LETTER

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Non-stabilized nucleophiles in Cu-catalysed dynamic kinetic asymmetric allylic alkylation

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The development of new reactions forming asymmetric carbon–carbon bonds has enabled chemists to synthesize a broad range of important carbon-containing molecules, including pharmaceutical agents, fragrances and polymers[1]. Most strategies to obtain enantiomerically enriched molecules rely on either generating new stereogenic centres from prochiral substrates or resolving racemic mixtures of enantiomers. An alternative strategy—dynamic kinetic asymmetric transformation—involves the transformation of a racemic starting material into a single enantiomer product, with greater than 50 per cent maximum yield[2,3]. The use of stabilized nucleophiles ($pK_a < 25$, where K_a is the acid dissociation constant) in palladium-catalysed asymmetric allylic alkylation reactions has proved to be extremely versatile in these processes[4,5]. Conversely, the use of non-stabilized nucleophiles in such reactions is difficult and remains a key challenge[6–9]. Here we report a copper-catalysed dynamic kinetic asymmetric transformation using racemic substrates and alkyl nucleophiles. These nucleophiles have a pK_a of ≥50, more than 25 orders of magnitude more basic than the nucleophiles that are typically used in such transformations. Organometallic reagents are generated *in situ* from alkenes by hydrometallation and give highly enantioenriched products under mild reaction conditions. The method is used to synthesize natural products that possess activity against tuberculosis and leprosy, and an inhibitor of *para*-aminobenzoate biosynthesis. Mechanistic studies indicate that the reaction proceeds through a rapidly isomerizing intermediate. We anticipate that this approach will be a valuable complement to existing asymmetric catalytic methods.

Two strategies for generating single enantiomer compounds using enantioselective catalysis have become widely used: the first strategy generates a chiral product by a selective reaction which introduces asymmetry to a prochiral substrate (Fig. 1a). This prochiral approach has proven important in the development of catalytic asymmetric reactions, despite the rather limited availability of prochiral substrates when compared to chiral substrates. The second widely used strategy is to start from a racemic mixture of chiral starting materials. Here the catalyst selectively reacts with one of the two enantiomers allowing differentiation (or resolution) of the enantiomers, but the yield is necessarily limited to 50%, as the undesired enantiomer remains as starting material. An efficient variation of this second strategy is to couple enantiomer differentiation with interconversion of the enantiomers, commonly called dynamic kinetic resolution. This strategy allows yields of more than 50% from chiral starting materials[2,3].

Transition-metal-catalysed asymmetric allylic alkylation (AAA) reactions have proven to be powerful tools for creating new carbon–carbon bonds[4,9–11]. Twenty years ago, palladium-catalysed AAA reactions were reported in which racemic mixtures were converted to single enantiomer products with high yield and enantioselectivity (Fig. 1b)[12]. The use of stabilized nucleophiles ($pK_a < 25$) in metal-catalysed AAA reactions is now well established in catalysis and synthesis[5,9]. These reactions are dynamic kinetic asymmetric transformations (DYKATs) as they form one enantiomer of a new product from both enantiomers of a racemic starting material, and no 'resolved' starting material is recovered[3,5]. Mechanistic studies reveal that Pd-catalysed DYKATs operate through a pathway where both enantiomers of the starting material are converted to a common pseudo-prochiral intermediate, and a subsequent enantioselective step creates the new stereogenic centre[6]. The use of non-stabilized nucleophiles in such reactions is a long-standing research goal[6–9] and efforts to broaden the scope of DYKAT to non-stabilized carbon nucleophiles now allows certain specific 'less-stabilized' partners to be used in Pd-catalysed asymmetric (for example, Fig. 1c)[7,13] and non-enantioselective procedures[8].

One difficulty in expanding the scope of DYKATs is that metal-catalysed AAAs do not rely on a single mechanistic pathway[4]. In particular, there is a significant mechanistic distinction between stabilized and non-stabilized nucleophiles (Fig. 1d)[4,6,7,10]. In the case of stabilized nucleophiles, the key bond-making event occurs outside of the coordination sphere of the metal, so that the stereochemistry is determined when the nucleophile attacks a carbon atom of a π-allyl-Pd intermediate[14]. In contrast, when using non-stabilized nucleophiles bond formation probably occurs through reductive elimination of an intermediate in which the nucleophile is bound to the metal centre[15].

Catalytic asymmetric reactions with non-stabilized nucleophiles often use copper catalysts[16,17]. These reactions have proven much more difficult to study mechanistically than their Pd-catalysed counterparts, as non-stabilized organometallic reagents are typically very reactive, hindering the isolation of intermediates and characterization of pathways. Copper-catalysed allylic alkylations are generally accepted to operate via

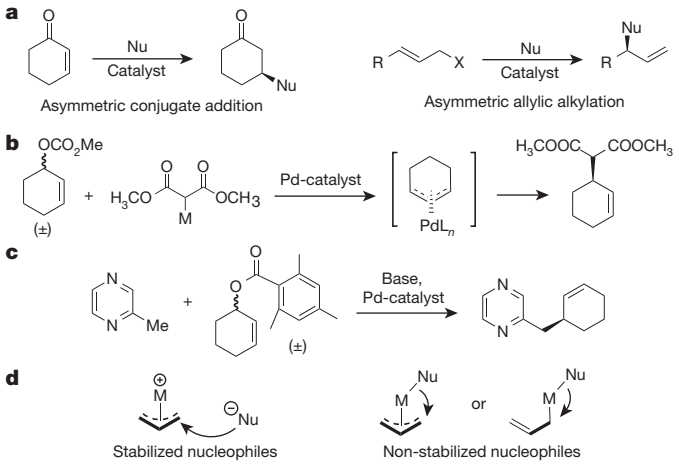

Figure 1 | Asymmetric allylic alkylation (AAA) procedures. **a**, Typical examples of the prochiral approach to asymmetric catalysis, in which a species selectively adds to one face of a prochiral substrate, exemplified (on the left) by asymmetric conjugate addition and (on the right) by AAA. Nu, nucleophile; R, generic substituent (or generic group); X, leaving group. **b**, A prototypical Pd-catalysed DYKAT, where AAA with a stabilized carbon nucleophile transforms a racemic mixture of starting materials into a single highly enantioenriched product. **c**, An example of DKYAT in AAA using heterocyclic nucleophiles with a $pK_a > 25$. **d**, Transition-metal-catalysed allylic substitution mechanisms with stabilized and non-stabilized nucleophiles.

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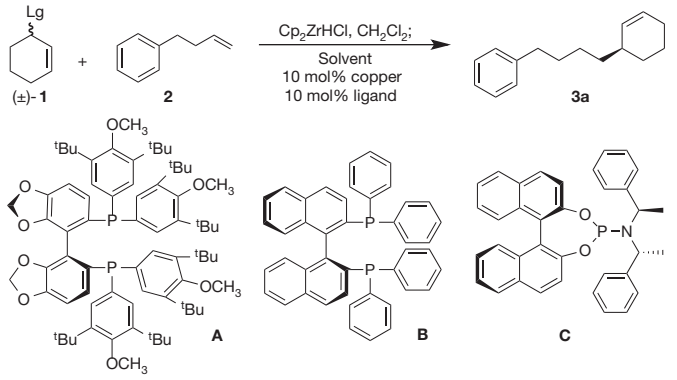
regiospecific *anti*-addition mechanisms, where selective rate-determining S_N2' oxidative additions give copper(III) intermediates, and fast reductive eliminations form the final product[16,17]. A key distinction between Cu- and Pd-AAA reactions is a lack of an efficient σ- to π- isomerization[18] in the case of copper, so that if reductive elimination is fast, a π-allyl-Cu species will not form and reactions involving racemic starting materials will lead to racemic products.

Copper-catalysed AAA on prochiral materials, where selective oxidative addition occurs on one enantiotopic face of the substrate, can be readily achieved[10,16–18]. However, the generally accepted Cu-catalysed mechanisms would seem to preclude efficient asymmetric reactions with chiral racemic substrates, where addition would be controlled by the stereogenic centre of the substrate, not the catalyst[18]. We note that racemization of enantiopure starting materials during Cu-catalysed allylic alkylation has been reported, suggesting the possibility of generating useful π-allyl-Cu species and DYKATs[19]. Building on this work, promising initial results have been obtained with Grignard reagents[20], but despite extensive examination, and the elucidation of interesting mechanistic pathways, generally useful procedures have not emerged[21,22].

Based on the observation that alkylzirconium reagents undergo highly enantioselective conjugate addition at ambient temperature[23,24], whereas procedures with traditional non-stabilized carbon nucleophiles (based on Mg, Al, and Zn species) are normally performed at very low temperatures[16,17], we hypothesized that alkylzirconium reagents may allow efficient AAA from racemic substrates. Here we describe AAA of racemic cyclic allylchlorides with alkylzirconocenes initiated by copper catalysts. Highly enantioenriched products are obtained at room temperature in convenient procedures, in which all of the reaction components are commercially available.

We began by exploring the coupling of racemic 3-substituted cyclohexenes **1** and the alkylzirconium species generated *in situ* from 4-phenyl-1-butene (**2** in Table 1) and the Schwartz reagent (Cp_2ZrHCl) under a variety of reaction conditions. The use of Pd- and Ir-based catalysts did not lead to product **3a**, but when Cu-catalysts were used, product **3a** was obtained with varying degrees of enantioselectivity. The combination of 3-chloro-cyclohexene **1d**, phosphoramidite **C**[11], and $(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$ in dichloromethane provided **3a** in quantitative yield with 71% enantiomeric excess (e.e.; Table 1, entry 6). Variation of the copper counterion under these conditions showed that CuI gave the highest e.e. (89% e.e., entry 10) and chloroform gave the best results of the solvents examined (93% e.e., entry 11). Varying the temperature (entries 12 and 13) showed that slightly higher enantioselectivity was obtained by cooling the reaction to 0 °C (93% versus 95% e.e.) but we chose to perform the rest of our studies at room temperature because of operational convenience and under these conditions full conversion was always observed overnight. Examination of bromide **1a** under these conditions (entry 14) showed that the less reactive chloride **1c** gave superior results.

Table 1 | Selected optimization experiments



Entry	Leaving group	Ligand	Copper source	Solvent	Temp. (°C)	e.e. (%)
1	Br (**1a**)	**A**	$(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$	CH_2Cl_2	25	4
2	$OP(O)(OEt)_2$ (**1b**)	**A**	$(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$	CH_2Cl_2	25	10
3	O_2CCF_3 (**1c**)	**A**	$(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$	CH_2Cl_2	25	10
4	Cl (**1d**)	**A**	$(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$	CH_2Cl_2	25	35
5	Cl	**B**	$(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$	CH_2Cl_2	25	1
6	Cl	**C**	$(t\text{BuCN})_2\text{Cu}\cdot\text{OTf}$	CH_2Cl_2	25	71
7	Cl	**C**	$CuCl/AgSbF_6$	CH_2Cl_2	25	51
8	Cl	**C**	CuCl	CH_2Cl_2	25	49
9	Cl	**C**	CuBr	CH_2Cl_2	25	73
10	Cl	**C**	CuI	CH_2Cl_2	25	89
11	Cl	**C**	CuI	$CHCl_3$	25	93
12	Cl	**C**	CuI	$CHCl_3$	0	95
13	Cl	**C**	CuI	$CHCl_3$	60	77
14	Br (**1a**)	**C**	CuI	$CHCl_3$	25	77

Optimization was performed for the AAA of racemic materials bearing different leaving groups and 4-phenyl-1-butene, which was hydrometallated using the Schwartz reagent. Different copper sources, ligands, solvents and temperatures were examined. The enantiomeric excess (e.e.) was determined by HPLC. Full conversion was observed in all cases shown.

The scope of the alkyl coupling partners was investigated using a variety of simple gaseous alkenes (giving products **3b**–**d**) and unfunctionalized primary alkenes (**3e**–**g**) (Fig. 2). High yields and consistently high enantioselectivities were obtained. Functionalized alkenes (**3h**–**3r**) were also examined: halogens, alkynes, aromatic rings, ethers, protected alcohols, trifluoromethyl groups and preformed stereogenic centres were all found to be compatible with the procedure. Electron rich alkenes such as allylsilane (to give **3i**) and styrenes (to give **3m**–**o**) also work well. We also examined the use of 5-membered rings with this procedure; we found that it is suitable for the direct preparation of highly enantioenriched cyclopentenes (**4a**–**c**) from an easily prepared racemic 5-membered allylchloride.

To probe practical aspects of this chemistry, scale-up reactions were performed (Fig. 3a). Despite excellent conversion (>90%), the yield of **4b** on a 15 mmol scale was low because the product and the residual alkene have similar polarities and boiling points, complicating isolation. Even so, we were easily able to obtain more than 1.8 g of pure **4b** (58% yield, 94% e.e.). When 1-hexene was used (to give **4a**), we arbitrarily reduced the ratio of alkene and Schwartz reagent used (to 2 and 1.8 equiv. respectively) and observed improved yield (86% yield, 91% e.e., 1.2 g) relative to using our standard test conditions (Fig. 2). Functionalized **3n** containing a bromide (Fig. 3b) was also synthesized on a preparative scale (88% yield, 87% e.e., 0.75 g) and a subsequent Heck reaction to provide *cis*-fused tricycle **5** (88% yield) demonstrates that these reactions can be used to rapidly access complex molecular frameworks.

To demonstrate that this method allows rapid access to important structural motifs, we performed asymmetric syntheses of biologically active cyclopentene-containing natural products (Fig. 3c). This approach provides short, straightforward, flexible syntheses which compare favourably to those previously reported[25], and will facilitate the study of structural analogues. Hydnocarpic acid (**6**) and chaulmoogric acid (**7**) are leprosy treatments used in ancient and traditional medicine: in both cases, the cyclopentenyl ring is a requirement for biological activity. Hydnocarpic acid is believed to act by blocking the activity of biotin or inhibiting microbial biotin synthesis[26], while the activity of chaulmoogric acid is probably due to incorporation into the cell wall lipids of *Mycobacterium leprae*[27]. Recent reports show that chaulmoogric acid and anthelminthicin C (**8**) significantly inhibit *Mycobacterium tuberculosis* growth with minimum inhibitory concentration values of 9.82 and 4.38 μM, respectively[28]. Anthelminthicin C has also recently been found to inhibit *para*-aminobenzoic acid biosynthesis (*p*ABAB)[28]; inhibitors of *p*ABAB are important leads for the development of new antibiotics, as this pathway is not found in humans[28].

On the basis of previously reported reactions it seemed likely that DYKAT was occurring by one of the four following pathways: (1) the reaction proceeds through a pseudo-*meso*- or prochiral π-allyl-Cu intermediate[19,20] similar to the Pd- or Ir-intermediates observed with stabilized nucleophiles[6]; (2) a related scenario, in which the reaction proceeds through rapidly interconverting intermediates derived from **1d** (such as σ-allyl-Cu species), one enantiomer of which undergoes a selective reaction[5]; (3) the two enantiomers of **1d** undergo two different

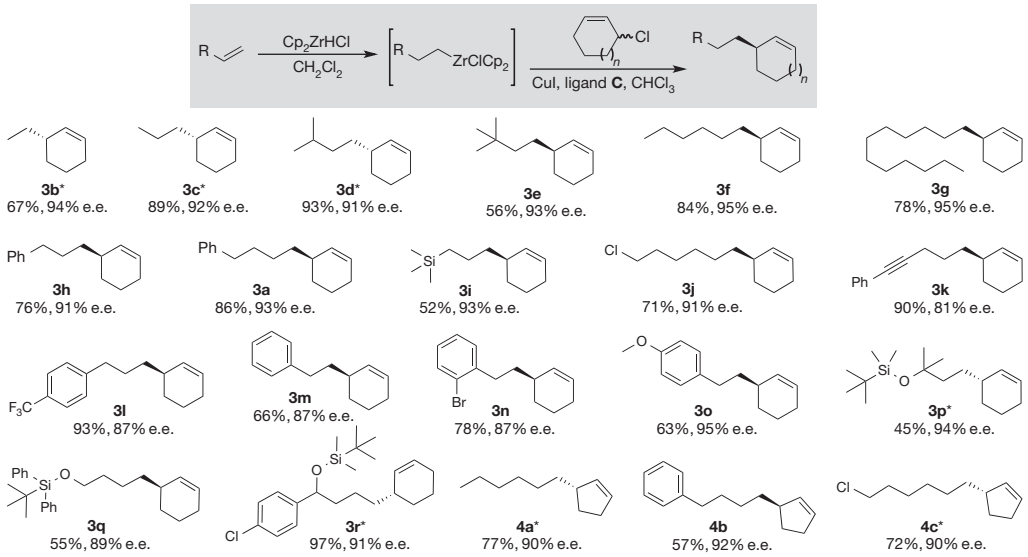


Figure 2 | Dynamic kinetic AAA with alkylzirconium nucleophiles generated from alkenes. Top row, alkenes react with the Schwartz reagent (Cp_2ZrHCl) in CH_2Cl_2 to generate alkylzirconocene species *in situ* which undergo AAA with racemic cyclic allylic chlorides. Cp, cyclopentadienyl. Conditions: 2.5 equiv. alkene, 2 equiv. Cp_2ZrHCl, 10 mol% CuI, 10 mol% ligand **C**, room temperature overnight, argon atmosphere. Lower rows, yield and enantiomeric excess of illustrated products. Yield refers to pure isolated compounds; the enantiomeric excess was either determined directly by high-performance liquid chromatography, or on the corresponding epoxides by gas chromatography, using a chiral non-racemic stationary phase. *Prepared using (*S*,*S*,*S*)-**C** (the enantiomer of the ligand shown in Table 1).

reactions, both giving the same product (an enantio-convergent transformation)[21]; or (4) **1d** racemizes during the reaction[2] and AAA is selective for one of the two enantiomers.

To gain insight into the mechanism, we followed reactions *in situ* using ^{1}H NMR spectroscopy. During these experiments, we observed clean conversion of **1d** to either **3a** or **3f**, and the formation of low, but fairly constant, concentrations of allyliodide **10** (Fig. 4a, also see Supplementary Information). The initial drop in the concentration of **1d** is an artefact of inconsistent NMR field inhomogeneities ('shimming') at early stages of the reaction. We were unable to observe the formation of alkyl-copper species (that would be produced by transmetallation from zirconium to copper) or σ- or π-allyl-copper species under these conditions, and we are unable to rule out the possibility of such species playing a role in the enantioselectivity of these reactions.

Examination of allyliodide **10** generated from **1d** (by CuI and **C** in $CDCl_3$) using 2-dimensional nuclear Overhauser effect NMR spectroscopy (NOESY) shows that the H_a and H_c protons of **10** rapidly interconvert (as indicated by cross-peaks between these proton signals, Fig. 4b, top right). At ambient temperature **1d** did not undergo observable dynamic processes, but at 55 °C (see Supplementary Information) we were able to detect interconversion between **1d** and **10**, demonstrating that the allyliodide and allylchloride interconvert, but not fast enough to be detected on the NMR timescale at room temperature. Under these conditions **1d** was not observed to isomerize directly. Monitoring an

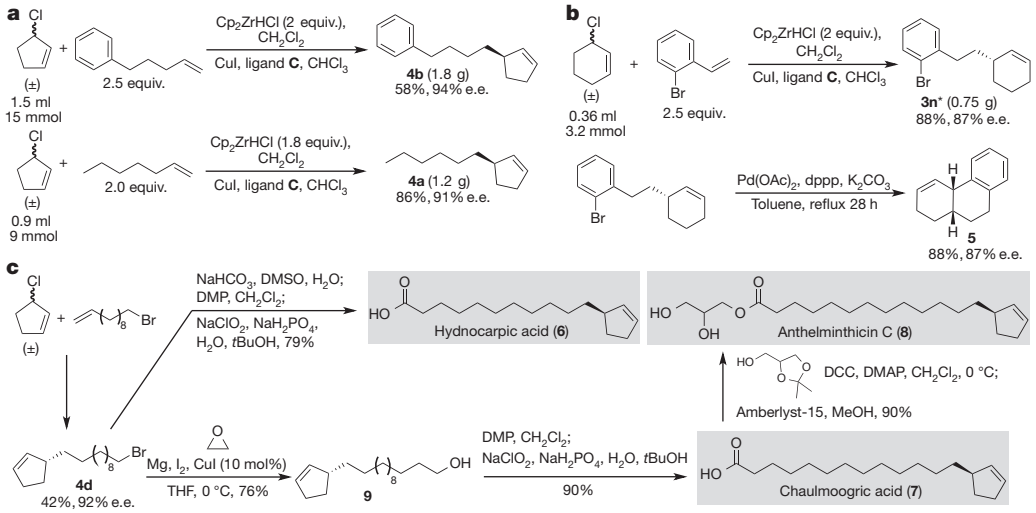


Figure 3 | Scale-up and applications of the method to access tricyclic structures and natural products. a, Experiments on a preparative scale to give >1 g of cyclopentene products. **b**, Preparative-scale reaction on a 6-membered ring followed by Heck reaction to give *cis*-fused tricycle **5**. **c**, Concise asymmetric synthesis of hydnocarpic acid (**6**), chaulmoogric acid (**7**) and anthelminthicin C (**8**). The syntheses start from commercially available 11-bromo-1-undecene to give bromo-substituted **4d** which is converted to **6** (by hydrolysis, then oxidation), or to **9** (by epoxide opening chain extension) followed by oxidation to **7**. Coupling **7** with racemic solketal, then acid catalysed deprotection, gave anthelminthicin C (**8**). *Made using (*S*,*S*,*S*)-**C** (the enantiomer of the ligand shown in Table 1). DMP, Dess-Martin periodinane; DCC, dicyclohexylcarbodiimide; dppp, 1,3-bis(diphenylphosphino)propane; DMAP, 4-dimethylaminopyridine. Amberlyst 15 is a polymeric acid resin. See Supplementary Information for full details.

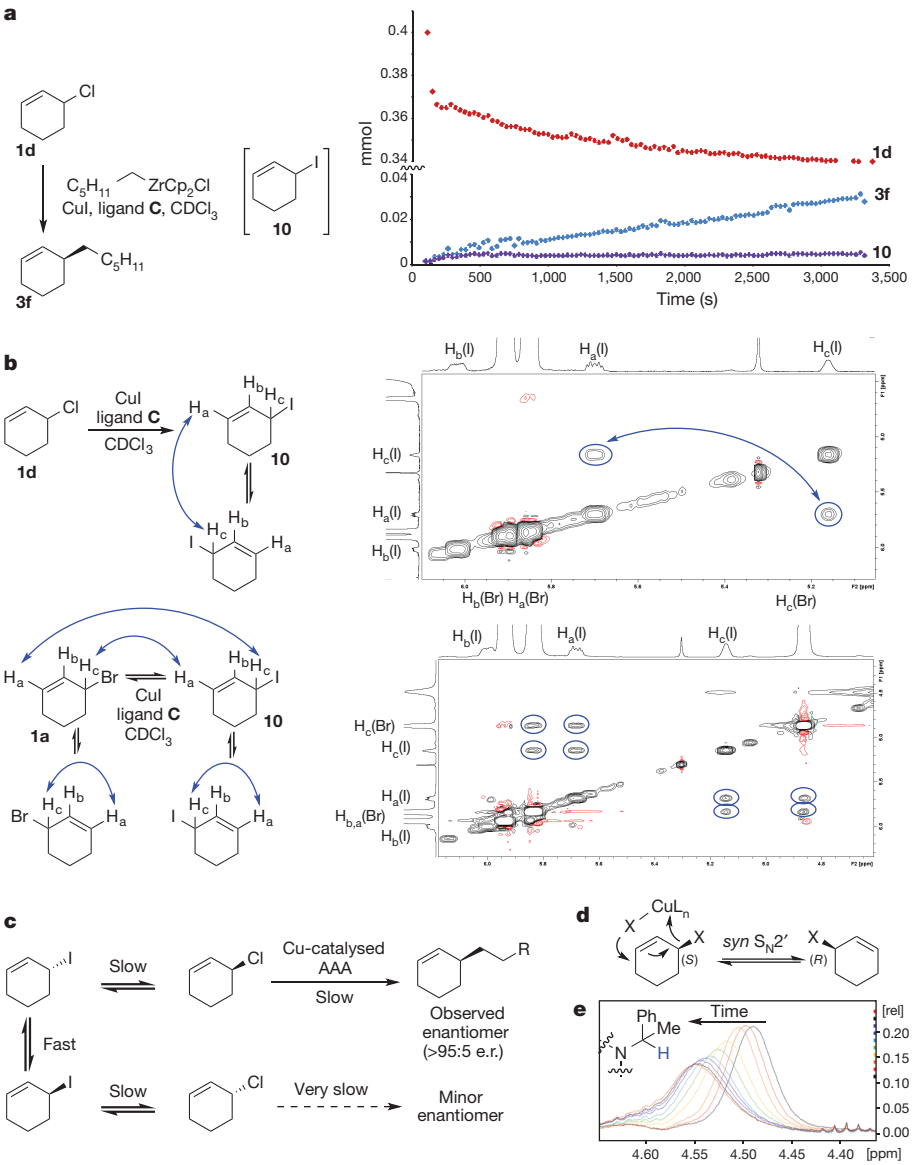


Figure 4 | Mechanistic analysis. **a**, Reaction kinetics as monitored by *in situ* ^{1}H NMR spectroscopy. Formation of an allyliodide intermediate (**10**) is observed. Plot at right shows concentration versus time. **b**, Examination of intermediates **10** (generated from CuI and **C** in $CDCl_3$) by NOESY: when generated from **1d** (top, proton chemical shifts on both axes, shift ranges as follows: vertical, 4.5–6.3 p.p.m.; horizontal, 6.2–5.05 p.p.m.), allyliodide protons labelled H_a and H_c exchange. When generated from **1a** (bottom, proton chemical shifts on both axes, shift ranges as follows: vertical, 4.1–6.3 p.p.m.; horizontal, 6.2–4.6 p.p.m.), rapid H_a/H_c isomerization is observed within both **1a** and **10**. Rapid exchange between **10** and **1a** is also observed. Cross peaks between H_a(Br)/H_c(I) and H_a(I)/H_c(Br), but not between H_a(Br)/H_a(I) or H_c(Br)/H_c(I), suggest interconversion occurs by an S_N2' pathway. **c**, Proposed mechanism for the DYKAT: as **1d** racemizes via **10**, one enantiomer of **1d** undergoes selective AAA. **d**, Possible racemization mechanism: metal-assisted *syn*-S_N2' attack. **e**, ^{1}H chemical shifts (vertical, relative intensity, 0.00–0.25; horizontal, chemical shift, 4.65–4.00 p.p.m.) of the benzylic protons of **C** are consistent with a change in metal-ligand aggregation, as a function of time (colours are for different spectra, taken at different times), from the initial $[L_nCuI]_n$ species.

AAA reaction to form **3a** from **1d** by *in situ* NOESY (see Supplementary Information) demonstrates that allyliodide **10** undergoes dynamic isomerization during the AAA itself.

When allylbromide **1a** is dissolved in $CDCl_3$ at room temperature, no dynamic processes are observed by NOESY (see Supplementary Information), but in the presence of CuI and **C** a variety of fast exchanges are observed (Fig. 4b, bottom right). Allyliodide **10** is formed, and both **1a** and **10** rapidly isomerize (as indicated by cross peaks between H_a(Br)/H_c(Br) of **1a** and H_a(I)/H_c(I) of **10**). Rapid interconversion of **1a** and **10** occurs as indicated by cross peaks between H_a(Br)/H_c(I) and H_a(I)/H_c(Br). As cross peaks between H_a(Br)/H_a(I) and H_c(Br)/H_c(I) are not observed, interconversion appears to exclusively occur by S_N2' mechanisms, although S_N2 exchange may occur through minor pathways not observable on the NMR timescale.

Taken together, these studies point to a mechanism (Fig. 4c) where **1d** racemizes, via **10**, and selective AAA of one of the enantiomers of **1d** gives a product with high enantiomeric excess. When using copper halides, higher enantioselectivities are obtained when the halide is a better nucleophile and leaving group (that is, I > Br > Cl, Table 1, entries 8–10), facilitating interconversion, but the overall reaction rates with CuCl and CuI are similar, suggesting that it is **1d** that undergoes AAA.

Racemization probably occurs through *syn*-S_N2' displacement reactions: S_N2' pathways are observed by NOESY, and *anti*-S_N2' reactions would not change the absolute sense of stereochemistry of the allylic halides. Many allylic substitutions are *syn*-S_N2' selective, and 'ion-pair' nucleophiles undergo selective *syn*-S_N2' reactions through cyclic transition structures[29]. Our studies are consistent with the copper-mediated *syn*- S_N2' pathway shown in Fig. 4d.

We followed the enantiomeric excess of **3f** formed as a function of time using CuCl, CuI and CuOTf. When using CuOTf, the reaction goes to completion much faster (<30 min) than with copper halides (overnight) and we did not detect any change in e.e. with time, so we tentatively speculate that CuOTf and Cu-halide catalysed reactions (Table 1, entry 6) are mechanistically distinct. Reactions using CuCl show a decrease of e.e. with increasing time (~82% e.e., 10 min; 68% e.e., 2 h; 54% e.e. at completion) and we speculate that when CuCl is used, the rapidly reacting enantiomer of **1d** is consumed, and not replenished by fast racemization. The reaction with the minor enantiomer therefore becomes significant and reduces the e.e. of **3f** as time progresses. We observed non-racemic **1d** (at least 11% e.e. at 2 h) during the reaction as judged by gas chromatography analysis (see Supplementary Information). In the case of CuI the initial reaction rate is slow, and only very small amounts of **3f** are formed after 10 and 30 min. Here the e.e. increases with time (~85% e.e., 10 min; 90% e.e., 2 h; 95% e.e. at completion) suggesting that a more enantioselective system is generated as the reaction progresses.

At least part of the role of CuI is to racemize **1d** via **10**, but the identity of the proposed highly enantioselective catalyst is unclear. Both CuCl and CuI give lower initial values of e.e. than are observed at later stages of the CuI-catalysed reaction. It may be that copper aggregates containing both 'Cl' and 'I' are more selective than those containing only one halogen. An experiment performed using 10% **C** + 5% CuCl + 5% CuI ambiguously gave **3f** with 90% e.e. (rather than 95% e.e.) at completion. Alternatively, salt effects may increase the e.e. of **3f** as time progresses by favouring the formation of more highly enantioselective copper-ligand complexes; the reaction produces Cp_2ZrCl_2 which may affect the relative solubility of other reaction components.

^{1}H NMR spectroscopy studies suggest that copper-ligand aggregates change during the reaction: we observe a shift in the benzylic proton signal of ligand **C**, from being characteristic of $[L_nCuI]_n$ complexes, towards new species as time progresses (Fig. 4e, see also Supplementary Information). Cu-halide phosphoramidite aggregates exhibit complex dynamic equilibria between several solution- and solid-phase species, which are sensitive to solvent as well as halide and salt effects[30], and so determining the actual composition of the copper species generated in the reaction will require further work. How the Cu-ligand complex selects for one enantiomer of **1d**, and how the Cu-ligand complex interacts with the alkylzirconium species, are also both currently unclear.

We have described a copper-catalysed enantioselective addition of alkyl zirconium reagents to racemic cyclic allylic chlorides. The reaction uses readily available starting materials and catalysts, tolerates a variety of functional groups and operates under convenient conditions. The reactions can be performed on gram scales, and we have applied the reaction to the asymmetric synthesis of biologically active cyclopentene natural products. Mechanistic studies suggest that this dynamic kinetic asymmetric transformation operates via a rapidly interconverting intermediate, racemizing the substrate, and the formation of a more highly selective copper-catalyst *in situ*. This reaction is expected to complement the well-established palladium and iridium-catalysed methods with stabilized nucleophiles. Additionally, we anticipate that the mechanistic insight will inspire future studies in the field.

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