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Synthesis of α-Quaternary Formimides and Aldehydes through Umpolung Asymmetric Copper Catalysis with Isocyanides

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Supporting Information

ABSTRACT: A highly regio- and enantioselective copper-catalyzed three-component coupling of isocyanides, hydrosilanes, and γ,γ-disubstituted allylic phosphates/chlorides to afford chiral α-quaternary formimides was enabled by the combined use of our original chiral naphthol−carbene ligand as a functional Cu-supporting ligand and LiO*t*Bu as a stoichiometric Lewis base for Si. The formimides were readily converted to α-quaternary aldehydes.

Isocyanides have been employed as one-carbon reagents through their 1,1-insertion reactions into metal−element (M−E) bonds to form imidoylmetal species [M−C(=NR)−E], which exhibit characteristic reactivities in various catalytic transformations.[1] Specifically, formimidoylmetal species [M−C(=NR)−H], which can be produced through isocyanide 1,1-insertion into metal−H bonds, are expected to be "formyl anion (HCO^-)" equivalents. In fact, about 50 years ago, Saegusa, Ito, and co-workers[2] reported the copper-catalyzed 1,1-hydrosilylation of cyclohexyl isocyanide with trimethylsilane to yield (*N*-cyclohexylformimidoyl)trimethylsilane (Figure 1a). This

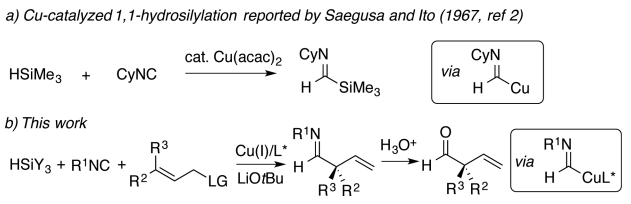

Figure 1. Isocyanides as precursors for formyl anion equivalents.

reaction should involve silylation of catalytically generated formimidoylcopper(I) species. In this regard, Saegusa, Ito, and co-workers showed for the first time the high synthetic potential of isocyanide 1,1-insertion into a metal−H bond as a means of generating a reactive "formyl anion" equivalent. Surprisingly, however, for a period of about a half century after this discovery, catalytic reactions involving 1,1-insertion of isocyanides into metal−H bonds or the formation of formimidoylmetal species were not explored except for the copper-catalyzed indole-forming reductive cyclization of a 2-alkenylaryl isocyanide reported by Chatani in 2010,[3] while it was well-documented that various hydride complexes of early or middle transition metals (group 3−5 transition metals and lanthanides) reacted with isocyanides in a stoichiometric manner to form η^1- or η^2-formimidoylmetal complexes.[1] As for copper, Sadighi recently reported the synthesis of an η^1-formimidoylcopper(I) complex through the stoichiometric reaction of benzyl isocyanide with isolated Cu(I) hydride dimers coordinated with N-heterocyclic carbene ligands, but its reactivity was not revealed.[4]

Here we report a highly regio- and enantioselective copper-catalyzed asymmetric three-component coupling reaction of isocyanides, hydrosilanes, and γ,γ-disubstituted primary allylic phosphates (chlorides) yielding chiral α-quaternary formimides, which can readily be converted to α-quaternary aldehydes (Figure 1b).[5−7] Acyl anion equivalents are important as umpolung reagents in organic synthesis,[8] and numerous efforts have been made to develop metal-catalyzed enantioselective allylic alkylation reactions using this type of nucleophile.[9] However, the reported protocols constructed only tertiary carbon stereogenic centers. The enantioselective construction of all-carbon quaternary stereogenic centers remains highly challenging.[10−12]

In our earlier studies on the copper-catalyzed enantioselective allylic substitution reactions of prochiral primary allylic phosphates with terminal alkyne or azole pronucleophiles, we synthesized some phenol−carbene chiral ligands and found them to be particularly efficient for enantioselective catalysis because of the functional roles of the phenolic OH groups.[13a,b] These ligands were also useful for copper-catalyzed enantioselective allylic substitution with allylboronate reagents.[13c]

The three-component coupling reaction of $PhMe_2SiH$ (0.18 mmol), cyclohexyl isocyanide (**1a**) (0.165 mmol), and (*Z*)-3-phenyl-2-buten-1-ol derivative **2a** (0.15 mmol) occurred efficiently and cleanly in the presence of a stoichiometric amount of LiO*t*Bu (0.195 mmol) and catalytic amounts of CuCl (10 mol %) and a chiral imidazolium salt (**L1**·HBF_4, 10 mol %) in THF at 25 °C to produce α-quaternary *N*-cyclohexylformimide (*S*)-**3aa**. This hydrolytically unstable compound was transformed to the corresponding α-quaternary aldehyde (*S*)-**4a** upon purification by silica gel chromatography. The yield of the purified (*S*)-**4a** was 93% based on **2a**, and its enantiomeric excess was as high as 96% (Table 1, entry 1). The γ-regioselectivity giving the γ,γ-double-branched product (**3aa**) over the achiral linear product (structure not shown) was exclusive (branched/linear >99:1). The enantioselectivity was further increased to 97% ee by lowering the reaction temperature to 0 °C (entry 2). The reaction in the presence of only 0.2 equiv of LiO*t*Bu (relative to **2a**), which should be consumed as a Brønsted base to form an oxyanion form of the **L1** ligand (**L1**−H) (10 mol %), under otherwise identical conditions resulted in no reaction (entry 3).

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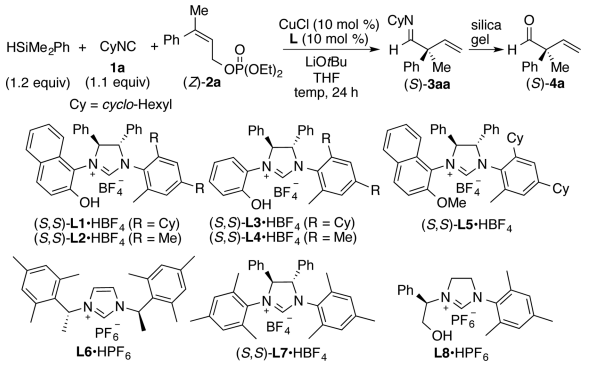
Table 1. Screening of Conditions[a]



entry	ligand	temp (°C)	yield of **4a** (%)	ee of **4a** (%)
1	**L1**·HBF_4	25	93	96
2	**L1**·HBF_4	0	88	97
3[b]	**L1**·HBF_4	25	0	–
4	**L2**·HBF_4	25	89	72
5	**L3**·HBF_4	25	90	81
6	**L4**·HBF_4	25	22	32
7	**L5**·HBF_4	25	0	–
8	**L6**·HPF_6	25	25	4
9	**L7**·HBF_4	25	0	–
10	**L8**·HPF_6	25	0	–

[a]Reaction conditions: $PhMe_2SiH$ (0.18 mmol), **1a** (0.165 mmol), (*Z*)-**2a** (0.15 mmol), CuCl/**L** (10 mol %), LiO*t*Bu (entries 1, 2, 4–6, 10, 0.195 mmol; entry 3, 0.03 mmol; entries 7–9, 0.18 mmol), THF (0.6 mL), 24 h. Yields of isolated **4a** are shown. The branched/linear ratio was >99:1 (as determined by ^{1}H NMR analysis of the crude product). **3aa** was hydrolyzed with silica gel. The enantiomeric excess was determined by HPLC analysis. [b]20 mol % LiO*t*Bu was used.

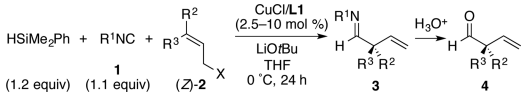
Other chiral carbene ligands bearing a naphthol or phenol group were less effective (Table 1, entries 4–6).[13] Thus, replacing the *N*-2,4-dicyclohexyl-6-methylphenyl group of **L1** with an *N*-mesityl group [(*S*,*S*)-**L2**] decreased the enantioselectivity to a moderate level (72% ee) (entry 4). Changing the naphthol group of **L1** to a phenol group [(*S*,*S*)-**L3**] also reduced the enantioselectivity (81%) (entry 5). The combination of phenol and *N*-mesityl groups [(*S*,*S*)-**L4**] significantly reduced the product yield (22%) and enantioselectivity (32%) (entry 6).

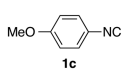
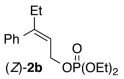
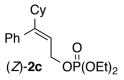
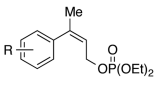
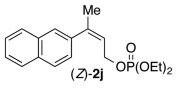
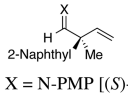
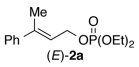
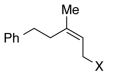
The use of phenol– or naphthol–carbenes was essential not only for the enantiocontrol but also for the catalytic activity (Table 1, entries 7–10). No reaction occurred with *O*-methyl-protected ligand **L5** (entry 7). Thus, the OH group in **L1** was essential. The ring-unsaturated C_2-symmetric carbene ligand having 1-(mesityl)ethyl groups on both N atoms (**L6**) gave nearly racemic product in low yield (25%), whereas the branch regioselectivity was exclusive (entry 8).[14] The ring-saturated C_2-symmetric carbene ligand with two stereogenic carbon centers in the imidazolidine ring and mesityl groups on both N atoms [(*S*,*S*)-**L7**] induced virtually no reaction (entry 9).[15] The *N*-hydroxyalkyl-substituted carbene ligand having a stereocenter in the *N*-alkyl side arm (**L8**) promoted no reaction (entry 10).[16] Thus, having the alkanol in place of the arenol was not suitable.

Siloxane-type hydrosilane $(Me_2HSi)_2O$ was as effective as $PhMe_2SiH$ (0 °C, 84% yield, 97% ee), but poly(methylhydrosiloxane) gave a low product yield (42%) but high enantioselectivity (95% ee). Trialkylsilanes such as Et_3SiH and *t*BuMe_2SiH did not participate in the reaction.

Other isocyanides also participated in the enantioselective reaction with $PhMe_2SiH$ and **2a** under identical conditions (Table 2). The reaction of benzyl isocyanide (**1b**) occurred with excellent enantioselectivity, affording, after hydrolysis, aldehyde (*S*)-**4a** with 99% ee in 89% yield (entry 1). The reaction of 4-

Table 2. Scope of Isocyanides and Allylic Phosphates[a]



entry	isocyanide	allylic substrate	formimide or aldehyde	yield (%)	ee (%)
1[b]	BnCN (**1b**)	(*Z*)-**2a**	(*S*)-**4a**	89	99
2	 **1c**	(*Z*)-**2a**	 (*S*)-**3ca**	94	99
3[b]	**1c**	(*Z*)-**2a**	(*S*)-**4a**	94	99
4[c]	**1c**	(*Z*)-**2a** (2 g, 7.04 mmol)	(*S*)-**3ca**	81	99
5[d]	**1c**	(*Z*)-**2a** (0.3 mmol)	(*S*)-**3ca**	90	99
6[e]	**1c**	(*Z*)-**2a** (0.6 mmol)	(*S*)-**3ca**	84	98
7	**1c**	 (*Z*)-**2b**	 (*S*)-**3cb**	90	96
8	**1c**	 (*Z*)-**2c**	 (*R*)-**3cc**	89	97
					
9	**1c**	R = *m*-MeO [(*Z*)-**2d**]	X = N-PMP [(*S*)-**3cd**]	93	98
10[b]	**1c**	R = *m*-MeO [(*Z*)-**2d**]	X = O [(*S*)-**4d**]	93	98
11	**1c**	R = *m*-THPO [(*Z*)-**2e**]	X = N-PMP [(*S*)-**3ce**]	90	99
12	**1c**	R = *p*-F [(*Z*)-**2f**]	X = N-PMP [(*S*)-**3cf**]	90	96
13	**1c**	R = *p*-EtO_2C [(*Z*)-**2g**]	X = N-PMP [(*S*)-**3cg**]	92	97
14	**1c**	R = *p*-Cl [(*Z*)-**2h**]	X = N-PMP [(*S*)-**3ch**]	88	95
15	**1c**	R = *p*-Me [(*Z*)-**2i**]	X = N-PMP [(*S*)-**3ci**]	95	98
16	**1c**	 (*Z*)-**2j**	 X = N-PMP [(*S*)-**3cj**]	90	97
17[b]	**1c**	(*Z*)-**2j**	X = O [(*S*)-**4j**]	90	97
18	**1c**	 (*E*)-**2a**	(*R*)-**3ca**	86	66
					
19[b]	**1a**	X = $(EtO)_2P(O)O$ [(*Z*)-**2k**]	X = O [(*R*)-**4k**]	89	83
20	**1c**	X = $(EtO)_2P(O)O$ [(*Z*)-**2k**]	X = N-PMP [(*R*)-**3ck**]	90	84
21[b]	**1c**	X = $(EtO)_2P(O)O$ [(*Z*)-**2k**]	X = O [(*R*)-**4k**]	90	84
22[b,f]	**1a**	X = Cl [(*Z*)-**2k'**]	X = O [(*R*)-**4k**]	60	86
					
23[b,f]	**1a**	R_3 = $Me_2C{=}CHCH_2CH_2$ [(Z)-**2l'**]	(*R*)-**4l**	60	88
24[b,f]	**1a**	R_3 = TBSO CH_2CH_2 [(Z)-**2m'**]	(*R*)-**4m**	46	84

[a]Reaction conditions: $PhMe_2SiH$ (0.18 mmol), **1** (0.165 mmol), **2** (0.15 mmol), CuCl/**L1** (10 mol %), LiO*t*Bu (0.195 mmol), THF (0.6 mL), 0 °C, 24 h. Yields of isolated products are shown. The branched/linear ratio was >99:1 (as determined by ^{1}H NMR analysis of the crude products). The enantiomeric excess was determined by HPLC analysis. [b]Entries 3, 10, 17, and 21: **3** was hydrolyzed with 2 M aqueous HCl. Entries 1, 19, and 22–24: **3** was hydrolyzed with silica gel. [c]Reaction over 36 h. [d]5 mol % CuCl/**L1** was used. Reaction over 48 h. [e]2.5 mol % CuCl/**L1** was used. Reaction over 72 h. [f]Poly(methylhydrosiloxane) was used.

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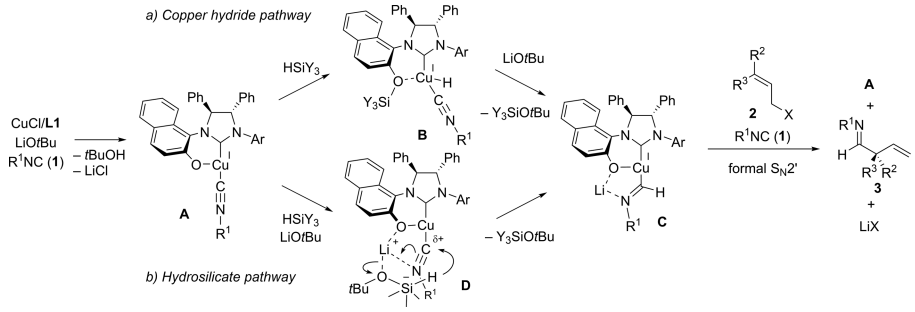

Figure 2. Possible reaction pathways.

methoxyphenyl isocyanide (**1c**) gave *N*-arylformimide (*S*)-**3ca** with 99% ee in 94% yield (entries 2 and 3).

The potential for scaling up the copper-catalyzed reaction was examined. Thus, the reaction of $PhMe_2SiH$ (1.19 g, 8.44 mmol), **1c** (1.06 g, 7.74 mmol), and **2a** (2 g, 7.04 mmol) yielded 1.51 g of (*S*)-**3ca** (81% yield) with 99% ee (Table 2, entry 4). The Cu loading could be reduced to 5 or 2.5 mol % with the high level of enantioselectivity retained (entries 5 and 6).

Table 2 also summarizes the results of the reactions of various (*Z*)-γ,γ-disubstituted allylic phosphates having aryl and alkyl substituents at the γ-position under the CuCl/**L1** catalyst system. **1c** was used as the isocyanide reagent because *N*-(4-methoxyphenyl)formimide products were more hydrolytically stable than *N*-alkylformimides. The former could be isolated by chromatography on silica gel. The *N*-(4-methoxyphenyl)-formimides were readily converted to the corresponding aldehydes upon acidic hydrolysis (2 M aqueous HCl). The methyl group of **2a** could be replaced with an ethyl group with virtually no deviation in enantioselectivity (entry 7). Remarkably, the allylic phosphate [(*Z*)-**2c**], with a sterically more demanding cyclohexyl group at the γ-position, also participated in the reaction to produce a significantly sterically congested quaternary stereogenic center with excellent enantioselectivity (entry 8). Various functional groups such as methoxy, THP ether, fluoro, ethoxycarbonyl and chloro substituents were tolerated at the meta or para position of the aromatic γ-substituent of the allylic phosphate (entries 9–14). The *p*-tolyl- and 2-naphthyl-substituted allylic substrates were also suitable (entries 15–17).

The reaction of (*E*)-**2a** with the *E* configuration under the optimized conditions provided the antipode of the product derived from the corresponding *Z* isomer (branched/linear >99:1) (Table 2, entry 18). This result suggests that (*Z*)-alkenes are more favorable substrates than (*E*)-alkenes and that the substitution pattern at the β-carbon is more important than that at the γ-carbon for enantioselection by the catalyst.

Furthermore, the copper catalyst system was applicable to the reaction of allylic substrates having two alkyl substituents at the γ-position, albeit with somewhat decreased enantioselectivity (Table 2). Thus, the reactions of allylic phosphate **2k** having methyl and phenylethyl groups with **1a** or **1c** occurred under the optimal reaction conditions with exclusive branch selectivities, affording the corresponding products [(*R*)-**4k** and (*R*)-**3ck**] in aldehyde or imine forms, respectively (entries 19–21). The combination of chloride as a leaving group and poly(methylhydrosiloxane) as a hydrosilane caused an increase in enantioselectivity (86% ee) (entry 22). Alkene [(*Z*)-**2l′**] and silyl ether [(*Z*)-**2m′**] moieties in the aliphatic γ-substituent of the allylic chloride were compatible with the reaction (entries 23 and 24). The reaction of γ-monosubstituted allylic substrates did not give the corresponding formimide products with tertiary stereogenic centers but instead gave trisubstituted alkenes and conjugated dienes that were produced through isomerization of the three-component coupling products and elimination reaction of the allylic substrates, respectively.

This copper-catalyzed three-component coupling presumably goes through the formation of a lithium aryloxo(formimidoyl)-cuprate species (**C**) followed by its formal S_N2' reaction with allylic substrate **2** (Figure 2). For the formation of formimidoylcopper(I) species **C**, two types of reaction pathways are conceivable. One involves isocyanide 1,1-insertion into a Cu–H bond (copper hydride pathway, Figure 2a), and the other is the direct reaction of hydrosilane, the isocyanide–Cu(I) complex (**A**), and LiO*t*Bu (hydrosilicate pathway, Figure 2b).

In the copper hydride pathway (Figure 2a), the reaction of CuCl, **L1**, LiO*t*Bu, and isocyanide **1** forms (**L1**–H)–Cu(I)–isocyanide complex **A**, in which the chiral carbene ligand coordinates to Cu as an anionic C,O-bidentate ligand (**L1**–H). Transmetalation between **A** and a hydrosilane produces copper(I) hydride species **B**.[17] Next, isocyanide insertion into the Cu–H bond accompanied by transmetalation between the aryloxysilane moiety and LiO*t*Bu forms intermediate **C**.

On the other hand, in the hydrosilicate pathway (Figure 2b) a Cu–H bond does not form. Thus, complex **A** recruits LiO*t*Bu through an O···Li^+···O ionic bridge to activate the hydrosilane reagent, forming hydrosilicate species **D**. The nucleophilic hydrosilicate moiety attacks the positively charged isocyanide terminal carbon that is in close proximity, producing **C**.

Although we do not rule out either reaction pathway at present, the hydrosilicate pathway (Figure 2b) better explains the critical roles of the ligand hydroxyl group (Table 1, entry 1 with **L1** vs entry 7 with **L5**) because the naphthoxo group directly participates in the formation of the formimidoylcopper structure only in the hydrosilicate pathway.[18]

When intermediate **C** assumed above reacts with the prochiral allylic substrate **2** in a formal S_N2' manner, either the Cu atom or the imidoyl C(sp^2) atoms may attack the γ-carbon of **2** (Figure 2). Furthermore, the possibility of the intervention of bond formation between the aryloxo O atom of **L1** and the α- or γ-carbon atom of **2** should not be ruled out. This complicated situation hampers the development of a model to explain the highly efficient enantioselection by the Cu/**L1** catalyst at present. However, it is likely that the Li^+ ion, which bridges the formimidoyl N and aryloxo O atoms in **C**, plays an essential role in the enantioselection. Thus, a Li^+ ion located at a well-defined position in a chiral environment would fix the rotation of the formimidoyl ligand around the Cu–C(imidoyl, sp^2) axis and assist the reaction of **C** with **2** in a cooperative manner through binding to the leaving group, limiting possible enantioselectivity-determining transition state conformers.

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The enantioenriched α-quaternary formimide and aldehyde products obtained by the enantioselective copper catalysis were used to demonstrate the synthetic utility of this methodology (Figure 3). Formimide (*S*)-**3ca** was readily converted to primary

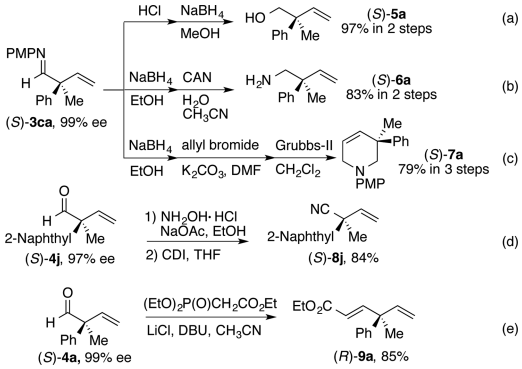

Figure 3. Derivatizations of α-quaternary formimide and aldehydes.

alcohol (*S*)-**5a** through acidic hydrolysis followed by $NaBH_4$ reduction (Figure 3a). Reduction of (*S*)-**3ca** with $NaBH_4$ followed by removal of the PMP group through treatment with cerium ammonium nitrate afforded primary amine (*S*)-**6a** (Figure 3b). The $NaBH_4$ reduction of (*S*)-**3ca** and N-allylation followed by ring-closing alkene metathesis produced the N-heterocyclic six-membered-ring compound (*S*)-**7a** (Figure 3c). The α-quaternary aldehydes (*S*)-**4j** and (*S*)-**4a** could be transformed to 2,2-disubstituted 3-butenonitrile (*S*)-**8j** and 2,5-dienoate (*R*)-**9a**, respectively, via the Horner–Wadsworth–Emmons reaction (Figure 3d,e).

In conclusion, a copper-catalyzed asymmetric three-component coupling reaction of isocyanides, hydrosilanes, and γ,γ-disubstituted primary allylic phosphates occurred with exclusive regioselectivity and high enantioselectivity to yield chiral α-quaternary formimides, which were readily converted to the corresponding aldehydes. This enantioselective copper catalysis was enabled by our original chiral naphthol–carbene ligand as a functional supporting ligand for Cu. Various functional groups in the substrates were tolerated. The formimidoyl and vinyl groups in the coupling products can be used as handles for further transformations. Mechanistic studies by intermediate analysis and theoretical calculations are underway. This enantioselective copper catalysis provides a new strategy for asymmetric synthesis using isocyanides as reagents for umpolung C1 synthons. Studies on expanding this strategy to include the use of different coupling partners will be carried out in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12881.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Preliminary NMR or FTIR studies on stoichiometric reactions with CuCl, **L1**, LiO*t*Bu, $PhMe_2SiH$, and benzyl isocyanide (**1b**) (1:1:3:1:1) in THF-d_8 (for NMR) or THF (for FTIR) at room temperature indicated coordination of the isocyanide to Cu in an asymmetric environment ($^2J_{H-H}$ = 17.2 Hz (AB quartet) for $CNCH_2Ph$; $\Delta\nu_{CN(isocyanide)}$ = +22 cm^{-1}), interaction of LiO*t*Bu with the Cu–isocyanide complex, and the formation of a formimidoyl species (δ 9.98 (s) for –N=C(R)–H; $\nu_{C=N}$ = 1680 cm^{-1}) upon addition of the hydrosilane (see the Supporting Information). During these spectroscopic experiments, no evidence of the formation of Cu–H species was obtained. Although definitive information concerning the formation of formimidoyl species was not obtained because of the complex and dynamic nature of the reaction mixtures, these spectroscopic results are in support of the hydrosilicate pathway.

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