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Catalytic asymmetric carbon–carbon bond formation via allylic alkylations with organolithium compounds

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Carbon–carbon bond formation is the basis for the biogenesis of nature's essential molecules. Consequently, it lies at the heart of the chemical sciences. Chiral catalysts have been developed for asymmetric C–C bond formation to yield single enantiomers from several organometallic reagents. Remarkably, for extremely reactive organolithium compounds, which are among the most broadly used reagents in chemical synthesis, a general catalytic methodology for enantioselective C–C formation has proven elusive, until now. Here, we report a copper-based chiral catalytic system that allows carbon–carbon bond formation via allylic alkylation with alkyllithium reagents, with extremely high enantioselectivities and able to tolerate several functional groups. We have found that both the solvent used and the structure of the active chiral catalyst are the most critical factors in achieving successful asymmetric catalysis with alkyllithium reagents. The active form of the chiral catalyst has been identified through spectroscopic studies as a diphosphine copper monoalkyl species.

Since their discovery by Wilhelm Schlenk in 1917 (ref. 1), and his vivid description of their chemical properties, alkyllithium reagents have beguiled the chemical community. Methyllithium was reported to be extremely reactive, burning in air with 'a brilliant red flame with a shower of golden sparks'[2], and, initially, alkyllithium compounds were not considered useful because of their instability. It is remarkable how dramatically this situation has changed over the intervening decades. Organolithium reagents have arguably become some of the most versatile and widely used reagents[3,4] in the daily repertoire of chemical synthesis, and are indispensable in the preparation of a myriad of industrial products from pharmaceuticals to polymers[5,6].

In recent decades, asymmetric catalysis has undergone substantial developments, and a broad range of C–C and C–X bond formations with high enantioselectivities are currently known[7–9]. In particular, less reactive organozinc[10–12], aluminium[13–15] and Grignard[16,17] reagents have been shown to be highly effective in asymmetric C–C bond formation[18]. In stark contrast, the only glimmer of hope for enantioselective reactions with organolithium reagents was in the stoichiometric use of chiral ligands[5,19,20]. Tantalisingly, catalytic asymmetric reactions of organolithiums using high catalyst loading with a specific substrate[21], catalytic asymmetric deprotonations[22,23] and additions to imines have been reported[24–28]. Despite these great efforts, a general method for the direct use of alkyllithium reagents for catalytic and highly enantioselective C–C bond formation, to the best of our knowledge, has not been developed[5,29]. Several factors complicate the control of stereochemistry in this organometallic-based transformation and cause unpredictable behaviour; this includes the high reactivity of organolithium reagents leading to uncatalysed reactions and the presence of the aggregates[30] common to organolithium reagents. Challenged by this long-standing problem of merging highly enantioselective C–C bond formation and the synthetic power and high reactivity of alkyllithium reagents, we have developed a practical chiral catalytic system for this purpose.

In our mechanistically guided investigations on the subtle interplay between catalyst structure and reaction parameters, we discovered that copper complexes generated *in situ* from CuBr and chiral phosphorus-based ligands in dichloromethane allowed us to harness the reactivity of alkyllithium compounds and provide an efficient and highly selective catalyst for the alkylation of allylic halides[31] (Fig. 1).

Results and discussions

Starting with ferrocenyl-type chiral diphosphines[32], which have been shown previously to be effective with organomagnesium reagents[17], we found that the enantioselectivity in the reaction between cinnamyl bromide **1a** and the most common organolithium reagent *n*-BuLi could be increased dramatically by changing the chiral ligand from (*R*,*Sp*)-JosiPhos **L1** to reversed (*S*,*Rp*)-**L2** (entries 1–2, Table 1). However, in both cases, the achiral linear compound **4** resulting from an S_N2 substitution reaction was predominantly found. It should be emphasized that at least four competing reaction pathways are possible, including transmetallation of the halide, formation of the homo-coupled product, S_N2 substitution leading to the achiral linear product **4**, and S_N2' substitution, with only the last reaction affording the desired branched chiral product **3**. These problems of chemo- and regioselectivity represent additional complicating factors typically associated with the use of

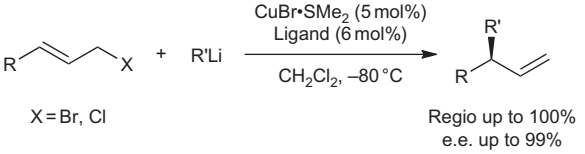

Figure 1 | Catalytic asymmetric allylic alkylation with organolithium reagents (X = bromide or chloride).

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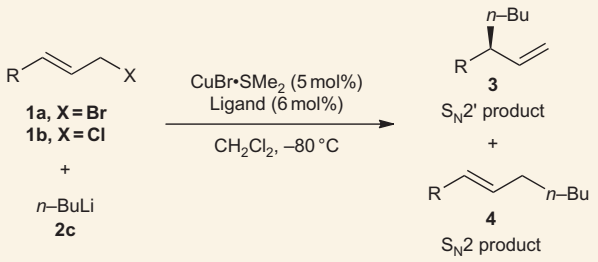
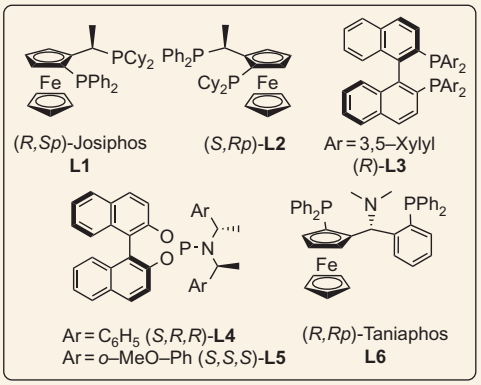
Table 1 | Screening of chiral ligands for asymmetric allylic alkylation.





Entry	X	Ligand	$S_N2':S_N2$ (%)	e.e. (%)
1	Br	**L1**	23:77	25
2	Br	**L2**	17:83	82
3	Br	**L3**	87:13	94
4	Br	**L4**	73:27	62
5	Br	**L5**	87:13	91
6	Cl	**L5**	91:9	95
7	Br	**L6**	83:17	98

Conditions: 1.5 equiv. *n*-BuLi diluted with hexane, 0.1 M in CH_2Cl_2, 2 h addition time.

highly reactive organolithium reagents in catalysis. A major increase in regioselectivity towards the branched product **3** was achieved using the ligands (*R*)-**L3** and phosphoramidites[9] (*S*,*R*,*R*)-**L4** and (*S*,*S*,*S*)-**L5** (entries 3–5, Table 1). Enantioselectivities (e.e.) up to 94% were obtained (entries 3 and 5, Table 1). Interestingly, high values of regio- and enantioselectivities were obtained not only when using cinnamyl bromide **1a**, but also with cinnamyl chloride **1b** (entry 6, Table 1). The highest enantioselectivities for allyl bromide **1a** were reached in the S_N2' allylic alkylation with the copper catalyst based on TaniaPhos (*R*,*Rp*)-**L6** (entry 7, Table 1).

An intriguing observation is that both monodentate (phosphoramidites **L4** and **L5**) and bidentate (**L2**, **L3** and **L6**) chiral ligands are effective in controlling the stereoselectivity in C–C bond formation with *n*-BuLi. Judicious selection of solvents, rate and order of addition of the reagents and reaction temperature, in combination with the chiral CuBr·SMe_2/TaniaPhos **L6** catalyst, resulted in an optimized catalytic system, allowing for almost full control with respect to side reactions and non-catalysed 'background' transformations. The choice of dichloromethane as the solvent is key to obtain high regio- and enantioselectivity. The use of ethereal solvents caused a drastic drop in both regio- and enantioselectivity.

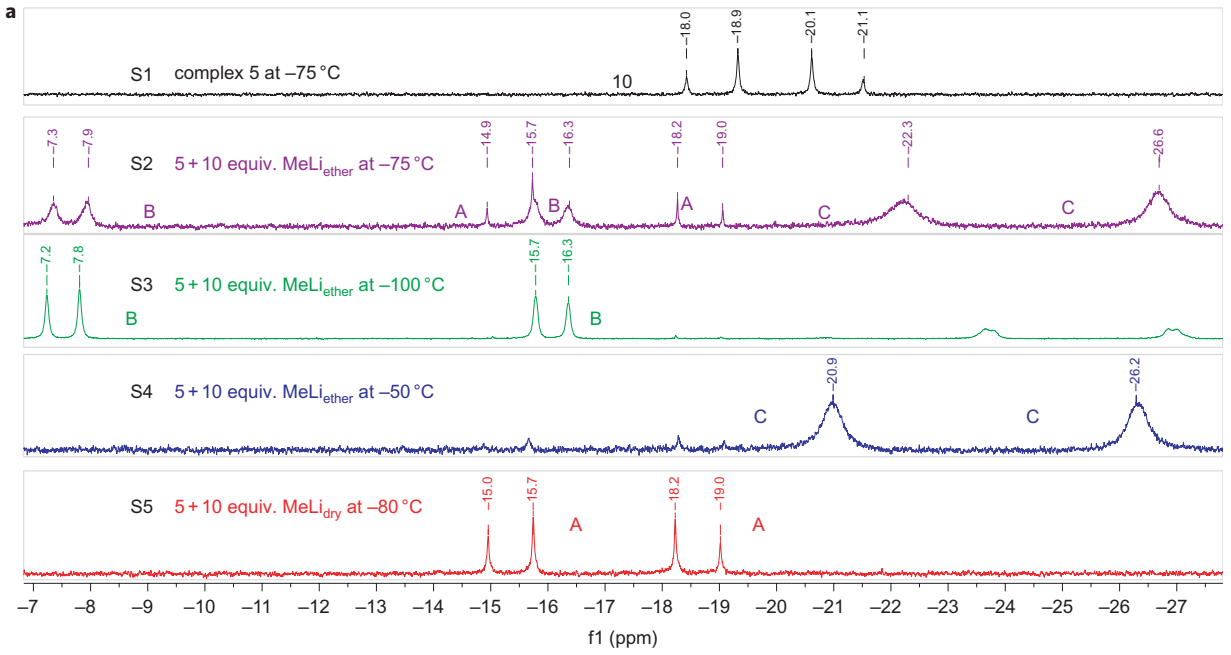
Using our optimized reaction protocol, involving the slow addition of 1.5 equiv. of MeLi (diluted with toluene) over 2.5 h to a solution of substrate **1a** and 5 mol% catalyst in dichloromethane at –80 °C, provided the corresponding chiral product **3aa** in 90% isolated yield, 90:10 ratio of regioisomers and 99% e.e. (entry 1, Table 2). The optimized CuBr·SMe_2/TaniaPhos **L6** catalyst system proved to be remarkably effective for a range of allylic substrates and alkyllithium reagents, with, in nearly all cases, excellent enantioselectivities (Table 2). Using longer alkyl moieties in the lithium reagent (in these cases 1.2 equiv. diluted with *n*-hexane) gave over 98% e.e. without exception (entries 1–4, Table 2). Importantly, allyl chloride **1b** is equally efficient in this transformation when chiral phosphoramidite ligand (*S*,*S*,*S*)-**L5** is used (entry 5, Table 2). With this protocol, it is not only primary organolithium reagents that can be used; secondary ones are well tolerated when phosphoramidite ligand (*S*,*R*,*R*)-**L4** is used in combination with CuBr·SMe_2. In stark contrast with other organometallic reagents, we could achieve regioselectivities of more than 90% and enantioselectivities up to 91% in the allylic alkylation of cinnamyl chloride **1b** with *i*-PrLi and *s*-BuLi (entries 6 and 7, Table 2). Our example demonstrates the highest value reported to date for the transfer of an *i*-Pr moiety (entry 6, Table 2) from organometallic reagents to this allylic substrate[33–35]. In addition, no examples have been reported for the synthesis of the compound with the addition of *s*-BuLi (entry 7, Table 2). This reaction system also tolerates more sterically demanding substrates; in particular, high e.e. values (96–99%) are achieved with allyl bromide **1c** bearing a 1-naphthyl substituent, using a copper catalyst based on ligand **L6** (entries 8 and 9, Table 2). Remarkably, the catalytic system can even tolerate the presence of halides in the aromatic moieties of the allylic substrates (entries 10–16, Table 2). There was no evidence of the common lithium–halogen exchange in the case of *p*-bromo-cinnamyl bromide **1e** (entry 16, Table 2), demonstrating the extremely high activity of the chiral catalyst, which can dominate over the reactivity of the organolithium compound towards competing reactions.

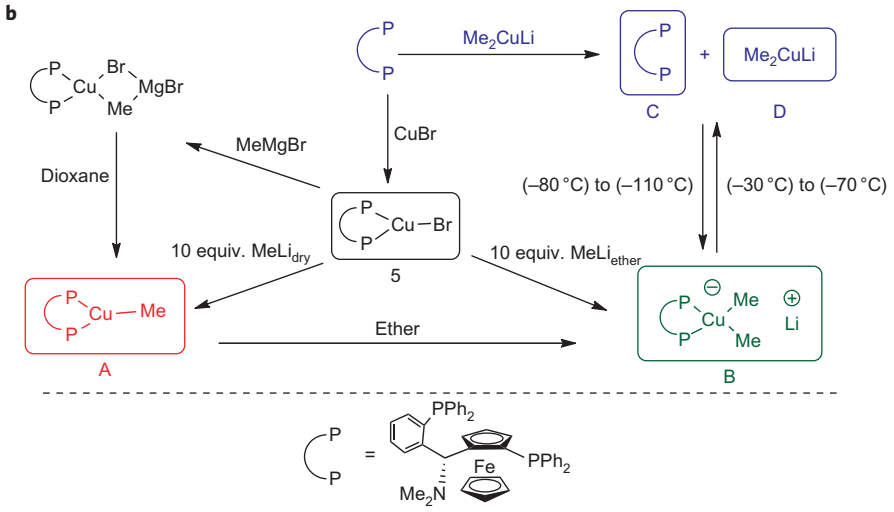
Addition of aryllithium compounds, in particular PhLi, provided more than 99% enantioselectivity when phosphoramidite ligand (*S*,*R*,*R*)-**L4** was used for the allylic alkylation of *p*-chloro-cinnamyl bromide **1d**. However, the regioselectivity in this case needs to be improved (entry 15, Table 2).

With aliphatic substrate **1f**, the TaniaPhos **L6** based catalyst was found to be the best, providing 95% e.e. (entry 17, Table 2). A major challenge and potential limitation of using alkyllithium compounds in synthesis is related to functional group tolerance, because of the high basicity and nucleophilicity of organolithium species. Allylic substrates with various functional groups known to be sensitive to organolithium reagents were therefore examined. Importantly, the catalyst system tolerates the benzyloxy and *N*-Boc-protected amine groups, with only a slight decrease in enantioselectivity, and provides chiral building blocks for natural product synthesis (entries 18–22, Table 2). It is well known that esters and alcohols are highly reactive to alkyllithium reagents, and the ultimate test of our catalytic system was therefore the allylic alkylations with *n*-BuLi and MeLi of a highly sensitive ester-substituted allylic substrate **1i** (ref. 36) bearing a heteroatom directly at the γ-position of the allyl bromide and substrate with unprotected alcohol **1j** (entries 23–25, Table 2). To our delight, the ester-protected allylic alcohol from the asymmetric S_N2' reaction with *n*-BuLi was obtained as the exclusive product in 82% isolated yield and 98% e.e., with only a small decrease in selectivity when MeLi was used (entries 23 and 24, Table 2). In addition, high regioselectivity and an e.e. of 90% were obtained with hydroxymethyl-substituted allyl bromide **1j** bearing an unprotected hydroxyl group without formation of any side products (entry 25, Table 2).

So, which chiral copper complex is responsible for this unique activity and selectivity, and what is the role of the solvent in the allylic alkylation with organolithium reagents?

As with the formation of organocuprates, we surmised that a transmetallation between the organolithium and copper bromide would occur before catalytic asymmetric C–C bond formation[37]. The formation of the chiral transmetallated copper catalyst in dichloromethane-d_2 was examined by ^1H, ^{31}P and $^6Li/^7Li$ nuclear magnetic resonance (NMR) spectroscopy using different combinations





c

Co-solvent in *n*-BuLi	$S_N2':S_N2$	e.e
Hexane	88:12	99
Et_2O	27:73	28
t-BuOMe	75:25	90
Toluene	81:19	97

d

CuX	$S_N2':S_N2$	e.e
CuBr•SMe_2	88:12	99
CuCl	83:17	98
CuI	85:15	99
Cu(TC)	81:19	97

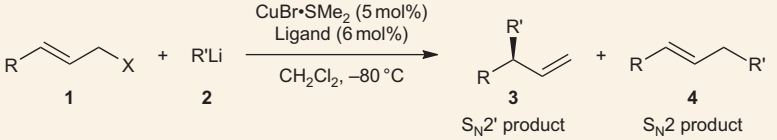
Figure 2 | Mechanistic study of chiral catalyst formation and the effect of copper salt and co-solvents present in the alkyllithium reagent. a, ^{31}P NMR spectroscopic studies of TaniaPhos–CuBr complex **5** in dichloromethane-d_2 with MeLi. S1 is the copper complex of TaniaPhos **5**, dissolved in dichloromethane-d_2 at -75 °C. S2 is **5** dissolved in dichloromethane-d_2 at -75 °C followed by addition of 10 equiv. of MeLi in Et_2O. In this case, the immediate formation of four different species (A, B, C and D) was observed. A temperature-dependent dynamic equilibrium was observed between species B and C. Species B is the major species between -80 and -110 °C (S3), but at temperatures higher than -80 °C, species C is dominant (S4). An equilibrated mixture of species B and C can also be obtained by mixing Me_2CuLi and TaniaPhos **L6** in dichloromethane-d_2. S5 is species A, which can be obtained exclusively by using nearly dry MeLi as well as Me_2Mg. Similarly, if diethyl ether is added to this mixture it causes dissolution of excess dry MeLi and formation of an equilibrated mixture of species B and C. Species D is only observed by ^1H NMR (see Supplementary Information) and corresponds to Me_2CuLi. **b**, Chemical structures and transformations proposed for species A, B, C and D. **c**,**d**, Dependence of regio- and enantioselectivity of *n*-BuLi addition to cinnamyl bromide **1a** on cosolvent (**c**) used to dilute *n*-BuLi and copper source (**d**).

of copper salt, solvents and quantities of MeLi over a range of temperatures (Fig. 2a).

A full account of our mechanistic studies will be reported in due course. However, the most striking observation is that in dichloromethane, in the presence of diethyl ether using 10 equiv. of MeLi and the copper bromide–TaniaPhos complex **5** (Fig. 2a), four distinct species are observed (Fig. 2a; Supplementary Fig. S2). In the absence of an ether, TaniaPhos–CuMe (complex **A**, Fig. 2a; Supplementary Fig. S5b) is found exclusively at –80 °C. This chiral monomethyl copper species was independently prepared using copper complex **5** with MeLi in the absence of ether or with Me_2Mg, confirming the proposed structure (for details, see Supplementary Information). To establish the relevance of species **A** in the catalytic allylic substitution, it was used in the stoichiometric alkylation of cinnamyl bromide **1a**, resulting in greater than 98% enantioselectivity. Additional control experiments confirmed the detrimental effect of ether on enantioselectivity, due to the formation of multiple copper species. We also observed an absence of any influence of the copper source used in the allylic alkylation (Fig. 2d) on the catalytic process, in accordance with the presence of the unique catalytic complex **A.**

Solvents and co-solvents (used for dilution of organolithium reagents) had a prominent effect on the stereo- and chemoselectivity

Table 2 | Scope of asymmetric allylic alkylation.



Entry*	1, R	X	2, R′	Ligand	3:4 (%)†	Yield‡ (%)	3, e.e. (%)§
1	**1a**, Ph	Br	**2a**, Me	**L6**	90:10	90	**3aa**, 99 (*S*)
2	**1a**, Ph	Br	**2b**, Et	**L6**	84:16	80	**3ab**, 98 (*S*)
3	**1a**, Ph	Br	**2c**, *n*-Bu	**L6**	90:10	88	**3ac**, 99 (*S*)
4	**1a**, Ph	Br	**2d**, *n*-Hex	**L6**	90:10	92	**3ad**, >99 (*S*)
5	**1b**, Ph	Cl	**2c**, *n*-Bu	**L5**	91:9	90	**3bc**, 95 (*S*)
6	**1b**, Ph	Cl	**2e**, *i*-Pr	**L4**	90:10	77	**3be**, 91 (*S*)
7‖	**1b**, Ph	Cl	**2f**, *s*-Bu	**L4**	97:3	80	**3bf**, 82 (+)
8	**1c**, 1-Naphthyl	Br	**2a**, Me	**L6**	80:20	96	**3ca**, 99 (-)
9	**1c**, 1-Naphthyl	Br	**2c**, *n*-Bu	**L6**	81:19	97	**3cc**, 96 (-)
10	**1d**, *p*-Cl-C_6H_4	Br	**2a**, Me	**L6**	85:15	90	**3da**, >99 (+)
11	**1d**, *p*-Cl-C_6H_4	Br	**2b**, Et	**L6**	82:18	91	**3db**, 96 (+)
12	**1d**, *p*-Cl-C_6H_4	Br	**2c**, *n*-Bu	**L6**	86:14	91	**3dc**, 97 (*S*)
13¶	**1d**, *p*-Cl-C_6H_4	Br	**2c**, *n*-Bu	**L6**	85:15	90	**3dc**, 97 (*S*)
14	**1d**, *p*-Cl-C_6H_4	Br	**2d**, *n*-Hex	**L6**	83:17	93	**3dd**, >99 (+)
15	**1d**, *p*-Cl-C_6H_4	Br	**2g**, Ph	**L4**	40:60	39#	**3dg**, 99 (*S*)
16	**1e**, *p*-Br-C_6H_4	Br	**2c**, *n*-Bu	**L6**	88:12	93	**3ec**, 98 (*S*)
17	**1f**, *n*-Pent	Br	**2b**, Et	**L6**	94:6	100**	**3fb**, 95 (ND)
18	**1g**, $BnOCH_2$	Br	**2a**, Me	**L6**	85:15	98	**3ga**, 90 (*S*)
19	**1g**, $BnOCH_2$	Br	**2b**, Et	**L6**	93:7	90	**3gb**, 91 (+)
20	**1g**, $BnOCH_2$	Br	**2c**, *n*-Bu	**L6**	86:14	>99	**3gc**, 90 (*S*)
21	**1g**, $BnOCH_2$	Br	**2d**, *n*-Hex	**L6**	85:15	96	**3gd**, 86 (+)
22	**1h**, TosN(Boc)CH_2	Br	**2b**, Et	**L6**	84:16	72	**3hb**, 86 (-)
23††	**1i**, $PhCO_2$	Br	**2c**, *n*-Bu	**L6**	100:0	82	**3ic**, 98 (+)
24	**1i**, $PhCO_2$	Br	**2a**, Me	**L6**	90:10	62	**3ia**, 96 (*S*)
25‡‡	**1j**, $HOCH_2$	Br	**2c**, *n*-Bu	**L6**	96:4	99**	**3jc**, 90 (ND)

*Conditions: 1.2 equiv. RLi diluted in hexane (1.5 equiv. diluted in toluene in the case of MeLi) was added over 2–5 h (see Supplementary Information) to the 0.1 M solution of substrate in CH_2Cl_2. †Ratio of S_N2':S_N2 products was determined by gas chromatography analysis. ‡Refers to the isolated yield of S_N2':S_N2 products. §Determined by gas or high-performance liquid chromatography analysis (see Supplementary Information). (*S*)-indicates absolute configuration; (+) and (-) are signs of optical rotation. ‖Ratio of diastereomers was determined as 1:1 with e.e. values of 82% and 81%, respectively. ¶Pre-formed CuBr·**L6** complex was used. #The S_N2' product could be isolated pure in this case. **This value refers to conversion; very volatile product. ††4% of double 1,2-addition product was isolated in this case. ‡‡2.2 equiv. of *n*-BuLi were used. ND, not determined.

of the organolithium reaction (Fig. 2c). The reactivity of alkyllithium reagents is highly dependent on their structure and aggregation state, which in turn is strongly dependent on solvent[30]. Thus, by excluding or minimizing ethereal solvents we were able to prevent the formation of highly reactive organolithium species, and by selecting dichloromethane as a solvent we were able to enhance the catalytic reaction exclusively.

Summary

In conclusion, for the first time since the discovery of organolithium compounds, it has been demonstrated that near absolute levels of enantioselectivity can be achieved in catalytic asymmetric C–C bond formation through allylic alkylation with these organometallic reagents. This is possible as a result of our ability to tune a dynamic system towards a unique and highly reactive catalyst featuring a chiral monoalkyl copper phosphine complex. Now that the elusive alkyllithium reagents have finally been tamed for catalytic asymmetric C–C bond formation, the stage is set for the discovery of a myriad of new catalytic applications for organolithium reagents, for the practical synthesis of highly valuable chiral products.

Methods

The general procedure for the copper-catalysed allylic alkylation of allyl halides **1** with organolithium reagents **2** is as follows. A Schlenk tube equipped with septum and stirring bar was charged with CuBr·SMe_2 (0.01 mmol, 2.06 mg, 5 mol%) and the appropriate ligand (0.012 mmol, 6 mol%). Dry dichloromethane (2 ml) was added and the solution was stirred under nitrogen at room temperature for 15 min. Allyl halide **1** (0.2 mmol) was then added and the resulting solution cooled to –80 °C. In a separate Schlenk tube, the corresponding organolithium reagent **2** (0.24 mmol, 1.2 equiv.) was diluted with hexane (combined volume of 1 ml; in the case of MeLi (**2a**; 1.5 equiv.) toluene was used) under nitrogen and added dropwise to the reaction mixture over 2 h (over 5 h when using phosphoramidite ligands) using a syringe pump. The flow of inert gas was turned off during the addition. Once the addition was complete, the mixture was stirred for another 2 h at –80 °C. The reaction was quenched with a saturated aqueous NH_4Cl solution (2 ml) and the mixture was warmed to room temperature, diluted with dichloromethane, and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 5 ml) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent evaporated *in vacuo*. Gas chromatography analysis was carried out to determine the S_N2':S_N2 ratio on a sample obtained after aqueous extraction with dichloromethane, which had been passed through a short plug of silica gel to remove transition-metal residues. Purification was performed by flash chromatography on silica gel using different mixtures of *n*-pentane:Et_2O as the eluent, and the enantiomeric excess was determined by gas or high-performance liquid chromatography analysis by comparison using authentic racemic material.

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Author contributions

M.P. and M.F.-M. studied solvent effects and optimized the reaction conditions. P.H.B. performed ligand screening. A.R. performed copper salt screening. S.R.H. carried out NMR studies. M.P., M.F.-M, P.H.B. and A.R. evaluated the scope of the organolithium addition reaction. All authors contributed to designing the experiments, analysing the data and editing the manuscript. S.R.H. and B.L.F. guided the research and wrote the manuscript.

Additional information

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