

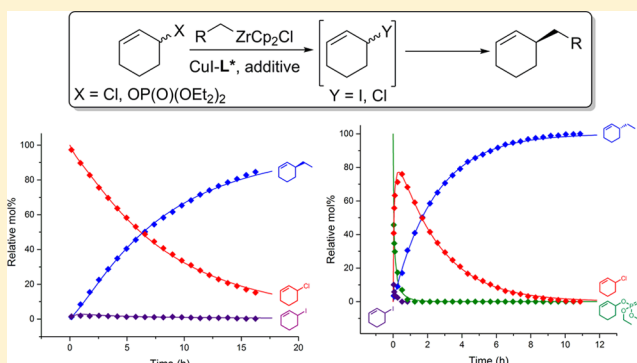
Mechanistic Studies on a Cu-Catalyzed Asymmetric Allylic Alkylation with Cyclic Racemic Starting Materials

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S Supporting Information

ABSTRACT: Mechanistic studies on Cu-catalyzed asymmetric additions of alkylzirconocene nucleophiles to racemic allylic halide electrophiles were conducted using a combination of isotopic labeling, NMR spectroscopy, kinetic modeling, structure–activity relationships, and new reaction development. Kinetic and dynamic NMR spectroscopic studies provided insight into the oligomeric Cu–ligand complexes, which evolve during the course of the reaction to become faster and more highly enantioselective. The Cu-counterions play a role in both selecting different pathways and in racemizing the starting material via formation of an allyl iodide intermediate. We quantify the rate of Cu-catalyzed allyl iodide isomerization and identify a series of conditions under which the formation and racemization of the allyl iodide occurs. We developed reaction conditions where racemic allylic phosphates are suitable substrates using new phosphoramidite ligand **D**. **D** also allows highly enantioselective addition to racemic seven-membered-ring allyl chlorides for the first time. ¹H and ²H NMR spectroscopy experiments on reactions using allylic phosphates showed the importance of allyl chloride intermediates, which form either by the action of TMSCl or from an adventitious chloride source. Overall these studies support a mechanism where complex oligomeric catalysts both racemize the starting material and select one enantiomer for a highly enantioselective reaction. It is anticipated that this work will enable extension of copper-catalyzed asymmetric reactions and provide understanding on how to develop dynamic kinetic asymmetric transformations more broadly.



INTRODUCTION

Copper is highly valued in synthetic organic chemistry, and a great number of asymmetric Cu-catalyzed methods have recently been developed.^{1–4} However, the mechanisms and structures of organocopper species involved in asymmetric addition reactions are poorly understood^{5,6} despite extensive studies on nonstereoselective processes.⁶

In the past decades, asymmetric allylic alkylation (AAA) reactions have emerged as powerful tools^{7–12} that may accommodate both achiral and chiral substrates. Enantioselective Cu-catalyzed AAA to prochiral materials can now be readily achieved by an array of nucleophiles, ligands, and leaving groups.^{1,2,10,12–18} While numerous mechanistic overviews have been outlined, detailed analyses of asymmetric Cu-catalyzed pathways are scarce and rely on analogy with work on stoichiometric nonenantioselective methods. To date, the most insight into these mechanisms has been brought by the Bäckvall,^{19–21} Nakamura,^{6,22–24} Alexakis,²⁵ and Feringa¹⁰ groups, all of which clearly emphasize the complexity of these mechanisms and the challenges associated with their study.

Most nonstabilized nucleophiles (R₂Zn, RMgX, and AlR₃) used in asymmetric Cu-catalyzed reactions are assumed to undergo transmetalation to Cu-species as a key step. However, to our knowledge, spectroscopic demonstration of trans-

metalation has only been observed in the addition of Grignard reagents to precatalytic Cu–ferrocenyl dimers,²⁶ addition of diorganozinc nucleophiles to Cu–phosphoramidite ligand complexes,²⁷ and for organolithium reagents used in Cu-catalyzed AAAs.²⁸ Upon addition of the allylic substrate, oxidative addition is believed to occur, providing many plausible σ- or π-Cu–substrate complexes, which may rapidly interconvert and involve various S_N2 or S_N2' and *syn* or *anti* mechanisms and is followed by reductive elimination (Figure 1a). What controls the overall chemo-, regio-, and enantioselectivity of these reactions is a subtle combination of variables and is not well understood.

Cu-AAAs using chiral racemic substrates are rare.^{25,29–35} Racemic electrophiles bring even more mechanistic complexity, as the relative rates of addition, isomerization, and elimination of two different chiral starting material/catalyst combinations must be considered. The vast majority of asymmetric reactions involving racemic substrates and a chiral catalyst are kinetic resolutions.^{36–41} To overcome the limitation of incomplete conversions (50% maximum theoretical yield), elegant processes have been designed to transform both enantiomers

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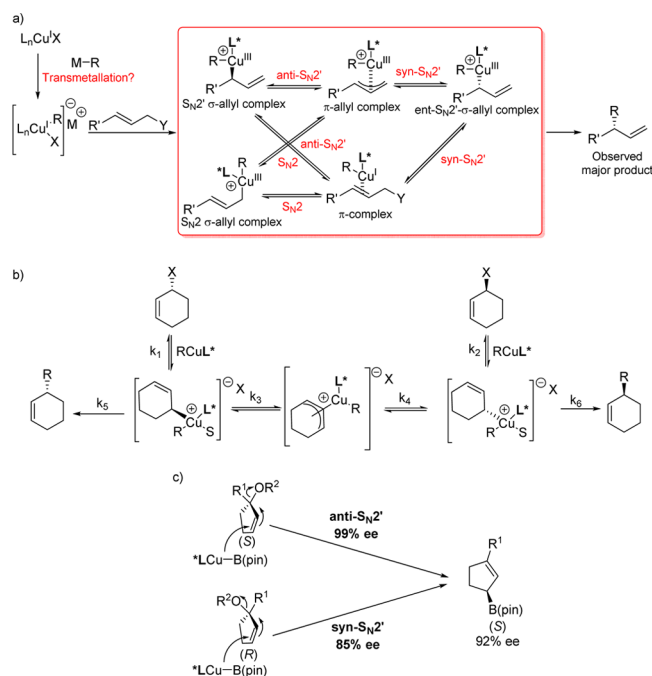


Figure 1. Mechanisms of copper-catalyzed asymmetric allylic alkylations. (a) Generally understood mechanism using prochiral starting materials; this process is highly complex and still not well understood. (b) Initially proposed mechanism for a Cu-catalyzed AAA with racemic allyl bromides and Grignard reagents.^{25,32,33} (c) Example of a Cu-catalyzed direct enantioconvergent transformation.³⁴

of racemic starting materials into a single enantiomer of product. Dynamic kinetic resolution^{38,42,43} (DKR) involves the rapid racemization of the starting material while only one enantiomer of the starting material reacts. As far as we are aware no Cu-catalyzed methods have been developed which apply the DKR strategy. Dynamic kinetic asymmetric transformations^{9,32,44–48} (DYKATs) are deracemization/symmetrization methods where both enantiomers of starting material are converted into a common intermediate, usually a pseudoprochiral π -complex as seen in Pd- or Ir-chemistry.

Alexakis reported Cu-AAAs of Grignard reagents with racemic cyclic allylic bromides which were initially suspected to proceed through DYKAT mechanisms^{25,32,33} (Figure 1b) where racemic allyl bromides would form diastereomeric σ -Cu complexes that rapidly desymmetrize via π -allyl complexes. However, a detailed study by Alexakis and co-workers using a combination of experimental and computational analyses upended the initially proposed mechanism.²⁵ A series of insightful studies concluded that in these reactions the catalyst promotes a distinct reaction pathway for each enantiomer to provide a common product. Such reactions are direct enantioconvergent transformations (DETs).^{25,34}

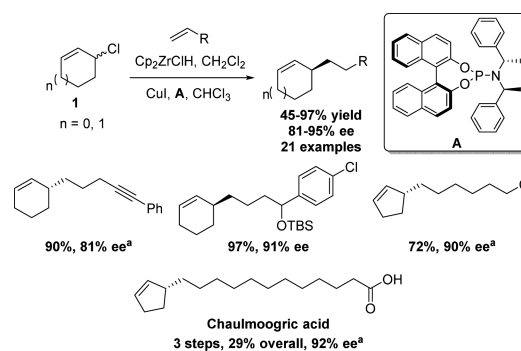
There are other examples of DETs providing very high yields and enantioselectivity, even though the design of DETs is presumably extremely challenging, as substrate- and catalyst-controlled selectivities need to be somehow balanced. For example, Sawamura³⁴ described a Cu-catalyzed DET of boronic ester nucleophiles to racemic cyclic esters (Figure 1c). This group has recently reported a different Cu-catalyzed AAA with linear racemic species that may involve multiple allylcopper(III) species in rapid equilibrium.³⁵

In some cases considerable mechanistic insight into complex organometallic reactions can be elucidated by *in situ* NMR

spectroscopic studies.^{6,49–53} Mechanistic NMR studies of asymmetric Cu-catalyzed methods are rare, presumably because of the high reactivity of the reagents (requiring cryogenic temperatures and rigorously dry conditions), the complexity of the reactions, the sensitivity of these processes to reaction parameters (requiring expensive NMR solvents), and the large quadrupole moment of Cu precluding its ready observation by NMR. Primary organocopper(I) species are dynamic and reactive entities with a tendency to aggregate, resulting in complex mixtures of species.⁵⁰ Here aggregation and reactivity are strongly linked to reaction outcome (yield, chemo- and enantioselectivity) and are highly dependent on solvent interactions, counterion and ligand effects, and more tractable variables such as concentration and temperature.^{3,26,50,54–56} Gschwind's elegant work shed light on the nature of precatalytic Cu-complexes in solution using NMR spectroscopy.^{27,57–60}

We recently reported a Cu-catalyzed AAA with racemic cyclic allyl chlorides **1** and alkylzirconocenes using Cu–A (Scheme 1).⁶¹ A variety of highly enantioenriched products could be

Scheme 1. Cu-AAA Using Racemic Cyclic Allyl Chloride 1 and Alkylzirconocenes⁶¹



^aPrepared using (R,R,R)-A.

obtained at room temperature in high yield, and the method was also used to synthesize bioactive natural products used as traditional treatments for tuberculosis and leprosy.

During this work we observed a clear dependence between ee and Cu-halides (**Figure 2a**, entries 1–3). CuI gave the best results which we attribute to the iodide promoting racemization of the starting material. However, CuOTf also provided products with reasonably high levels of ee (71% ee, entry 5).

¹H NMR spectroscopic studies aimed at identifying the pathways involved were carried out by *in situ* NMR and showed clean and slow conversion of allyl chloride **1** to product, as well as the constant presence of allyl iodide **2** in low (~3 mol %) concentrations. The CuI-A catalyst is believed to form **2** from **1** via S_N2' chemical exchanges, as observed by EXSY (Figure 2b) and we speculated that this reaction would racemize **2**. Further studies using allyl bromide showed that CuI-A both formed allyl iodide **2** and mediated isomerization of the allyl bromide. Further, interconversion between allyl bromide and **2** occurs solely by S_N2' mechanisms on the NMR time scale. We also observed deshielding of catalyst benzylic signals over the course of the reaction by ¹H NMR spectroscopy (Figure 2c).⁶² Interestingly, this correlates well to an increase in the ee of the product over time: from 85% ee at 10 min, 90% ee at 2 h, and 95% ee overnight. It would seem that the catalytic species are evolving toward a more highly enantioselective catalyst, and we

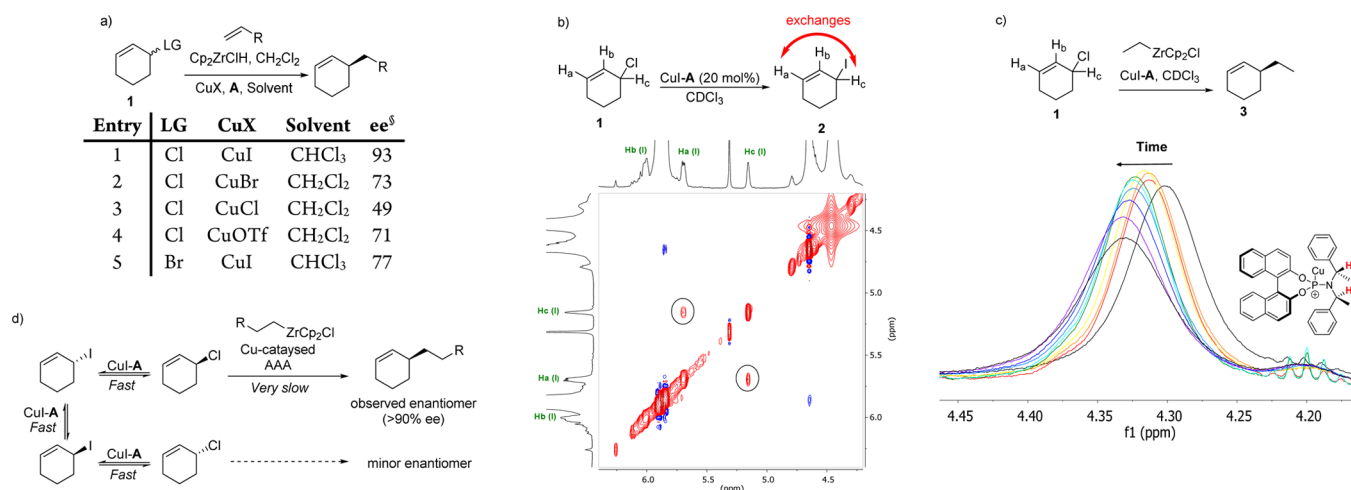


Figure 2. Previously described experiments and initial mechanistic observations. (a) Selected screening experiments. (b) 2D NMR EXSY (800 ms mixing time) during Cu-AAA reaction. (c) The chemical shift of a ligand benzylic ¹H signal over the course of the reaction. Spectra taken at different times following the visible light spectrum of color for clarity. (d) Proposed mechanism of Cu-catalyzed AAA of allyl chloride 1 using alkylzirconocenes.

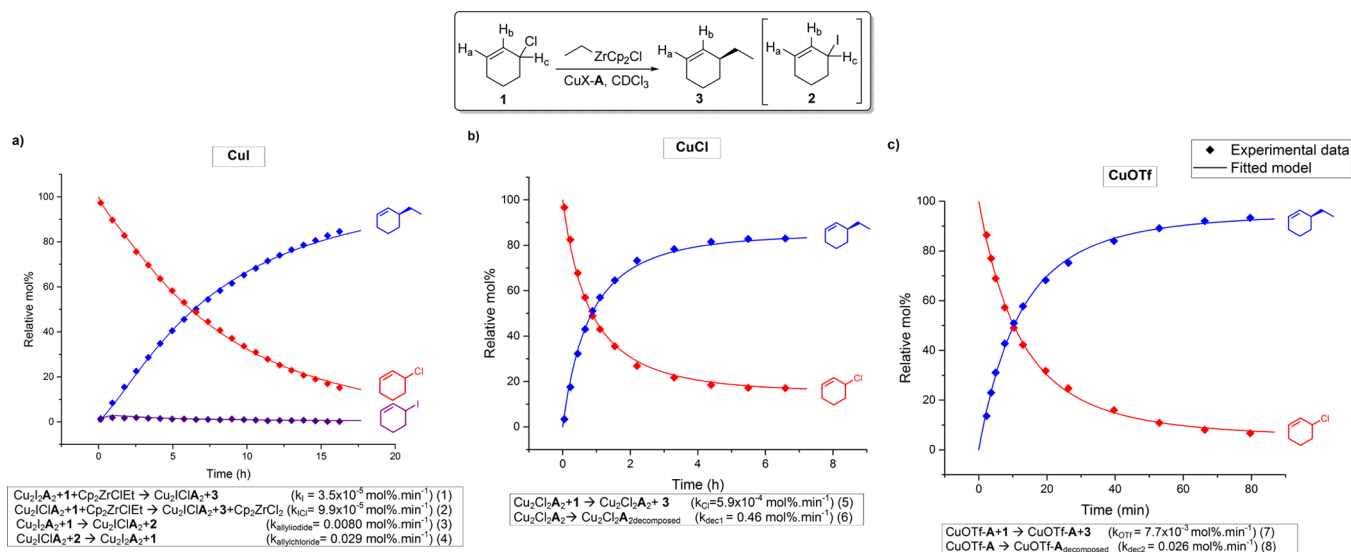


Figure 3. Experimental and modeled kinetic data of Cu-AAA with 1 as monitored by *in situ* ¹H NMR spectroscopy using (a) CuI, (b) CuCl, and (c) CuOTf. Conditions: ethylene (1 atm), Cp₂ZrClH (2.0 equiv), CD₂Cl₂, CuX (10 mol %), (S,S,S)-A (10 mol %), allyl chloride 1 (1.0 equiv), in CDCl₃, 298 K. The experimental data recorded by ¹H NMR are shown as diamonds. Based on those data points, modeling was performed using Dynafit4. The fitted curves are shown as solid lines, and the input equations with their rates are below the corresponding graphs.

speculated that the catalyst species evolved to contain chloride anions during the reaction.

Based on these experiments we proposed the mechanism shown in Figure 2d. This does not provide any insight into the C–C bond-forming step, but is suggestive of a generally useful pathway for racemic starting materials where a catalyst selects one enantiomer of an allylic substrate for the reaction, while racemization of the starting material replenishes the more reactive enantiomer. Overall such a process may be highly stereoselective, depending on the kinetics (as well as selectivity and robustness) of all of these different processes. A Cu-catalyzed heterocyclic AAA of alkylzirconocenes to racemic 3,6-dihydro-2H-pyrans was also developed.⁶³ Unfortunately these systems do not work well, but showed remarkable mechanistic diversity for *a priori* similar conditions.

Several aspects of these AAA mechanisms remain to be elucidated, in particular, details of the Cu-catalyzed AAA step,

the structure and dynamics of the catalyst, and also the rate, robustness, and generality of the racemization process. Here we describe detailed studies using a combination of structure–activity relationships, new reaction development, isotopic labeling, NMR spectroscopy, and kinetic modeling.

RESULTS AND DISCUSSION

Kinetics via *in situ* ¹H NMR Spectroscopy. Based on our previous insights using ¹H NMR spectroscopy, we decided to obtain kinetic data *in situ*. We were able to follow the reaction in time, showing consumption of starting material 1, formation of product 3, and the presence of allyl iodide intermediate 2 on a CuI-catalyzed reaction as shown in Figure 3a. Using nonlinear least-squares regression on Dynafit4,⁶⁴ we attempted to build a simple model of the reaction while taking into account the reversible formation of 2. Attempts to fit the data always led to significant divergence of the model from experiment (see

Supporting Information (SI) p S46). In order to obtain a reasonable fit we had to take into account the modification of the catalyst observed by NMR (Figure 2c)⁶¹ and speculate that the leaving group generates chloride anions during AAA (Figure 3a, eq 1) which become incorporated into the catalyst and generates a more enantioselective catalyst as the reaction proceeds; perhaps the simplest form of the second generation catalyst would be Cu₂IClA₂, a dimer of CuIA where one halogen has been replaced by Cl. A model using Cu₂IClA₂ as a second “reaction-enhanced” catalyst (eq 2) suggested that this AAA is 3 times faster than AAA with the starting catalyst (eq 1). Chemical exchange between 2 and 1 is relatively fast: $k_{\text{allyl iodide}} = 0.0080 \text{ mol \%} \cdot \text{min}^{-1}$ for formation of 2 (eq 3) with regeneration of 1 being more than 3 times faster ($k_{\text{allyl chloride}} = 0.029 \text{ mol \%} \cdot \text{min}^{-1}$, eq 4). This model supports the idea that AAA is slow compared to isomerization of 1 and 2 (>10² times slower), allowing replenishment of the reactive enantiomer of 1.

In situ ¹H NMR spectroscopic kinetic studies were also carried out for the CuCl and CuOTf catalyzed AAA (Figure 3b and 3c respectively). The obtained experimental data were fitted by nonlinear least-squares regression.⁶⁴ In the case of CuCl (Figure 3b) we observe clean conversion of 1 to 3, but the reaction ceases in the NMR tube after 5 h and has a half-life of 1 h. In reaction flasks, the ee of the product obtained using the CuCl catalyst decreases over time: 82% ee at 10 min, 68% ee at 2 h, and 54% ee at completion. EXSY experiments suggest that CuCl–A does not isomerize 1 on the NMR relaxation time scale (see SI p S73). This is consistent with studies on recovered 1 during the CuCl catalyzed reactions, which show the formation on nonracemic 1 (~7% ee after 1 h, >11% ee after 2 h) as judged by GC analysis (see SI p S51).

With CuOTf, AAA is much faster than with Cu halides and stops within ~80 min as determined by *in situ* ¹H NMR spectroscopy (Figure 3c). Another feature of the OTf[–] reaction is that the ee of the product stays constant over time (71% ee). In the modeling, a good fit was obtained by taking into account that the reaction does not go to completion because of catalyst decomposition. Decomposition was calculated to occur at $k_{\text{dec2}} = 0.026 \text{ mol \%} \cdot \text{min}^{-1}$, ~3× faster than the CuOTf–A catalyzed C–C bond formation ($k_{\text{OTf}} = 7.7 \times 10^{-3} \text{ mol \%} \cdot \text{min}^{-1}$). This catalyst instability is consistent with our qualitative observations on the reactivity of CuOTf complexes.

As the CuI AAA is ~10 times slower than with CuCl ($k_{\text{Cl}} = 5.9 \times 10^{-4} \text{ mol \%} \cdot \text{min}^{-1}$) and 10² times slower than with CuOTf ($k_{\text{OTf}} = 7.7 \times 10^{-3} \text{ mol \%} \cdot \text{min}^{-1}$), the Cu counterion impacts the catalytic species present throughout the reaction.

Upon addition of Cp₂ZrClEt to CuI–A, we do not observe any color changes or significant changes in ¹H and ³¹P NMR spectra. We speculate that CuI–A and Cp₂ZrClEt do not react before addition of 1 even though most mechanistic proposals with nonstabilized nucleophiles involve transmetalation processes.^{1,2,26,27,65} In contrast, upon addition of Cp₂ZrClEt to CuCl–A, a yellow to dark brown color change occurs within a few minutes and changes are observed by ¹H and ³¹P NMR spectroscopy (see SI p S50). In the ³¹P NMR spectra, the peak associated with CuCl–A drastically broadens without a significant change of chemical shift. At completion, the strong ³¹P NMR signals earlier seen at 140–120 ppm disappear, suggesting catalyst decomposition, consistent with our kinetics and modeling (see Figure 3b). It appears that precatalytic CuOTf–A exists as at least two entities in a 1:0.3 ratio in CDCl₃ at 298 K as there are two sets of distinct benzylic and

methyl signals in the ¹H NMR and two signals in the ³¹P NMR spectrum (see SI p S23). With CuOTf–A, upon addition of Cp₂ZrClEt the reaction mixture turns brown instantaneously and changes are observed in the ¹H and ³¹P NMR spectra suggesting the formation of a single species. From the information gathered, the mechanism of CuOTf–A catalyzed AAA appears to be different than that of Cu-halide–A complexes.

Supramolecular Structures of the Precatalytic Complexes. In an attempt to gain insight into the structure of the active catalysts we carried out diffusion NMR spectroscopy experiments. Gschwind extensively used these to study precatalytic Cu-phosphoramidite complexes at 220 K^{58,59,66} and found that the diffusion coefficients obtained are accurate enough to determine the number of ligands in a complex, but not the number of salt units.^{57,58} Morris et al.⁶⁷ have described a pragmatic correlation function, using the concept of an effective mean density for solute and solvent molecules, to estimate the molecular weight of a small-molecule species based on its diffusion coefficient. We note that although the correlation was developed and demonstrated only for molecules comprising light atoms (<Cl), the estimated molecular weights would nevertheless help us establish the presence of supramolecular assemblies of CuX–A complexes since the ligand unit makes up the bulk of the molecular weight (540 g·mol^{–1}) as opposed to the heavy atom Cu (64 g·mol^{–1}) and halides (35 g·mol^{–1} for Cl, 127 g·mol^{–1} for I).

Alternatively, calibration curves have also been used to determine the molecular weight of supramolecular complexes.^{68–70} We thus ran diffusion experiments on known Rh and Pd complexes in CDCl₃ to generate a calibration curve (see SI p S54). These experiments show, similar to Gschwind’s results, that D has limited ability to predict the stoichiometry of small bridging salts such as halides, but as stated above, these methods may still be used to estimate the molecular weight of the supramolecular complexes here, as ligands make up the bulk of the molecular weight.

We therefore carried out diffusion experiments with convection compensation^{71,72} of different CuX–A complexes at 298 K in CDCl₃. These experiments were measured in triplicate at 0.05 M, the same concentration as the catalytic species in the reaction. First as a control, we measured the diffusion coefficient of free ligand A to be $(8.74 \pm 0.16) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ (Table 1 – entry 1). The diffusion coefficient of A correlates to an estimated molecular weight of $542 \pm 21 \text{ g} \cdot \text{mol}^{-1}$ using Morris’ correlation, close to the actual value of 540 g·mol^{–1}.

The diffusion coefficient of CuI–A in CDCl₃ at 298 K was measured to be $(6.13 \pm 0.05) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ (entry 2) which correlates to an estimated molecular weight of $1163 \pm 20 \text{ g} \cdot \text{mol}^{-1}$. As the measured diffusion coefficient is consistent with a complex containing two ligands A (>1080 g·mol^{–1}), we propose the species is a dimer of the formula Cu₂I₂A₂ (1460 g·mol^{–1}) rather than a monomer (CuIA, 730 g·mol^{–1}). We however note that we cannot rule out other species, as there are uncertainties in these measurements.

CuCl–A in CDCl₃ had a diffusion coefficient of $(5.87 \pm 0.09) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ (entry 3), which suggests a molecular weight of $1279 \pm 46 \text{ g} \cdot \text{mol}^{-1}$. Unlike the above result with I atoms, this prediction actually correlates very well with a Cu₂Cl₂A₂ dimer (MW = 1277 g·mol^{–1}). We also measured the diffusion coefficient of mixed CuI–A/CuCl–A complexes in a 1:1 ratio (entry 4) in an attempt to mimic the possible structure

Table 1. Diffusion Coefficients *D*, and Estimated Molecular Weight, As Measured by NMR Spectroscopy^{a,b}

$\text{CuXA} \quad \text{A-Cu}^{\oplus} \text{X}^{\ominus} \text{ or } \text{A-Cu-X} \quad \text{Monomer}$			
$\text{Cu}_2\text{X}_2\text{A}_2 \quad \text{A-Cu}^{\oplus} \text{X}^{\ominus} \text{---} \text{Cu-A} \quad \text{Dimer}$			
$\text{Cu}_2\text{IClA}_2 \quad \text{A-Cu}^{\oplus} \text{Cl}^{\ominus} \text{---} \text{Cu-A} \quad \text{Mixed halide dimer}$			
species		<i>D</i> (10 ^{−10} m ² ·s ^{−1})	predicted MW ^{b,67}
1	A (control)	8.74 ± 0.16	542 ± 21
2	CuI-A	6.13 ± 0.05	1163 ± 20
3	CuCl-A	5.87 ± 0.09	1279 ± 46
4	CuI/CuCl-A ^c	5.89 ± 0.11	1269 ± 55
5	CuI-A + Cp ₂ ZrClEt ^d	5.95 ± 0.18	1243 ± 83
6a	CuOTf-A	6.70 ± 0.11	956 ± 36
6b ^e		5.83 ± 0.17	1298 ± 86

^aConditions: CuX (10 mol %), (S,S,S)-A (10 mol %) in CDCl₃ at 298 K. ^bNote that this technique is not accurate enough to determine halide numbers,^{57,58} see accompanying text. ^cCuI (5 mol %), CuCl (5 mol %), (S,S,S)-A (10 mol %) in CDCl₃, 298 K. ^dEthylene (1 atm), Cp₂ZrClH (2.0 equiv) in CD₂Cl₂, CuX (10 mol %), (S,S,S)-A (10 mol %) in CDCl₃ at 298 K. ^eCalculated for a broader component at 7.072–6.761 ppm. The error values were calculated from the standard deviation of diffusion coefficient found for the CH-N signals at 4.65–4.31 ppm and the aromatic signals of the catalyst in each diffusion experiment, which were run in triplicate.

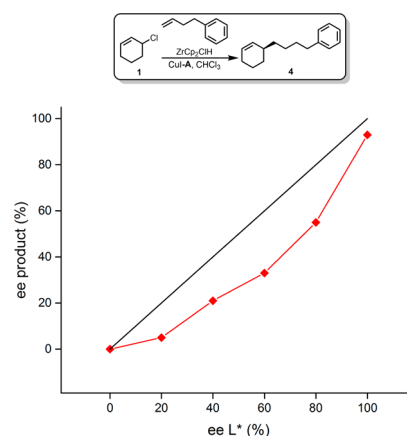
of the enhanced enantioselective catalyst generated during AAA. The diffusion coefficient was $(5.89 \pm 0.11) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$, a value very close to that observed with the CuCl-A complex.

When adding Cp₂ZrClEt to CuI-A, the diffusion coefficient was $(5.95 \pm 0.18) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ (entry 5), within experimental error of the diffusion coefficient for both CuI-A and CuCl-A, which, taken together with the lack of change observed in the ¹H and ³¹P NMR spectra when Cp₂ZrClEt and CuI-A are mixed, suggests that the dimeric aggregates do not change significantly in the presence of the nucleophile.

The diffusion coefficient of CuOTf-A, which the ¹H and ³¹P NMR spectra suggest is two complexes in solution at 298 K, was $(6.70 \pm 0.11) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ (entry 6a), associated with a molecular weight of $956 \pm 36 \text{ g} \cdot \text{mol}^{-1}$. Even with the assumption that ionic triflate pseudohalides are absent from the complex, this value is too low for a dimer (Cu₂A₂²⁺, 1206 g·mol^{−1}) but too high for a monomer (CuA⁺, 603 g·mol^{−1}) and the observed diffusion coefficient may be an average of the two CuOTf-A complexes found in solution. Measuring the diffusion coefficient for a broader component at 7.072–6.671 ppm resulted in a diffusion coefficient of $(5.83 \pm 0.17) \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$, corresponding to a molecular weight of $1298 \pm 86 \text{ g} \cdot \text{mol}^{-1}$ (entry 6b) and possibly dimeric Cu₂A₂OTf₂ (1504 g·mol^{−1}). Due to extensive NMR signal overlap we were unable to obtain diffusion ordered (DOSY) data, in which each complex could be separated.

Examining the correlation between the ee of the ligand and the ee of the product in the CuI catalyzed reaction shows a negative nonlinear effect (Figure 4),^{73–75} consistent with the active catalyst being an oligomer in ligand.

Isomerization of Allyl Iodide 2. We first decided to examine various conditions which may mediate the formation of 2 from 1 and its isomerization. Using CuI and CDCl₃, 2 was only observed when used in combination with a phosphine ligand (A, BINAP, or PPh₃, Table 2, entries 1–3). The absence

**Figure 4.** Negative nonlinear effect observed in the CuI-A catalyzed AAA of 1. Conditions: 4-phenyl-1-butene (2.5 equiv), Cp₂ZrHCl (2.0 equiv) in CH₂Cl₂, CuX (10 mol %), (S,S,S)-A (10 mol %), allyl chloride 1 (1.0 equiv), in CHCl₃, room temperature.**Table 2.** Testing the Generality of Allyl Iodide 2 Formation/Isomerization^a


entry	I [−] source	ligand	solvent	allyl iodide	exchanges
1	CuI	A	CDCl ₃	yes	yes
2	CuI	Binap	CDCl ₃	yes	yes
3	CuI	PPh ₃	CDCl ₃	yes	yes
4	CuI	NHC ^b	CDCl ₃	no	—
5	CuI	Me ₂ S	CDCl ₃	traces	no
6	CuI	—	CDCl ₃	no	—
7	TBAI	—	CDCl ₃	yes	no
8	TMSI	—	CDCl ₃	yes	yes
9	CuI	A	benzene-d ₆	yes	yes
10	CuI	A	THF-d ₈	yes	yes
11	CuI	A	CD ₃ CN	yes	yes

^aConditions: Iodide source (10 mol % for CuI, 1.0 eq for TMSI and TBAI), ligand (10 mol %), allyl chloride 1 (1.0 equiv), in solvent, 298 K. ^bNHC ligand used: 1-(S)-Leucinol-3-(2,4,6-trimethylphenyl)-3H-imidazolium hexafluorophosphate.

of ligand (entry 6) or use of N-heterocyclic carbene (NHC) (entry 4) or sulfur (entry 5) based ligands either gave no 2 or only traces of 2. Alternative I[−] sources such as tetrabutylammonium iodide (TBAI) (entry 7) and iodotrimethylsilane (TMSI) (entry 8) formed 2 in 4% and 70% yield, respectively. Although 2 was formed in the presence of TBAI, no exchanges by EXSY were observed (entry 7), whereas in other cases when 2 was formed it was rapidly isomerizing. Using CuI-A, formation and isomerization of 2 occurred in all solvents examined (CDCl₃, benzene, THF, MeCN).

CuCl-A catalyzed reactions (which normally give 49% ee, Figure 2a, entry 3) carried out in the presence of 10 mol % TMSI gave 4 in 76% ee, while a reaction with 10 mol % TBAI gave 4 in 52% ee, supporting the idea that allyl halide isomerization (Table 2, entries 7 vs 8) is crucial to obtaining high enantioselectivity in these reactions.

Under the reaction conditions used for the highly enantioselective AAA we set out to quantify the exchange observed in 2 using NMR spectroscopy (Table 3). We first used selective 1D-EXSY^{76,77} at various temperatures and

Table 3. Allyl Iodide Isomerization Rate Measurements by Multiple NMR Experiments^a


entry	experiment	T (K)	rate of isomerization (s ⁻¹)
1	1D-EXSY	273	0.02
2	1D-EXSY	298	0.11
3	1D-EXSY	313	0.60
4	inversion recovery	298	0.10
5	SSTD	298	0.08

^aConditions: CuI (10 mol %), (S,S,S)-A (10 mol %), allyl chloride 1 (1.0 equiv), in CDCl₃, room temperature. NMR spectra recorded at indicated temperature.

derived the Ha/Hc exchange rate constants from the initial slopes of normalized intensity build-up profiles (entries 1–3; see SI p S75). These results show the rate of Ha/Hc exchange in 2 exponentially increases with respect to temperature. To corroborate these data, we also ran selective inversion transfer^{53,78–80} (entry 4) and spin saturation transfer difference (SSTD)⁸¹ experiments (entry 5) at 298 K (see SI p S75). All three methods gave similar results emphasizing the validity and accuracy of the results. The data analyses also yielded longitudinal relaxation time constants (T₁'s) for the protons of 2 which were observed to be unusually large, with values ranging from 15 to 25 s for Ha, Hb, and Hc (see SI p S75). These values were comparable to those determined from (nonselective) inversion recovery experiments for 1 and 2, and

we attribute these large values to use of the argon degassing and lack of paramagnetic O₂ in the sample.

Development of a New AAA System. It would also be desirable to use less reactive electrophiles than allyl chlorides. These may be more chemically stable and less prone to isomerization during formation or routine manipulations. Furthermore, we anticipated that less reactive starting materials would aid mechanistic studies described in the next section. From this perspective, we attempted to develop a new AAA with alternative allyl species. Different cyclic allylic alcohol derivatives were tested using our previous conditions.

Allyl acetate did not react under these conditions (Figure 5a, entry 1), both the trifluoroacetate and pivalate derivatives behaved poorly (entries 2 and 3), but a phosphate gave promising results (>95% conversion, 40% ee, entry 4).

With allyl phosphate 5, different copper sources (Figure 5b, entries 1–3) and ligands (entries 4–8) were tested. A phosphoramidite D bearing a chiral amine (see SI p S26 for preparation) gave the highest ee (81% ee, entry 6). We examined the effect of solvents and found that nonchlorinated solvents were poorly selective. We thus tried different chlorinated solvents such as CHCl₃ which gave high (85%) ee (entry 9), CCl₄ which inhibited the reaction (entry 10), and dichloroethane which gave 57% ee (entry 11). Although we were able to obtain 85% ee, the procedure was not very reproducible. We suspected that an impurity was causing variations in our results from run to run and tested several additives (for example entries 12–16). The AAA was surprisingly tolerant to many additives and improved to 89% ee when using diethylchlorophosphate (entry 12). After substantial experimentation, 1.0 equiv of TMSCl reproducibly gave 80% yield and 89% ee (entry 15), although additional

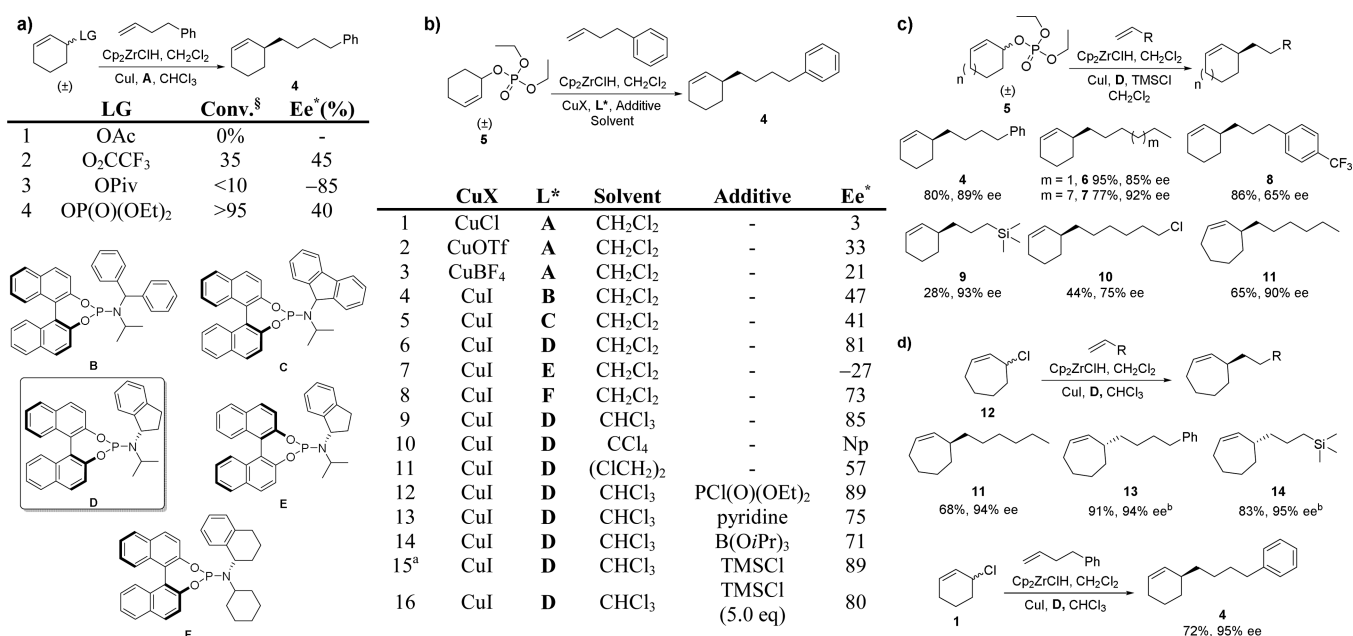


Figure 5. Development of a new AAA system. (a) Leaving group screening. Conditions: substrate (1.0 equiv), 4-phenyl-1-butene (2.5 equiv), Cp₂ZrHCl (2.0 equiv), CH₂Cl₂, CuI (10 mol %), A (10 mol %), CHCl₃, room temperature, overnight. [§]Conversion was determined by crude NMR. ^{*}Ee was determined by HPLC. (b) Optimizing conditions. Conditions: allyl phosphate (1.0 equiv), 4-phenyl-1-butene (2.5 equiv), Cp₂ZrHCl (2.0 equiv), CH₂Cl₂, CuX (10 mol %), L* (10 mol %), solvent, additive (1.0 eq unless specified), overnight. ^{*}Ee was determined by HPLC. (c) Scope of AAA of allyl phosphate. Conditions: alkene (2.5 equiv), Cp₂ZrHCl (2.0 equiv), CH₂Cl₂, CuI (10 mol %), D (10 mol %), allyl phosphate (1.0 equiv), TMSCl (1.0 equiv) in CHCl₃, room temperature. (d) AAA using ligand D with 6- and 7-membered ring allyl chlorides. Conditions: alkene (2.5 equiv), Cp₂ZrHCl (2.0 equiv), CH₂Cl₂, CuI (10 mol %), D (10 mol %), allyl chloride (1.0 equiv), in CHCl₃, room temperature. ^a Using CH₂Cl₂ gave the same results and was used in subsequent scope for convenience. ^b Prepared using (R,R)-D.

TMSCl decreased the ee (for example, 5.0 equiv, 80% ee, entry 16). When using 1.0 equiv of TMSCl, using CHCl_3 and CH_2Cl_2 gave the same results.

We then tested the scope of alkenes (Figure 5c). Products bearing simple alkyl chains (compounds 6 and 7) were obtained in high yields (>77%) and ee's (>85% ee). The presence of more elaborate functional groups such as 4- CF_3 -Ph (8, 86%, 65% ee), TMS (9, 28%, 93% ee), and Cl (10, 44%, 75% ee) were tolerated but caused a decrease in the ee or the yield. We note that this AAA of allyl phosphates is more sensitive to the presence of functionalized alkene starting materials than the corresponding reactions with allyl chlorides.

When using a seven-membered allyl phosphate, we obtained 11 in good yield (65%) with excellent 90% ee. The ability to use seven-membered rings here is important because these were not suitable substrates for the previous AAA with allyl chlorides (use of 12 gave 23% ee). We tested ligand D in an AAA using the seven-membered chloride 12, and excellent (94–95% ee) enantioselectivity and good yield (>68%) were observed for the three alkenes tested (Figure 5d).

Generally, ligand D appears to be an excellent alternative to A in these AAA reactions, as it allows reactions with seven-membered substrates. Also, in the case of six-membered allyl chloride 1 we obtained a 72% yield and 95% ee, a similar result obtained with A (88% yield, 93% ee).

Substituted Starting Materials. We next studied substituted racemic cyclic starting materials, which can “desymmetrize” the substrates and give rise to diastereomeric intermediates and products. This work probes the scope and limitations of these processes and suggests realistic synthetic applications. We also hoped these studies would shed light on the reaction mechanism, but interpretation is complicated.

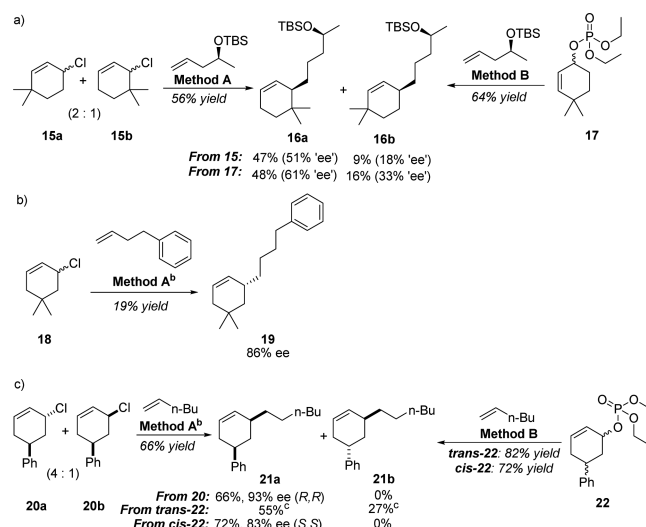
Synthesis of allyl chloride 15 always produced an inseparable mixture of 15a and 15b in an ~2:1 ratio, despite several synthetic approaches. Some enantiomerically enriched methyl substituted allyl chlorides are known, but these are reported to rapidly racemize.^{82,83} During AAA of 15 with 4-phenyl-1-butene, regioisomeric products were obtained using stoichiometric nonchiral CuBr-DMS (DMS, dimethyl sulfoxide) as the catalyst (1:1 ratio) or catalytic CuI–A (2:1 ratio), but the ee's of the mixture could not be determined due to their aliphatic nature. Using a single enantiomer (>99% ee) a chiral alkene nucleophile allowed us to determine the “ee” of the products by measuring the diastereotopic ratios of 16a and 16b isomers by NMR spectroscopy.⁸⁴ We obtained 16a and 16b in a 5:1 ratio with 51% “ee” and 18% “ee” respectively (Scheme 2a, left).

In contrast to 15, allyl phosphate 17 could be prepared as a single racemic regioisomer, and optimized conditions gave $\text{S}_{\text{N}}2/\text{S}_{\text{N}}2'$ products 16a and 16b in 3:1 ratio in favor of $\text{S}_{\text{N}}2'$ with poor enantioselectivity (61% and 33% “ee” respectively) (Scheme 2a, right). Overall, these results are difficult to interpret, but these AAA reactions favor formation of the (more hindered) $\text{S}_{\text{N}}2'$ product, albeit not with synthetically useful enantioselectivity, and we are uncertain of the structure of the allylic species that actually undergo C–C bond formation.

5,5-Disubstituted allyl chloride 18 was found to give 19 with high ee (86%) but only low (30%) conversion resulting in a very poor yield (19%), so it appears that bulky disubstitution impairs reactivity (Scheme 2b).

5-Phenyl-substituted allyl chlorides 20, prepared and used as a racemic 4:1 *trans/cis* diastereomeric mixture, provided a single product, *cis*-21a, in 66% yield with 93% ee (Scheme 2c, left). This result is remarkable, as it shows that, in appropriately

Scheme 2. Cu-Catalyzed AAA of Substituted Allyl Chlorides and Allyl Phosphates^a



^aMethod A: alkene (2.5 equiv), Cp_2ZrCl_2 (2.0 equiv), CH_2Cl_2 , CuI (10 mol %), A (10 mol %), allyl chloride (1.0 equiv) in CHCl_3 , room temperature. Method B: alkene (2.5 equiv), Cp_2ZrCl_2 (2.0 equiv), CH_2Cl_2 , CuI (10 mol %), D (10 mol %), allylphosphate (1.0 equiv) TMSCl (1.0 equiv) in CH_2Cl_2 , room temperature. Isolated yields. Ee was determined by NMR or HPLC. ^bPrepared using (R,R,R)-A. ^cThe ee of these products could not be determined due to overlapping signals (see SI, p S113).

designed substrates, a mixture of four isomers (two racemic diastereomers) may be converted into a single diastereomerically and enantiomerically pure product. We speculate that rapid CuI–A mediated isomerization of substrates 20 allows the catalyst to select one isomer of starting material for a highly enantioselective reaction.

5-Phenyl-substituted phosphate 22 could be isolated as either the *trans*- or *cis*-isomer. *trans*-22a gave a 2:1 ratio of products (Scheme 2c, middle). *cis*-22b solely gave the *cis*-product 21a in 72% yield with 83% ee (Scheme 2c, bottom). These empirical results show divergence in reactivity between the allyl chloride and allyl phosphate substrates.

NMR Studies on AAA Reactions Using Allyl Phosphate

5. In an AAA of allyl phosphate 5 followed by *in situ* ^1H NMR spectroscopy, we observe clean conversion of 5 to product 3 (Figure 6a). 5 was consumed much more rapidly (<1 h) than product was formed (11 h to completion). We identified allyl chloride 1 as an important intermediate. The presence of allyl iodide 2 was also observed, but 2 behaves differently than described above (Figure 2). Here 2 rapidly forms at the beginning of the reaction, reaches a maximum concentration of ~10 mol % after ~2 min, and is consumed within 30 min. Signals characteristic of $\text{S}_{\text{N}}2'$ isomerization processes were never observed by *in situ* EXSYs during this AAA (see SI p S43).

We modeled these kinetics,⁶⁴ assuming AAA preferentially uses allyl chloride 1 as a substrate, but some allyl phosphate 5 undergoes AAA. The model fits formation of 3 from 1 being 20 times faster ($k_1 = 0.042 \text{ mol \%} \cdot \text{min}^{-1}$) (eq 9) than from 5 ($k_2 = 0.023 \text{ mol \%} \cdot \text{min}^{-1}$) (eq 10). We assume TMSCl forms 1 from 5 ($k_{\text{TMSCl}} = 0.212 \text{ mol \%} \cdot \text{min}^{-1}$) (eq 11) and formation of 1 is measured to be ~5 times faster than AAA. This model requires that AAA generates stoichiometric Cl^- which reacts with 5 to

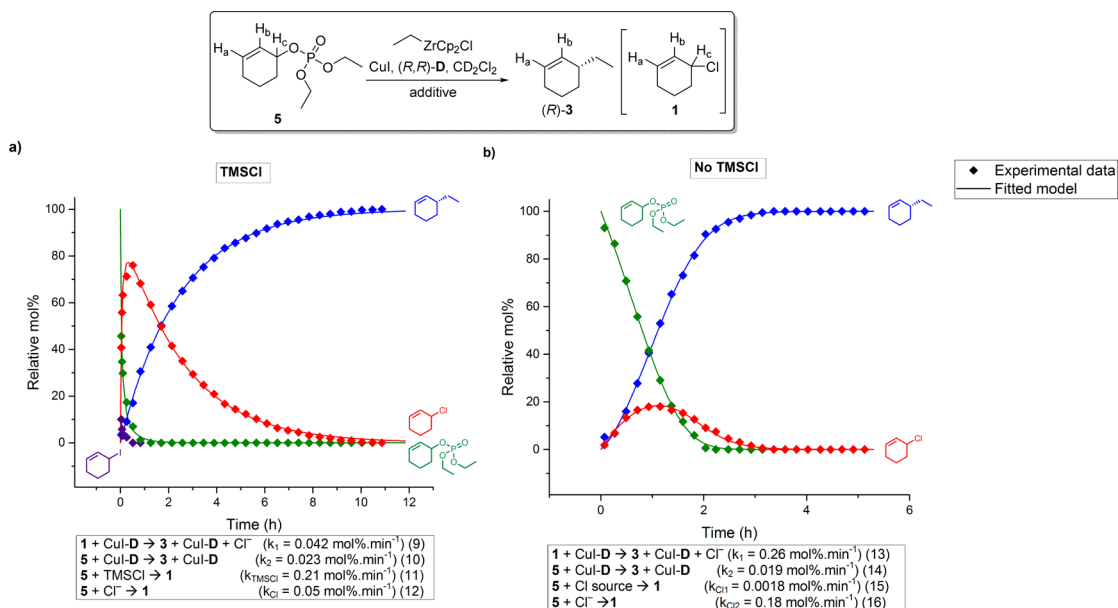


Figure 6. Reaction kinetics of Cu-AAA with allyl phosphate **5** monitored by ^1H NMR spectroscopy (a) with TMSCl and (b) without TMSCl and modeled. Conditions: ethylene (1 atm), Cp_2ZrClEt (2.0 equiv) in CD_2Cl_2 , CuI (10 allyl iodide), (*R,R*)-**D** (10 mol %), allyl phosphate **5** (1.0 equiv), TMSCl (0 or 1.0 equiv) in CD_2Cl_2 , 298 K. Experimental data recorded by ^1H NMR spectroscopy are shown as diamonds. Based on those data points, modeling was performed using Dynafit4 and the resulting fitted curves are shown as solid lines and the input equations, with their rates, below the corresponding graphs.

generate more **1** (eq 12) at a similar rate ($k_{\text{Cl}} = 0.05 \text{ mol\%}\cdot\text{min}^{-1}$) to AAA with **1**.

We also followed AAA with phosphate **5** by *in situ* ^{31}P NMR spectroscopy. Upon addition of Cp_2ZrClEt to CuI-D in CD_2Cl_2 no change was observed. Upon addition of **5** and TMSCl, **5** is observed at -1.5 ppm and a new peak is formed at 9.2 ppm (the phosphate leaving group anion; see SI p S118). At completion, $(\text{Et}_2\text{O})_2\text{P}(\text{O})\text{O}^-$ is still present while **5** is fully consumed and a variety of new, small, unsymmetrical broad peaks were observed.

Simply adding TMSCl to **5** in CD_2Cl_2 shows quantitative formation of **1** in 1 h, but **1** was not observed to isomerize by EXSY. Addition of CuI-D to **5** did not result in any observable changes to the ^1H or ^{31}P NMR spectra (see SI p S120). So it appears that, contrary to experiments with chloride **1**, phosphate **5** does not directly react with the catalyst to form iodide **2**. However, upon addition of TMSCl to a mixture of **5** and CuI-D, allyl phosphate **5** is rapidly transformed to allyl chloride **1**. Allyl iodide **2** is also formed and reaches a maximum concentration of 10 mol % and is then consumed within 10 min to give **1**. Contrary to experiments carried out on the actual Cu-AAA of **5**, isomerization of **2** was observed by EXSY when **5**, TMSCl, and CuI-D are mixed in CD_2Cl_2 .

Upon mixing Cp_2ZrClEt and **5** in CD_2Cl_2 , the ^1H and ^{31}P NMR spectra of **5** remain unaffected, and addition of TMSCl forms **1**. Under these conditions formation of **1** reaches completion in 150 min, ~ 2.5 times slower than without Cp_2ZrClEt . In the presence of Cp_2ZrClEt and TMSCl, **1** is not observed to undergo $\text{S}_{\text{N}}2'$ isomerization by EXSY. Overall, **1** seems to originate from addition of TMSCl, but its rate of formation is affected by other reaction components.

We became curious about the mechanism of AAA with **5** in the absence of TMSCl (Figure 5b, entry 6). Using *in situ* ^1H NMR spectroscopy, and the same conditions as above but without TMSCl, we surprisingly observed that this reaction also proceeds through allyl chloride **1** (Figure 6b). Allyl iodide **2**

was also briefly present at a concentration of <2 mol % and consumed within the first 10 min. Here, no isomerization of **2** or **1** was observed by EXSY. TMSCl is known to accelerate Cu-catalyzed conjugate addition reactions, but not without some lingering mechanistic ambiguity.^{85–91} In contrast, here the overall reaction is faster in the absence of TMSCl and reaches completion in 3.5 h, as opposed to 11 h with TMSCl, but both AAAs have similar half-lives (~ 1.5 h). However, despite the overall lower rate of reaction, TMSCl facilitates conversion of allyl phosphate **5** to allyl chloride **1**. In the absence of TMSCl consumption of **5** is slower (2 h) than in the presence of TMSCl (1 h) and **1** reaches a maximum of 20 mol % at 1 h (compared to 75 mol % with TMSCl), as **1** presumably gets transformed to **3**, limiting its concentration. ^{31}P NMR spectroscopy of the TMS-free AAA also shows **5** (-1.5 ppm) is consumed within ~ 2 h and many nonsymmetrical broad signals appear in that region within 12 h (see SI p S120).

In the AAA of **5** without TMSCl, a model⁶⁴ fits formation of **3** being 10 times faster from **1** ($k_1 = 0.26 \text{ mol\%}\cdot\text{min}^{-1}$, eq 13) than from **5** ($k_2 = 0.019 \text{ mol\%}\cdot\text{min}^{-1}$, eq 14) and faster than in the presence of TMSCl ($k_1 = 0.042 \text{ mol\%}\cdot\text{min}^{-1}$). As Cp_2ZrClEt and CH_2Cl_2 are the only possible initial sources of chloride, we modeled formation of **1** using Cp_2ZrClEt as the source (eq 15). The formation of **1** is very slow ($k_{\text{Cl1}} = 0.0018 \text{ mol\%}\cdot\text{min}^{-1}$) (eq 15), but generating **1** from Cl⁻ produced during AAA is fast ($k_{\text{Cl2}} = 0.18 \text{ mol\%}\cdot\text{min}^{-1}$; eq 16) and of the same order of magnitude as formation of **3** from **1**.

TMSCl plays a role in the formation of **1**, and also affects the catalyst. Upon addition of TMSCl to a solution of CuI-D, instantaneous changes are observed in ^1H and ^{31}P NMR spectra suggesting formation of two species (see SI p S130). The minor component of the two newly formed species resembles CuCl-D complexes, but the major component is unknown and is not observed during AAA of **5** in the presence of TMSCl. Curiously these catalytic modifications do not occur in the presence of Cp_2ZrClR .

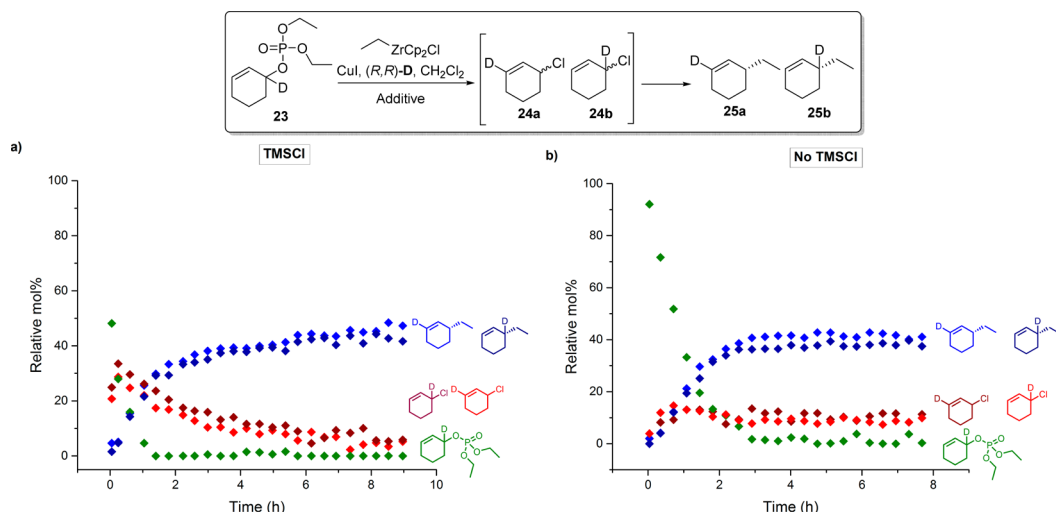


Figure 7. Reaction kinetics of Cu-AAA with d-23 as monitored by ^2H NMR spectroscopy (a) with TMSCl and (b) without TMSCl. Conditions: ethylene (1 atm), Cp_2ZrClEt (2.0 equiv) in CH_2Cl_2 , CuI (10 mol %), (*R,R*)-**D** (10 mol %), d-allyl phosphate **23** (1.0 equiv), TMSCl (0 or 1.0 equiv) in CH_2Cl_2 , 298 K.

We also synthesized deuterated allyl phosphate **23**. In AAAs with TMSCl monitored by *in situ* ^2H spectroscopy (Figure 7a), d-**23** is rapidly consumed to form d-allyl chlorides **24a** and **24b** in approximately equal amounts and the d-allyl chlorides in turn form D-products **25a** and **25b** in a 1:1 ratio. ^2H NMR spectroscopy on d-**23** without TMSCl *in situ* (Figure 7b) similarly showed that d-**23** is consumed slowly to form equal amounts of d-allyl chlorides **24a** and **24b**, which in turn form an ~1:1 mixture of **25a** and **25b**.

Adding TMSCl (1.0 equiv) to d-**23** (1.0 equiv) shows that it is completely transformed to d-chlorides **24a** and **24b** within 20 min. Both $\text{S}_{\text{N}}2'$ and $\text{S}_{\text{N}}2$ products are formed, but reaction of **23** with TMSCl appears to prefer $\text{S}_{\text{N}}2'$ pathways (65 mol % β -d-**24a** vs 35 mol % **24b**; see SI p S136). As the ratio of **24a** and **24b** remains largely unchanged under these conditions, d-allyl chlorides **24** appear not to isomerize through $\text{S}_{\text{N}}2'$ mechanisms spontaneously, suggesting that TMSCl alone is not responsible for the 1:1 ratio of **24a** and **24b** observed during AAA.

We studied the effect of Cp_2ZrClEt (2.0 equiv) on the formation of d-**24a** and d-**24b** with TMSCl (1.0 equiv). Within 200 min, 65 mol % of **24b** was formed while 35 mol % of **24a** was obtained (see SI p S137), so (for reasons that are not understood) addition of Cp_2ZrClEt appears to reverse the selectivity observed with TMSCl alone.

We investigated the effect of CuI-**D** (10 mol %) on the formation of **24a** and **24b** from d-**23**. Upon addition of TMSCl, **24a** and **24b** are formed instantaneously as well as trace amounts of d-allyl iodides (see SI p S137). Here, the D-isomers are formed in equal amount suggesting that CuI-**D** facilitates isomerization of the allyl halide species in the AAA reaction itself.

Finally, we investigated the use of enantiomerically pure allylphosphates (+)-**5** and (–)-**5** using CuI-**D** and TMSCl in a reaction to form **4**. Although these experiments are difficult because of the very small amount of product formed at early stages of the reaction (~10 min), no significant difference in the enantiomeric excess of **4** formed from (–)-, (+)-, or (±)-**5** was observed (ee values obtained varied from run to run and range from 84% ee to 93% ee).

In the AAA of **5**, we did not observe the constant presence of allyl iodide **2** or see evidence of the $\text{S}_{\text{N}}2'$ isomerization of **1** or **2**

by EXSY. However, these pathways may still operate at rates undetectable by NMR. It seems likely that, regardless of the source of chloride-**1**, both CuI-L* catalyzed AAAs with **1** occur via similar mechanisms and that both reactions involve rapidly racemizing starting materials and a DKR type mechanism. But it is not inconceivable that the reaction of phosphate **5** to give **3** goes through other pathways.

CONCLUSION

High yield and enantioselectivity can be achieved in the Cu-catalyzed addition of alkylzirconium reagents to racemic allyl chloride and allyl phosphate electrophiles. Our work suggests a simple but powerful mechanism where CuI-mediated racemization of the starting materials coupled with a highly selective C–C bond forming catalyst allows highly enantioselective addition.

A number of different isomerizing agents have been identified potentially facilitating the extension of this strategy to a broader range of reactions. We have also shown that it is possible to quantify the rate of allyl halide isomerization using three different NMR techniques. Here experiments show the rate of CuI-**A** mediated isomerization of allyl iodide **2** is $0.10 \pm 0.01 \text{ s}^{-1}$, and kinetic modeling suggests that **1** and **2** interchange much faster than C–C bond formation.

The catalysts involved in C–C formation are aggregates of Cu and phosphoramidite which involve at least two ligands. A critical dependence of the copper counterion was demonstrated, which affects many mechanistic aspects of the reaction. Kinetic modeling suggests that the catalyst is modified during the reaction to contain both I and Cl ions and becomes more enantioselective and 3 times faster than the starting catalyst.

A second AAA system was developed using racemic allyl phosphates and new ligand **D** which is also an excellent alternative to **A** in AAAs with **1** and is superior with seven-membered-ring substrates. Structure–reactivity relationships demonstrated that, in some cases, excellent stereochemical control can be achieved where racemic mixtures of diastereomers are converted to a single diastereoisomer of product with high ee.

AAA reactions with these allyl phosphates, as judged by NMR spectroscopy and isotopic labeling studies, proceed via

allyl chlorides formed *in situ*, either by the action of TMSCl or from adventitious Cl^- generated from reaction components. The ability to generate rapidly isomerizing allyl halide species *in situ* from these phosphates is likely to be useful in chemistry far beyond the present studies. We anticipate that this work will aid development of new asymmetric addition reactions using racemic starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02440.

Experimental procedures, characterization data and relevant NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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