nature communications

Article

https://doi.org/10.1038/s41467-025-61726-w

Diastereoselective synthesis of multi-substituted cyclobutanes via catalyst-controlled regiodivergent hydrophosphination of acyl bicyclobutanes

Received: 7 February 2025

Accepted: 1 July 2025

Published online: 18 July 2025

Check for updates

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Although ring-opening reactions of bicyclo[1.1.0]butanes (BCBs) provide a reliable platform for synthesizing functionalized cyclobutanes, current methods frequently encounter challenges such as poor diastereoselectivity, regioselectivity issues, and a lack of α- and β'-selective transformations. Herein, we report a catalyst-controlled, regiodivergent α- and β'-selective hydrophosphination of acyl BCBs, which expands the chemical space of tertiary phosphines with multi-substituted cyclobutane backbones derived from identical starting materials. Utilizing a Cu(I) catalytic system, we achieve an α-selective nucleophilic addition to 1,3-disubstituted BCBs. This reaction exhibits a broad substrate scope under mild conditions, yielding valuable 1,1,3-functionalized cyclobutanes predominantly as single diastereoisomers. In contrast, the unusual β'-selective pathway facilitated by a Cu(II) catalytic system produces 1,2,3-trisubstituted variants with up to >20:1 *d.r.* The developed method holds promise for accessing structurally diverse cyclobutanes with potential applications in medicinal chemistry and the design of organophosphorus catalysts.

Controlling the selectivity of reactions is a primary goal in the field of synthetic organic chemistry. Among them, controllable regiodivergent synthesis is particularly appealing yet challenging, as it provides a unique platform for obtaining diverse products through regioselective functionalization of the same functional group in identical starting materials[1–4]. Multi-substituted cyclobutanes, especially the 1,1,3- and 1,2,3-functionalized variants, are essential components of various biologically active molecules. These molecules demonstrate significant pharmaceutical activities, including antidopaminergic effects, as well as antiviral and anticonvulsive properties (Fig. 1a)[5–8]. Furthermore, they could also be employed as conformationally restricted bioisosteres for flexible ethyl or propyl linkers[9]. Although many state-of-the-art strategies, such as [2 + 2] cycloadditions[10,11], ring contractions[12,13], ring expansions of cyclopropanes[14], and functionalization of existing four-membered ring substrates[15–18], have been developed, constructing multi-substituted cyclobutane frameworks with high stereoselective control remains a significant challenge. This difficulty arises from the inherent ring strain and congested environment compared to their five- and six-membered congeners[19–23]. Therefore, developing a highly selective and divergent synthesis strategy to expand the chemical space of multi-substituted cyclobutanes from the same starting materials is of significant interest and importance.

Bicyclo[1.1.0]butanes (BCBs) represent one of the most intriguing classes of "spring-loaded" reagents[24–30], capable of being ring-opened by various nucleophiles[31–36], electrophiles[37,38], as well as by radicals[39–42].

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https://doi.org/10.1038/s41467-025-61726-w

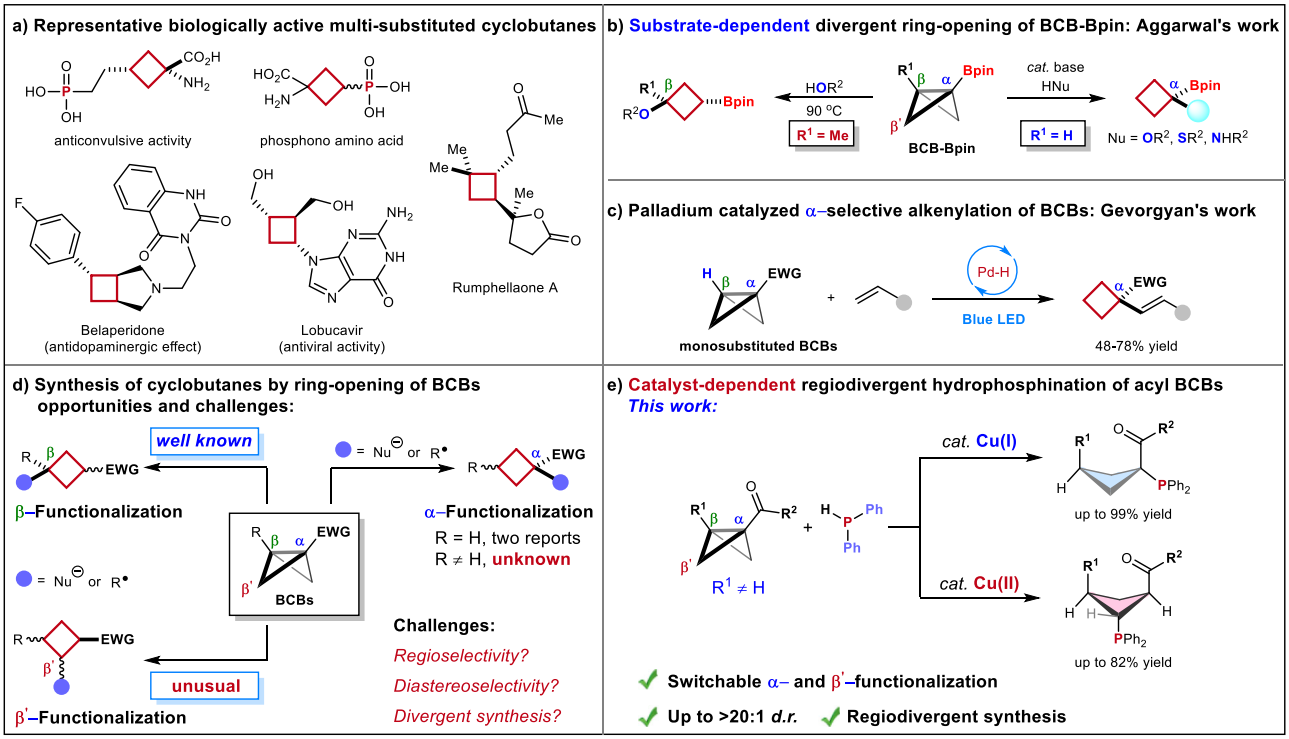

Fig. 1 | Outline of this work. a Representative biologically active multi-substituted cyclobutanes. **b** Substrate-dependent divergent ring-opening of BCB-Bpin. **c** Palladium catalyzed α-selective alkenylation of BCBs. **d** Synthesis of cyclobutanes by ring-opening of BCBs. **e** Catalyst-dependent regiodivergent hydrophosphination of acyl BCBs.

Following Baran's fundamental work on strain-release amination in 2016[43], the ring-opening reaction of BCBs has been revived as a reliable synthetic toolkit for functionalized cyclobutanes. The highly strained, "bent" central σ-bond in BCBs can participate in conjugation, enabling BCBs substituted with electron-withdrawing groups (EWGs) to function as electrophiles in Michael-type additions or as radical acceptors in Giese reactions. Consequently, β-selective heterolytic and homolytic ring-opening processes involving BCBs have been extensively developed and are now well-established[30]. For instance, Wipf conducted pioneering research on the base-promoted β-selective phosphination of BCB nitriles using phosphine boranes or *H*-phosphonates. However, similar to most β-selective ring-opening reactions of BCBs, this reaction suffers from low diastereoselectivity (1.1:1 to 3.3:1)[44]. In contrast, α-selective ring-opening process of BCBs is rare. In 2021, Aggarwal group developed α-selective ring-opening reactions of BCBs with a variety of *O*-, *S*-, and *N*-nucleophiles[45]. The application of monosubstituted bicyclo[1.1.0]butyl boronic ester (BCB-Bpin) to form a boronate complex with nucleophiles is essential for enabling a consecutive 1,2-migration process, thereby achieving exclusive α-selectivity. When 1,3-disubstituted BCB was employed as the substrate, only the β-functionalized cyclobutane product was produced (Fig. 1b). Subsequently, Gevorgyan reported an elegant palladium hydride-enabled regioselective hydroalkenylation of monosubstituted BCBs, leading to α-alkenylated 1,1-disubstituted cyclobutanes (Fig. 1c)[46]. Complementary to the aforementioned two impressive studies, we have recently accomplished the α-selective radical addition to acyl bicyclobutanes, which facilitates the synthesis of cyclobutene products[47]. Although progress has been made, several challenging issues related to ring opening of BCBs remain (Fig. 1d): (1) How to achieve α-selective ring-opening reactions of 1,3-disubstituted bicyclo[1.1.0]butanes (BCBs) for the synthesis of valuable 1,1,3-trisubstituted cyclobutanes with high diastereoselectivity? (2) How to achieve regiodivergent ring-opening functionalization of BCBs to rapidly expand the chemical space of multi-substituted cyclobutanes derived from the same starting materials. (3) Due to the presence of a fragile central C–C bond, nearly all BCB ring-opening reactions result in the formation of new bonds with the bridgehead carbon of BCB. The ring-opening β'-selective functionalization of BCBs[48], which generates 1,2,3-functionalized cyclobutanes, is rare and is limited to the cyclization of BCBs as reported by Glorius[49,50].

Recently, strain-release-driven hydrophosphination reactions have garnered considerable attention in organic synthesis[51–54]. This approach is highly valued for its atom-economical and streamlined nature, enabling the construction of organophosphorus architectures that feature cyclopropane[55–58], cyclobutane[44,59], and bicyclo[1.1.1]pentane backbones[60–63]. Motivated by these advancements, we herein report a catalyst-controlled, switchable unusual α- and β'- phosphination of acyl bicyclobutanes. This method effectively addresses the three aforementioned challenges associated with BCB ring-opening reactions (Fig. 1e).

Results

Reaction optimization

We initiated our investigation using BCB ester **1a** as the model substrate and diphenyl phosphine (**2**) as the nucleophile for the ring-opening reaction (Table 1). We tested various transition metal catalysts, including MgI_2, $ZnCl_2$, and copper salts (Table 1, entries 1–7; See the Supplementary Tables 1, 2 for the complete set of data). In contrast to Wipf's β-selective phosphination of BCB[44], the model reaction unexpectedly yielded α-phosphanyl-substituted cyclobutyl ester **3a** without the use of a base. While monovalent copper catalysts, including CuI, CuBr and $Cu(CH_3CN)_4PF_6$ (entries 3–4 and 6), as well as the divalent copper salt $Cu(OAc)_2$ (entry 7), afforded the cyclobutyl phosphine product **3a** with low to moderate diastereoselectivity, the use of CuCl as the catalyst exclusively produced the desired product with a 95% yield and a diastereomeric ratio (*d.r.*) of 16:1 (entry 5). A range of solvents were evaluated, among which tetrahydrofuran, an ether-type solvent, and toluene, a nonpolar solvent, exhibited superior performance in terms of both yield and selectivity (entry 5 and entries 11–13). While the addition of Cs_2CO_3 resulted in a slight decrease in

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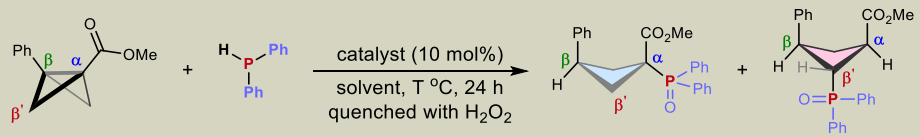
Table 1 | Optimization of the reaction conditions[a]



1a 2 3a 4a

Entry	Catalyst	Solvent	T (°C)	3a Yield (%)[b]	3a d.r.[c]	4a Yield (%)[b]	4a d.r.[c]
1	MgI_2	THF	25	17	7:1	<5	–
2	$ZnCl_2$	THF	25	23	2:1	0	–
3	CuI	THF	25	80	3:1	0	–
4	CuBr	THF	25	78	4:1	<5	–
5	CuCl	THF	25	95	16:1	0	–
6	$Cu(CH_3CN)_4PF_6$	THF	25	92	6:1	0	–
7	$Cu(OAc)_2$	THF	25	81	3:1	0	–
8	CuF_2	THF	25	38	1:1	10	2:1
9	$CuCl_2$	THF	25	49	5:1	38	6:1
10	$CuBr_2$	THF	25	17	2:1	44	7:1
11	CuCl	toluene	25	90	18:1	0	–
12	CuCl	CH_2Cl_2	25	97	6:1	0	–
13	CuCl	MeOH	25	50	15:1	0	–
14	CuCl	THF	25	93	12:1	0	–[d]
15	CuCl	THF	60	97	>20:1	0	–
16	–	THF	25	0	–	0	–
17	–	THF	60	22	–	0	–[e]
18	$CuBr_2$	toluene	25	9	4:1	33	3:1
19	$CuBr_2$	CH_2Cl_2	25	12	2:1	15	2:1
20	$CuBr_2$	DMSO	25	24	2:1	64	3:1
21	$CuBr_2$	DMA	25	19	1:1	56	4:1
22	$CuBr_2$	DMF	25	13	2:1	55	12:1
23	$CuBr_2$	DMF	25	26	3:1	69	6:1[f]
24	$CuBr_2$	DMF	25	64	15:1	36	9:1[g]
25	$CuBr_2$	DMF	25	8	1:1	70	9:1 [f,h]
26	$CuBr_2$	DMF	60	16	1:1	78	>20:1[f,h]

[a]**1a** (0.2 mmol), **2** (0.24 mmol) and catalyst (10 mol%) in solvent (2.0 mL) stirred at T °C for 24 h, then quenched with H_2O_2.
[b]Combined NMR yield determined by ^{1}HNMR spectroscopy with CH_2Br_2 as an internal standard.
[c]Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product.
[d]Cs_2CO_3 (0.5 equiv) was added.
[e]The reaction mixture was stirred at 60 °C for 48 h.
[f]**1a** (0.2 mmol) and **2** (0.4 mmol) were used.
[g]**1a** (0.4 mmol) and **2** (0.2 mmol) were used.
[h]LiBr (1.0 equiv) was added.

yield and diastereoselectivity (entry 14), elevating the reaction temperature to 60 °C was found to effectively enhance both the yield and diastereomeric ratio of the product (entry 15). Control experiments demonstrated that the desired product was undetectable by ^{1}H NMR spectroscopy when the reaction was conducted at room temperature (entry 16), whereas a 22% yield of the desired diastereoisomer of **3a** was observed when the reaction was performed at 60 °C for 48 h (entry 17). Eventually, a 97% NMR yield of product **3a**, a *d.r.* value exceeding 20:1, and exclusive α-selectivity were achieved under optimal conditions A: the reaction of BCB (1.0 equiv), diphenyl phosphine (1.2 equiv), in the presence of CuCl (10 mol%), in THF at 60 °C (entry 15). To our surprise, during the screening of copper catalysts, we observed that the presence of copper(II) halides in the current ring-opening reaction resulted in the formation of both α-phosphinated product **3a** and β'-phosphinated product **4a** (entries 8–10). In comparison to nonpolar solvents (e.g. toluene), halogenated solvents (e.g. CH_2Cl_2), and polar protic solvents (e.g. MeOH), the polar aprotic solvents such as DMSO, DMA, and DMF yielded a higher amount of product **4a** (entries 18–22). Altering the stoichiometry of substrates **1a** and **2** has substantially influenced the distribution of products (entry 23 *versus* entry 24). After further optimization of additives and reaction temperature (entries 25–26), the desired β'-phosphinated product **4a** was obtained in 78% NMR yield with >20:1 *d.r.* (entry 26). The reaction employed substrates **1** (1.0 equiv) and diphenyl phosphine (2.0 equiv), $CuBr_2$ (10 mol%) as the catalyst, and LiBr as the additive in DMF at 60 °C (conditions B).

Substrate scope

With the optimized conditions in hand, we first investigated the generality of this protocol for constructing trans-1,1,3-trisubstituted cyclobutanes via the α-selective ring-opening reaction of BCBs, and the results are summarized in Fig. 2. The variation in ester groups, including methyl (**3a**), ethyl (**3b**), benzyl (**3 d**), phenyl (**3e**), and the

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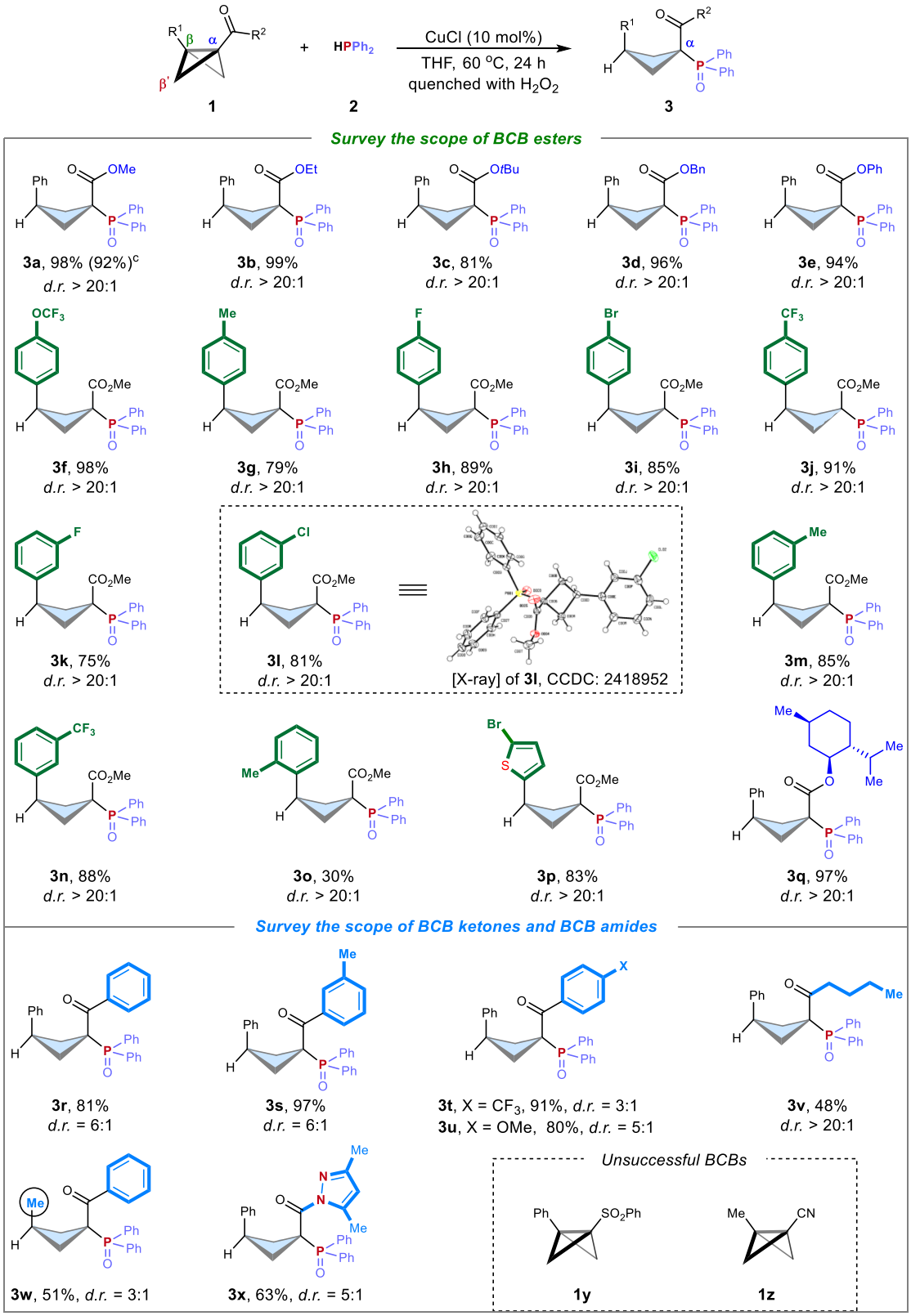

Fig. 2 | Construction of phosphine-containing 1,1,3-trisubstituted cyclobutane scaffolds[a,b]. [a]Conditions A: 0.2 mmol BCB 1, 1.2 equiv. diphenyl phosphine, and 10 mol% CuCl in 2.0 mL THF at 60 °C for 24 h. [b]Isolated yield. [c]1.0 mmol scale.

sterically hindered *tert*-butyl (**3c**), led to the formation of the corresponding cyclobutylated products with excellent yields (81–99%) and diastereoselectivity (>20:1). Notably, the scale-up synthesis of **3a** (1.0 mmol) was performed almost without loss of efficiency and selectivity (92% yield, *d.r.* > 20:1). Both *para*- and *meta*-substituted aryl moieties were smoothly engaged in the ring-opening reaction, yielding the expected products (**3f**–**3n**) with good yield. Notably, BCBs bearing electron-donating (e.g. methyl group) and electron-withdrawing (e.g. CF_3 group) bridgehead aryl substituents afforded the corresponding cyclobutanes **3g** and **3j** in yields of 79% and 91%, respectively. The

experimental results indicated that the current α-selective ring-opening reaction may occur without the formation of a benzyl cation intermediate. The structure and relative stereochemistry of **3l** were unambiguously determined by X-ray crystallography analysis. The BCB substrate containing a substituent at the *ortho* position of the phenyl group was tolerated, although it resulted in a lower yield (**3o**). In addition, not only the phenyl moiety but also the 2-thienyl derived BCB (as in **3p**) produced the expected product with a high yield and excellent diastereomeric ratio (>20:1). BCB **1q**, derived from the natural product *L*-menthol, furnished the desired phosphine **3q** in 97% yield. Besides BCB esters, the substituted phenyl BCB ketones (**3r**–**3u**) reacted efficiently with diphenyl phosphine (**2**) to yield the corresponding products in satisfactory yields ranging from 80% to 97%, although with moderate d.r. values. The alkyl-substituted BCB ketone is a suitable substrate for the selective formation of the desired phosphine **3v** with >20:1 d.r. The methylsubstituted phenyl BCB ketone also exhibited smooth reactivity, yielding 51% of product **3w** under the conditions A. While the BCB amide substrate (**1x**) is suitable for this reaction, BCB substrates modified with sulfonyl (**1y**) and nitrile (**1z**) groups are incompatible with the α-selective ring-opening reaction.

In parallel, the β′-selective functionalization of BCBs was employed to synthesize phosphines containing 1,2,3-trisubstituted cyclobutane scaffolds (Fig. 3). The regio- and diastereoselective ring-opening reaction was not restricted to methyl ester-derived BCBs; ethyl (as in **4b**), *tert*-butyl (as in **4c**), benzyl (as in **4d**) and phenyl (as in **4e**) substituted BCB esters also produced the target products in good yields and excellent *d.r.* value. The molecular connectivity of **4e** has been confirmed by X-ray crystallographic analysis. Notably, the reaction between **1a** and **2a** could be scaled up to yield **4aa** at 72% efficiency using 1.0 mmol of **1a**. Aryl-substituted BCB ester **1d** successfully yielded phosphine **4d**, whereas BCB **1bb**, which contains a methyl group in the β-position of the BCB, did not produce the desired product. This emphasizes the critical role of the β-phenyl ring in the ring-opening reaction. BCBs, which contain various substituents including OCF_3 (**4f**), alkyl groups (methyl in **4g**), and halogen groups (4-F in **4h**, 4-Br in **4i**, 3-F in **4k**, 3-Cl in **4l**), at the *meta*- or *para*-position of the phenyl ring, are compatible with standard conditions B. These reactions yielded the corresponding phosphines with moderate to good yields and excellent stereoselectivity. For BCB substrates **1j** and **1m**, lower reaction temperature (25 °C) are necessary to achieve improved diastereoselectivity. As a trend, BCBs bearing electron-rich aryl substituents generally afforded the corresponding products in higher yields compared to those with electron-poor aryl substituents (**4g** *versus* **4j**; **4m** *versus* **4n**). Moreover, the BCB ester containing a 2-thienyl group yielded the desired product **4p** at a 50% yield as a single diastereoisomer. The use of *L*-menthyl as a chiral auxiliary resulted in the formation of the desired chiral phosphine **4q**, containing six chiral carbon centers, in 75% yield. Furthermore, the substituents at the *meta*- and *para*-positions of the phenyl ring in BCB ketones were systematically examined, and each successfully delivered the desired β′-ring-opening products (**4r**–**4u**) while maintaining high diastereoselectivity. Notably, BCB amide (**1aa**) was found to be compatible with this reaction system, affording the cyclobutane product (**4aa**) in 74% yield with excellent diastereoselectivity. In contrast, BCB derivatives containing an acyl pyrazole unit (**1x**) or a sulfonyl group (**1y**) failed to undergo the desired ring-opening process.

Synthetic applications & proposed mechanism

To demonstrate the practical applicability of this methodology in expanding the chemical diversity of organophosphines, we performed a series of transformations on the ring-opening products (Fig. 4). Due to the oxygen sensitivity of the phosphine group in the ring-opening product, $Me_2S{\bullet}BH_3$ and S_8 were introduced during the work-up phase, respectively, to form the corresponding phosphine-borane complexes (**5** and **6**) and phosphine sulfides (**7** and **8**) in a one-pot sequence. The cyclobutane-derived phosphine-borane **6** can also be efficiently prepared through the reduction of phosphine oxide **4a**. The treatment of compounds **3a, 4a, 5**, and **6** with $LiBH_4$ effectively reduced the ester groups, resulting in the formation of the corresponding primary alcohols **24, 21, 9**, and **18**. The Swern oxidation of compound **9** afforded the corresponding aldehyde **10** in 80% yield. The reaction of **3a** with Grignard reagent afforded tertiary alcohol **25** in quantitative yield and unharmed *d.r.* value. Hydrolysis of **3a** and **4a** produced the corresponding carboxylic acids **26** and **22**, with yields of 86% and 95%, respectively. This result facilitates subsequent esterification. For instance, the distinctive cyclobutyl phosphine scaffold can be integrated into bioactive molecules, such as estrone (**22** → **23**), and chiral urea catalysts (**26** → **27**). Phosphine-nitrogen-based ligands, particularly phosphine oxazolines, represent a versatile class of ligands that have been widely employed in various transition-metal-catalyzed asymmetric reactions[64]. While phosphines incorporating cyclopentane or cyclohexane backbones are commonly utilized in ligand design, phosphine ligands featuring a cyclobutane backbone are relatively rare. This may be due to the challenges associated with their synthesis. Therefore, an efficient mothod was developed for the synthesis of phosphine oxazoline ligands with multisubstituted cyclobutane backbones (**26** → **28** and **29**). The deprotection of compounds **6** and **9** with diethylamine effectively removed the borane groups, affording the free tertiary phosphines **15** and **11** in quantitative yields. The transformation of tertiary phosphines to iminophosphoranes (**13** and **16**), as well as phosphonium methyl iodides (**14** and **17**), is also feasible. Notably, based on the current selective ring-opening reaction, the synthesis of diphosphine ligands containing cyclobutyl phosphine scaffolds has been achieved, as exemplified by the efficient synthesis of compound **19** and chiral diphosphine ligand **12**. Compound **19** was treated with $CpRuCl(PPh_3)_2$ to yield ruthenium complex **20** with a 60% yield. Moreover, ligand **19** demonstrated efficacy in the palladium-catalyzed hydroamidation of isoprene[65]. The preliminary application of chiral diphosphine ligand **12** in asymmetric catalysis was explored through a palladium-catalyzed enantioselective allylic alkylation reaction, yielding the corresponding product **37** with 67% *ee* (Fig. 5). The aforementioned results highlight the potential of regiodivergent hydrophosphination of BCBs as a strategy for designing new phosphine ligands and advancing asymmetric catalysis.

To gain insight into this transformation, we conducted a series of control experiments designed to probe the reaction pathway. Initially, radical quenching experiments were conducted by introducing various radical inhibitors, specifically 2,6-*di*-*tert*-butyl-4-methylphenol (BHT) and 1,1-diphenylethylene, into the α-phosphination reaction system under controlled conditions. The addition of these scavengers had a minimal impact on the progression of the reaction, suggesting that a radical pathway may not be involved in this process. In contrast, when BCB **1a** was treated with diphenyl phosphine (**2**), LiBr, and $CuBr_2$ in the presence of BHT or 1,1-diphenylethylene at room temperature, the yield and diastereomeric ratio of **4a** decreased; however, the yield of **3a** increased (Fig. 6a). Furthermore, no corresponding radical trapping products were detected by ^1H NMR and HRMS.

Heating BCB **1a** in THF for 24 h in the presence of CuCl did not yield cyclobutene **38a**. In contrast, mixing BCB **1a** with $CuBr_2$ in DMF at room temperature resulted in the isomerization of **1a** to cyclobutene **38a**, achieving a 27% NMR yield. The yield of cyclobutene can be enhanced to 70% through the addition of LiBr (Fig. 6b). These results prompt an investigation into whether cyclobutene **38a** serves as the key intermediate for the synthesis of the current cyclobutylphosphine products. The CuCl-catalyzed hydrophosphination of cyclobutene did not produce the product **3a**; however, it yielded **4a** with 40% NMR yield and >20:1 diastereomeric ratio. A comparable phenomenon was observed when $CuBr_2$ was employed as a catalyst (Fig. 6c). Under

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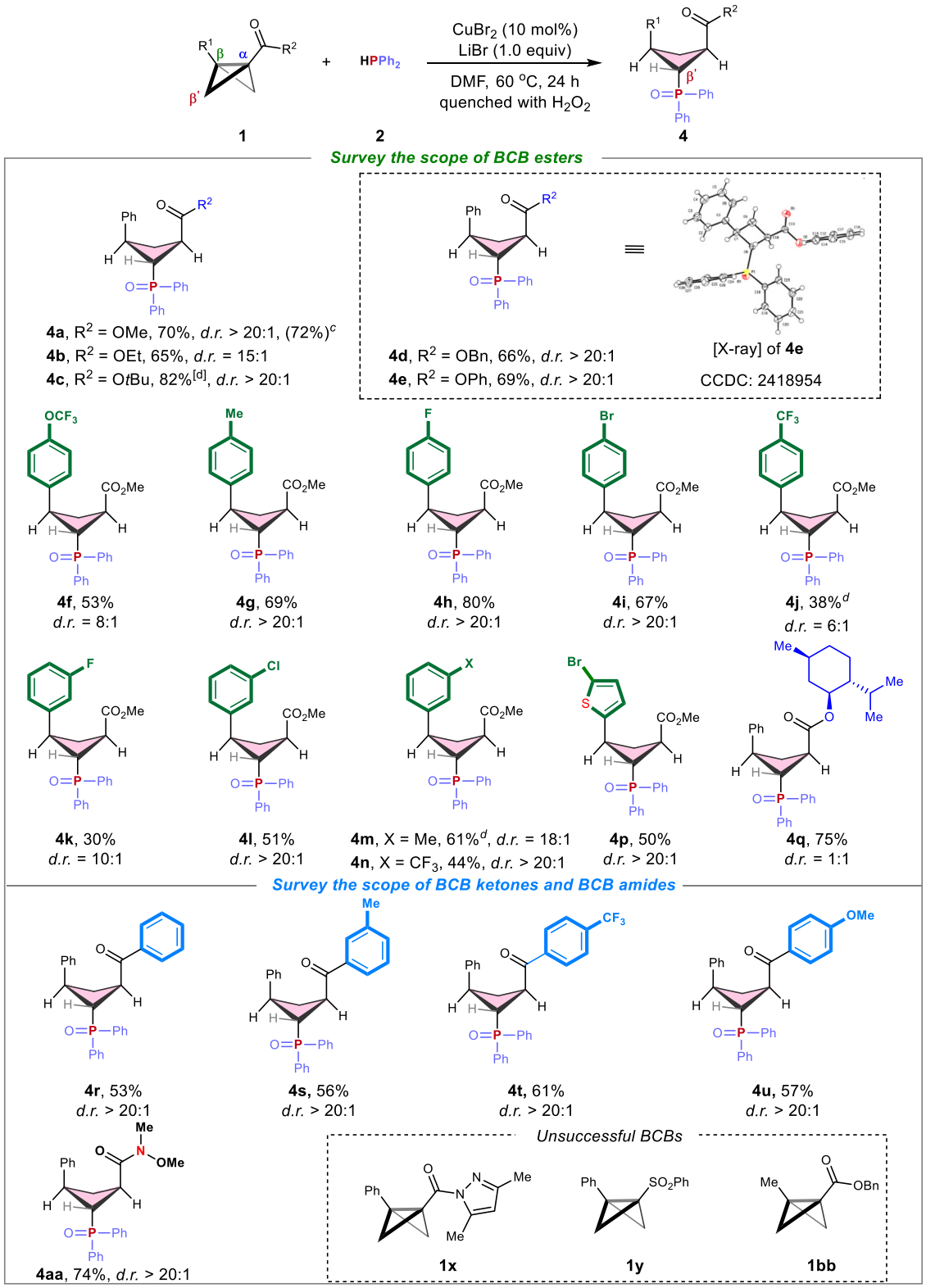

Fig. 3 | Construction of phosphine-containing 1,2,3-trisubstituted cyclobutane scaffolds[a,b]. [a]Conditions B: 0.2 mmol BCB **1**, 2.0 equiv. diphenyl phosphine, 1.0 equiv. LiBr and 10 mol% $CuBr_2$ in 2.0 mL DMF at 60 °C for 24 h. [b]Isolated yield. [c]1.0 mmol scale, **4a**: *d.r.* = 15:1.[d]Run at 25 °C.

standard conditions A and B, the hydrophosphination of monosubstituted BCB ketone regioselectively yielded the 1,3-disubstituted cyclobutane **40**, while the corresponding α- or β′-phosphinated cyclobutane products were not detected (Fig. 6d).

Based on the experimental results presented above and previous studies on copper-catalyzed hydrophosphination reactions[57,58], we propose a possible mechanism for the selective ring-opening reaction of **1** with **2**, as illustrated in Fig. 7. Initially, the diarylphosphorus group is transferred to the copper(I) catalyst, resulting in the formation of a nucleophilic copper(I)-diphenylphosphide intermediate (**INT-I**). Subsequently, this intermediate **INT-I** coordinates with acyl bicyclobutane **1** to generate the intermediate **INT-II**. When R^1 is hydrogen (R^1 = H),

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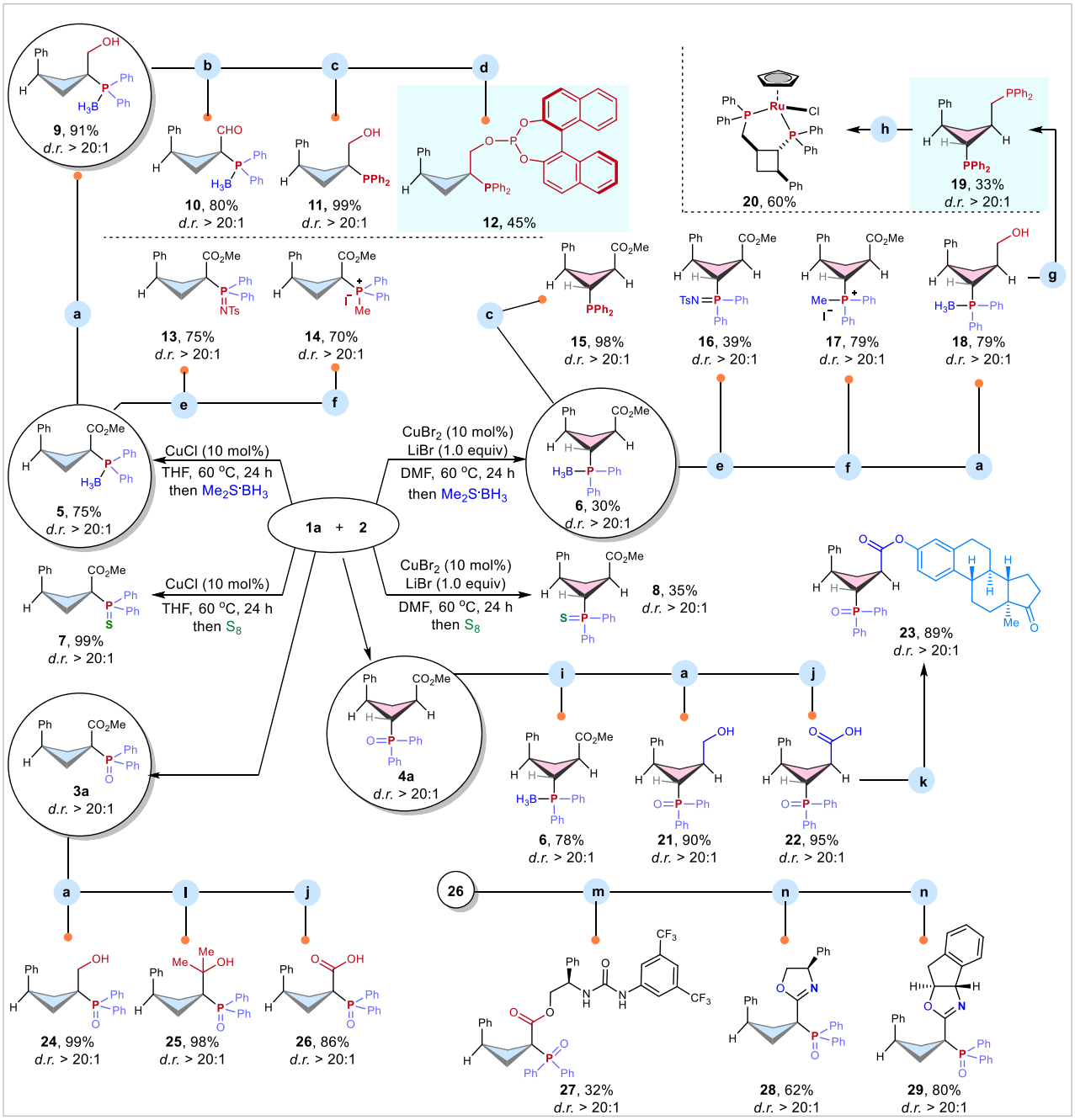

Fig. 4 | Synthetic transformation. a $LiBH_4$, THF. **b** Oxalyl dichloride, DMSO, Et_3N, CH_2Cl_2, −78 °C. **c** Et_2NH, 65 °C. **d** (1) Et_2NH, 65 °C; (2) (*S*)-BINOL, PCl_3, DMAP, Et_3N. **e** Et_2NH then TsN_3. **f** Et_2NH then MeI. **g** (1) PPh_3, CBr_4, CH_2Cl_2, 0 °C to RT; (2) Ph_2PH, *n*BuLi, THF, −78 °C to RT; (3) Et_2NH, 65 °C. **h** $CpRuCl(PPh_3)_2$, toluene, 90 °C. **i** $Cu(OTf)_2$, TMDS, toluene then $Me_2S{\cdot}BH_3$. **j** LiOH, THF/H_2O. **k** Estrone, EDC·HCl, DMAP, DMF. **l** MeMgBr, THF, RT. **m** (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-hydroxy-1-phenylethyl)urea, DMAP, EDC·HCl, Et_3N, CH_2Cl_2. **n** (1) oxalyl dichloride, DMF, CH_2Cl_2; (2) Amino alcohol, Na_2CO_3, CH_2Cl_2; (3) TsCl, Et_3N, CH_2Cl_2.

a β-selective nucleophilic addition occurs, followed by protonolysis with HX present in the system. This sequence of events leads to the formation of 1,3-disubstituted cyclobutane **40′** and concomitantly regenerates the original copper catalyst. However, when a sterically hindered group is present at the β-position of BCB **1**, the transition state for the α-selective ring-opening pathway (**TS-II**) is favored. This preference arises due to steric repulsion from the R^1 substituent (**TS-I**) as the diarylphosphorus group on the copper atom approaches the β-position of the BCB **1**. Consequently, the ring-opening reaction proceeds with exclusive α-selectivity, yielding 1,1,3-trisubstituted cyclobutane **3′**.

Regarding the β′-selective ring-opening functionalization of BCBs, the divalent copper salt $CuBr_2$ was employed as a catalyst, which facilitated the Lewis-acid-catalyzed isomerization of BCBs and led to the formation of cyclobutenes **38** through the carbocation species **INT-IV**[37,66,67]. Stabilization of the carbocation intermediate via an aryl group (R^1 = aryl) through resonance facilitates the subsequent intramolecular E1 elimination. In the presence of $HPPh_2$, the copper(II) salts can be reduced to copper(I), which serves as the active catalyst[68,69]. LiBr can act as a mediator to facilitate the reduction of divalent copper salt[70]. Subsequently, 1,2,3-trisubstituted cyclobutane **4′** is generated through a copper(I)-catalyzed regioselective hydrophosphination of cyclobutene.

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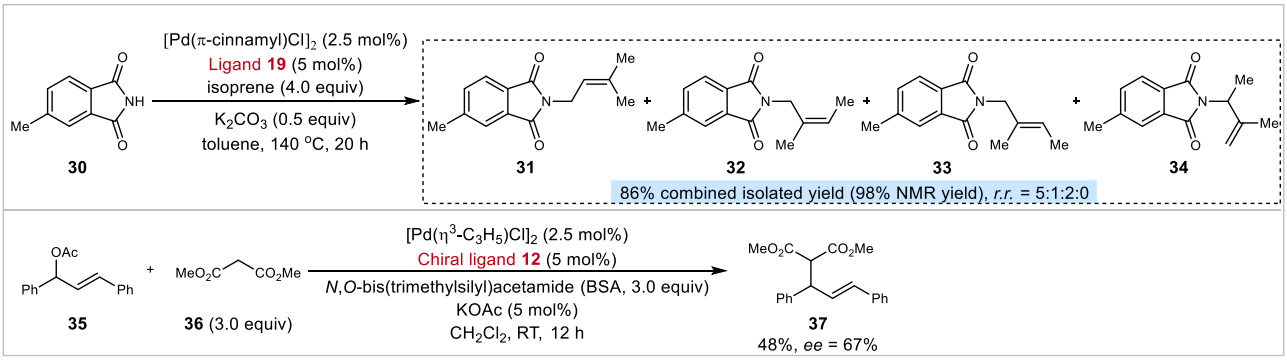

Fig. 5 | Applications of new phosphine ligands. Compounds **12** and **19**, serving as novel phosphine ligands, are applied to the palladium-catalyzed hydroamidation of isoprene and the enantioselective allylic alkylation reaction.

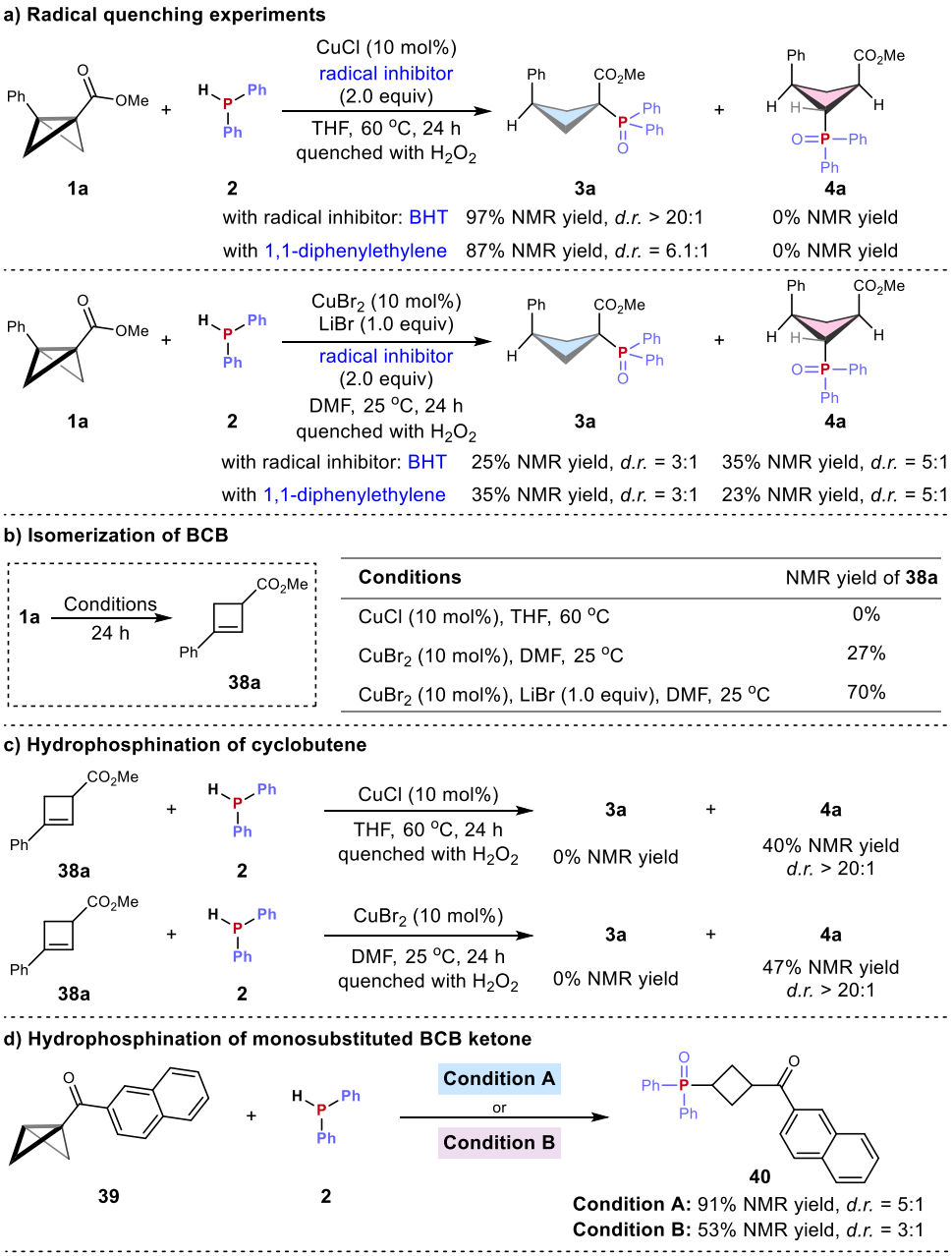

Fig. 6 | Control experiments. a Radical quenching experiments. **b** Isomerization of BCB. **c** Hydrophosphination of cyclobutene. **d** Hydrophosphination of monosubstituted BCB ketone.

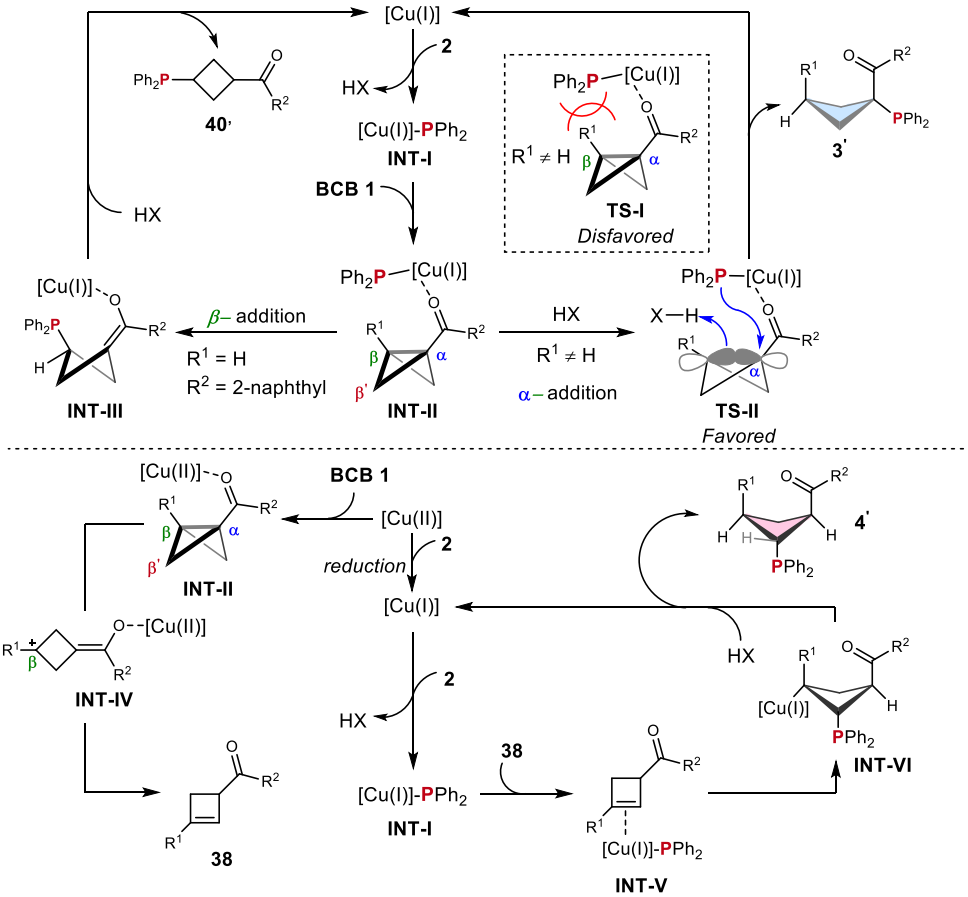

Fig. 7 | Proposed mechanism. BCBs undergo α-, β, and β′-selective ring-opening reactions with $HPPh_2$ under copper catalysis.

Discussion

In conclusion, we report a catalyst-controlled regiodivergent synthesis of multi-substituted cyclobutanes from BCBs. By modulating the catalytic system with varying copper oxidation states, we have achieved precise control over the regioselective ring-opening pathways of acyl BCBs. The α-selective hydrophosphination pathway delivers 1,1,3-trisubstituted cyclobutane-derived phosphines, while the unusual β′-selective process affords 1,2,3-trisubstituted variants, both with excellent regio- and diastereoselectivity control (up to >20:1 *d.r.*). This strategy addresses long-standing challenges in BCB chemistry, including the limited availability of α-selective transformations for 1,3-disubstituted BCBs and the rarity of β′-selective functionalization. Moreover, the reaction system demonstrates good functional group tolerance, underscoring its robustness and versatility. The scalability of the process, along with the successful derivatization of products, particularly facilitates the preparation of new phosphine ligands that incorporate cyclobutane frameworks and allow for late-stage modification of bioactive compounds. The (chiral) diphosphine ligands, synthesized through the divergent hydrophosphination of BCBs, have shown promising potential in regioselective reactions and asymmetric catalysis. This further emphasizes the practical utility and synthetic value of the protocol. This divergent ring-opening phosphination strategy for BCBs paves the way for the development of innovative methodologies aimed at the selective synthesis of valuable cyclobutane derivatives and tertiary phosphine compounds.

Methods

General procedure for the α-selective ring-opening functionalization of BCBs

Under an atmosphere of N_2, to a 25 mL oven-dried Schlenk tube were added BCBs 1 (0.20 mmol, 1.0 equiv), CuCl (2.0 mg, 0.020 mmol) and diphenylphosphane (44.7 mg, 42 µL, 0.24 mmol, 1.2 equiv), followed by 2.0 mL of anhydrous THF. The mixture was stirred at 60 °C for 24 h. Upon cooling to room temperature, the reaction was quenched with H_2O_2 (0.10 mL, 30% w/w) and stirred for an additional 1 h. The reaction mixture was subsequently diluted with ethyl acetate (5 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using a CH_2Cl_2/MeOH mixture (100:1, v/v) as the eluent, yielding the desired product 3.

General procedure for the β′-selective ring-opening functionalization of BCBs

Under an atmosphere of N_2, to a 25 mL oven-dried Schlenk tube were added BCBs 1 (0.20 mmol, 1.0 equiv), $CuBr_2$ (4.5 mg, 0.020 mmol), LiBr (17.4 mg, 0.20 mmol, 1.0 equiv) and diphenylphosphane (74.5 mg, 70 µL, 0.40 mmol, 2.0 equiv), followed by 2.0 mL of anhydrous DMF. The mixture was stirred at 60 °C for 24 h. Upon cooling to room temperature, the reaction was quenched with H_2O_2 (0.10 mL, 30% w/w) and stirred for an additional 1 h. The reaction mixture was subsequently diluted with ethyl acetate (5 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using a CH_2Cl_2/MeOH mixture (75:1, v/v) as the eluent, yielding the desired product 4.

Data availability

The data supporting the findings of this study are available within this article and its Supplementary Information, which contains experimental details, characterization data, copies of NMR spectra and HPLC spectra for all new compounds, and X-ray structural analysis.

Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2418952 (**3l**) and CCDC 2418954 (**4e**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. All other data are available from the corresponding author upon request.

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Acknowledgements

We are grateful to the National Natural Science Foundation of China (22471068 for J.-J.F.) and Fundamental Research Funds for the Central Universities for financial support. 1H, 13C NMR spectra, single crystal X-ray diffraction and HRMS were performed at Analytical Instrumentation Center of Hunan University.

Author contributions

J.-J.F. conceived the study. H.-X.H. and F.W. carried out the experiments and data analysis work. K.-J.W. and L.W. synthesized the bicyclobutanes. The paper was written by J.-J.F. All authors contributed to discussions. H.-X.H. and F.W. contributed equally.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-025-61726-w.

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Peer review information *Nature Communications* thanks Jet Tsien and the other anonymous reviewer(s) for their contribution to the peer review of this work. A peer review file is available.