Engaging Aldehydes in CuH-Catalyzed Reductive Coupling Reactions: Stereoselective Allylation from 1,3-Diene Pronucleophiles

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ABSTRACT: Recently, CuH-catalyzed reductive coupling processes involving carbonyl compounds and imines has become an attractive alternative to traditional methods for stereoselective addition to carbonyls due to the ability to use readily accessible and stable olefin-derived pronucleophiles as surrogates for organometallic reagents. However, the inability to use aldehydes, which traditionally reduce too rapidly in the presence of copper hydride complexes to be viable substrates, has been a major limitation. We show that by exploiting relative concentration effects through slow addition, we can invert this intrinsic reactivity and achieve the reductive coupling of 1,3-dienes with aldehydes. Using this method, both aromatic and aliphatic aldehydes can be transformed to valuable products with high levels of diastereo- and enantioselectivity and in the presence of many useful functional groups. Furthermore, using a combination of theoretical (DFT) and experimental methods, important mechanistic features of this reaction related to stereo- and chemoselectivity were uncovered.

INTRODUCTION

The addition of nucleophilic organometallic reagents, such as those based on Mg (Grignard), B, Si, Sn and Zn, to carbonyl derivatives is a key reaction for C–C bond formation.[1] Accordingly, the development of methods to accomplish this transformation in a catalytic, stereoselective manner have been the subject of widespread research efforts.[2] Recently, breakthroughs in transition metal catalysis have enabled the use of olefin-derived nucleophiles, one of the most convenient and readily available classes of compounds, as surrogates of traditional organometallic reagents in carbonyl addition processes.[3-10] Following pioneering work by Krische using Rh[4a,b], Ru[5], Ir[6], and Ni catalysts,[7e] several research groups, including ours, have developed a number of CuH-catalyzed processes for reductive C–C bond formation from π-unsaturated pronucleophiles (Figure 1A).[9,10]

Each of these metals is associated with distinct catalytic mechanisms and complementary reactivity, and hence, features respective advantages and deficiencies. In the case of Cu, the most notable advantages include mild conditions, high stereoselectivity, and exceptional tolerance for polar functional groups.[9,10] On the other hand, the proclivity of CuH intermediates to participate in direct reduction of carbonyl compounds has so far limited the generality of this strategy: to date, only the functionalization of ketones and imines using relatively activated alkenes such as allenes, enynes, styrenes have been successfully accomplished (Figure 1B).[9,10] The conspicuous absence of aldehydes, the most common class of electrophiles in carbonyl addition reactions, can be explained by the rate of their direct reaction with CuH species, which is sufficiently high that the olefinic partner typically does not have the chance to participate in hydrocupration.[11]

With the aim of addressing this important limitation, we herein report the expansion of the scope of CuH-catalyzed reductive olefin–carbonyl coupling to aldehyde starting materials, using a combination of ligand-conferred regioselectivity and kinetic control through metered addition. To prove our concept, we selected 2-substituted 1,3-dienes as relatively unactivated model pronucleophiles (Figure 1B). 2-Substituted allyl groups are difficult to introduce using stoichiometric organometallic reagents, and few catalytic methods have been reported for their stereoselective installation.[2,12]

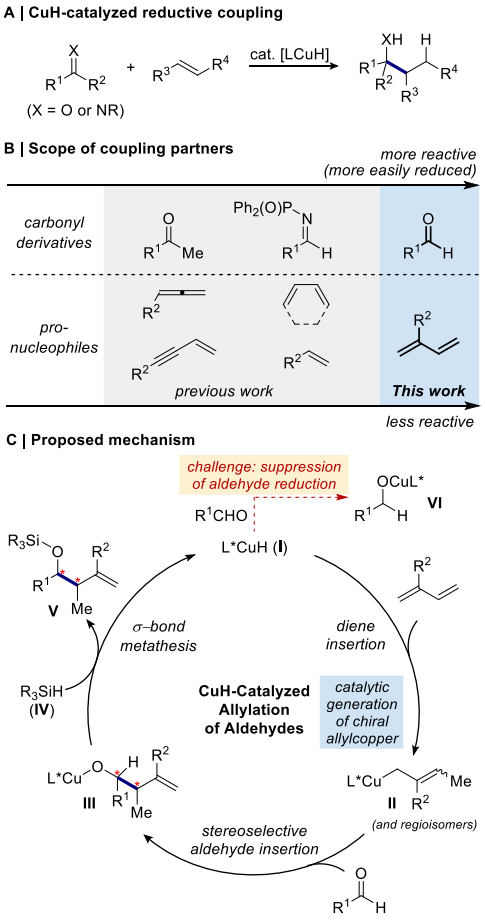


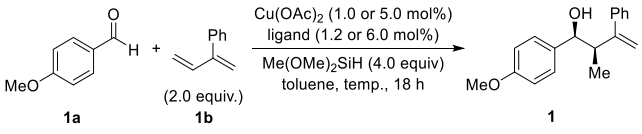
Figure 1. Overview of CuH-catalyzed reductive coupling of π-unsaturated pronucleophiles with carbonyl derivatives.

Considering previous mechanistic studies,[9f] we envisioned that our proposed transformation would proceed through hydrocupration of a diene to generate a mixture of allylcopper complexes represented by **II** (Figure 1C). One or more of these species could engage an aldehyde coupling partner in a stereoselective migratory insertion process to form the copper alkoxide **III**, from which metathesis with a hydrosilane (**IV**) would regenerate LCuH (**I**) and the desired product (**V**) in silyl-protected form. Clearly, the diene hydrocupration must be faster than the rapid direct reduction of the aldehyde, which is contrary to the intrinsic kinetic preferences of these elementary reactions (18.5 vs. 13.9 kcal/mol calculated free energy barriers for diene and aldehyde hydrocupration respectively, see below). In this article, we describe the optimization of a reaction system that displays this inverted chemoselectivity, its applications to the highly regio-, diastereo- and enantioselective allylation of both aliphatic and aromatic aldehydes, and mechanistic studies that explain the origin of these selectivities.

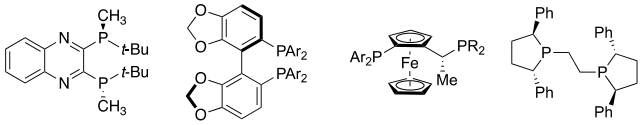
RESULTS AND DISCUSSION

We initiated our study by examining reactions of *p*-anisaldehyde (**1a**) and 2-phenyl-1,3-butadiene (**1b**) under reaction conditions previously described for CuH-catalyzed ketone allylation.[9e,f] With (*S*,*S*)-QuinoxP*(**L1**) as the ligand, the desired product **1** was obtained in 48% yield, with exclusive branched-selectivity and excellent preference for the indicated diastereomer (11:1 dr). However, the major diastereomer was formed with only a moderate level of enantioselectivity (68:32 er, Table 1, entry 1). No desired homoallylic alcohol **1** was obtained when (*R*)-DTBM-SEGPHOS (**L2**) was used as the ligand: complete reduction of the aldehyde was observed instead (Table 1, entry 2). JosiPhos[13] derivative SL-J011-1 (**L3**), a ligand which had been employed with good results in ketone allylation,[9f] was also examined. The corresponding test reaction provided **1** in moderate (57%) yield, with 8:1 dr and 85:15 er (Table 1, entry 3). Further evaluation of commercially available common chiral ligands revealed (*S*,*S*)-Ph-BPE (**L4**) to be optimal (Table 1, entry 4), providing 75% yield of **1** was obtained with excellent dr (21:1) and er (96.5:3.5).

Table 1. Evaluation of Reaction Conditions for the CuH-Catalyzed Allylation of 4-Methoxybenzaldehyde.[a]



Entry	Ligand	Cat. (%)	Temp. (°C)	Yield[b] 1 (%)	dr	er[c] (major)
1	**L1**	5	rt	48	11:1	68:32
2	**L2**	5	rt	0	--	--
3	**L3**	5	rt	57	8:1	85:15
4	**L4**	5	rt	75	21:1	96.5:3.5
5	**L4**	5	40	71	24:1	95.5:4.5
6	**L4**	1	rt	90	13:1	94:6
7	**L4**	1	0	94	13:1	95:5
8[d]	**L4**	1	0	33	9:1	95:5
9[e]	**L4**	1	0	97	10:1	91:9



[a]Conditions: **1a** (0.1 mmol, 1 equiv), **1b** (2 equiv), $Cu(OAc)_2$ (0.01 or 0.05 equiv), ligand (0.012 or 0.06 equiv), dimethoxy(methyl)silane (4.0 equiv) in solvent (0.2 mL). **1a** was added slowly by syringe pump (1.0 mol/L, 1.0 uL/min); see the Supporting Information for details. [b]Yield and diastereomeric ratio were determined by ^{1}H NMR spectroscopy of the crude reaction mixture, using dibromomethane as an internal standard. [c]Enantiomeric ratio was determined by HPLC or SFC analysis on commercial chiral columns, and the relative configuration of **1** was determined by comparing its NMR and optical rotation data with reported data.[14] [d]Without metered addition. [e]With slower addition rate (1.0 mol/L, 0.5 uL/min).

With a slight increase in reaction temperature (40 ˚C), both the yield and er diminished slightly (Table 1, entry 5). Furthermore, the results were very sensitive to the catalyst loading: excellent yield (90%) was achieved without losing high diastereo- and enantioselectivity (13:1 dr, 94:6 er) by decreasing the catalyst loading from 5.0 to 1.0 mol% (Table 1, entry 6). Lowering the temperature to 0 ˚C proved to be beneficial, increasing the yield to 94% (Table 1, entry 7). Metered addition of the aldehyde is also important for this allylation process: by adding the aldehyde in a single batch at the start of the reaction, only 33% of target product could be observed. However, extremely slow addition rates will decrease the enantioselectivity slightly and are not advantageous for the yield (Table 1, entry 8 and 9).

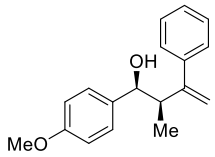
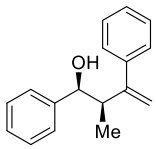
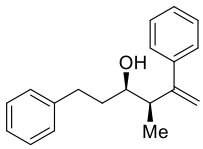
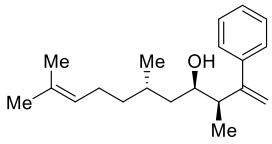
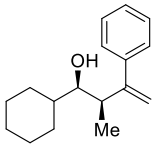
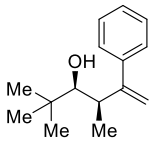
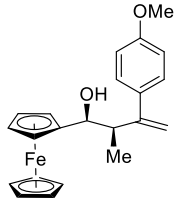
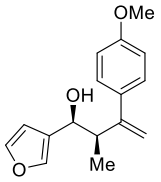
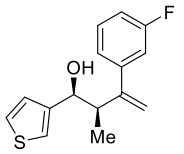
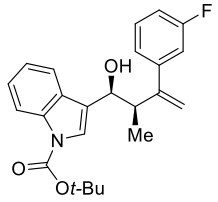
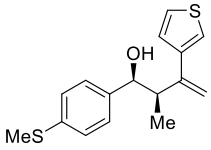
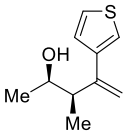
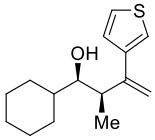
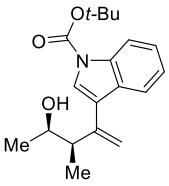
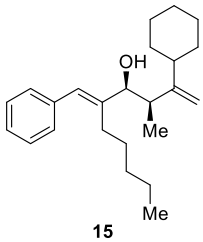
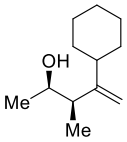
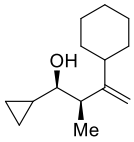
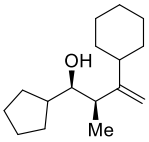
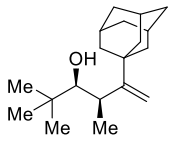
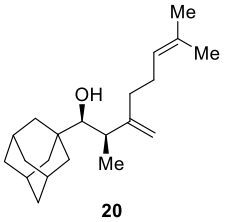
We next explored the scope of the asymmetric reductive coupling of aldehydes with 1,3-dienes. As depicted in Table 2, a range of chiral homoallylic alcohols were prepared in excellent yields and levels of enantiomeric purity. Simple benzaldehyde was successfully transformed into the corresponding homoallylic alcohol **2** in good yield with moderate diastereoselectivity, but high enantioselectivity. Notably, aliphatic primary (**3**, **4**), secondary (**5**), and tertiary (**6**) aldehydes were also compatible substrates with our protocol, providing uniformly excellent yield, dr and er. Using ferrocenecarboxaldehyde, we obtained enantiomerically enriched ferrocene derivative **7**. Furthermore, substrates containing heterocycles, such as a furan (**8**), a thiophene (**9**) and an indole (**10**), were all tolerated under the reaction conditions. A thioether could also be effectively converted into secondary alcohol **11** with good stereoselectivity.

Next, we assessed the scope of 1,3-diene pronucleophiles (Table 2). The reaction proceeded efficiently with dienes bearing electron-donating (**7**, **8**) or electron-withdrawing (**9**, **10**) aryl substituents at 2-position. Various heterocycles are well tolerated on the diene component, including a thiophene and an indole, reacting efficiently with both aromatic and aliphatic aldehyde partners (**11**-**14**) with excellent diastereo- and enantioselectivity.

2-Alkyl substituted dienes could also be effectively converted. For instance, 2-cyclohexyl-1,3-butadiene coupled well with a range of vinyl (**15**) and aliphatic aldehydes (**16**-**18**) with high selectivities, although the yields are moderate. In particular, simple aliphatic aldehydes such as acetaldehyde are suitable starting materials for this reaction (**16**). Even extreme steric bulk on both components could be tolerated: using pivaldehyde and an adamantyl-substituted diene, homoallyl alcohol **19** was obtained with moderate yield (48%) and excellent diastereo-

and enantioselectivity (>20:1 dr, 99.5:0.5 er). Finally, a naturally occurring diene, myrcene, proved to be an effective reagent, providing **20** with good yield and useful stereoselectivity.

Table 2. Evaluation of the Scope of the Aldehyde Allylation with Branched Dienes.[a]

 **1** 87% yield, 11:1 dr, 95.5:4.5 er	 **2** 86% yield, 5:1 dr, 94.5:5.5 er	 **3** 68%, 9:1 dr, 98:2 er	 **4** 77% yield, >20:1 dr
 **5** 82% yield, >20:1 dr, 97:3 er	 **6** 87% yield, >20:1 dr, 99.5:0.5 er	 **7** 90% yield, 7:1 dr, 95:5 er	 **8** 86% yield, 8:1 dr, 97:3 er
 **9** 85% yield, 7:1 dr, 97:3 er	 **10** 79% yield, 8:1 dr, 99:1 er	 **11** 92% yield, 6:1 dr, 94:6 er	 **12** 84% yield, >20:1 dr, 99:1 er
 **13** 81% yield, >20:1 dr, 96:4 er	 **14** 88% yield, 13:1 dr, 98.5:1.5 er	 **15** 81% yield, 10:1 dr, 95:5 er	 **16** 50% yield, >20:1 dr, 93.5:6.5 er
 **17** 66% yield, 14:1 dr, 97:3 er	 **18** 57% yield, >20:1 dr, 95:5 er	 **19** 48% yield, >20:1 dr, 99.5:0.5 er	 **20** 73% yield, 5:1 dr, 85:15 er

[a]Yields indicate the isolated yield of product as a mixture of two diastereomers on a 1.0 mmol scale. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy for both the crude and purified products; enantiomeric ratios were determined by HPLC, SFC or chiral GC analysis on commercial chiral columns. Yields, diastereomeric ratios, and enantiomeric ratios are the averages for two identical runs. See Supporting Information for full details.

MECHANISTIC STUDIES

By analogy to other copper-catalyzed reductive olefin–keton[9b,f] and olefin–imine coupling[9a] reactions, we proposed that the current reaction proceeds through the mechanism illustrated in Figure 1C. Previous computational and experimental investigations of related transformations have revealed, in intricate detail, the sequence of events and controlling factors that dictate the regio-, diastereo- and enantioselectivity observed in these transformations.[9f] However, we were interested in several questions pertaining to the mechanism and selectivity that are particular to this aldehyde allylation. First, we wanted to confirm the feasibility of our proposed series of elementary steps, as well as their relative rates, their reversibility, and the identity of the selectivity-determining step(s). It is important to note, however, that metered addition of the aldehyde, which presumably maintains a low steady-state concentration of aldehyde, is crucial to obtaining high yields of product. Thus, it is necessary that our model to account for this effect. Second, we hoped to explain the stereochemical outcome of our reaction. Specifically, our rationale should both identify the step(s) that control the diastereo- and enantioselectivity (allylcopper isomerization, C–C bond formation, σ-bond metathesis, or a combination thereof), as well as the specific ligand–substrate interactions responsible for destabilizing the disfavored stereoisomeric pathways. Finally, we wanted to confirm experimentally that competing aldehyde vs. diene insertion into a copper(I) hydride complex determines the chemoselectivity with regard to reduction vs. the desired coupling.

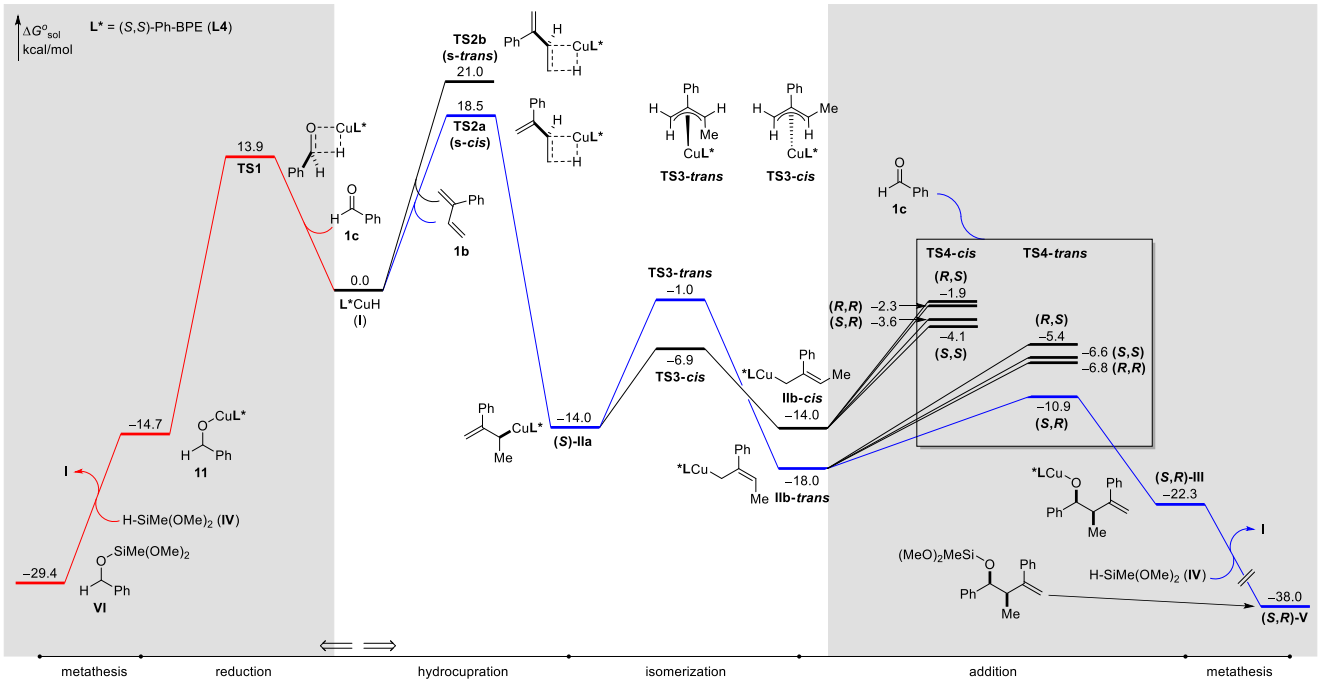


Figure 2. Computed energy profiles for CuH-catalyzed allylation (blue) and reduction (red) of benzaldehyde (**1c**). These calculations were performed at the M06-2X/SDD–6-311+G(d,p)/SMD(toluene)//B3LYP/SDD–6-31G(d) level of theory. Standard free energies are relative to infinitely separated **I** and reactants (**1c** and **1b**). See the Supporting Information for details.

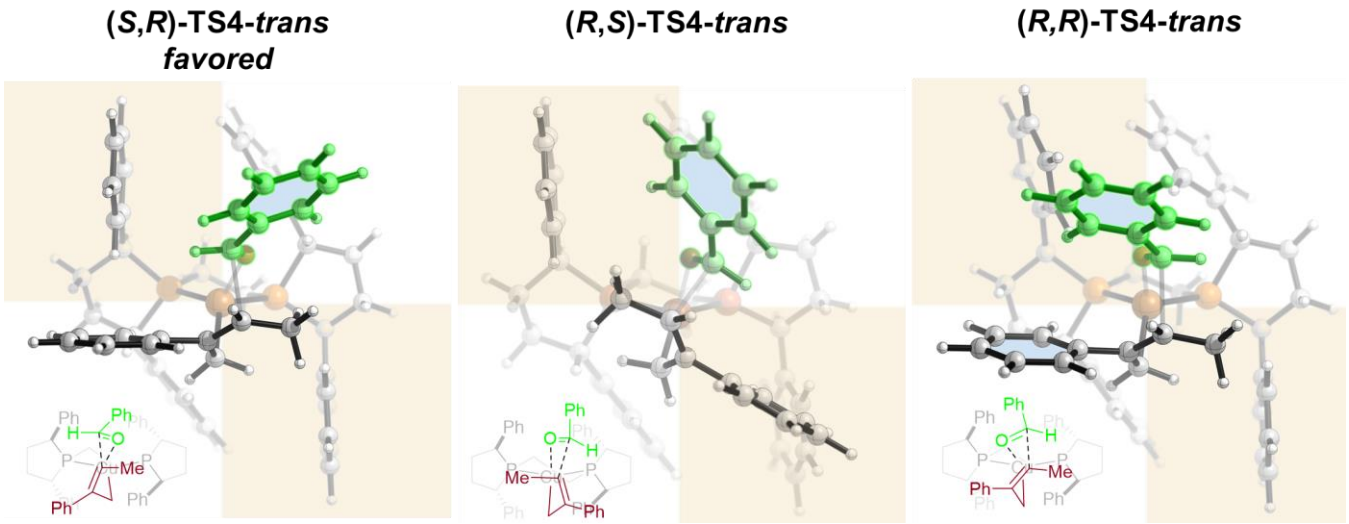


Figure 3. Stereochemical model for the CuH-catalyzed aldehyde allylation process. DFT-optimized lowest energy transition state structures for the C–C bond formation step, leading to the major stereoisomer (left), the minor diastereomer (middle) and the minor enantiomer (right) of product **2**. See the Supporting Information for details.

We first turned to DFT-based modeling to address the first two questions. The computed Gibbs free energy profile, using model diene **1b** and benzaldehyde (**1c**) as model substrates, is shown in Fig. 2. Starting from **L***CuH (**I**), where **L*** = (*S*,*S*)-Ph-BPE, irreversible hydrocupration of **1b** takes place preferentially through its s-*cis* conformation and with facial selectivity to generate the *S* enantiomer of branched allylcopper complex **IIa**. We found that (*S*)-**IIa** can isomerize rapidly to a nearly isoenergetic linear isomer **IIb-*cis***, in which the Ph and Me alkene substituents are mutually *cis*. While this isomerization is associated with an energetic barrier of 7.1 kcal/mol (**TS3-*cis***), there also exists a second, slower isomerization pathway (13.0 kcal/mol barrier) leading to more stable linear isomer **IIb-*trans*** (4.0 kcal/mol more stable than **IIa**), in which the Ph and Me are mutually *trans*.

In accordance with the Curtin–Hammett principle, the isomer of **II** (e.g., **IIa**, **IIb-*cis*, IIb-*trans***) through which the reaction proceeds will depend on the rate of the subsequent addition step relative to the isomerization processes. However, prior to further elaboration on this aspect, we first need to more precisely consider the effect of slow addition of aldehyde on the mechanistic model in general. While it is conventional to plot energy diagrams using standard thermodynamic parameters, (i.e., those at 1 M solution for solutes), true relative free energies depend on the concentrations of the species involved. In cases where two reactants might have concentrations differing by many orders of magnitude during steady-state catalyst turnover, it is particularly important to consider relative concentration effects in the interpretation of an energy diagram.[15]

Accordingly, in the reaction under consideration, we noted that the metered addition of aldehyde over several hours should ensure that the concentration of the aldehyde is very low relative to the other reactants. The presence of this concentration disparity is equivalent to raising the free energy of all states wherein aldehyde is associated with the catalyst (Figure 2, highlighted in grey) relative to states in which the aldehyde is free (in white). Indeed, we find that if, by relative concentration effects, **TS1** is raised in energy by more than about 4.6 kcal/mol relative to **TS2a**, hydrocupration can be favored over direct reduction of the aldehyde, as is observed in the reaction.

A less obvious consequence is that the reaction of the copper allyl species is also slowed, which has implications on reversibility of allylcopper isomerization. We examined eight diastereomeric transition states for allylcopper addition to the aldehyde (Figure 4, boxed and labeled **TS4-*cis*/*trans***). Considering standard free energies alone, it would appear that reaction of the *cis*-allyl complex **IIb-*cis*** through **(*S*,*S*)-TS4-*cis*** is sufficiently facile that competing isomerization to the more stable **IIb-*trans*** should be kinetically precluded. However, with species highlighted in grey raised in energy by the amount (>4.6 kcal/mol) required to avoid direct aldehyde reduction, reaction of **IIb-*cis*** with aldehyde through the **TS4-*cis*** transition states necessarily become more challenging than reversible isomerization to **IIb-*trans***. In this scenario, the predicted major reaction pathway (highlighted in blue) proceeds through **(*S*,*R*)-TS4-*trans***, leading to the diastereomer of product that is experimentally observed to be predominant (**(*S*,*R*)-V**).

We next examined the transition state structures to elucidate the origin of stereoselectivity in the addition step. Monomeric complexes of Ph-BPE-ligated copper are known adopt a conformation whose steric profile is well approximated by a quadrant model.[16] For instance, in the preferred six-membered cyclic transition state (Figure 3, left panel),[17] the largest substituents of both the allyl component and the aldehyde component are directed into the less hindered (white) quadrants during the C–C bond formation. In contrast, minor enantiomer of product can form if the aldehyde attacks the opposite face of the diene (Figure 3, center panel). However, a steric clash is created between the aryl substituent of the diene and the Ph substituent of the ligand (bottom-right quadrant), which destabilizes this structure. Furthermore, unfavorable steric interactions between the aldehyde substituent and the other Ph group on the ligand (top-left quadrant) causes the structure to distort from its ideal, chair-shaped cyclic geometry. Finally, a minor diastereomer can form if, relative to the favored transition state, the opposite face of the aldehyde is attacked (Figure 3, right panel). The dominant destabilizing interaction in this case is between the aldehyde substituent and the Ph group of Ph-BPE in the top-left quadrant. Overall, this model determines the correct sense of selectivity, although the magnitude is somewhat overestimated relative to experiment (95:5 er, 5:1 dr).

We also performed kinetic experiments to further explore the effect of slow addition on the chemoselectivity of our reaction (Figure 4). Under the standard conditions, except with no diene present, the reduction of aldehydes is extremely rapid. In our experiment, benzaldehyde was fully consumed within 40 min, forming the silyl-protected benzyl alcohol (Figure 4, top panel). If a single equivalent of diene is added at the beginning of the reaction, the corresponding reductive coupling product is observed to form in a roughly 1:9 ratio with the reduction product (Figure 4, middle panel). Notably, however, the overall consumption of starting material has been retarded, with the reaction now requiring over 3 h to reach full consumption of starting material. Finally, when a large excess of diene is added at the beginning of the reaction (5.0 equiv diene, Figure 4, bottom panel), the reductive coupling product is observed to form at a higher ratio relative to the reduction product. Simultaneously, the total consumption of starting material is further retarded.

Two conclusions can be drawn from these data. First, the correlation of the product-to-reduction ratio with the diene-to-aldehyde concentration ratio supports the proposed the role of slow addition in our mechanistic scheme. In Figure 2, higher concentration of diene lowers the energy of the blue pathway relative to the red pathway, and therefore leads to increased formation of the coupling product. Second, the seemingly inhibitory effect of the diene explains why the slow addition protocol must be conducted over a relatively long timespan (~3.5 h), in spite of the fact that we are trying to outcompete an extremely rapid reaction (half-life on the order of several min). Under the conditions of our protocol, at large excesses of diene relative to aldehyde, the rate of both the reduction and desired coupling are slow.

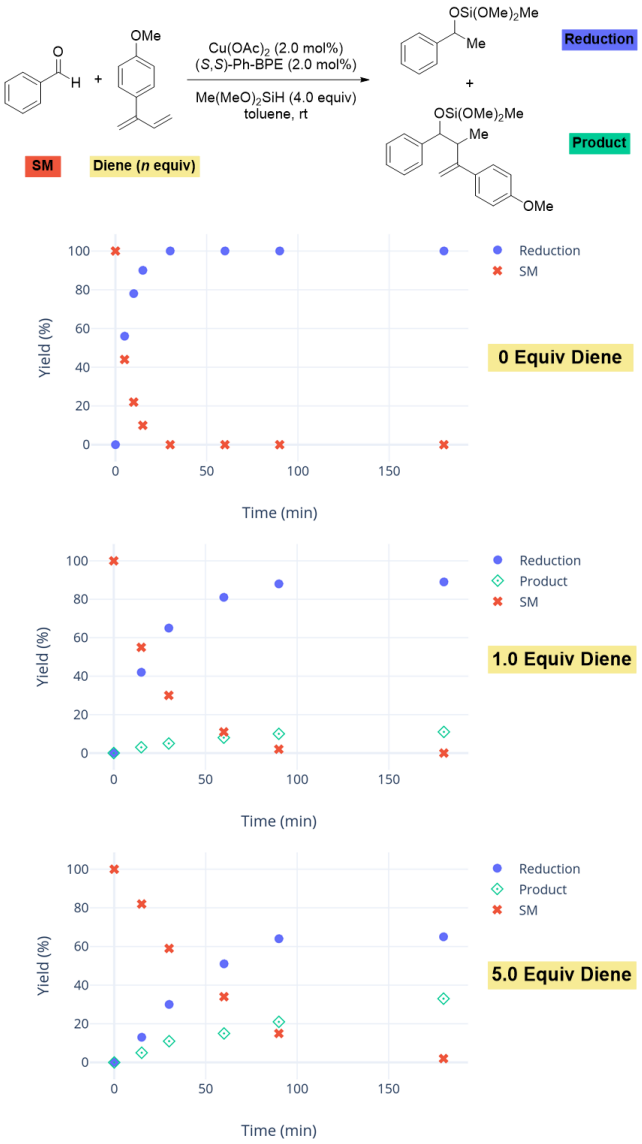


Figure 4. Kinetic profiles of the competing reductive coupling and reduction processes as a function of diene concentration. See the Supporting Information for experimental details.

CONCLUSION

In summary, we have developed a highly efficient copper-catalyzed allylation of aldehydes using dienes as allylmetal surrogates. Computational studies were performed which indicate that a reversible isomerization of copper(I) allyl species is formed, from which reaction of the *trans*-linear isomer with the aldehyde yields the major stereoisomer of product. Transition state models are provided, which show the specific steric interactions between ligand and substrates that are responsible for the stereoselectivity. Finally, kinetic experiments were performed, demonstrating effect of aldehyde–diene relative concentration on the chemoselectivity of this reaction.

ASSOCIATED CONTENT

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

Experimental procedures and characterization data for all compounds (PDF)
NMR spectra (PDF)
SFC and HPLC traces (PDF)
Computational details and Cartesian coordinates of optimized geometries (PDF)

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Notes

The authors declare no competing financial interest.

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(15) In general, away from equilibrium, the Gibbs free energy of reaction ΔG differs from the standard free energy of reaction $\Delta G^{\ddagger}$ by a quantity related to the reaction quotient Q:

$$\Delta G - \Delta G^{\ddagger} = RT \ln Q$$

In our system of interest, the aldehyde concentration is presumably maintained at a very low value, meaning that states involving free aldehyde are lowered in free energy relative to those involving the aldehyde bound to the catalyst. Although this effect is not reflected in Figure 2, which shows only the standard free energies, it is a useful mnemonic to associate the effect of decreasing the steady-state aldehyde concentration with raising the energies of the grey-highlighted states relative to the white ones.

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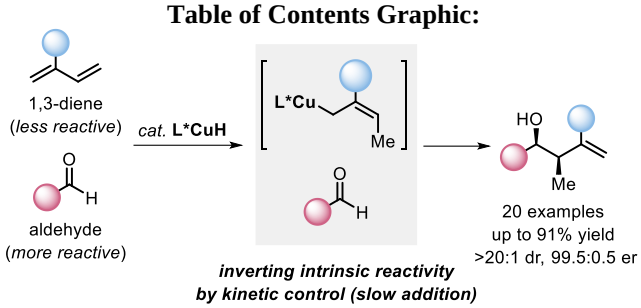
Table of Contents Graphic:



inverting intrinsic reactivity by kinetic control (slow addition)