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A general asymmetric copper-catalysed Sonogashira C(sp^3)–C(sp) coupling

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Continued development of the Sonogashira coupling has made it a well established and versatile reaction for the straightforward formation of C–C bonds, forging the carbon skeletons of broadly useful functionalized molecules. However, asymmetric Sonogashira coupling, particularly for C(sp^3)–C(sp) bond formation, has remained largely unexplored. Here we demonstrate a general stereoconvergent Sonogashira C(sp^3)–C(sp) cross-coupling of a broad range of terminal alkynes and racemic alkyl halides (>120 examples) that are enabled by copper-catalysed radical-involved alkynylation using a chiral cinchona alkaloid-based P,N-ligand. Industrially relevant acetylene and propyne are successfully incorporated, laying the foundation for scalable and economic synthetic applications. The potential utility of this method is demonstrated in the facile synthesis of stereoenriched bioactive or functional molecule derivatives, medicinal compounds and natural products that feature a range of chiral C(sp^3)–C($sp/sp^2/sp^3$) bonds. This work emphasizes the importance of radical species for developing enantioconvergent transformations.

Carbon–carbon bond formation represents one of the most fundamental tasks of chemical synthesis and lies at the heart of organic chemistry[1]. Over the past fifty years, transition metal-catalysed cross-coupling reactions have changed the way organic compounds are constructed through the evolution of a wide variety of carbon–carbon bond-forming reactions, the importance of which has been recognized with the 2010 Nobel Prize in Chemistry[2,3]. There are three types of carbon–carbon cross-coupling reactions: C–C(sp^3), C–C(sp^2) and C–C(sp) (Fig. 1a), and investigations and applications of the first two (for example, the Heck, Suzuki–Miyaura, Negishi and Kumada couplings, as well as many others) have greatly outcompeted those of the last one. This is possibly mainly due to the higher stability and geometric versatility of sp^3 and sp^2 carbons, which predominate in carbon skeletons of natural organic molecules, medicines, agrochemicals and material molecules. Nevertheless, the unsaturation of an sp carbon renders it innately more amenable to versatile transformations that deliver sp^3 and sp^2 carbons as products[4] while under mild reaction conditions. In this sense, mild and versatile C–C(sp) cross-couplings, if well established, would offer substantial complementary approaches to C–C(sp^3)/C(sp^2) couplings, which typically require organometallic and/or pre-functionalized reagents with potential compatibility and cost issues.

Among others, the traditional Sonogashira C–C(sp) coupling reaction[5–7] between terminal alkynes and aryl/alkenyl halides or pseudohalides in the presence of various transition metal catalysts has become a popular and reliable method to forge C–C bonds (Fig. 1b)[8]. Continued interest in this reaction has recently culminated with the expansion of the electrophile scope to alkyl halides[9,10]. Despite continuous development of the Sonogashira coupling, the exploration of its asymmetric variants for expedited access to chiral C–C bonds has been met with limited success. Highly enantioselective C(sp^2)–C(sp) Sonogashira cross-coupling for the construction of axial or planar chirality has been only achieved once in the presence of a chelating group[11]. As for C(sp^3)–C(sp) Sonogashira cross-coupling, the few relevant examples are all asymmetric allylic alkylation reactions between allylic electrophiles and terminal alkynes or their derivatives to afford mostly γ-alkynylation (or seldom α-alkynylation) products[12–15]. The development of complementary enantioconvergent pathways that highly selectively deliver one α-alkynylation enantiomer from a broad range of readily available racemic alkyl halides[16–18] thus constitutes a major challenge. Furthermore, their difficult oxidative addition by a transition metal catalyst and the high propensity of the ensuing alkyl–metal intermediate for β-hydride elimination compared with their aryl/alkenyl counterparts also need to be dealt with (Fig. 1b)[10,19]. Aside from these, a considerable challenge lies in the accommodation of acetylene gas—an abundant, inexpensive and widely used industrial feedstock (Fig. 1e)—as a suitable starting material for an asymmetric Sonogashira cross-coupling reaction in terms of cost efficiency and step economy[20,21]. Its lack of substituents renders it distinct from its homologues and often inapplicable for suitable transformations of the latter[21]. Accordingly, transition metal-catalysed asymmetric transformations that use acetylene gas have been scarce[22–27] and may suffer from decomposition and/or polymerization of acetylene as well as undesired displacement of the chiral ligand used for enantiocontrol.

In light of the aforementioned challenges, we were intrigued to develop an efficient catalyst system to realize catalytic enantioconvergent Sonogashira C(sp^3)–C(sp) cross-coupling of common alkyl electrophiles, which, if successful, would provide not only an excellent complementary approach to established enantioconvergent C(sp^3)–C(sp^3/sp^2) cross-couplings, but also immediate access to chiral C(sp^3)–C(sp) bonds that are essential to a number of important natural products and drugs (Fig. 1c). Copper catalysis holds high potential for economical and operational benefits thanks to its low toxicity[19], ready commercial availability at low cost and complementary reactivity compared with heavier late d-block metals,

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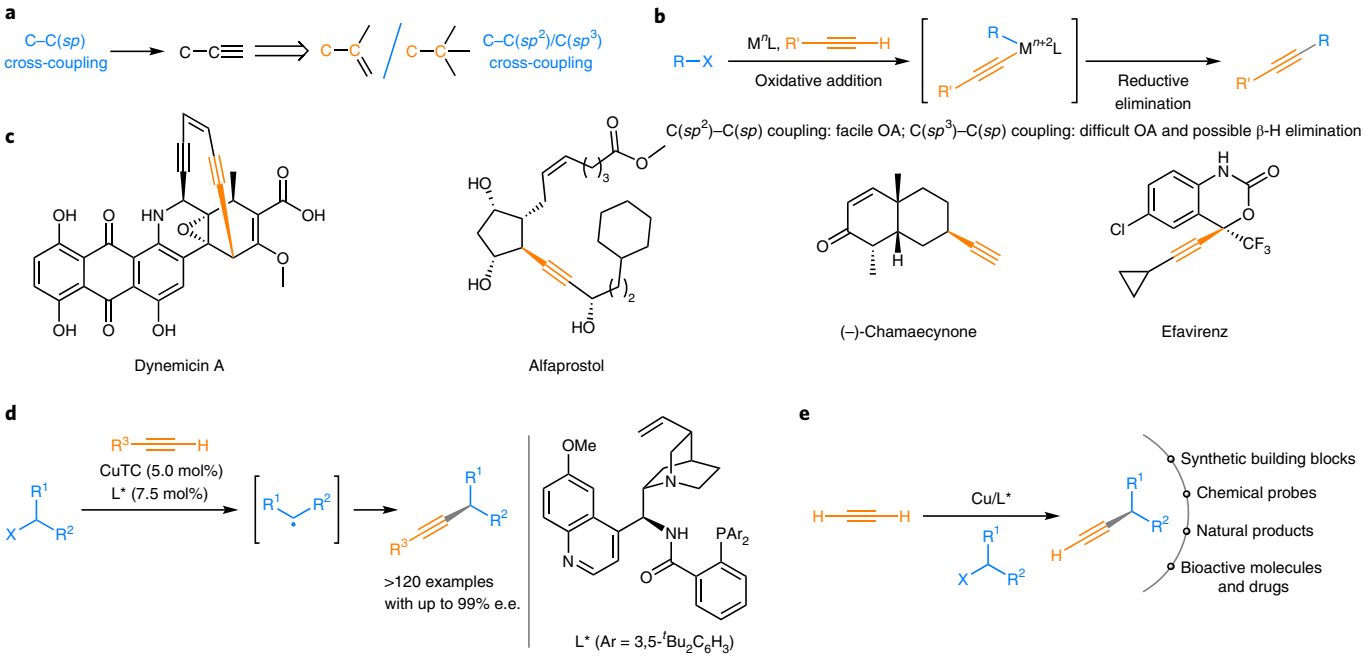
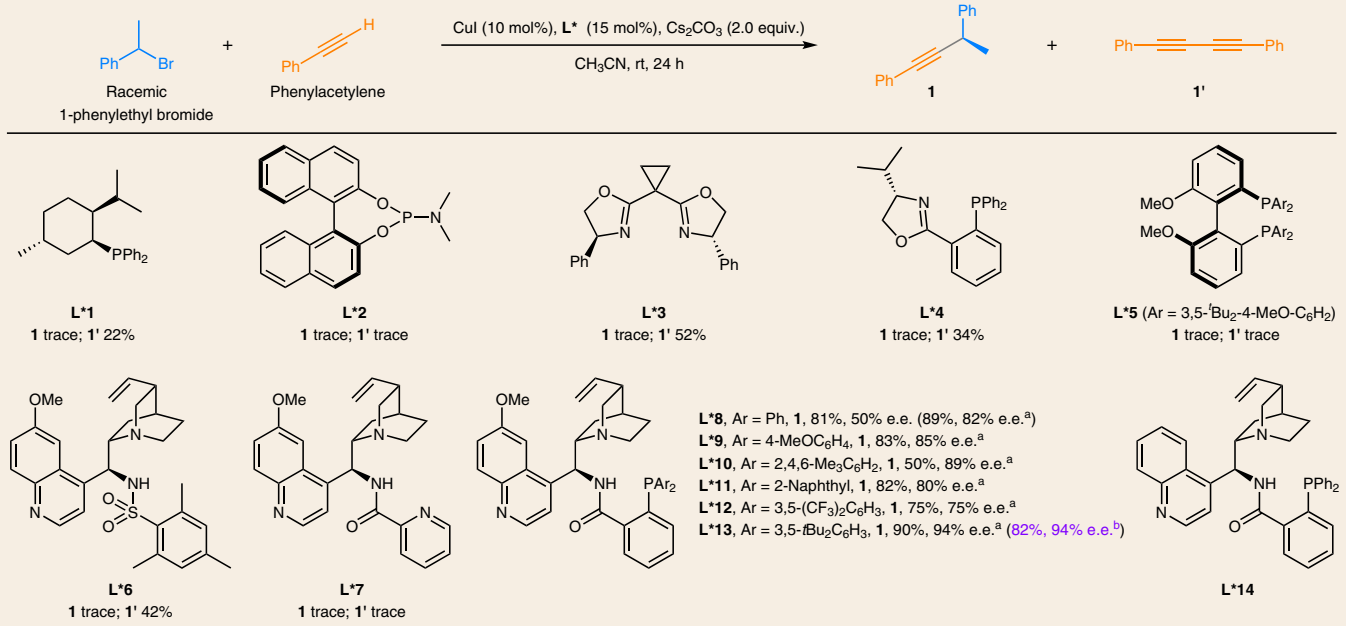


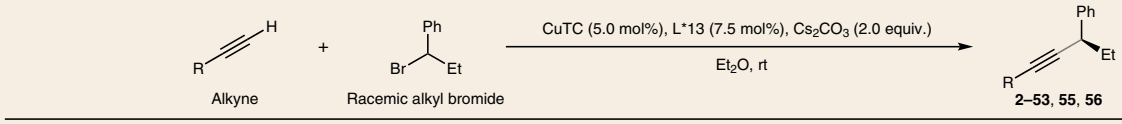
Fig. 1 | Motivation and design of catalytic enantioselective Sonogashira C(sp^3)–C(sp) cross-couplings. a, The C–C(sp) cross-coupling (for example, the Sonogashira coupling) provides not only facile access to alkyne compounds, but also excellent complementary approaches to C–C(sp^2) and C–C(sp^3) cross-couplings (for example, Suzuki–Miyaura, Negishi, Kumada and Heck couplings) when allied with versatile further transformations. Nevertheless, the development and application of C–C(sp) cross-coupling lags far behind the other two. **b**, Sonogashira C(sp^3)–C(sp) cross-coupling is more difficult than C(sp^2)–C(sp) cross-coupling due to its more challenging oxidative addition (OA), as well as the potential for β-H elimination. **c**, Important chiral alkyne natural products ((−)-chamaecynone and dynemicin A) and drugs are shown (dynemicin A, anti-cancer drug; alfaprostol, veterinary drug for breeding control; efavirenz, antiretroviral drug for HIV/AIDS). **d**, This work involves a Cu(I)/cinchona alkaloid-based P,N-ligand catalyst for catalytic, enantioconvergent Sonogashira cross-couplings of racemic alkyl electrophiles via a radical intermediate. **e**, The current methodology well accommodates the industrial feedstock acetylene gas and the resulting chiral terminal alkynes are amenable to versatile applications in various areas.

Table 1 | The effect of different ligands in the model reaction and the optimal results

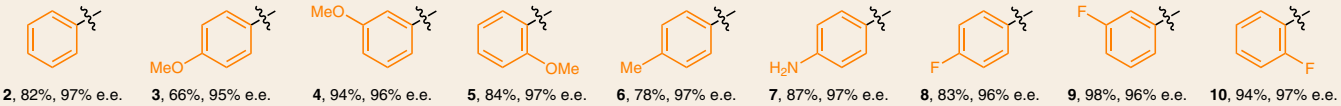


Standard reaction conditions: racemic 1-phenylethyl bromide (0.050 mmol, 1.0 equiv.), phenylacetylene (1.5 equiv.), CuI (10 mol%), ligand (15 mol%) and Cs_2CO_3 (2.0 equiv.) in CH_3CN (0.50 ml) at room temperature (rt) for 24 h. [a]CuTC (10 mol%) and Et_2O (1.0 ml) were used. [b]CuTC (5.0 mol%), ligand (7.5 mol%) and Et_2O (1.0 ml) were used.

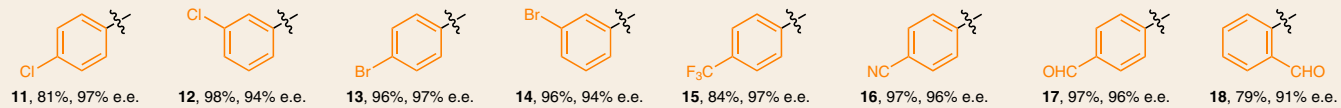
Table 2 | The substrate scope of the alkynes



Aryl alkynes (R)



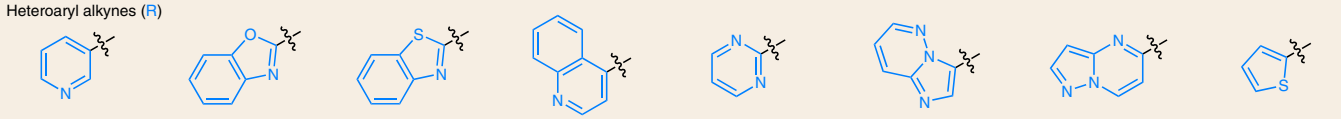
2, 82%, 97% e.e. **3**, 66%, 95% e.e. **4**, 94%, 96% e.e. **5**, 84%, 97% e.e. **6**, 78%, 97% e.e. **7**, 87%, 97% e.e. **8**, 83%, 96% e.e. **9**, 98%, 96% e.e. **10**, 94%, 97% e.e.



11, 81%, 97% e.e. **12**, 98%, 94% e.e. **13**, 96%, 97% e.e. **14**, 96%, 94% e.e. **15**, 84%, 97% e.e. **16**, 97%, 96% e.e. **17**, 97%, 96% e.e. **18**, 79%, 91% e.e.

19, 92%, 96% e.e. **20**, 94%, 98% e.e.[a] **21**, 94%, 96% e.e. **22**, 77%, 96% e.e. **23**, 65%, 96% e.e. **24**, 93%, 97% e.e. **25**, 75%, 98% e.e. **26**, 88%, 98% e.e.

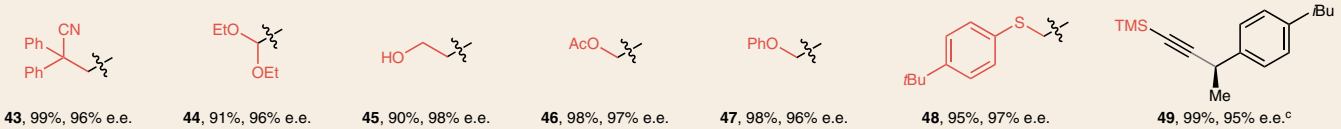
Heteroaryl alkynes (R)



27, 86%, 95% e.e. **28**, 88%, 97% e.e. **29**, 99%, 96% e.e. **30**, 99%, 94% e.e. **31**, 97%, 97% e.e. **32**, 91%, 96% e.e. **33**, 99%, 96% e.e. **34**, 91%, 97% e.e.

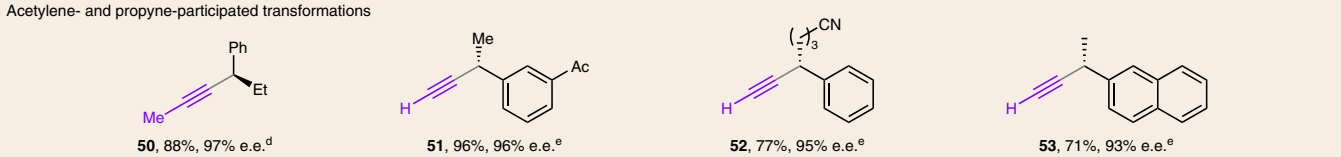
Other alkynes (R)

35, 92%, 96% e.e. **36**, 88%, 98% e.e.[b] **37**, 74%, 97% e.e. **38**, 81%, 97% e.e. **39**, 88%, 97% e.e. **40**, 78%, 97% e.e. **41**, 96%, 97% e.e. **42**, 98%, 98% e.e.

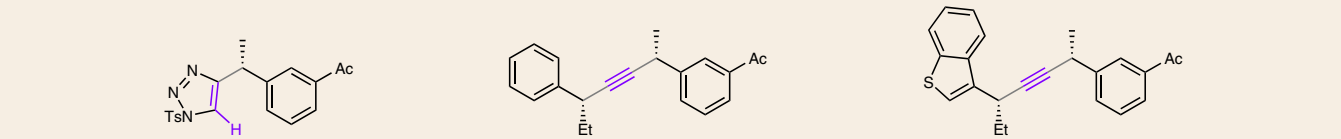


43, 99%, 96% e.e. **44**, 91%, 96% e.e. **45**, 90%, 98% e.e. **46**, 98%, 97% e.e. **47**, 98%, 96% e.e. **48**, 95%, 97% e.e. **49**, 99%, 95% e.e.[c]

Acetylene- and propyne-participated transformations



50, 88%, 97% e.e.[d] **51**, 96%, 96% e.e.[e] **52**, 77%, 95% e.e.[e] **53**, 71%, 93% e.e.[e]



54, 81%, 95% e.e.[f] **55**, 68%, 95% e.e.[g] **56**, 49%, 95% e.e.[g]

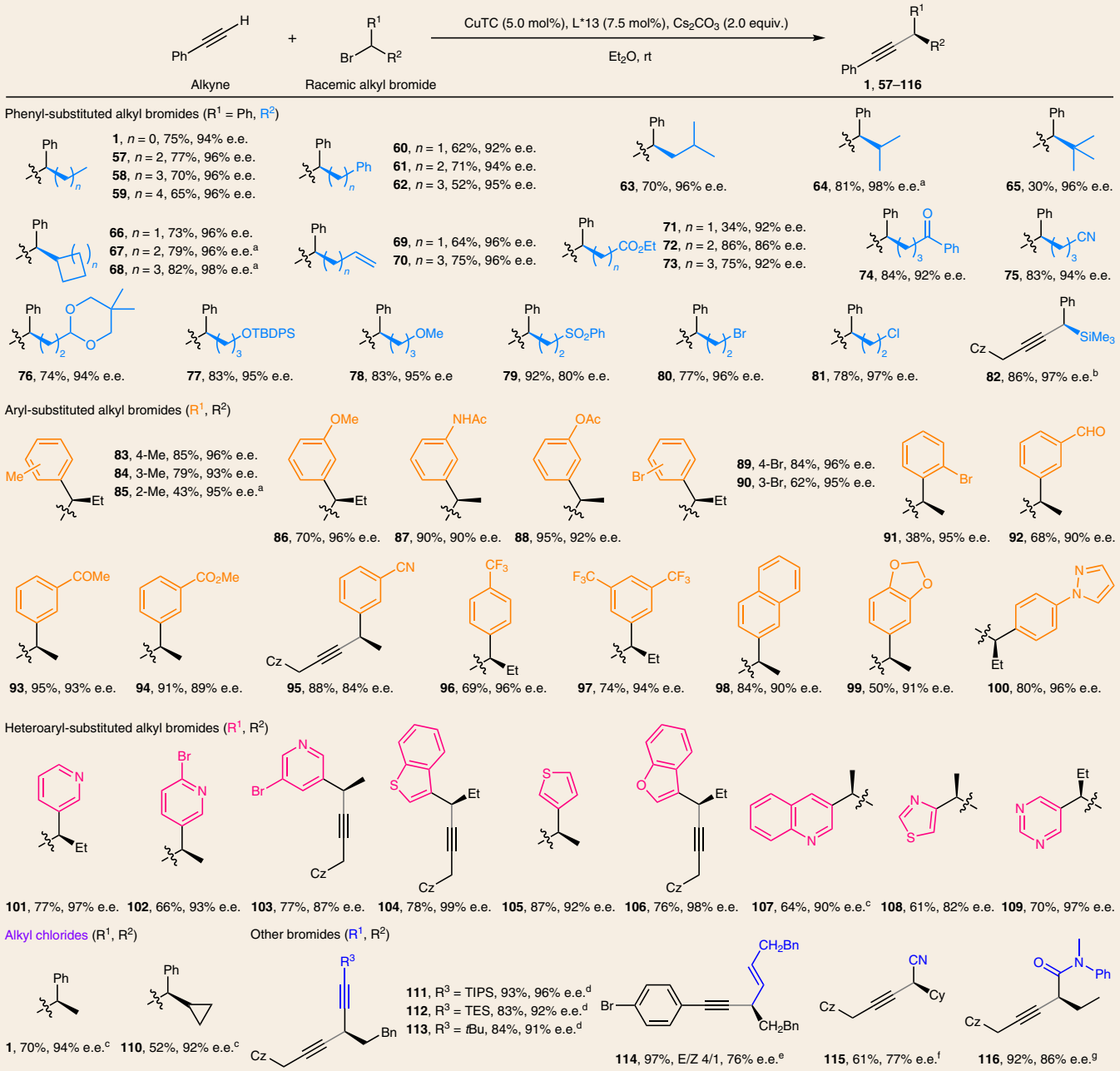
Standard reaction conditions: alkyne (0.20 mmol), racemic alkyl bromide (1.5 equiv.), CuTC (5.0 mol%), **L*13** (7.5 mol%) and Cs_2CO_3 (2.0 equiv.) in Et_2O (4.0 ml) under argon at room temperature. The yields are isolated yields. [a]The reaction was at −10 °C. [b]Alkyne (1.5 equiv.), racemic alkyl bromide (0.20 mmol) and KO^{t}Bu (2.0 equiv.) were used. [c]The e.e. was determined after desilylation and the yield given is the crude yield. [d]Propyne (2.5 equiv.) and racemic 1-phenyl-1-propyl bromide (0.20 mmol) were used. [e]An acetylene balloon and racemic alkyl bromide (0.20 mmol) were used. [f]Crude **51** (~0.20 mmol), CuTC (5.0 mol%) and TsN_3 (1.0 equiv.) in toluene (2.0 ml) were used at room temperature (r.t.) under argon. [g]Crude **51** (~0.20 mmol), racemic alkyl bromide (1.5 equiv.), CuTC (5.0 mol%), **L*13** (7.5 mol%) and Cs_2CO_3 (2.0 equiv.) in Et_2O (4.0 ml) were used under argon. The diastereomeric ratio (d.r.) was roughly estimated by HPLC to be larger than 20:1. Pin, pinacolato; PMP, *para*-methoxyphenyl; Phth, phthalyl; Cz, 9-carbazolyl; TMS, trimethylsilyl; Ac, acetyl; Ts, *para*-toluenesulfonyl.

especially palladium[28,29]. Furthermore, copper acetylide could be readily formed from terminal alkyne and copper salt in the presence of mild base[30]. We then questioned whether a copper salt together with an appropriate chiral ligand would overcome all of the challenges described above. Here we present a copper(I)/cinchona alkaloid-based P,N-ligand catalyst system for enantioconvergent Sonogashira C(sp^3)–C(sp) cross-coupling via a radical intermediate. This reaction exhibits a broad scope (>120 examples, Fig. 1d) across a range of both terminal alkyne and racemic alkyl halide coupling partners while under operationally simple and mild reaction conditions. Moreover, this process well accommodates industrial feedstock acetylene gas to provide valuable chiral terminal alkyne synthons with high monosubstitution selectivity (Fig. 1e). Most importantly, this protocol was compatible with various core structures of bioactive and functional molecules (five examples) and provides facile access to chiral C–C(sp^3), C–C(sp^2) and C–C(sp) bonds in enantioenriched drugs and drug leads (four examples) as well as natural products (formal syntheses).

Results and discussion

Reaction development. In comparison with the considerable advances pioneered by Fu and co-workers[16–18] of enantioconvergent

Table 3 | The substrate scope of racemic secondary alkyl halides



Standard conditions: racemic alkyl halide (0.20 mmol), alkyne (1.5 equiv.), CuTC (5.0 mol%), **L*13** (7.5 mol%) and Cs_2CO_3 (2.0 equiv.) in Et_2O (4.0 ml) under argon. The yields are isolated yields. [a]**L*8** (7.5 mol%). [b]Alkyne (0.20 mmol) and racemic alkyl halide (1.5 equiv.) were used. [c]CuTC (10 mol%) and **L*13** (15 mol%) were used. [d]Alkyne (0.20 mmol), racemic alkyl halide (1.5 equiv.), CuTC (8.0 mol%) and **L*13** (12 mol%) in dichloromethane (4.0 ml) were used. [e]1-Bromo-4-ethynylbenzene (2.0 equiv.) and $Cu(PPh_3)Br$ (5.0 mol%) in 1,4-dioxane (4.0 ml) were used. [f]Alkyne (0.20 mmol) and racemic alkyl halide (1.5 equiv.) at −40 °C. [g]CuTC (8.0 mol%) and **L*13** (12 mol%) were used. TBDPS, *tert*-butyl-diphenylsilyl; TIPS, triisopropylsilyl; TES, triethylsilyl; Cy, cyclohexanyl.

radical-involved C–C cross-couplings of racemic alkyl electrophiles using chiral nickel catalysis, the use of a chiral copper catalyst for such transformations remains rare[31]. This deficit may be attributed to its relatively difficult oxidative addition compared with a nickel catalyst under similar conditions[19,28,32–37]. An exhaustive screening of various types of monodentate and bidentate ligands—including monophosphine (**L*1**), monophosphoramidite (**L*2**), bis(oxazoline) (**L*3**), phosphinooxazoline (**L*4**) and biphenylphosphine (**L*5**)—for the model coupling of racemic 1-phenylethyl bromide and phenylacetylene resulted in the formation of trace amounts of desired coupling product **1**, although occasionally together with the Glaser homocoupling product **1′** (Table 1). To promote the oxidative addition of a Cu(I) catalyst, we envisaged using an electron-rich amine ligand[38] to increase the electron density on copper, and we resorted to multidentate ligands to depress undesired Glaser coupling[39]. As such, we chose a series of cinchona alkaloid-derived P,N-ligands (**L*6–L*13**) that feature a bridgehead tertiary amine for such a reaction[40] (Table 1). The reaction using bidentate quinine-derived sulfonamide (**L*6**) still suffered from the alkyne homocoupling whereas tridentate picolinamide (**L*7**) did not. Although both of these ligands failed to deliver the desired coupling, Dixon's tridentate ligand[41] **L*8**, which possesses an electron-rich phosphine coordination motif,

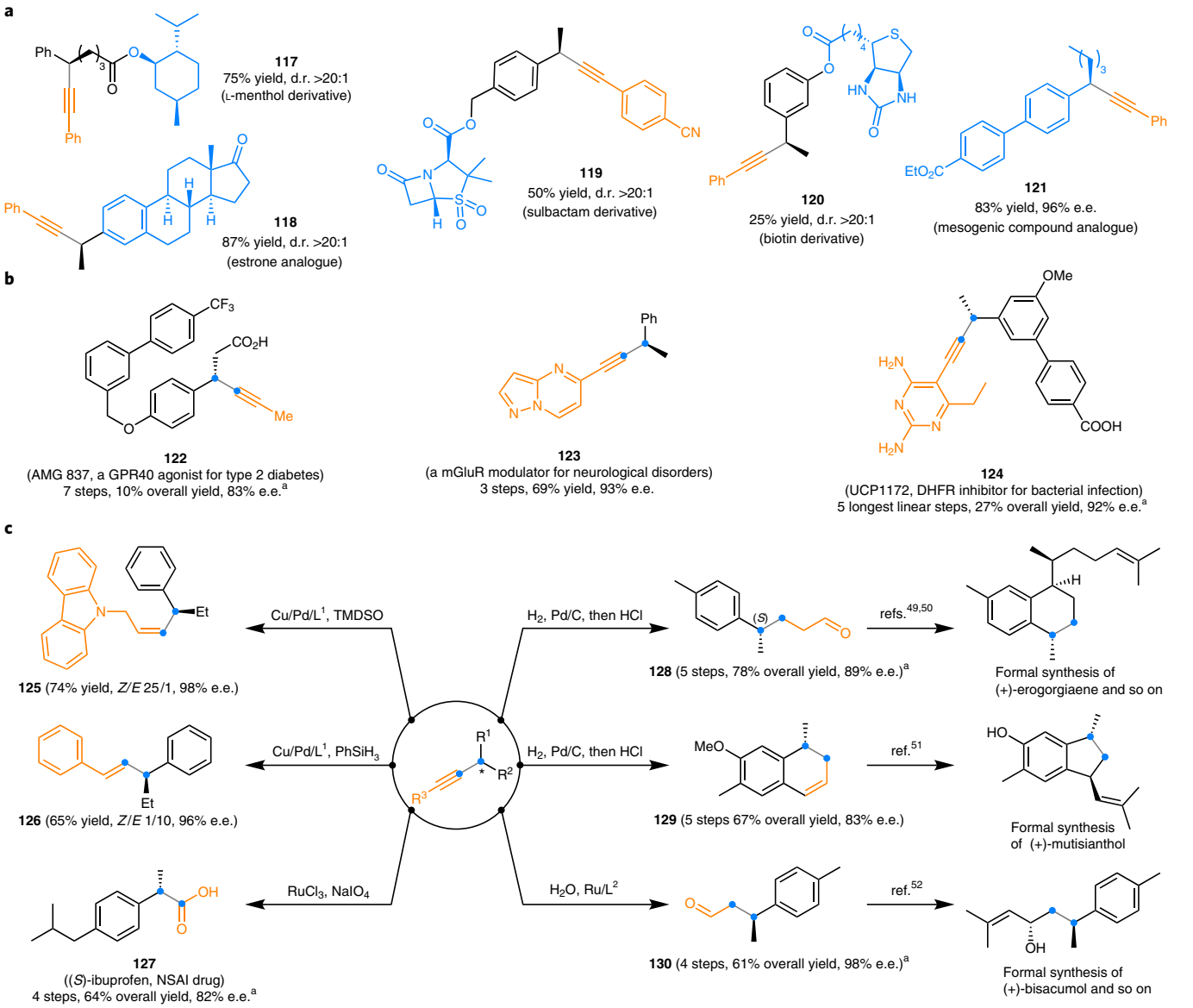


Fig. 2 | Synthetic applications of the catalytic enantioselective Sonogashira cross-coupling. a, Examples where the reaction exhibited excellent compatibility with core structures of bioactive molecules and a mesogenic compound are shown. **b**, Examples where the reaction provided practical and convenient synthetic routes towards drug leads are shown. **c**, The current asymmetric C(sp^3)–C(sp) coupling easily delivered chiral C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bonds in drugs and natural products following further manipulations in one or two steps, thus constituting excellent complementary approaches to established asymmetric C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) couplings. [a]The e.e. values were determined on an immediate precursor or derivative of the product (see the Supplementary Information for details). NSAI, non-steroidal anti-inflammatory; GPR40, G-protein-coupled receptor 40; mGluR, metabotropic glutamate receptor; DHFR, dihydrofolate reductase; Cu/Pd/L[1], [1,3-bis[2,6-bis(1-methylethyl)phenyl]-2-imidazolidinylidene] chlorocopper/palladium acetate/dicyclohexyl(2′-methoxy[1,1′-biphenyl]-2-yl)phosphine; TMDSO, 1,1,3,3-tetramethyldisiloxane; Ru/L[2], cyclopentadienyltris (acetonitrile)-ruthenium hexafluorophosphate/5,5′-bis(trifluoromethyl)-2,2′-bipyridine.

successfully provided **1** in 81% yield with 50% e.e. without the formation of **1′**. Encouraged by this finding, we systematically evaluated different copper salts, inorganic bases and solvents (Supplementary Table 1) and found that the copper salt CuTC (TC = thiophene-2-carboxylate) and solvent Et_2O performed better to give **1** in 89% yield with 82% e.e. Considering the substantial role that the phosphine motif might play in the reaction, we then examined several analogues of **L*8** with different steric and electronic properties (**L*9**–**L*13**) and observed favourable effects for electron-donating and steric bulky *P*-substituents on enantioselectivity (Table 1). Accordingly, the best ligand (**L*13**) afforded **1** in 90% yield with 94% e.e. at ambient conditions, and reducing the catalyst loading by half did not affect the enantioselectivity. The optimal conditions in terms of cost efficiency thus involve CuTC (5.0 mol%) as well as **L*13** (7.5 mol%) in Et_2O (0.05 M) at room temperature.

The substrate scope. With the optimal reaction conditions established, we next examined the generality of this enantioselective Sonogashira C(sp^3)–C(sp) cross-coupling. With regards to the alkyne scope (Table 2), a broad series of substituted aryl alkynes—including those that have monosubstituted phenyl rings with electron-donating or -withdrawing groups at different positions (*ortho*, *meta* or *para*), a disubstituted phenyl ring, a naphthalene ring and a ferrocene ring—can readily participate in this reaction to afford **2**–**26** in 65–98% yield with 91–98% e.e. Many common functional groups, such as methoxyl (**3**–**5**), free amino (**7**),

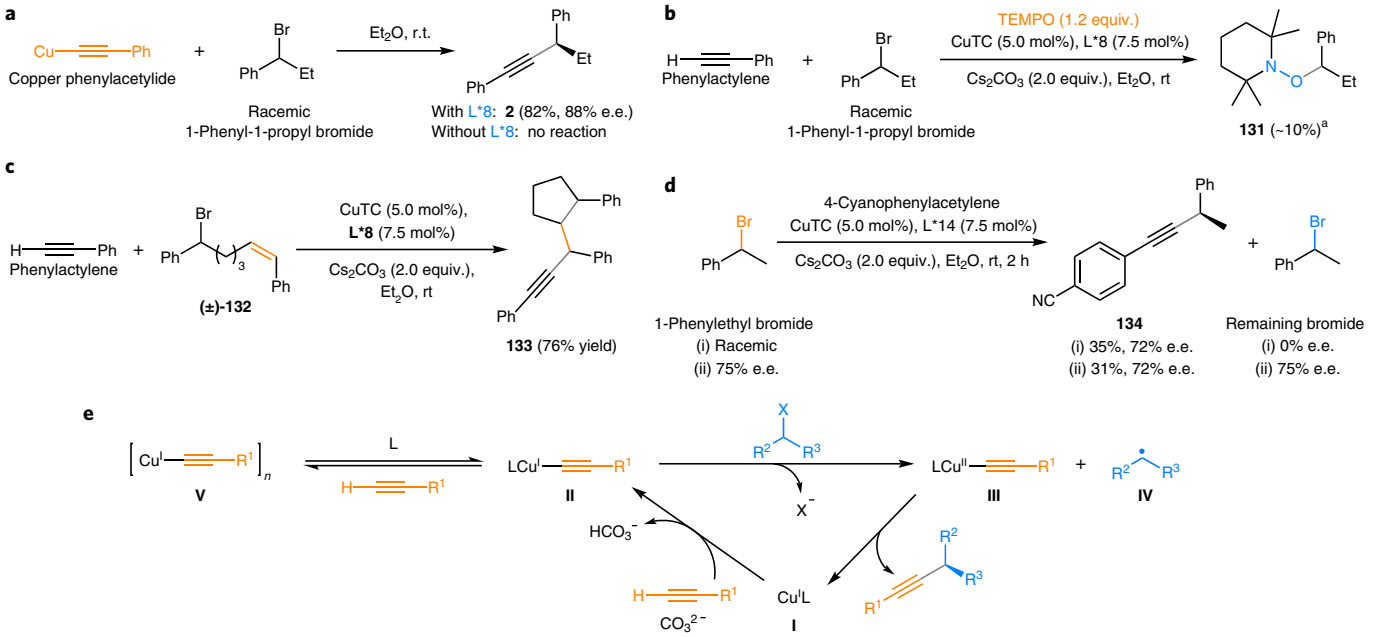


Fig. 3 | Mechanistic studies of the catalytic enantioconvergent Sonogashira cross-coupling. a, Copper phenylacetylide participated directly in the reaction, which was greatly promoted by ligand **L*8**. **b**, The reaction was completely inhibited by the radical inhibitor TEMPO and TEMPO-trapped product **131** was formed, supporting the involvement of a benzylic radical. **c**, Alkene-tethered substrate **132** led to formation of **133** under standard conditions, suggesting the generation of a benzylic radical and its subsequent 5-*exo*-*trig* cyclization and C(sp^3)–C(sp) coupling. **d**, No changes to the enantiopurities of the starting alkyl bromide were observed in the reactions on racemic and chiral 1-phenylethyl bromide, respectively, therefore probably excluding pathways that involve kinetic resolution or fast racemization of alkyl bromide. Values aligned horizontally belong to one experiment. **e**, The reaction was proposed to proceed via a single-electron transfer between in situ generated copper acetylide complexes **II** and racemic alkyl halides to form Cu(II) complexes **III** and alkyl radicals **IV** and subsequent C(sp^3)–C(sp) coupling. Alkyne substrates might form polymeric Cu(I) complexes **V** that are catalytically inactive. [a]No desired product **2** was observed.

halo (**8**–**14**), cyano (**16**), formyl (**17** and **18**), methoxylcarbonyl (**19**), nitro (**20**) and pinacolborato (**21**)—as well as terminal olefin (**22**) and alkyne (**23**)—were all compatible with the mild reaction conditions. As for the scope of heteroaryl alkynes, we find that many alkynes that contain medicinally relevant heterocycles[42]—such as pyridine (**27**), benzo[*d*]oxazole (**28**), benzo[*d*]thiazole (**29**), quinoline (**30**), pyrimidine (**31**), imidazo[1,2-*b*]pyridazine (**32**), pyrazolo[1,5-*a*]pyrimidine (**33**) and thiophene (**34**)—were competent substrates, providing the desired products in excellent yields with excellent enantioselectivity. With respect to alkyl alkynes, barely functionalized aliphatic alkynes **35** and **36** successfully underwent efficient cross-coupling. Most importantly, a wide range of functional groups, such as conjugating alkene (**37**), cyclopropane (**38**), primary chloride (**39**), amide (**40**), imide (**41**), carbazole (**42**), nitrile (**43**), acetal (**44**), free alcohol (**45**), ester (**46**) and ether (**47**)—as well as coordinating thioether (**48**)—were well tolerated at different distances away from the reacting alkynes, providing high chemoselectivity and excellent enantioselectivity in this cross-coupling process. Furthermore, silyl alkyne worked well under standard conditions to provide **49** in almost quantitative yield with 95% e.e.

The direct conversion of industrial feedstocks to medicinally and agriculturally relevant chiral products is an important goal of chemical research. To this end, we first tested our reaction using the industrially relevant propyne—a key component of the readily available methylacetylene-propadiene propane welding gas[43]—as a substrate (Table 2). We obtained the desired product **50** from a commercial solution of pure propyne in 88% yield with 97% e.e. under standard conditions. We then noted that industrial-grade acetylene gas (an important industrial raw material mainly produced from coal[44], 500 kilotonnes were produced in 2014 at ~US$26 cents per mol[45]) chemoselectively coupled with various secondary alkyl bromides (Fig. 1d) to provide chiral terminal alkynes **51**–**53** in excellent yields with excellent e.e. The high monosubstitution selectivity makes this reaction an ideal tool for preparing chiral terminal alkyne building blocks. The crude product **51** thus participated well in the following click reaction without purification, yielding cycloaddition product **54** in high yield and enantioselectivity. This crude product was also suitable for a second Sonogashira coupling to provide internal alkynes **55** and **56** in high diastereoselectivity and enantioselectivity.

In the following study, we switched our attention to evaluate the scope of the other coupling partner; that is, racemic alkyl halides (Table 3). Using phenylacetylene as a model alkyne, we observed that simple unfunctionalized linear benzyl bromides all worked well to give **1** and **57**–**59** with good results (Table 3, 65–77% yield and 94–96% e.e.). As for the effect of steric hindrance around the chiral centre, most substituents in the alkyl branch did not greatly affect the reaction efficiency or enantioselectivity (**60**–**64** and **66**–**68**) and even a *tert*-butyl group was moderately tolerated (**65**). With regards to potentially reactive functional groups, a gamut of functionalities, such as terminal olefin (**69** and **70**), ester (**71**–**73**), ketone (**74**), nitrile (**75**), acetal (**76**), silyl ether (**77**), ether (**78**) and sulfone (**79**), were left unscathed under the coupling reaction conditions. Perfect chemoselectivity was observed for the secondary benzylic bromide over primary bromide and chloride (**80** and **81**, respectively). Notably, an α-bromo silane also smoothly underwent the desired coupling to afford the valuable α-chiral silane **82**, which has recently been receiving increasing synthetic and application interest[46]. With respect to the phenyl ring of alkyl bromides, a broad series of electron-donating or -withdrawing substituents at different positions (*ortho*, *meta*, *para*, 3,4- or 3,5-), and even a naphthalene ring, were all well accommodated in this process to deliver **83**–**100** in 38–95%

yield with 84–97% e.e. Alkyl bromides that contain different types of medicinally relevant heterocycles—including pyridines (**101**–**103**), benzo[*b*]thiophene (**104**), thiophene (**105**), benzo[*b*]furan (**106**), quinoline (**107**), thiazole (**108**) and pyrimidine (**109**)—were viable substrates. The less reactive alkyl chloride also underwent the desired Sonogashira coupling reaction with slightly increased catalyst loading to afford **1** in comparable efficiency and enantioselectivity. Notably, with this protocol we were able to incorporate a small cyclopropane ring (**110**)—a chemically and metabolically stable bioisostere for alkyl groups[47]—into the chiral internal alkyne product. All of these results highlight the potential of our methodology in the process of drug discovery. The scope with respect to the electrophile is not limited to the racemic α-aryl and -heteroaryl substituted alkyl halides. For example, various racemic propargylic bromides were found to be suitable substrates to afford the expected bis-alkynyl products **111**–**113** in 83–93% yield with 91–96% e.e. Furthermore, allylic and α-cyano/aminocarbonyl alkyl bromides all are well applicable to this transformation, delivering various alkynylation products **114**, **115** and **116** in good to excellent enantioselectivity, respectively. These results emphasize the high substrate diversity of the current cross-coupling reaction.

Synthetic applications. To illustrate the utility of this transformation, we initially examined this asymmetric Sonogashira C(sp^3)–C(sp) cross-coupling reaction using the core structures of several bioactive molecules, such as L-menthol (**117**), estrone (**118**), sulbactam (**119**) and biotin (**120**), and a mesogenic compound (**121**) (Fig. 2a). All of the desired alkynylated products were obtained in high stereoselectivity, irrespective of existing chiral centres and complex molecular structures.

As for the immediate potential in medicinal chemistry (Fig. 2b), we have easily prepared chiral alkyne drug leads **122** (AMG 837 a G-protein coupled receptor GPR40 agonist) and **123** (a patented mGluR modulator) in high enantiopurity through a key asymmetric Sonogashira C(sp^3)–C(sp) cross-coupling (Supplementary Figs. 1 and 2). We have also prepared the newly reported highly potent DHFR inhibitor UCP1172 (**124**) for drug-resistant bacteria treatment via a convergent synthetic route culminating in an asymmetric Sonogashira coupling and subsequent hydrolysis (Supplementary Fig. 3). This convergence emphasizes the endowed capacity of this newly devised coupling reaction for enabling novel synthetic planning, leading to the possibility of more facile construction of a structurally diverse molecular library for further drug optimization.

To demonstrate the potential for chiral C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) formation (Fig. 2c), the highly stereoselective hydrogenation of two chiral alkyne products is shown, giving *Z*-alkene **125** and *E*-alkene **126**, respectively, by following Lalic's recent protocols[48]. Furthermore, we have oxidatively cleaved one alkyne product to carboxylic acid (*S*)-ibuprofen (**127**), which is the more biologically active enantiomer of this common NSAID (for details on its synthesis and that of its enantiomer, see Supplementary Fig. 4). Notably, the preparations of AMG 837 and (*S*)-ibuprofen involved industrially relevant propyne and acetylene gas raw materials as coupling substrates, respectively, demonstrating great potential of this methodology for industrial applications in the future. Furthermore, we have fully hydrogenated two alkyne products to aldehyde **128** and alkene **129** following palladium catalysis and further acidic treatments, and hydrated another alkyne product to aldehyde **130** through ruthenium catalysis. These three compounds are all synthetic precursors of a range of natural products, such as (+)-erogorgiaene[49,50], (+)-mutisianthol[51], (+)-bisacumol[52] and so on (for details on the total synthesis or formal synthesis of several families of natural products, see Supplementary Figs. 5–9). In summary, these diverse transformations showcase the robust capability of our asymmetric C(sp^3)–C(sp) cross-coupling allied with a variety of subsequent manipulations for forging chiral C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bonds, which would be particularly invaluable when functionalities that have low compatibility with organometallics, such as carboxylic acid and aldehyde, are desired.

Mechanistic considerations. Our mechanistic study revealed that copper phenylacetylide participated in the reaction while in the presence of **L*8**, whereas no reaction occurred in its absence (Fig. 3a). This result confirmed the ligand-promoting effect of this reaction. Control experiments with the radical inhibitor TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) demonstrated complete inhibition of the desired reaction and TEMPO-trapped product **131** was isolated in ~10% yield (Fig. 3b). Moreover, substrate **132** with a tethered alkene underwent tandem cyclization and alkynylation to provide product **133** under standard conditions (Fig. 3c). No enantioenrichment or enantioerosion of recovered starting materials were observed when racemic or scalemic 1-phenylethyl bromide were used, respectively (Fig. 3d), indicating that kinetic resolution or fast racemization of alkyl bromide is unlikely. These pieces of evidence strongly support the formation of alkyl radical species. Further kinetic experiments on the reaction disclosed first-order dependences of reaction rates on the alkyl bromide and copper catalyst (Supplementary Figs. 10 and 11, respectively), indicating that related species are involved in the reaction step(s) until the rate-determining step. Moreover, elemental analyses were carried out on both the copper catalyst and the crude reaction mixture, and control experiments were conducted to exclude possible catalysis by trace metal impurities (Supplementary Tables 2–8). With regards to acetylene, the reaction rate was initially increased and then slightly decreased following its concentration increase (Supplementary Fig. 12), highlighting the multifaceted roles it played in the reaction.

On the basis of the above-mentioned mechanistic results, as well as the literature[53], we propose a possible reaction mechanism (Fig. 3e). The reaction starts with the formation of monomeric copper acetylide **II** from copper complex **I** by reacting with terminal alkyne in presence of base. This copper complex **II** may transform to catalytically inactive polymeric copper acetylide **V** in the presence of excessive terminal alkyne, leading to reaction inhibition[54]. Subsequent oxidative addition of **II** with alkyl halide (through either inner- or outer-sphere electron transfer[38]) results in the formation of alkyl radical **IV**. Next, C(sp^3)–C(sp) bond coupling via either a Cu(III) intermediate or radical addition to the acetylide triple bond gives rise to enantioenriched product and Cu(I) complex **I**. Further experimental and computational studies are underway in our laboratory to delineate the mechanistic details.

Conclusion

We have established a robust strategy for the practical and versatile enantioconvergent Sonogashira C(sp^3)–C(sp) cross-coupling—via a radical intermediate—by combining a copper catalyst with a cinchona-based chiral P,N-ligand, providing a tool for the construction of chiral C–C bonds. The successful direct incorporation of acetylene gas in this reaction demonstrates important potential for industrial-grade applications. We envision that this methodology will not only open up new avenues for enantioconvergent C–C bond formation but also inspire the discovery of more novel catalyst systems that can handle challenging asymmetric radical transformations.

Data availability

All of the characterization data and experimental protocols are provided in this article and its Supplementary Information. Data are also available from the corresponding author on request.

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Author contributions

X.-Y.D., Y.-F.Z., C.-L.M., Q.-S.G. and F.-L.W. designed the experiments and analysed the data. X.-Y.D., Y.-F.Z., C.-L.M., F.-L.W., Z.-L.L. and S.-P.J. performed the experiments. All authors participated in writing the manuscript. X.-Y.L. conceived and supervised the project.

Competing interests

The authors declare no competing interests.

Additional information

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