane was optimized with a new family of copper N-heterocyclic carbene complexes. These catalysts do not require activation and show high activity (TOF > 15 000 h^{-1}) as well as some anti diastereoselectivity.

Since the first example of an N-heterocyclic carbene (NHC) copper(I) complex was reported less than 15 years ago by Arduengo,[1] the use of these complexes in catalysis has been developed thanks to their easy synthesis and stability. They have exhibited excellent reactivity in a wide range of transformations.[2] Notably, (NHC)copper−halogen complexes have been shown to be effective precursors of copper hydride species[3] which can be used in useful reduction processes such as in the hydrosilylation of carbonyl compounds[4] and electrophilic double bonds,[5] Copper(I) hydride complexes have been recently used in intramolecular tandem reduction-aldol cyclization with Stryker's reagent $[(PPh_3)CuH]_6$ as the copper hydride source.[6] Riant and Shibasaki reported the first examples of enantioselective copper hydride-catalyzed domino reduction−aldol reaction of methyl acrylate with aldehydes and ketones.[7] In these catalytic systems, copper hydride complexes bearing various chiral diphosphine ligands are generated and react with the acrylate to generate copper enolate nucleophiles. After the subsequent reaction of the

[†] Unité de Chimie Organique et Médicinale, Université catholique de Louvain.

[‡] Institute of Chemical Research of Catalonia.

[§] Unité de Chimie Structurale et des Mécanismes Réactionnels, Université catholique de Louvain.

(1) Arduengo, A. J., III; Rasika Dias, H. V.; Calabrese, J. C.; Davidson, F. *Organometallics* **1993**, *12*, 3405−3409.

(2) Selected examples in catalysis: Allylic alkylation: (a) Tominaga, S.; Oi, Y.; Kato, T.; Keun, An D.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585−5588. (b) Larsen, A. O.; Leu, W. L.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130−11131. Asymmetric conjugated addition of organometallics to enones: (c) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083−2086. (d) Pytkowics, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087−2089. (e) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345−348. (f) Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182−7183. (g) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416−8417. Carbene transfer: (h) Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Diaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 10846−10847. Boration of alkenes and aldehydes (i) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics* **2006**, *25*, 2405−2408. (j) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036−11038.

(3) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369−3371.

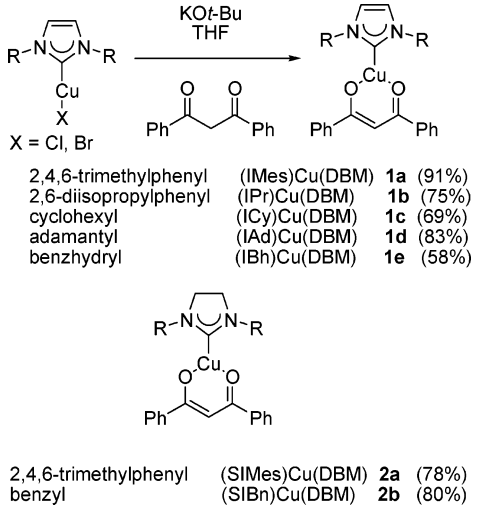
10.1021/ol062495o CCC: $33.50
Published on Web 11/24/2006

enolate with the electrophile, the copper hydride catalysts are regenerated by reaction of the copper aldolates with a hydrosilane. High reactivities could be reached with the proper choice of diphosphine ligand and we were interested to investigate the performance of NHC ligands in such catalytic reactions.

As for the (NHC)CuX complexes, their main drawback is the mandatory use of an activator such as NaO-*t*-Bu (1−6 equiv per copper atom).[4,5] This permits a halide−alkoxide exchange on the copper atom which in turn can react with the hydrosilane to generate the copper hydride active species. To avoid the use of an activator, variation of the co-ligand on the metal center was envisaged to design a "ready to use" copper hydride precursor. The choice of the co-ligand was made on the assumption that a weak Cu−O bond on the co-ligand should allow direct activation of the complex to generate the desired copper hydride catalyst. After several experiments, we found that dibenzoylmethanoate was an acceptable ligand (DBM) (Scheme 1). Complexes **1** and **2** could be prepared in high yield by simply reacting the corresponding (NHC)CuX complex with the potassium salt of DBMH. Alternatively, a two step "one-pot" procedure was devised by mixing the imidazolium salt, copper(I) chloride, DBMH, and 2 equiv of KO-*t*-Bu in dry THF. The corresponding DBM complexes were isolated as stable orange crystalline solids after simple filtration crystallization. All complexes can be prepared on a multigram scale as air stable solids except the ones bearing unhindered alkyl- or benzyl-substituted NHC ligands such as **1c** and **2b**. In the latter case, rapid decomposition was observed when the complex was handled in aerobic conditions both in the solid state and in solution, and therefore, they were kept in a glovebox. The structure of (IMes)Cu(DBM) complex **1a** was also confirmed by X-ray crystallography (Figure 1).

We were pleased to find that direct activation of the complex **1b** by a hydrosilane afforded the copper hydride species. This was confirmed by ^{1}H NMR spectra of degassed solutions of (IPr)Cu(DBM) in anhydrous C_6D_6 in the presence of various silanes. In all cases, a sharp singlet located at 4.46 ppm was observed that was attributed to the corresponding Cu−H resonance. Although the resonance for the corresponding dimer was reported at 2.67 ppm by Sadighi et al.,[3] the presence of the silylated DBM ligand on copper is presumably responsible for this chemical shift.

Scheme 1. Synthesis of (NHC)Copper Complexes **1** and **2**



Preliminary optimization experiments were carried out on the reaction of methyl acrylate with cyclohexane carboxaldehyde (Table 1) which gave the correponding aldol adducts after deprotection of the silyl aldolates (NH_4F, MeOH) along with the alcohol **6** arising from the competitive direct reduction of the aldehyde **3**. Various reaction parameters were examined such as solvent, temperature, silane, and the catalyst structure. In all cases, excellent reactivity was achieved, and we examined the influence of those parameters on the chemoselectivity and diastereoselectivity of this reaction. The reaction can be carried out in various solvents (Et_2O, DCM, CH_3CN, THF, PhMe) but we found

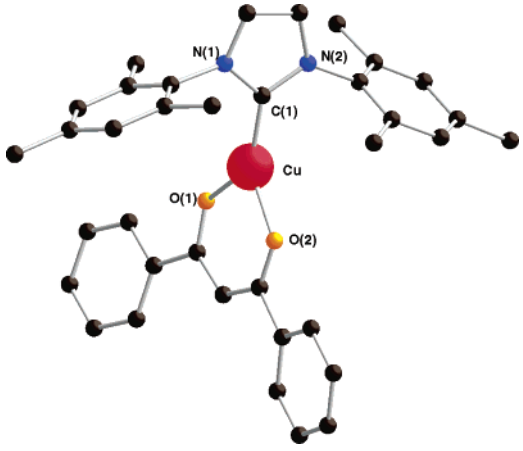


Figure 1. Ball-and-stick drawing of **1a**. Hydrogen atoms were omitted for clarity. Selected bond lengths and angles: Cu−C(1), 1.861 Å; Cu−O(1), 1.974 Å; Cu−O(2), 1.986 Å; C(1)−Cu−O(1), 136.0°; C(1)−Cu−O(2), 132.5°; O(1)−Cu−O(2), 91.3°.

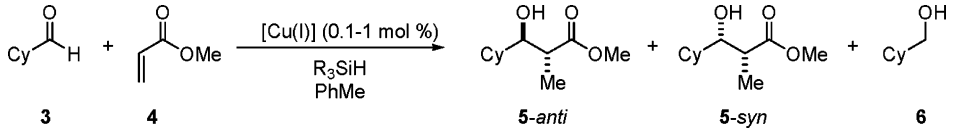
(4) (a) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157−1160. (b) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784−4796. (c) Bantu, B.; Wang, D.; Wurst, K.; Buchmeiser, M. R. *Tetrahedron* **2005**, *61*, 12145−12152. (d) Díez-González, S.; Scott, N. M.; Nolan, S. P. *Organometallics* **2006**, *25*, 2355−2358.

(5) (a) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417−2420. (b) Yun, J.; Kim, D.; Yun, H. *J. Chem. Soc., Chem. Commun.* **2005**, 5181−5183.

(6) For intramolecular reductive aldol reaction with a stoichiometric amount of Stryker's reagent, see: (a) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229−9232. (b) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901−1903. (c) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091−4093. For intramolecular reductive aldol reaction with a catalytic amount of Stryker's reagent, see: (d) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308−2309. (e) Chiu, P. *Synthesis* **2004**, 2210−2215. For intramolecular reductive aldol reactions catalyzed by $Cu(OAc)_2{\cdot}H_2O$, see : (f) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225−4228. (g) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743−5746.

(7) (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1297. (b) Zhao, D. B.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403−1407. (c) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O. Submitted for publication.

Table 1. Optimization Studies on the Reductive Aldol Reaction[a]



3 **4** **5**-*anti* **5**-*syn* **6**

entry	complex	T (°C)	silane	cat. loading (mol %)	chemoselectivity[b,c]	anti/syn[b]
1	**1a**	25	$PhSiH_3$	1	82	68/32
2	**1a**	25	$PhSiH_3$	0.1	93	69/31
3	**1a**	−20	$PhSiH_3$	1	90	74/26
4	**1a**	−50	$PhSiH_3$	1	88	72/28
5	**1a**	25	Ph_2SiH_2	1	67	73/27
6	**1a**	25	$Me_2(EtO)SiH$	1	n.r.	
7	**1a**	25	$Me(EtO)_2SiH$	1	93	66/34
8	**1b**	25	$PhSiH_3$	1	75	73/27
9	**1c**	25	$PhSiH_3$	1	91	70/30
10	**1d**	25	$PhSiH_3$	1	90	65/35
11	**1e**	25	$PhSiH_3$	1	96	73/27
12	**2a**	25	$PhSiH_3$	1	77	69/31
13	**2b**	25	$PhSiH_3$	1	84	68/32

[a] All reactions were carried out at 25 °C under an oxygen-free argon atmosphere containing **3** (1 equiv), **4** (1.1 equiv), the copper catalysts (1 mol %), and $PhSiH_3$ (1.2 equiv) unless otherwise stated. [b] Determined by GC analysis after deprotection (NH_4F, MeOH) of the silyl ether. [c] Chemoselectivity = (**5**/(**5** + **6**)100).

that toluene afforded the highest reaction rates. We were very pleased to see that very high reactivity was indeed reached with complex **1a**, as the reaction was completed in less than 4 min when 0.1 mol % of the catalyst was used, reaching thus a TOF > 15 000 h^{-1} (entry 2). It should also be noted that reaction of (NHC)CuCl in the absence of an activator does not lead to any activity while the addition of KO-*t*-Bu restores the catalytic activity of the carbene complex.

Under these reaction conditions, very little competitive reduction of the aldehyde occurred and the anti aldol adduct was always observed as the major isomer. Fast reactions also occurred at lower temperature (1 h at −50 °C), although little influence on the anti/syn ratio was observed (entries 3 and 4). The influence of the steric bulk around the copper atom was also studied with the NHC complexes **1a**−**e** (entries 1 and 9−11). This catalytic system is quite insensitive as little modification in the anti/syn ratio was observed when the NHC steric hindrance was modified. Saturated ligands SIMes and SIBn also gave similar diastereoselectivities, albeit with a slightly reduced chemoselectivity (entries 12 and 13). The lack of influence of the structure of the ligand on the diastereoselectivity suggests that the aldol reaction goes through an open transition state in which the aldehyde is not coordinated to the copper enolate. This hypothesis is also supported by the low Lewis acidity of copper(I) coordinated to a strong σ-donor ligand and by the important steric congestion around the metal center, although the hypothesis of a closed chairlike Zimmerman−Traxler transition state with low *E*/*Z* selectivity cannot be completely excluded.

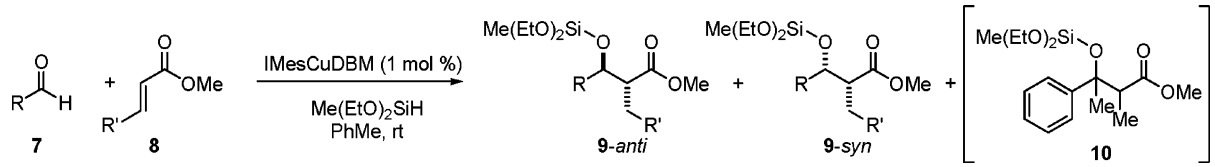
All optimization experiments were carried out with a strongly reactive, albeit expensive silane ($PhSiH_3$). To develop a practical experimental protocol, we searched for more economical alternatives. While little or no activity was observed for silanes such as tetramethyldisiloxane (TMDS), heptamethyltrisiloxane (HMTS), and $Me_2(EtO)SiH$, excellent reactivity was obtained when more reactive silanes such as Ph_2SiH_2 and $Me(EtO)_2SiH$ were used (entries 5 and 7). Methyldiethoxysilane was finally selected for further optimization as it is one of the less expensive silane reagent available.[8] Furthermore, the corresponding aldol adducts are fairly stable to hydrolysis, which allow the isolation of fully protected adducts bearing a methyldiethoxysilyl protecting group on the alkoxy moiety. This optimized procedure using (IMes)Cu(DMB) **1a** (1 mol %) complex as a precatalyst was then used to analyze the scope of the tandem reaction (Table 2).[9] Good yields were obtained with various aliphatic and aromatic aldehydes, the anti isomer being always the major product. We were also pleased to see that the catalytic system was not restricted to the use of aldehydes and acrylate as Michael acceptors. Indeed, good reactivity was also observed with methyl crotonate as the enolate precursor, albeit with reduced chemoselectivity (entry 2). This problem could be easily overcome by the use of an excess (2 equiv) of the Michael acceptor. Promising results were also obtained with ketones as the adduct of methyl acrylate, and acetophenone **10** was obtained in a 78% yield with our catalysts (erythro/threo 57:43).

We also tested variation of the electron withdrawing groups on the Michael acceptor and preliminary tests with

(8) Cost: $Me(EtO)_2SiH$, 265 euros/mol; Et_3SiH, 180 euros/mol.

(9) **Typical Procedure for Tandem Hydrosilylation−Aldolization.** A flame-dried flask under argon was loaded with the (NHC)copper complex (0.01 mmol, 0.01 equiv) under argon. A 5 mL portion of freshly distilled toluene was introduced, followed by sequential addition of the electrophilic olefin (1.1 mmol, 1.1 equiv), the electrophile (1 mmol, 1 equiv), and the silane (1.2 mmol, 1.2 equiv). After being stirred for 1 h, the solution was stirred for an additional 1 h under air. The volatile compounds were removed under reduced pressure, and the residue was purified by chromatography on triethylamine-pacified silica gel.

Table 2. (NHC)Copper-Catalyzed Reductive Aldol Reaction[a]

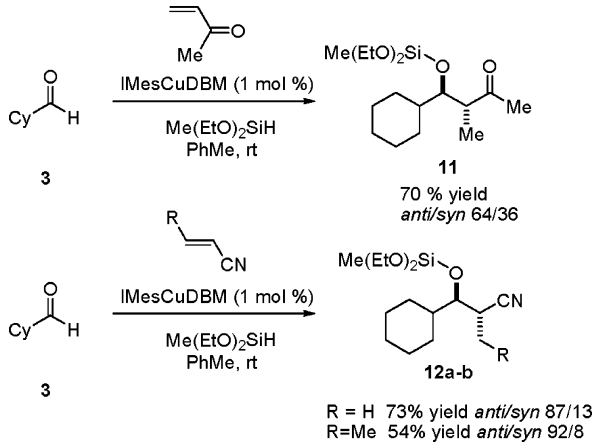


entry	electrophile	R′	product	chemoselectivity[b,c]	anti/syn[b]	yield[d] (%)
1	CyCHO	H	**9a**	95	70/30	70
2	CyCHO	Me	**9b**	77	71/29	75
3	EtCHO	H	**9c**	93	57/43	75
4	*i*-PrCHO	H	**9d**	95	67/33	78
5	*t*-BuCHO	H	**9e**	90	68/32	80
6	PhCHO	H	**9f**	97	71/29	72
7	2-PyrCHO	H	**9g**	93	73/27	72
8	2-ThCHO	H	**9h**	98	69/31	72
9	$PhCOCH_3$	H	**10**	>95	57/43[e]	78

[a] All reactions were carried out in toluene at 25 °C under an oxygen-free argon atmosphere containing **3** (1 equiv), **4** (1.1 equiv), the copper catalysts (1 mol %), and $Me(EtO)_2SiH$ (1.2 equiv) unless otherwise stated. [b] Determined by GC analysis. [c] Chemoselectivity = (**9**/(**9** + alcohol)100). [d] Isolated yield. [e] Erythro/threo.

unsaturated ketones, and nitriles also gave the corresponding adducts with cyclohexane carboxaldehydes in good yields and promising diastereoselectivities (Scheme 2).

Scheme 2. Reductive Aldol Reaction with Various Electrophilic Alkenes



The selectivities in favor of the anti adduct were especially high in the case of crotononitrile with a 92:8 anti/syn ratio. These equivalents of aldols adducts should be particularly interesting for the preparation of new building blocks such as γ-amino alcohols.

In conclusion, we have shown that a new family of (NHC)-copper(I) complexes could efficiently catalyze the three component reaction of electrophilic double bonds and aldehydes with dimethylethoxysilane without the need of an activating agent. We are currently studying the scope of this catalytic system in view of developing efficient enantioselective versions for the construction of useful enantiomerically enriched building blocks.

Acknowledgment. Université catholique de Louvain and FNRS are gratefully acknowledged for financial support of this work. Shimadzu Benelux is also gratefully acknowledged for financial support for the acquisition of a FTIR-8400S spectrometer. S.P.N. acknowledges the ICIQ Foundation and ICREA for a Research Professorship. Eli Lilly (assistance with materials) and Boehringer Ingelheim (unrestricted grant) are gratefully acknowledged for support of this work.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062495O