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Application of a C_2-Symmetric Copper Carbenoid in the Enantioselective Hydrosilylation of Dialkyl and Aryl−Alkyl Ketones

Abigail Albright and Robert E. Gawley*

Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, Arkansas 72701, United States

Supporting Information

ABSTRACT: We report excellent reactivity and enantioselectivity of a C_2-symmetric copper-bound *N*-heterocyclic carbene (NHC) in the hydrosilylation of a variety of structurally diverse ketones. This catalyst exhibits extraordinary enantioselctivity in the reduction of such challenging substrates as 2-butanone and 3-hexanone. Even at low catalyst loading (2.0 mol %), the reactions occur in under an hour at room temperature and often do not require purification beyond catalyst and solvent removal. The scope of this transformation was investigated in the reduction of 10 aryl−alkyl and alkyl−alkyl ketones.

The asymmetric hydrosilylation of prochiral ketones yielding enriched silylethers or alcohols is an attractive alternative to asymmetric hydrogenation, avoiding the use of expensive precious metal catalysts and occurring under very mild conditions.[1] The first catalytic ketone hydrosilylation was effected with tris-(triphenylphosphine)-rhodium chloride in 1972,[2] and this transformation has since become an important route to access the silyl ether and alcohol functionalities. Over the same period of time, silanes have emerged as an important class of protecting group for alcohols, fortuitously making the products of ketone hydrosilylation—before hydrolysis—useful in their own right. Furthermore, hydrosilylation generally occurs under mild reaction conditions which avoid over-reduction of the substrate and utilizes affordable and easy-to-handle reagents.[3]

Hydrosilylation catalysts are most frequently developed as complexes of group 9 metals such as rhodium and iridium, although recent advances have shown group 11 metals to be attractive (less expensive) alternatives.[4] In particular, stabilized copper hydride species are powerful reducing agents for numerous reductive transformations, among them hydrosilylation of ketones.[5] Tertiary phosphines are widely employed as ligands for hydrosilylation catalysts, particularly chiral ones, owing to their highly tunable steric and electronic properties. Comparable in their attributes but much less extensively employed are N-heterocyclic carbene (NHC) ligands.[6] The copper(I)-*N*,*N*′-bis-(2,6-diisopropylphenyl)imidazol-2-ylidine (CuIPr) NHC, a number of its analogs, and its cationic dimer, have shown promise in the hydrosilylation of a wide variety of ketones.[7]

A handful of chiral NHC catalysts have been employed with some success in the enantioselective hydrosilylation of prochiral ketones; key examples are depicted in Figure 1.[8−11] While some aryl−alkyl ketones can be reduced with excellent enantioselectivity using these NHC hydrosilylation catalysts, the rhodium complex developed by Gade is notable in that it can achieve moderate enantioenrichment in the hydrosilylation of *dialkyl* ketones. The enantioselective reduction of linear ketones remains an elusive goal: the best selectivity achieved for the hydrosilylation of 2-butanone is 83:17 er.[11,12]

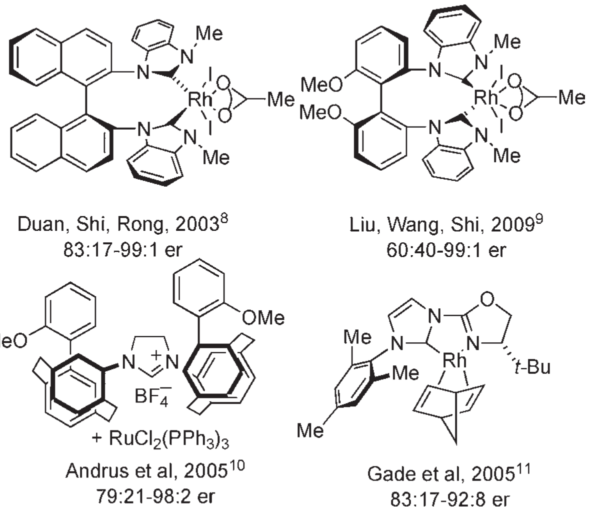

Figure 1. Previously reported NHC-catalysts for asymmetric hydrosilylation.

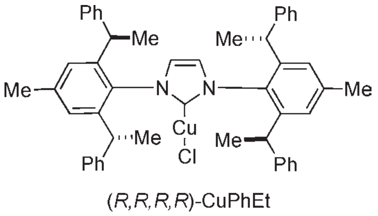

Figure 2. Cl−CuPhEt precatalyst.

Of course, many enantioselective hydrosilylation catalysts not containing NHC ligands can also be found in the literature. Pioneering work by Nishiyama showed chiral bisoxazoline catalysts to be effective in the asymmetric hydrosilylation of aryl−alkyl ketones.[13] Ito was among the first to demonstrate the utility of enriched silyl ethers as donors in cross coupling reactions.[14] More recently, Fu showed chiral P,N-ligands to be excellent catalysts for asymmetric hydrosilylation of both aryl akyl and dialkyl ketones, achieving the reduction of 2-octanone in 86:14 er.[15]

We recently disclosed the design and synthesis of three N-heterocyclic carbene ligands that have a stereocenter γ to the

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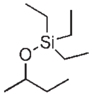
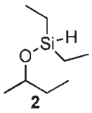
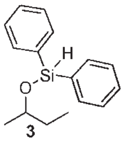
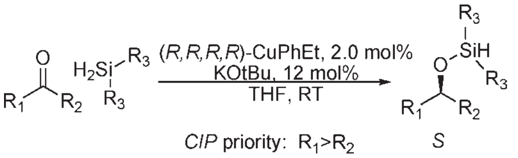
Table 1. Role of the Silane on the Time for 100% Conversion and Enantioselectivity in Reactions Catalyzed by (*R*,*R*,*R*,*R*)-CuPhEt

Product	Reaction Time (h)	%Conversion*	er (*S*:*R*)
 **1**	1.5	100	85:15
 **2**	0.5	100	98:2
 **3**	0.5	100	98:2

*GC conversions.

Scheme 1. CuPhEt-catalyzed Hydrosilylation of Prochiral Ketones

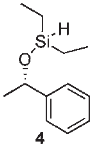
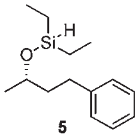
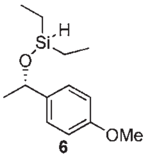
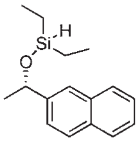
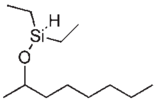
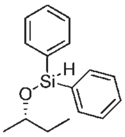
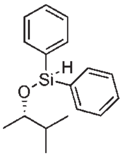
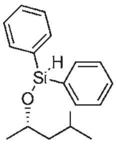
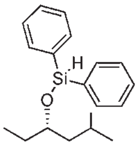
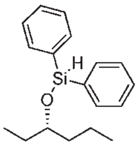


heterocyclic nitrogen.[16] One of these, a C_2-symmetric chiral copper NHC (Cl−CuPhEt, Figure 2), showed excellent activity and enantioselectivity in the hydrosilylation of acetophenone. The CuPhEt catalyst is air-stable and can be synthesized from *p*-toluidine in five steps. We consider it a chiral analog of the widely used Cl−CuIPr catalyst.

We now report the highly enantioselective reduction of a variety of aryl−alkyl ketones and, more importantly, simple linear ketones. The selectivity we observe with this class of substrates is exceptional, and it is achieved in less than an hour under very mild reaction conditions at room temperature. Interestingly, CuPhEt was found to be significantly more reactive than the CuIPr in the hydrosilylation of acetophenone, achieving full conversion in a fraction of the time (<1 h for CuPhEt vs 3−4 h for CuIPr). Furthermore, the synthetic protocol in many cases makes use of a highly volatile silane, which—though used in 3-fold excess—can be easily removed under reduced pressure. The enantioenriched silylether products are thus obtained without the need for extensive purification.

We first investigated the effect of the silane reagent on the enantioselectivity and percent conversion of 2-butanone to silyl ethers of 2-butanol. The results are summarized in Table 1. We observed that diethylsilane and diphenylsilane are more reactive than triethylsilane, as indicated by more rapid consumption of the ketone; triphenylsilane is unreactive with CuPhEt. This observation is consistent with evidence in the literature suggesting that hydrosilylation with trisubstituted silanes may be mechanistically distinct from hydrosilylation with disubstituted silane

Table 2. Scope of (*R*,*R*,*R*,*R*)-CuPhEt-catalyzed Hydrosilylation

Entry	Product	%conversion (Isolated Yield)	er (*S*:*R*)	Time (h)
1	 **4**	100 (90)	99:1	0.75
2	 **5**	100 (81)	98:2	0.75
3	 **6**	100 (85)	97:3	1
4	 **7**	100 (92)	99:1	1
5	 **8**	100 (77)	97:3	0.75
6	 **3**	100 (69)	98:2	0.5
7	 **9**	100 (88)	99:1	0.5
8	 **10**	100 (74)	96:4	0.5
9	 **11**	100 (77)	96:4	0.75
10	 **12**	100 (77)	95:5	0.75

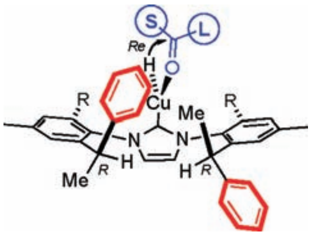


Figure 3. Predictive model for steric course of CuPhEt hydrosilylation. S = small, L = large.

reagents.[17] Significantly, the disubstituted silanes produce a more highly enantioenriched product than triethylsilane. Use of either diphenyl- or diethylsilane provided for isolation of the silyl ether of 2-butanol in 98:2 er. The dependence of enantioselectivity on the silane reagent has been observed with chiral BINAP-copper(I) catalysts used for hydrosilylation.[18] Also notable is the chemoselectivity of the CuPhEt catalyst. The use of a dihydrosilane reagent could lead to formation of the dialkoxy silane products, but di-*sec*-butoxysilanes were not detected in our experiments.

The optimized reaction conditions are detailed in Scheme 1. Less volatile ketone substrates (Entries 1−5, Table 2) were hydrosilylated with diethylsilane, providing for easy removal of excess silane during work up and obviating the need for chromatographic purification of the product. To prevent loss of product by evaporation, the more volatile dialkyl ketones (Entries 6−10, Table 2) were converted to diphenylsilyl ethers instead.

CuPhEt shows a high degree of reactivity and enantioselectivity in the hydrosilylation of a variety of aryl−alkyl ketones and simple linear ketones. 2-Butanone (entry 6) and 3-hexanone (entry 10) are respectively reduced in 98:2 and 95:5 er! Remarkably, hydrosilylation using CuPhEt is able to distinguish a methyl from an ethyl and an ethyl from a propyl group.

The absolute configurations of the silyl ethers derived from acetophenone, 2-butanone, 3-methyl-2-butanone, and 2-octanone were assigned by CSP-GC coinjection of an authentic, enantiopure silyl ether, or by hydrolysis of the silyl ether to the corresponding alcohol and comparison of optical rotation with an authentic sample. The configuration of the silylethers was in all cases found to be *S* via hydride addition to the *Re* face of the ketone using (*R,R,R,R*)-CuPhEt. For the examples for which an authentic enantiopure silane or alcohol was not available, absolute configuration was assigned by analogy. A predictive model, based on DFT calculations of an acetophenone complex with CuPhEt-H is offered in Figure 3.[16] This model is consistent with modeling and kinetic studies recently reported by Bellemin-Laponnaz et al.[19]

There is evidence that hydrosilylation catalyzed by achiral copper carbenoids proceeds via the formation of a copper hydride followed by coordination of the ketone and sigma bond metathesis.[7,20] The importance of aggregation of the copper hydride active catalyst has been established, and it is possible that the extraordinary activity of CuPhEt may be attributable in part to diminished ability to aggregate due to its steric bulk.[19] The kinetics and mechanism of CuPhEt-catalyzed hydrosilylations are under current investigation and will be reported in due course.

In conclusion, copper carbenoid CuPhEt has been synthesized and its activity in the hydrosilylation of prochiral ketone substrates has been investigated. CuPhEt exhibits extraordinary reactivity and enantioselectivity in this transformation, most notably in the reduction of simple dialkyl ketones. To our knowledge, the selectivity reported herein for the reduction of dialkyl ketones is unmatched by any asymmetric hydrosilylation or hydrogenation catalyst reported to date.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Spectroscopic and chromatographic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

bgawley@uark.edu

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