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Direct enantio-convergent transformation of racemic substrates without racemization or symmetrization

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Asymmetric reactions that transform racemic mixtures into enantio-enriched products are in high demand, but classical kinetic resolution produces enantiopure compounds in <50% yield even in an ideal case. Many deracemization processes have thus been developed including dynamic kinetic resolution and dynamic kinetic asymmetric transformation, which can provide enantio-enriched products even after complete conversion of the racemic starting materials. However, these dynamic processes require racemization or symmetrization of the substrates or intermediates. We demonstrate a direct chemical enantio-convergent transformation without a racemization or symmetrization process. Copper(I)-catalysed asymmetric allylic substitution of a racemic allylic ether afforded a single enantiomer of an α-chiral allylboronate with complete conversion and high enantioselectivity (up to 98% enantiomeric excess). One enantiomer of the substrate undergoes an *anti*-S_N2'-type reaction whereas the other enantiomer reacts via a *syn*-S_N2' pathway. The products, which cannot be prepared by dynamic procedures, have been used to construct all-carbon quaternary stereocentres.

Efficient methods to produce enantiopure compounds from racemic starting materials are in high demand, especially in the pharmaceutical and agricultural industries, as are enantioselective catalysis methods that convert pro-chiral starting materials to desired enantio-enriched products (Fig. 1)[1–4]. The reaction of a racemic substrate with a chiral catalyst usually results in kinetic resolution where the two enantiomers of the racemate react at different rates (Fig. 1a)[4–6]. When the reaction rate of one enantiomer of the starting material ($\mathbf{S_A}$) is significantly higher than the other ($k_A \gg k_B$), that enantiomer is converted far more rapidly than the opposite enantiomer. An enantio-enriched product ($\mathbf{P_A}$) is thus obtained with high selectivity; however, the other substrate enantiomer with lower reactivity ($\mathbf{S_B}$) remains unreacted and the theoretical maximum yield of the desired product ($\mathbf{P_A}$) is only 50% even in an ideal case.

To overcome the limitation caused by this incomplete conversion, many elegant deracemization processes have been designed that can transform both enantiomers of the racemic starting materials into a single enantiomer of the product. Dynamic kinetic resolution (DKR)[7–9] and dynamic kinetic asymmetric transformation (DYKAT)[10–18] are examples (Fig 1b,c). Dynamic kinetic resolution can be achieved by combining an enantioselective reaction with the rapid racemization of the starting materials (Fig. 1b). In this case, the less reactive substrate enantiomer ($\mathbf{S_B}$) can be converted into the more reactive enantiomer ($\mathbf{S_A}$) through the racemization process; when the reaction rate of the racemization is much higher than the favourable enantioselective step (from $\mathbf{S_A}$ to $\mathbf{P_A}$) and the rate of the favourable enantioselective step is sufficiently larger than that of the disfavoured one ($k_A \gg k_B$), the desirable enantiomer ($\mathbf{P_A}$) can be obtained with high enantiomeric purity after complete conversion of the starting material. For dynamic kinetic asymmetric transformation (Fig. 1c), both enantiomers are initially converted into a common intermediate (**I**) in which the substrate stereogenic centre disappears. This is typically achieved by forming pseudo *meso*- or C_2-symmetric complexes with chiral catalysts. The new chiral centre is then established by the subsequent enantioselective step ($k_A \gg k_B$, Fig. 1c)[10–18]. However, the majority of racemic compounds have significantly robust chiral centres, and reaction procedures such as DKR or DYKAT are therefore ineffective: most racemic starting materials have no suitable means for racemization, which is essential for DKR; and DYKAT requires the disappearance of the stereogenic centre in the reaction intermediate, but many chiral compounds cannot take symmetrical structures (pseudo *meso*- or C_2-symmetric) even in the transformation pathway to other chiral products. Deracemization of racemates with such robust chiral centres remains an unsolved problem in the field of asymmetric synthesis.

If each enantiomer of a racemic mixture is converted into the same enantiomer of the product through different reaction pathways, the problems raised by racemization or symmetrization can be circumvented (Fig. 1d)[1,2,19,20]. However, the requirements to achieve such a reaction in a single operation with a single catalyst are challenging. The catalyst should promote two distinctive reaction pathways with opposite enantiomeric preference of the substrate ($k_{AA} \gg k_{AB}$ and $k_{BA} \gg k_{BB}$), and each pathway should have opposite stereoselectivity to produce the same enantiomer of the products. Furthermore, the two preferred pathways should proceed at similar reaction rates ($k_{AA} \approx k_{BA}$) to avoid kinetic resolution of the substrate. Studies describing such direct enantio-convergent reactions are scarce and are limited to a few biocatalytic reactions[19,20]. To our knowledge, artificial catalysts that can promote this type of transformation with a practically useful level of selectivity are unknown. We recently reported the copper(I)-catalysed enantioselective boryl substitution of pro-chiral allylic carbonates to produce enantio-enriched allylboronates, which are useful building blocks for the asymmetric preparation of compounds with multiple chiral centres[21–23]. This is the first direct chemical enantio-convergent transformation to occur without a racemization or symmetrization process when the substrate

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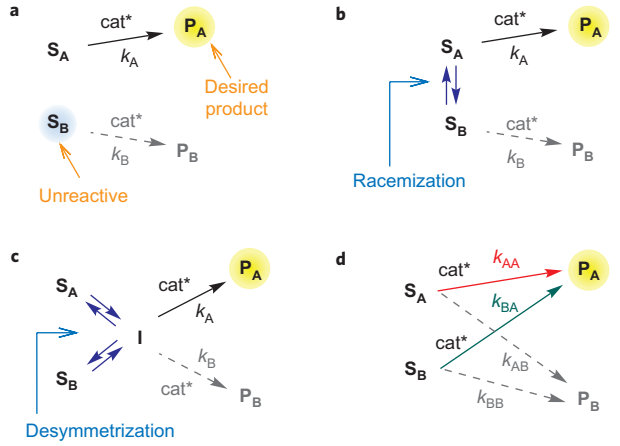


Figure 1 | Conceptual schemes for asymmetric reactions of racemic chiral substrates for production of enantio-enriched compounds. Solid arrows represent faster reaction pathways and dotted arrows show slower ones. Racemization and desymmetrization processes are shown by blue arrows. **a**, Kinetic resolution. One of the substrate enantiomers ($\mathbf{S_A}$) is converted into the product ($\mathbf{P_A}$) at a higher reaction rate in the presence of a chiral catalyst (cat*), whereas the other substrate enantiomer ($\mathbf{S_B}$) reacts at a much lower rate ($k_A \gg k_B$). **b**, Dynamic kinetic resolution. The rapid racemization process of the substrate enables the conversion of two enantiomers ($\mathbf{S_A}$ and $\mathbf{S_B}$) into one enantiomer of the product ($\mathbf{P_A}$). **c**, Dynamic kinetic asymmetric transformation. A desymmetrization process first converts the two substrate enantiomers ($\mathbf{S_A}$ and $\mathbf{S_B}$) into an intermediate (**I**), where the substrate chiral centre disappears. The subsequent enantioselective path produces one enantiomer ($k_A \gg k_B$). **d**, Direct enantio-convergent transformation. One substrate enantiomer ($\mathbf{S_A}$) is converted preferentially into one product enantiomer ($\mathbf{P_A}$) (red arrow, $k_{AA} \gg k_{AB}$) and the other enantiomer ($\mathbf{S_B}$) is also converted into the same product ($\mathbf{P_A}$) ($k_{BA} \gg k_{BB}$) through a different reaction pathway (green arrow).

racemic allylic ethers have a 'robust' chiral centre that cannot be treated by known deracemization processes such as DKR or DYKAT. The synthetic use of the allylboronates, which can only be prepared by this direct enantio-convergent transformation, was demonstrated by construction of all-carbon quaternary stereocentres through stereoselective aldehyde allylation[24–26].

Results

Direct enantio-convergent reaction. Racemic allylic ether **1a** has a cyclic structure with an asymmetric substituent pattern around the allylic system (Table 1). This appears to be an example of a compound that cannot be applied to the known deracemization procedures. There are no efficient ways to racemize such tertiary ethers, indicating that DKR is not applicable. Although DYKAT of some racemic allylic esters have been reported in transition-metal-catalysed asymmetric allylic alkylation[10,11,13–18], successful cases are limited to the acyclic allylic esters or cyclic ones bearing symmetrical substituents about the allylic system or an electron withdrawing group. Such structures enable DYKAT by racemization through $\pi-\sigma-\pi$ isomerization[10,11,15,16] or symmetrization via the formation of pseudo-*meso* π allylmetal complexes[10,11,17,18].

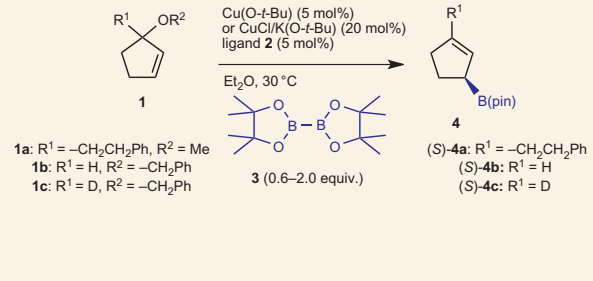
The reaction of (*rac*)-**1a** was first carried out with bis(pinacolato)diboron **3** ((pin)B–B(pin), pin = pinacolato; 1.5 equivalents) in the presence of 5 mol% of Cu(O-*t*-Bu) and a chiral phosphine ligand [(*R*,*R*)-QuinoxP* (**2a**)][27] in diethyl ether at 30 °C (Table 1). Complete conversion of (*rac*)-**1a** was reached within 24 h and the corresponding allylboronate (*S*)-**4a**, the S_N2' product of boryl substitution, was obtained in high yield (98%) with a high enantioselectivity (97% enantiomeric excess (e.e.); entry 1). The reaction was also performed with the readily available catalyst CuCl/K(O-*t*-Bu) instead of Cu(O-*t*-Bu), but a longer reaction time was required (entry 2, 96 h). Reaction with (*R*,*R*)-Me-Duphos (**2b**) instead of (*R*,*R*)-QuinoxP* (**2a**) also proceeded as the enantio-convergent transformation with a lower enantioselectivity (99%, 88% e.e., entry 3). Reaction with (*R*)-BINAP (**2c**) did not reach completion even after a long reaction time and gave poor enantioselectivity (59 h, 54%, 18% e.e., entry 4). Reactions of enantiopure substrates, (+)-**1a** and (−)-**1a**, also afforded the same enantiomer of the product (*S*)-**4a** with a high degree of enantiomeric excess (97% e.e., entries 5 and 6). These results represent the successful deracemization of the robust chiral compound (*rac*)-**1a**.

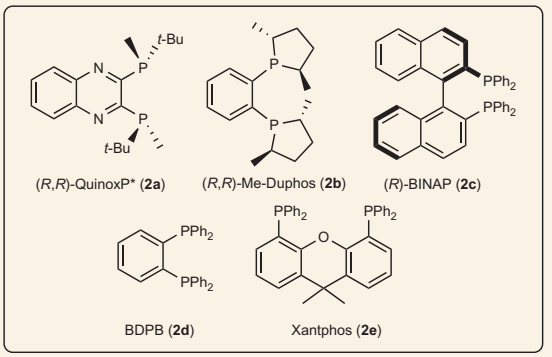
We next applied this enantio-convergent transformation catalysis to the secondary allylic ether **1b** to investigate details of the reaction stereochemistry; the use of **1b** eases the stereochemical characterization of the starting material and the product. Reaction of (*rac*)-**1b** using the enantio-convergent transformation catalysis approach gave the corresponding allylboronate (*S*)-**4b** in good yield with high enantiomeric purity (92% yield, 92% e.e.; entry 7). The reaction of deuterium-labelled (*rac*)-**1c** exclusively afforded the allylboronate (*S*)-**4c** with high enantioselectivity (92% e.e.; entry 8) without transposition of the deuterium atom. This indicates that the reaction does not include a pseudo-*meso* π allylmetal intermediate, which is observed in other transition-metal-catalysed DYKAT processes (entry 8)[10,11,17,18]. In addition, both enantio-enriched forms of the starting material, (*S*)-**1b** (93% e.e.) or (*R*)-**1b** (94% e.e.) were converted into the same enantiomer, (*S*)-**4b** (entries 9 and 10). The reaction of (*S*)-**1b** resulted in a higher enantiomeric excess (99% e.e.) than that obtained from (*rac*)-**1b**, and the reaction of (*R*)-**1b** gave a lower enantiomeric excess (85% e.e.). The stereochemical outcomes indicate that the reactions of (*S*)-**1b** and (*R*)-**1b** proceed via two distinct pathways, *anti*-S_N2' with higher enantioselectivity and *syn*-S_N2' with slightly lower enantioselectivity. The enantiomeric excess of the product prepared from (*rac*)-**1b** (92%; entry 7) is roughly the average of the values from (*S*)-**1b** (99% e.e.; entry 9) and (*R*)-**1b** (85% e.e.; entry 10). The reaction of (*S*)-**1b** with a low amount of **3** (0.6 equivalents), where the reaction did not reach completion, gave (*S*)-**4b** in 46% yield with 99% e.e.; (*S*)-**1b** was recovered in 44% yield with a slightly lower enantiomeric purity (89% e.e.) compared with the starting material (entry 11). Conversely, a similar reaction of (*R*)-**1b** with 0.6 equivalents of **3** gave (*S*)-**4b** with a lower product enantiomeric purity (43%, 85% e.e.) and the recovered (*R*)-**1b** showed a higher enantiomeric purity (45%, 98% e.e.) than that of the starting material (entry 12). The enantiomeric excess values of the recovered **1b** indicate that the reaction does not involve racemization of the starting material and that the consumption rate of (*S*)-**1b** is slightly higher than that of (*R*)-**1b**, resulting in partial kinetic resolution (entries 11, 12). Reaction of (*rac*)-**1b** with 0.6 equivalents of **3** resulted in 50% yield of (*S*)-**4b** with high enantioselectivity (95% e.e.) and 48% recovery of the starting material with moderate enantiomeric excess (34% e.e. (*R*); entry 13). This result is consistent with the assumption that (*S*)-**1b** reacts slightly faster than (*R*)-**1b**.

The reaction of enantiomerically pure (*S*)-**4b** with an achiral ligand BDPB (**2d**), which has a similar backbone structure to chiral ligands **2a** and **2b**, proceeded via *anti*-S_N2' to afford (*S*)-**4b** (84%, 77% e.e. (*S*); entry 14). Conversely, the reaction with Xantphos (**2e**), which showed high reactivity in our former copper(I)/diboron catalyst systems, preferentially gave a *syn*-S_N2' product with a low enantiomeric excess (17% e.e. (*R*); entry 15). We suppose that the steric interaction between the catalyst with BDPB (**2d**) and the benzyloxy group is responsible for the *anti*-stereoselectivity, whereas the catalyst with Xantphos (**2e**) has no significant difference in the steric interactions in both pathways.

Mechanism. Further experiments with deuterated substrates clearly showed that the two enantiomers were converted via distinct

Table 1 | Examination of direct enantio-convergent transformation in copper(I)-catalysed asymmetric allylic boryl substitution.





Entry	Substrate	Ligand 2	Equiv. of 3	Time (h)	Yield of 4 (%)*	e.e. of 4 (%)†	Recovery of 1 (%)*	e.e. of 1 (%)‡
1	(*rac*)-**1a**	(*R*,*R*)-QuinoxP* (**2a**)	1.5	24	98	97 (*S*)	0	-
2§	(*rac*)-**1a**	(*R*,*R*)-QuinoxP* (**2a**)	2.0	96	98	95 (*S*)	0	-
3	(*rac*)-**1a**	(*R*,*R*)-Me-Duphos (**2b**)	2.0	16.5	99	88 (*S*)	0	-
4	(*rac*)-**1a**	(*R*)-BINAP (**2c**)	2.0	59	54	18 (*S*)	46	28
5	(+)-**1a** (99% e.e.)	(*R*,*R*)-QuinoxP* (**2a**)	1.5	24	95	97 (*S*)	0	-
6	(−)-**1a** (>99% e.e.)	(*R*,*R*)-QuinoxP* (**2a**)	1.5	24	92	97 (*S*)	0	-
7	(*rac*)-**1b**	(*R*,*R*)-QuinoxP* (**2a**)	1.5	12	92	92 (*S*)	0	-
8	(*rac*)-**1c**	(*R*,*R*)-QuinoxP* (**2a**)	1.5	12	91	92 (*S*)	0	-
9‖	(*S*)-**1b** (93% e.e.)	(*R*,*R*)-QuinoxP* (**2a**)	1.5	10	88	99 (*S*)	0	-
10‖	(*R*)-**1b** (94% e.e.)	(*R*,*R*)-QuinoxP* (**2a**)	1.5	10	90	85 (*S*)	0	-
11‖	(*S*)-**1b** (93% e.e.)	(*R*,*R*)-QuinoxP* (**2a**)	0.6	7.5	46	99 (*S*)	44	89 (*S*)
12‖	(*R*)-**1b** (94% e.e.)	(*R*,*R*)-QuinoxP* (**2a**)	0.6	7	43	85 (*S*)	45	98 (*R*)
13	(*rac*)-**1b**	(*R*,*R*)-QuinoxP* (**2a**)	0.6	5.5	50	95 (*S*)	48	34 (*R*)
14¶	(*S*)-**1b** (>99% e.e.)	BDPB (**2d**)	1.5	9	84	77 (*S*)	0	-
15¶	(*S*)-**1b** (>99% e.e.)	Xantphos (**2e**)	1.5	8	88	17 (*R*)	0	-

Reaction conditions: **1** (0.5 mmol), Cu(O-*t*-Bu) (0.025 mmol), ligand **2** (0.025 mmol), **3** (0.75 mmol) in diethyl ether at 30 °C. *Yield of the allylboronate and recovery of the starting material were determined by ^{1}H NMR of an unpurified reaction mixture using an internal standard. †The value of the enantiomeric excess was determined by HPLC analysis of an oxidative derivative or a carbonyl addition product of the allylboronate. ‡Enantiomeric ratio was determined by HPLC analysis. §CuCl (0.1 mmol) and K(O-*t*-Bu) (0.1 mmol) were used instead of Cu(O-*t*-Bu). ‖The reaction was carried out at a 0.25 mmol scale with 5 mol% of catalyst. ¶The reaction was carried out at a 0.20 mmol scale with 10 mol% of catalyst.

pathways, *anti*-S_N2' and *syn*-S_N2' (Fig. 2a,b). The reaction of (1*S*,5*R*)-**1d**, deuterated at the 5-position, gave the *anti*-S_N2' product, (1*S*,4*R*)-**4d**, without regio- and stereochemical disposition of the deuterium (Fig. 2a). (1*R*,5*S*)-**1d**, which is the enantiomer of (1*S*,5*R*)-**1d**, afforded the diastereomeric *syn*-S_N2' product, (1*S*,4*S*)-**4d** (Fig. 2b). The two opposite stereogenic centres at the α-carbon of the alkoxy group in the allylic systems in **1d** disappeared and a new chiral centre at the γ-carbon with the same absolute configuration was formed in **4d**. However, the chiral centres around the deuteride remained unchanged. This led to the formation of two product diastereomers from two substrate enantiomers. This stereo-divergent behaviour is characteristic of this type of enantio-convergent transformation when the substrate racemates have multiple chiral centres[1].

As shown in Fig. 2c, the experimental results are clearly explained by assuming a direct enantio-convergent reaction. The substrate (*S*)-**1b** is attacked by the borylcopper(I), a catalytic intermediate generated from alkoxycopper(I) and diboron **3**. When

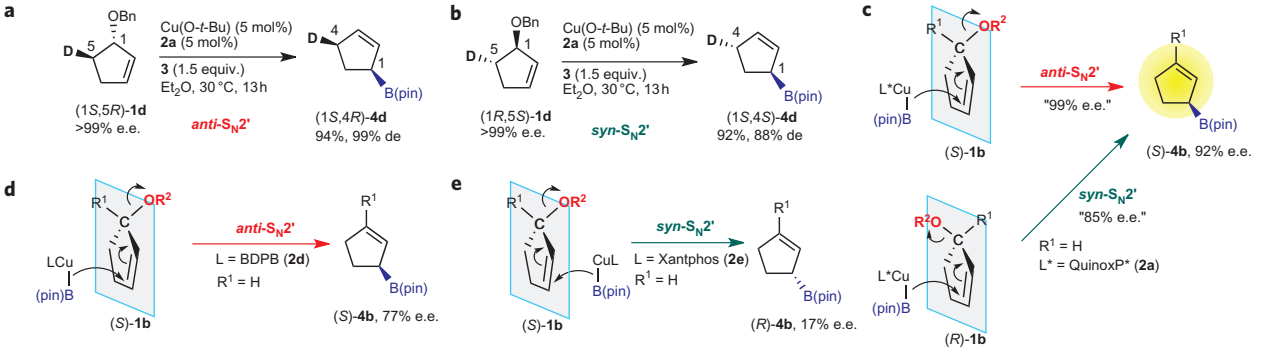


Figure 2 | Experimental studies and plausible schematic explanations on the mechanism of the direct enantio-convergent transformation. a, The reaction of a deuterium-labelled substrate, (1*S*,5*R*)-**1d**, resulted in *anti*-S_N2' product (1*S*,4*R*)-**4d**. **b**, The reaction of (1*R*,5*S*)-**1d**, which is the enantiomer starting material in **a**, afforded the *syn*-S_N2' product (1*S*,4*S*)-**4d**, which is the diastereomer of the product in **a. c**, The mechanistic scheme for the direct enantio-convergent transformation. The chiral borylcopper(I) intermediate with the chiral ligand (**2a**) reacts with (*S*)-**1b** via an *anti*-S_N2' pathway (red arrow) and with (*R*)-**1b** via a *syn*-S_N2' pathway (green arrow). The same product, (*S*)-**4b**, is produced from both substrate enantiomers by the two distinct pathways. **d**, Reaction of borylcopper(I) with achiral ligand BDPB (**2d**) via an *anti*-S_N2' route. **e**, Reaction of borylcopper(I) with achiral ligand Xantphos (**2e**) tends to proceed via an *syn*-S_N2' route.

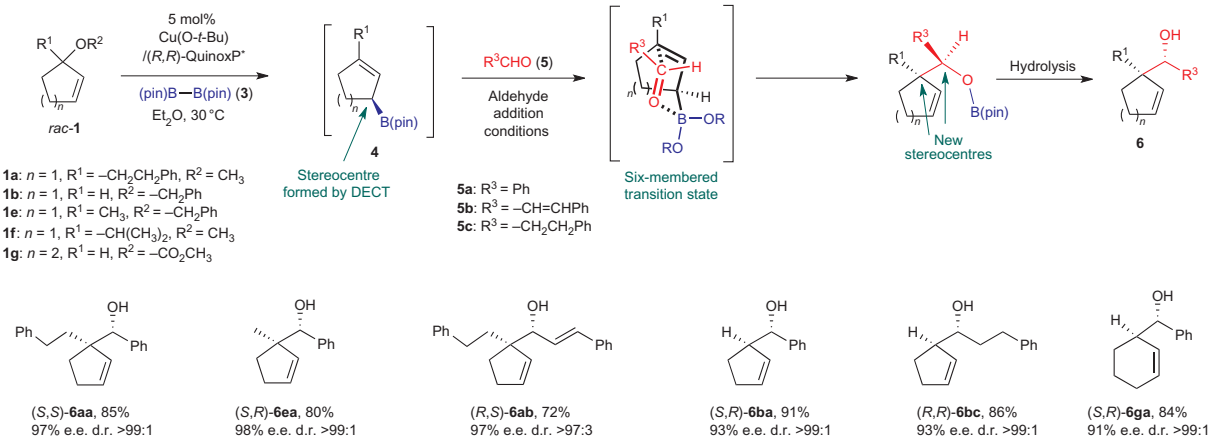


Figure 3 | Synthesis of enantio-enriched homoallylic alcohols with an all-carbon quaternary or tertiary stereocentre. The direct enantio-convergent reaction of allylic ether or carbonate (*rac*-**1**) with diboron **3** was first conducted in the presence of a Cu(O-*t*-Bu)/QuinoxP* catalyst at 30 °C. After completion of the copper(I)-catalysed reaction and rough purification of the allylboronate **4**, a subsequent reaction with aldehyde **5** was carried out in either the presence (BF_3·OEt_2, −78 °C in CH_2Cl_2) or absence of a Lewis acid catalyst (30 °C in toluene). The addition reaction proceeded via a six-membered ring transition state to produce homoallylic alcohol **6** with two newly formed chiral stereocentres after hydrolysis. The enantiomeric excess values of **6** were determined by high-performance liquid chromotography analysis with a chiral stationary phase. In the case of substrate **1f**, the best result was obtained by using (R,R)-Me-Duphos as ligand—product (*S*)-**4f** was obtained in 78% yield and 85% e.e. DECT = direct enantio-convergent transformation.

(*R*,*R*)-QuinoxP* (**2a**) was used as the ligand, in the reaction of (*S*)-**1b**, the nucleophilic attack took place on the opposite face (of the carbon–carbon double bond) to the leaving alkoxy group (OR^2) to afford (*S*)-**4b** via an *anti*-S_N2'-type pathway with 99% e.e. (Fig. 2c). In contrast, the same borylcopper(I) intermediate approaches (*R*)-**1b** from the same side as the leaving alkoxy group (OR^2) to give (*S*)-**4b** through a *syn*-S_N2'-type reaction with 85% e.e.

As shown in Fig. 2c,d the reaction of (*S*)-**1b** predominantly proceeds through an *anti*-S_N2' pathway when an achiral BDPB ligand is used, whereas when Xantphos is used the reaction tends to proceed via a *syn*-S_N2' pathway (Table 1, entries 14 and 15). These results indicate that the *anti*- or *syn*-S_N2'-type reaction route is flexible and controllable by the ligand structure. Thus, it is reasonable to assume that catalysts with the (*R*,*R*)-QuinoxP* ligand have sound face selectivity on the double bond and that this overcomes the inherent stereoselectivity (*anti*- or *syn*- S_N2') of the borylcopper(I) intermediate toward the allylic substrate. Density functional theory calculations (M05-2X/6-31G(d)) using model compounds were carried out for four distinct reaction pathways (*anti*- or *syn*-S_N2' pathways from (*S*)-**1** or (*R*)-**1**). The results support our proposed mechanism. For the reaction of (*S*)-**1**, *anti*-S_N2' is favourable over *syn*-S_N2'; for the reaction of (*R*)-**1**, *syn*-S_N2' is favourable over the *anti*-S_N2' reaction (see Supplementary Information).

Construction of all-carbon quaternary stereocentre. The enantio-enriched allylboronates prepared by the enantio-convergent transformation through copper(I)-catalysed asymmetric boryl substitution are valuable synthetic reagents[28–30]. In particular, α-chiral cyclic allylboronates bearing a substituent at the 3-position can be prepared only by this reaction, and these can be used to produce homoallylic alcohols with an all-carbon quaternary stereocentre by stereoselective aldehyde allylation; selective construction of such molecules is a challenging issue in synthetic chemistry. The racemic substrates **1a–e** were initially subjected to the copper(I)-catalysed enantio-convergent transformation to afford enantio-enriched allylboronates, which were subsequently reacted with aldehydes (Fig. 3). The aldehyde addition proceeded in a highly stereoselective manner through a six-membered transition state to give homoallylic alcohols **6** with an all-carbon quaternary or tertiary stereocentre in high yields with high diastereo- and enantioselectivities (72–91%, 93–98% e.e., diastereomeric ratio (d.r.) >99:1–> 97:3). The borylation reaction with a substrate with a bulky isopropyl substituent (**1f**) gave the corresponding allylboronate in good yield with slightly lower enantioselectivity (78%, 85% e.e.) when a (*R*,*R*)-Me-Duphos ligand (**2b**) was used; however the subsequent aldehyde addition was very slow. A carbonate with cyclohexenyl structure (**1g**) also gave a good result with 10 mol% catalyst (84%, 91% e.e., d.r. > 99:1); however the reaction with a similar seven-membered ring substrate, 2-cyclohepten-1-yl methyl carbonate, resulted in a poor enantioselectivity (65%, 44% e.e.). Interestingly, the reaction of a linear substrate with unsymmetrical substituents, (*Z*)-methyl (6-phenylhex-3-en-2-yl) carbonate, proceeded in a typical kinetic resolution manner (allylboronate product, 47%, 80% e.e.; recovered starting material, 46%, 82% e.e.; see Supplementary Information).

Discussion

The present transformation shows interesting similarity to a class of asymmetric reactions called 'divergent reactions on a racemic mixture' by Kagan[3], which may include parallel kinetic resolution, regio- and stereo-divergent reactions[31–37]. In such reactions, two enantiomers of a racemic mixture were converted into 'distinct' enantio-enriched products through different pathways. Contrary to this, the present reaction transforms the substrate enantiomers into the 'same' enantio-enriched product through different pathways. The divergent or parallel asymmetric reactions are advantageous compared with classical kinetic resolution in terms of efficiency because the efficiency of the resolution is the simple sum of the selectivity of the two independent pathways when the two pathways have similar reaction rates[3,31]. A similar feature was observed in the present transformation (Table 1, entries 11–13). This enantio-convergent transformation can be considered as a special 'convergent' case of the 'divergent reactions on a racemic mixture'.

The key to success in the present enantio-convergent reaction, as well as other divergent-type reactions, is the ability of the external chiral reactive species to control the selectivity. This is significantly superior to the influence of the internal chiral structure of the racemic substrate. Tomioka *et al.* reported a relevant two-step enantio-convergent procedure, which includes a reagent-controlled reaction[38]. In our reaction, the single catalytic reaction promotes the reagent-controlled enantioselective addition and the elimination of the stereogenic leaving groups.

In summary, we have presented the first direct chemical enantio-convergent transformation promoted by an artificial catalyst without a racemization or symmetrization process. The known

dynamic processes (for example, DKR and DYKAT) require racemization or symmetrization of the substrates or the intermediates and can thus only treat 'labile' racemates. In contrast, the present reaction can access racemates with structural features that are not suitable for racemization or symmetrization. Reaction of such 'robust' racemic compounds with a chiral catalyst usually results in kinetic resolution because the substrate-controlled stereoselectivity and reagent-controlled enantioselectivity of the catalyst are in conflict with the conversion of the less reactive substrate enantiomer. In our direct enantio-convergent reaction, convergence of both substrate enantiomers into the single chiral product is enabled because of the decisive superiority of reagent-controlled enantioselectivity over substrate-controlled stereoselectivity. Although the present reaction is effective on rather limited substrates, we believe that our study provides a novel principle for the development of chemical enantio-convergent reactions for the robust racemates that cannot be treated by known dynamic methods.

Methods

In a nitrogen-filled glove box, copper(I) *tert*-butoxide (3.4 mg, 0.025 mmol), the ligand **2** (0.025 mmol) and bis(pinacolato)diboron **3** (190 mg, 0.75 mmol) were placed into a vial and mixed with dry diethyl ether (0.5 ml) with stirring. After being sealed with a rubber septum, the reaction vial was removed from the glovebox and connected to an argon line through a needle. Allylic ether **1** (0.5 mmol) was added dropwise to the mixture at 30 °C. After the reaction was complete, the reaction mixture was directly subjected to column chromatography (SiO_2, hexane:diethyl ether = 100:0–99.0:1.0) to give the crude allylboronate **4** as a colourless oil. The yield was estimated by ^{1}H NMR using mesitylene as the internal standard.

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Author contributions

H.I. directed this study. Experiments were carried out by S.K. and H.I. Density functional theory calculations (Supplementary Information) were carried out by H.I. M.S. gave comments on the reaction mechanism and the preparation of the enantio-enriched starting materials.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/. Correspondence and requests for materials should be addressed to H.I.