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Enantioselective Conjugate Silyl Additions to α,β-Unsaturated Aldehydes Catalyzed by Combination of Transition Metal and Chiral Amine Catalysts

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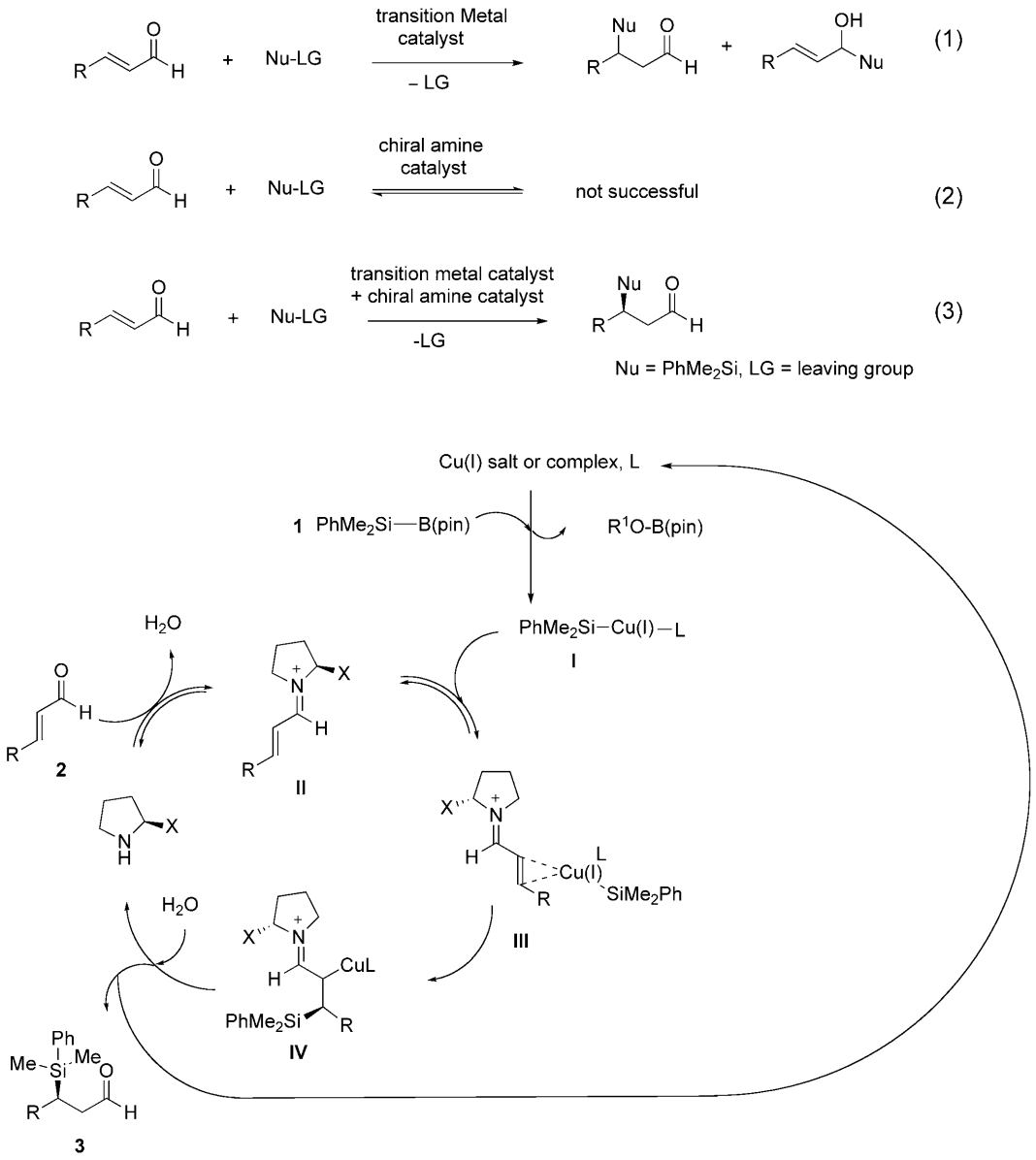
Abstract: We report that transition metal-catalyzed nucleophilic activation can be combined with chiral amine-catalyzed iminium activation as exemplified by the unprecedented enantioselective conjugate addition of a dimethylsilanyl group to α,β-unsaturated aldehydes. These reactions proceed with excellent 1,4-selectivity to afford the corresponding β-silyl aldehyde products 3 in high yields and up to 97:3 *er* using inexpensive bench stable copper salts and simple chiral amine catalysts. The reaction can also generate a quaternary stereocenter with good enantioselectivity. Density functional calculations are performed to elucidate the reaction mechanism and the origin of enantioselectivity.

Keywords: asymmetric catalysis; organocatalysis; β-silyl aldehydes; transition metal catalysis; α,β-unsaturated aldehydes

The development of methods for the catalytic enantioselective formation of C–Si bonds is an important challenge in organic synthesis.[1] In this context, the transition metal-catalyzed enantioselective conjugate addition (ECA) of *in situ* generated Si nucleophiles derived from readily available sources [e.g., $Cl_2PhSi–SiMe_3$ and $Me_2PhSi–B(pin)$ **1**, (pin) = pinacolato] to α,β-unsaturated acceptors is particularly attractive as it provides direct access to synthetically useful β-silyl carbonyl compounds.[2–7] For example, they can be readily transformed to the corresponding β-hydroxy carbonyl compounds without competing reactions (e.g., retro-aldol).[8] There are reports on the enantioselective silyl conjugate addition to α,β-unsaturated carbonyls.[4–6] However, to the best of our knowledge the ECA of a silyl group to α,β-unsaturated aldehydes **2** has not been disclosed. The enantioselective disilylation of enones has been reported using Pd as the catalyst and BINAP [2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl] as the chiral ligand.[4] Enantioselective silyl conjugate additions can also be performed using $Me_2PhSi-B(pin)$ **1** as the reagent, Rh as the metal catalysts and BINAP as the chiral ligand.[5] Recently, an elegant Cu-catalyzed asymmetric silyl addition to α,β-unsaturated ketones or lactones using monodendate chiral imidazolinium salts as ligand precursors was presented.[6] It is noteworthy that this system cannot be used with α,β-unsaturated aldehydes due to 1,2-addition.[6b]

In 2006, we reported that the catalytic cycles of a transition metal's activation of an electrophile and an amine's enamine activation of an aldehyde or ketone could be merged.[9] Since then several applications of this concept have been developed.[10] However, the catalytic cycles of a transition metal's activation of a nucleophile[11] and a chiral amine's iminium activation of an enal[12] have not been merged (Scheme 1). This strategy should allow for the employment of nucleophiles (e.g., Si nucleophile) that would not successfully react in catalytic ECAs without both the transition metal and amine catalysts present [Eqs. (1)-(3)].

Based on our research interest of merging transition metal-catalysis with aminocatalysis, we became intrigued whether we could test and develop this concept. The recent report of Hoveyda inspired us to begin with the catalytic enantioselective silyl addition to α,β-unsaturated aldehydes (Scheme 1).[6] Herein, we report that transition metal-catalyzed nucleophilic activation can be combined with chiral amine-catalyzed iminium activation as exemplified by the unpre-



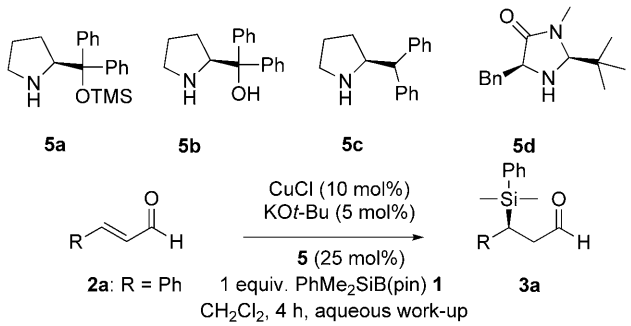
Scheme 1. A proposed reaction pathway for the combined catalytic cycles. B(pin) = pinacolatoboron, L = ligand.

cedented ECA of a dimethylsilanyl group to α,β-unsaturated aldehydes. Reactions proceed with excellent 1,4-selectivity and good to high enantioselectivity (up to 97:3 *er*) giving the corresponding β-silylaldehyde products **3** in high yields using inexpensive bench stable copper salts and simple chiral amine catalysts.

We envisioned that a Cu salt or complex would react with a sterically hindered Me_2PhSi-B(pin) **1** to deliver an L-Cu(I)-Silane **I**. For example, the driving force for its formation can be the creation of the B–O bond of the leaving pinacolatoboron alkoxide.[6,12] In this case, the chemoselectivity can be rationalized because formation of a Si–O bond is energetically less favored as compared to a B–O bond as shown by Hoveyda and co-workers.[6] In parallel, a simple chiral amine would form iminium intermediate **II** with the α,β-unsaturated aldehyde **2**. Next, the catalytic cycles would merge and the L-Cu-Silane **I** would stereoselectively react with the chiral iminum intermediate **II** *via* possible intermediate **III** to form a C–Si bond (**IV**). Subsequent hydrolysis of imiunium ion **IV** would give the corresponding β-silyl aldehyde product **3** as well as regenerate the Cu(I)-Silane **I** and chiral catalyst.

We began investigating the ability of *in situ* generated Cu complexes in catalyzing the addition of **1** to cinnamic aldehyde **2a** to afford β-silyl aldehyde **3a**. Only a trace amount of product was observed (e.g., Table 1, entries 1 and 2). The ability of a chiral amine such as **5a** to catalyze the same reaction without the

Table 1. Initial examination of the catalytic ECA of **1** to **2a**.[a]

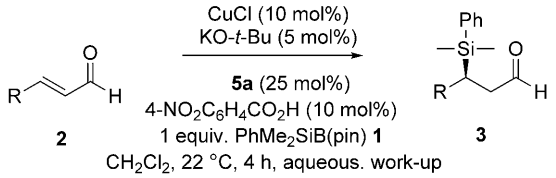


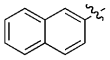
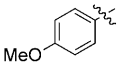
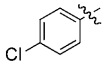
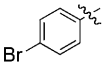
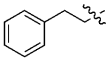
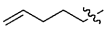
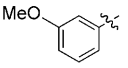
Entry	Cat. **5**	Temp. [°C]	Conv. [%][b]	*er*[c]
1	none	22	<3	n.d.
2	none	40	4	n.d.
3	**5a**[e]	22	<3	n.d.
4	**5a**	22	55 (50)[f]	63:37
5	**5a**[d]	40	80 (77)[f]	93.5:6.5
6	**5b**[d]	40	45	64.4:35.5
7	**5c**[d]	40	60	77:23
8	**5d**[d]	40	47	66.5:33.5
9	**5a**[g]	40	81	92:8
10	**5a**[h]	40	79	92.5:7.5
11	**5a**[d]	–15	35	95:5
12	**5a**[d]	22	80 (78)[f]	95:5
13	**5a**[i]	22	40	93:7
14	**5a**[j]	22	50	92:8
15	**5a**[d,k]	22	45	90:10
16	**5a**[d,k,l]	22	55	87.5:12.5

[a] Under an N_2 atmosphere.
[b] Determined by analysis of ^{1}H NMR spectra of unpurified mixtures.
[c] By HPLC analysis of alcohol **6a** derived by reduction of **3a**; see Supporting Information for details.
[d] 10 mol% 4-$NO_2C_6H_4CO_2H$ added.
[e] No CuCl.
[f] Yields of purified products.
[g] 10 mol% 3,5-$(NO_2)_2$-$C_6H_3CO_2H$ added.
[h] 10 mol% 4-F-$C_6H_4CO_2H$ added.
[i] Reaction performed with CuBr.
[j] Reaction performed with 20 mol% **5a** and 5 mol% CuCl.
[k] Reaction run without *t*-BuOK.
[l] Reaction run for 12 h; n.d. = not determined.

CuCl catalyst did also render a small amount (< 3% conversion) of **3a** (e.g., entry 3). Thus, we began probing the ability of a combination of an *in situ* generated Cu complex and a chiral amine **5** in catalyzing the ECA of **1** to **2a**. The key results, after 4 h reaction time, are summarized in Table 1.

Table 2. Combined Cu- and chiral amine **5a**-catalyzed ECA of silane **1** to enals **2**.[a]



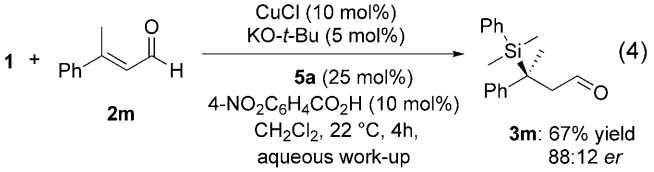
Entry	R	Product	Yield [%][b]	*er*[c]
1		**3a**	78	95:5
2		**3b**	69	96:4
3		**3c**	71	96.5:3.5
4		**3d**	70	97:3
5		**3e**	71	94:6
6		**3f**	70	94:6
7	*n*-Pr	**3g**	80	90:10
8	*n*-Bu	**3h**	70	90:10
9		**3i**	65	90:10
10	Me	**3j**	78	86:14
11		**3k**	65	94:6
12		**3l**	74	94.5:5.5

[a] Under an N_2 atm with 10 mol% CuCl, 25 mol% **5a**, 5 mol% KO-*t*-Bu and 10 mol% 4-nitrobenzoic acid at 22 °C for 4 h.
[b] Yields of purified products.
[c] By HPLC analysis of alcohol **6** derived by reduction of **3**; see Supporting Information for details.

To our delight, we found that simple commercially available chiral amines **5a**–**5d** with CuCl or CuBr were able to catalyze the ECA of **1** to **2** with excellent 1,4-selectivity (entries 4–14). The addition of an organic acid additive improved the *er* of the β-silylaldehyde **3**. Of the investigated chiral amines, catalyst **5a**[14] together with CuCl co-catalyzed the asymmetric assembly of **3a** with the highest enantioselectivity. It is noteworthy that none of the products derived from the formation of a C–B bond are observed. The optimal result gave **3a** in 78% isolated yield and 95:5 *er* (entry 12). Running the reaction for more than 4 h

did not significantly improve the conversion or *ee* of **3a** under our investigated reaction conditions. We also investigated the reaction without the addition of KO-*t*-Bu and found that the co-catalytic enantioselective β-silylaton of **2a** occurred (entries 15 and 16). However, the reaction rate decreased. With these results in hand, we decided to probe the scope of the catalytic β-silyl ECA of **1** to enals **2** using CuCl as the transition metal catalyst, **5a** as the amine catalyst, 4-nitrobenzoic acid as the additive in the optimal solvent CH_2Cl_2 (Table 2).

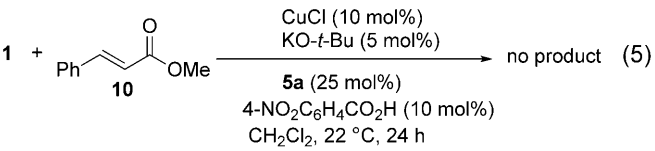
The reactions were efficient and proceeded with excellent chemo- and 1,4-selectivity to give the corresponding β-silyl aldehyde products **3a–3l** in high yields and good to high enantiomeric ratios (entries 1–12). The reaction tolerated enals with either an aryl substituent or an aliphatic moiety at the β-position. We observed a substituent effect for the catalytic β-silylation of cinnamic aldehydes where an electron-donating group gave a higher *er* as compared with an electron-withdrawing group at the phenyl group. Thus, the highest enantioselectivity was achieved in the co-catalytic reaction between **1** and 4-methoxycinnamic aldehyde **2d** to give **3d** in a 97:3 *er* (entry 4). Good enantioselectivity was observed for the transformations with aliphatic enals **2g–2k** (entries 7 to 11). The co-catalytic β-silyl additions to functionalized acceptor aldehydes **2i** and **2k** afforded the corresponding product aldehydes such as **3i** and **3k** in a 90:10 and 94:6 *er*, respectively (entries 9 and 11). The β-silyl aldehydes **3** are readily reduced in high yields to the corresponding β-silyl alcohols **6**. The co-catalytic asymmetric β-silylation reaction did also work with β-disubstituted enals **3**, which are useful starting materials for the synthesis of tertiary alcohols.[15] This was exemplified by the reaction between **1** and enal **2m** to give the corresponding product aldehyde **3m** with a quaternary stereocenter in good enantiomeric ratio [Eq. (4)].



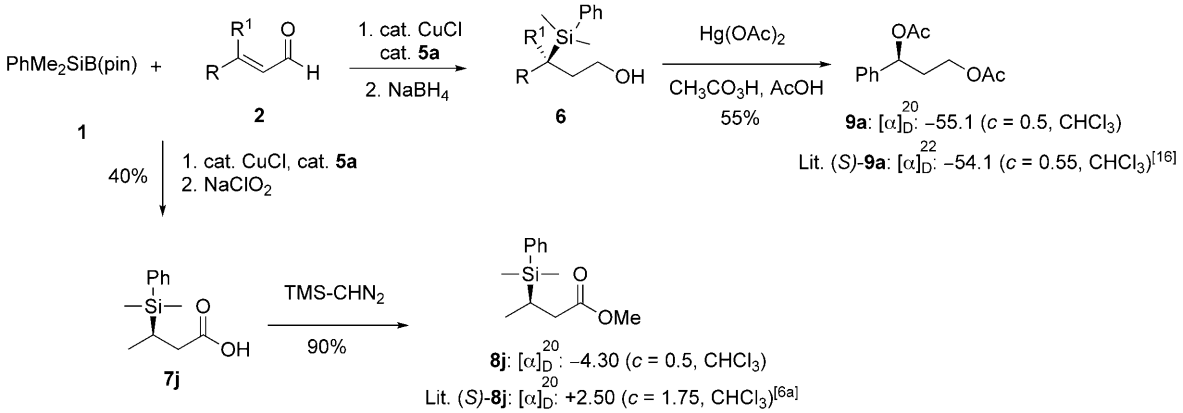
(4)

To establish the absolute configuration, β-silyl aldehyde **3j** was converted to the known β-silyl methyl ester **8j** *via* acid **7j** in two-steps (Scheme 2). Comparison with the literature revealed that the stereochemistry at C-3 is (*R*) {$[\alpha]_D^{20}$: −4.30 (*c* 0.5, $CHCl_3$); Lit. (*S*)-**8j**: $[\alpha]_D^{20}$: +2.50 (*c* 1.75, $CHCl_3$)[6]}. The synthetic utility of the reaction was shown by conversion of alcohol **6a** to diacetylated diol **9a** in 55% yield with a 91:9 *er* by a one-pot operation.[15] Thus, the silyl group can be readily converted to a useful acetoxy or hydroxy moiety. Comparison with the literature revealed that the stereochemistry at C-3 is (*S*) {$[\alpha]_D^{20}$: −55.1 (*c* 0.5, $CHCl_3$); Lit. (*S*)-**9a**: $[\alpha]_D^{22}$: −54.1 (*c* 0.55, $CHCl_3$)[16]}. Thus, the absolute configuration of aldehydes **3** is *S* when R = aryl.

^{1}H NMR and HR-MS analyses of the crude reaction mixture confirmed that a chiral iminium intermediate was formed between catalyst **5a** and enal **2a**. Furthermore, no ECA product was formed when cinnamic esters were used as substrates [Eq. (5)]. Thus, iminium activation must be essential for the aminocatalysis to occur. Based on the absolute configuration determinations and these results, we propose that the Cu(I)-Silane **I** approaches the less sterically hindered



(5)



Scheme 2. Enantioselective synthesis of alcohols **6**, ester **8j** and diacetylated diol **9a**.

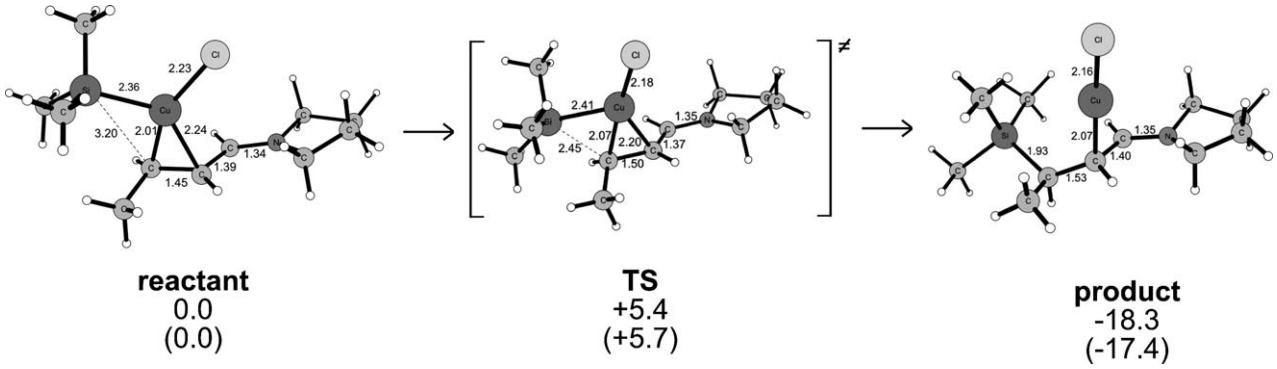


Figure 1. Optimized structures of the silylation step for the small model system. Distances in Ångstroms.

Re-face (R = aliphatic) of the β-carbon of chiral iminium intermediate **III** to give intermediate **IV** as shown in Scheme 1. In addition, HR-MS and ^{1}H NMR analyses of the crude reaction mixture confirmed the direct formation of product aldehyde **3** while no product boron enolate[6] could be observed by these methods, indicating that such a species is not present in significant amounts in our reaction system.

To shed more light on the reaction mechanism we performed density functional theory (DFT) calculations on the silylation step.[17–19]

We first modeled the key silylation step using a small system in which the chiral catalyst was replaced by a pyrrolidine, the phenyldimethylsilyl moiety by a trimethylsilyl group and (*E*)-2-butenal was chosen as the substrate (see Figure 1). The presence and the nature of the ligand on copper were first investigated (see Scheme 1). The reaction can in principle occur without a ligand (with the species R_3SiCu being the reactant) or with a neutral or anionic ligand (Cl^-, catalyst **5a** or the acid used as an additive). It turns out that the alternative that has the lowest energy barrier is when the reaction occurs on the iminium intermediate with chloride as a ligand to the copper. The barrier for the silylation step is calculated to be 5.4 kcal mol^{-1} (5.7 without inclusion of solvation effects). The optimized structures of the reactant, transition state (TS), and resulting product are shown in Figure 1. In the initial complex the copper coordinates both the α and β carbons (with distances 2.24 Å and 2.01 Å, respectively). In the TS, the nucleophilic silicon approaches the β carbon, with a distance of 2.45 Å, while the copper-carbon distances are almost unchanged (2.20 Å and 2.07 Å, respectively). After the attack, the Cu–Si bond is broken and the copper shifts to the α carbon. We also considered the possibilities of the reaction taking place with either the organocatalyst or the acidic additive as ligands to the copper instead of the chloride. The barriers for these two are calculated to be 6.3 and 7.5 kcal mol^{-1}, respectively (optimized transition states are shown in Figure 2). Both these values are very similar to the chloride case and it is therefore not possible from the current calculations to determine the nature of the

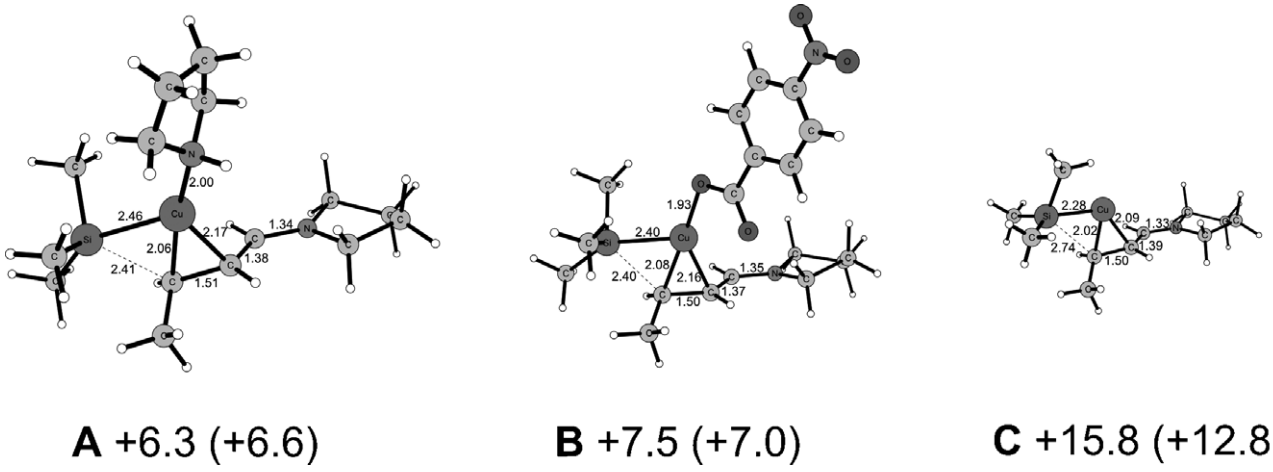


Figure 2. Optimized transition state structures for silylation on the small model system considering **A**) pyrrolidine as copper ligand, **B**) 4-nitrobenzoate as copper ligand, and **C**) no ligand on the copper. Respective barriers (kcal mol^{-1}) in CH_2Cl_2 and in the gas phase (in parentheses) are given.

copper ligand. However, performing reactions in order to investigate the *ee* of the product **3g** as a function of the *ee* of the chiral amine catalyst **5a** did not exhibit a significant non-linear effect (Supporting Information). Thus, it is most likely that one chiral amine molecule is present in the transition state. The option of not having any ligand on the copper was also considered (Figure 2) and the barrier was found to be considerably higher, 15.8 kcal mol^{-1}, ruling out this possibility.

It should also be mentioned that we also explored the possibility of the 1,4-addition occurring on the aldehyde, (*E*)-2-butenal **2g**, instead of the iminium intermediate, either with the chlorine or the pyrrolidine as ligands to the copper. Both these options have much higher barriers, 18.9 and 20.0 kcal mol^{-1}, respectively. These results establish the catalytic effect of the amine, that is, that the reaction occurs on the iminium intermediate. In addition, the transition state for the 1,2-addition on the iminium has been optimized, but it has been found to be 10.3 kcal mol^{-1} higher than the 1,4-addition. The possibility of the reaction occurring by a direct attack of compound **1** (modeled with an Me_3Si group and substituting the pinacolato moiety with an ethylene glycol) could be ruled out, since the transition state for this process has a very high energy (34.9 kcal mol^{-1}). Finally, a possible mechanism involving the conjugate addition of the silyl group on the hemiaminal formed by the attack of the amine on the aldehyde was also considered. The transition state for this reaction was, however, found to be prohibitively high in energy compared to the 1,4-addition on the iminium (barrier calculated to be 34.2 kcal mol^{-1}). The optimized transition state structures of all these mechanistic options are given in Supporting Information. Taken together, these results support the mechanistic proposal depicted in Scheme 1.

Next, in order to investigate the origin of enantioselectivity, the transition states for the 1,4-additions were optimized for a larger model comprising the whole catalyst **5a**, the proposed silylating complex **I** and (*E*)-2-hexenal as the acceptor substrate. The copper ligand was considered to be either chlorine or a model pyrrolidine, and the results were very similar in terms of absolute and relative barriers. Here, only the former case is discussed.[20] In Figure 3, we show the transition states leading to the *R* (**TS-*R***), and *S* (**TS-*S***) products. The calculations show that attack at the *Re*-face of the iminium, which is not shielded by the bulky group of the catalyst, is 2.3 kcal mol^{-1} lower than attack on the shielded *Si*-face (7.0 *vs.* 9.3 kcal mol^{-1}). This energy difference is in good agreement with the experimentally observed enantioselectivity (Table 2, entry 7). The calculations thus show that the source of enantioselectivity is the steric repulsion between the nucleophile and the bulky substituent on the organocatalyst, a feature that is now well-established in asymmetric enamine/iminium catalysis.[21]

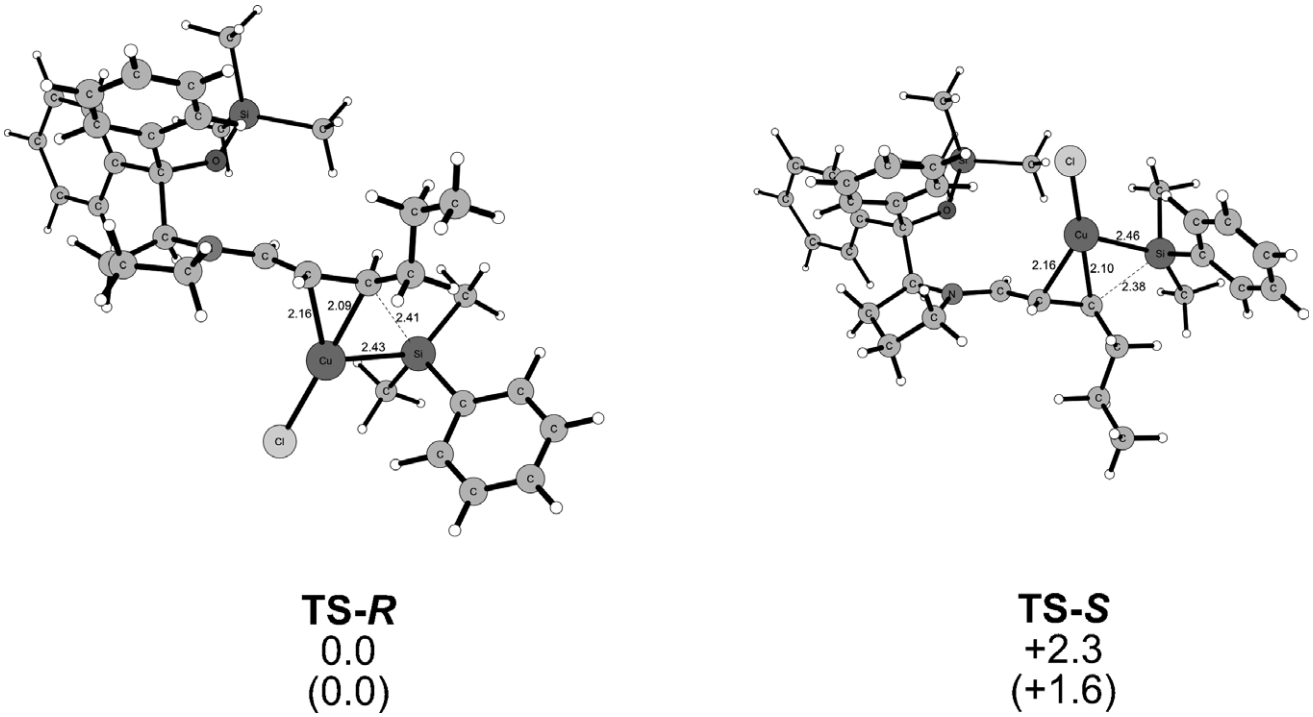


Figure 3. Optimized transition state structures for silylation of iminium ion. Relative energies (kcal mol^{-1}) in CH_2Cl_2 and in the gas phase (in parentheses) are given.

In summary, we have shown that it is possible to merge the catalytic cycles of transition metal-catalyzed nucleophilic activation and amine-catalyzed iminium activation to achieve enantioselective bond formation. This concept was exemplified by the first report of an enantioselective β-silyl addition to α,β-unsaturated aldehydes using simple and commercially available Cu salts and chiral amines to give the corresponding β-silyl aldehydes in up to 97:3 *er*. The products can be efficiently converted to protected 1,3-diols and β-functionalized esters. It is also noteworthy that a quaternary stereocenter can be generated by this co-catalytic transformation. Furthermore, DFT calculations have been used to investigate the reaction mechanism. The reaction is shown to proceed through a nucleophilic attack of the silyl moiety from a $PhMe_2SiCuL$ species on the iminium intermediate. The origin of the enantioselectivity has been shown to be the steric repulsion between the nucleophile and the bulky group of the organocatalyst. Future studies will involve investigating the possibilities of developing more efficient chiral amine catalysts and the employment of other nucleophiles based on the concept presented herein.

Experimental Section

Representative Procedure for Iminium-Cu-Catalytic Enantioselective Conjugate Silyl Additions

A 6-mL oven-dried vial with a magnetic stir bar was charged with KO-*t*-Bu (1.0 mg, 8.75 μmol, 5 mol%) and CuCl (2.0 mg, 17.5 μmol, 10 mol%). The vial was sealed and purged with a stream of N_2 before CH_2Cl_2 (875 μL) was added. The solution was allowed to stir for one hour at 22 °C under an N_2 atmosphere. The resulting solution was charged with $PhMe_2Si(Bpin)$ **1** (48.0 μL, 0.175 mmol, 1.0 equiv.). In a separate oven-dried vial (6×1 cm), aldehydes **2** (0.350 mmol, 2.0 equiv.) and the catalyst **5a** (14.2 mg, 43.8 μmol, 25 mol%) were dissolved in CH_2Cl_2 (875 μL) with *para*-nitrobenzoic acid (3.0 mg, 17.5 μmol, 10 mol%) under N_2, and then transferred by syringe to the solution of KO-*t*-Bu and CuCl (final substrate concentration = 0.1 M). The resulting mixture was allowed to stir for 4 h at 22 °C. Next, the resulting brown reaction mixture was directly loaded upon a silica gel column and immediate chromatography (hexane:EtOAc-mixtures) furnished the β-silyl aldehyde products **3**.

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