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Controlled semi-Pinacol rearrangement on a strained ring: Efficient access to multi-substituted cyclopropanes by group migration strategy

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ABSTRACT

We describe a versatile electrophile addition/SPR sequence of readily available cyclopropyl carbinols that affords multi-substituted carbonylated cyclopropanes with high stereo-fidelity. This approach tolerates various heteroatom electrophiles, migration of carbon moiety of all possible hybridization states, facile ring reorganization and natural compound valorization. The examples represent an unprecedented version of SPR wherein migration to a non-benzylic bulky tertiary carbo-cation is realized with promising enantiocontrol.

The cyclopropane scaffold is present in numerous bioactive natural and artificial compounds and ranks 10th in the most prevalent cyclic scaffolds of clinical drugs [1–4], of which carbonylated cyclopropane is a prominently featured subclass (Fig. 1) [5–10]. While many synthetic bioactive molecules feature sparsely-substituted cyclopropane moieties, increasing substitution at the cyclopropane scaffold have been recognized to improve their biological effects [11,12]. Despite of the numerous strategies being developed toward cyclopropane synthesis, access to stereo-defined polysubstituted cyclopropanes remains a daunting task. Traditional methods, such as metal-catalyzed olefin cyclopropanation with diazo derivatives [13–16] and Michael addition initiated ring-closure of sulfur ylides with α,β-unsaturated carbonyl compounds [17,18] usually fall short in multisubstituted cyclopropane synthesis due to increased steric-hindrance or plagued selectivity issues [19]. Transition metal-catalyzed C–H functionalization of cyclopropane backbone becomes an efficient straightforward approach [20–23]. Recent efforts in metal-catalyzed ring-retentive cyclopropene functionalization has blossomed as an exciting alternative, although available modes are limited to only a few intermediates [24]. Although exciting new strategies are being continually uncovered to address the cyclopropane synthesis [25–28], assembly of multi-substituted cyclopropanes with diverse structural patterns and defined stereocontrol remains an unsolved object.

The semi-Pinacol rearrangement (SPR) has been widely applied in the synthesis of β-functionalized ketones [29] and as key steps in natural product total syntheses (Scheme 1a) [30]. While allylic alcohol bearing substituted olefins have been intensively studied, examples of SPR on a strained ring were only reported very recently with (aza)bicyclo[1.1.0]butyl carbinols (Scheme 1b) [31,32], which are intrinsically limited to unimolecular processes, posing severe limitation to the synthetic versatility, and the intermolecular reactivity of highly strained olefins remains unestablished due to facile ring-opening [33,34].

Based on our interest in cyclopropane synthesis [35–38], we envisioned that electrophilic activation of cyclopropane carbinols, readily available from bromoalkene and an aldehyde or ketone *via* two steps, may generate highly reactive yet under-exploited cyclopropyl cation that may undergo group migration to provide an avenue to multi-substituted, carbonylated cyclopropanes, a highly useful synthetic target and an increasingly important synthon [39]. Envisioned challenges include (1) involvement of tertiary cationic centers may increase the steric hindrance and lower the driving force, and (2) the presence of multiple competing ring-opening processes involving the high-energy structures may steer the reaction away from productive migration reactivity. Herein we present the realization of this process, which can be used for late-stage cyclopropane formation, a well-known challenge in cyclopropane syntheses (Scheme 1c).

Our studies commenced by evaluating the SPR of cyclopropene carbinol **1a**, which can be readily assembled *via* a 2-step procedure from 2–bromo-2-butene, bromoform, and acetophenone. After brief optimization (Table S1 in Supporting information), we found that treatment of **1a** with 2 equiv. of PhSeBr at –40 °C in THF in the presence of 2 equiv. of 2,6-di-*tert*-butylpyridine (DTBP) afforded the phenyl migrated product **3a** facilely in 82% yield as a

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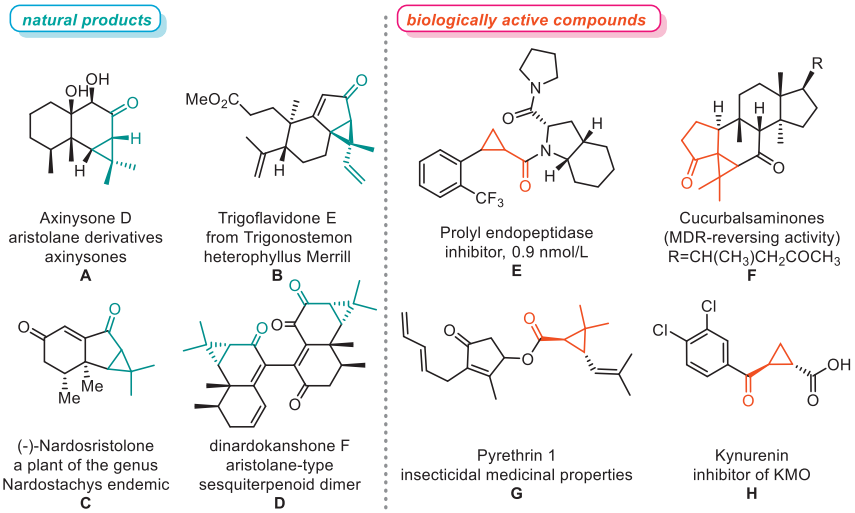
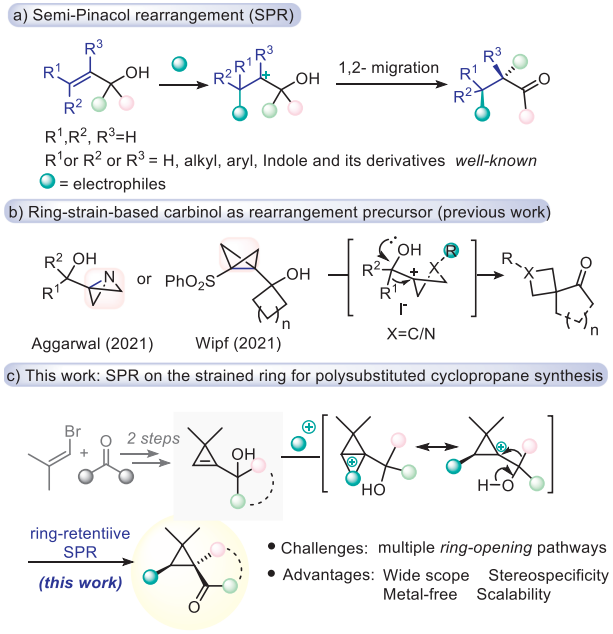


Fig. 1. The multi-substituted cyclopropane moiety: occurrence in functional molecules.



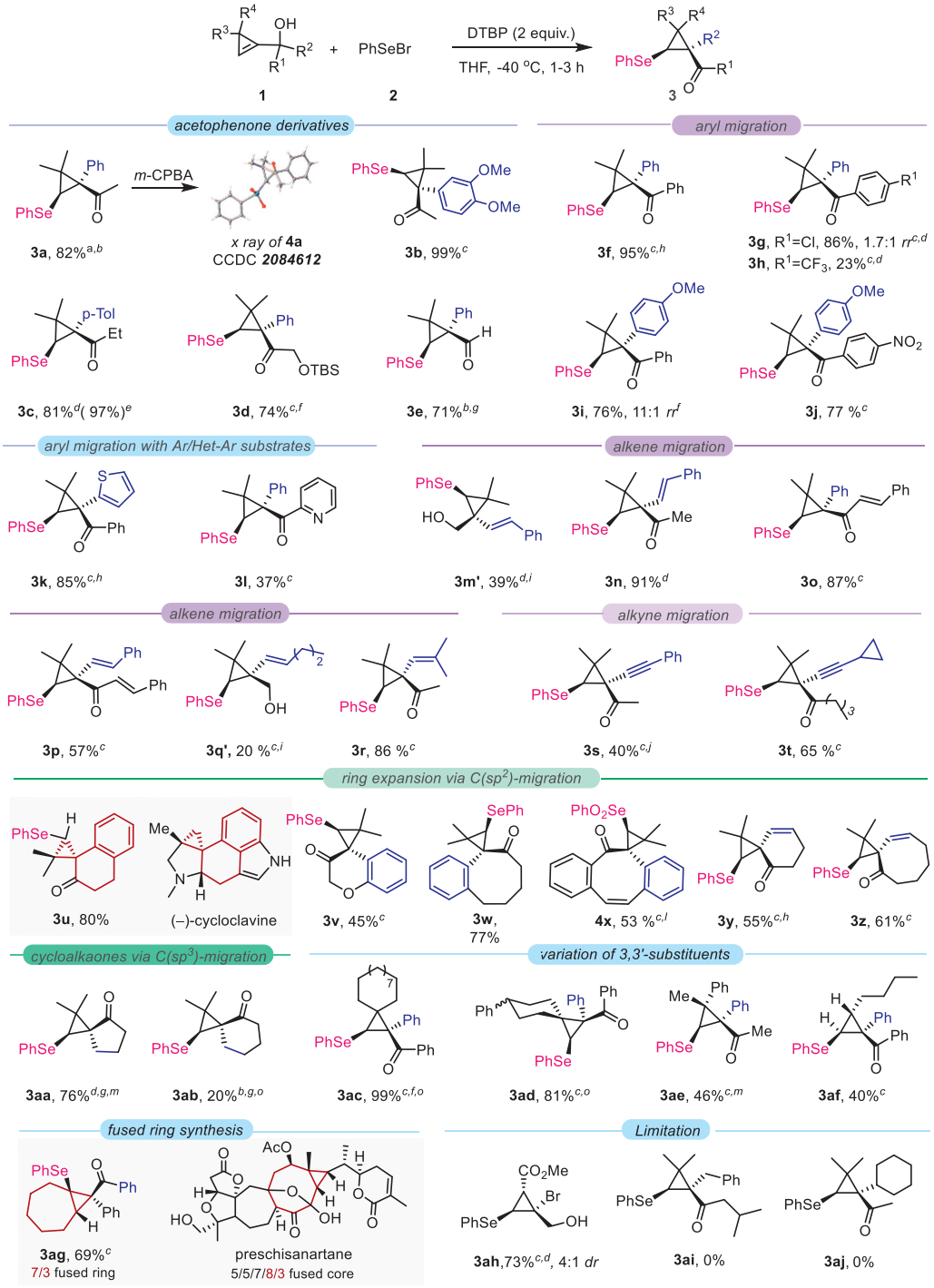
Scheme 1. Background and reaction synopsis.

single diastereoisomer, as shown in the X-ray structure of its oxidized product **4a** (Scheme 2).

We then turned to interrogate the scope of the selenylation initiated SPR (Scheme 2). Electron-rich aryls migrated efficiently (**3b** and **3c**). The reaction can be performed on a gram scale with a higher yield of **3c** (97%). Functionalities such as *tert*-butyldimethylsilyl ether and secondary alcohols are also tolerated (**3d**-**3e**). For substrates bearing tertiary allyl alcohol moieties derived from benzophenone derivatives, the more electron-rich aryl group migrated preferentially (**3f**-**3j**). Introduction of heteroaryl such as thienyl (**3k**) and 2-pyridinyl (**3l**) onto the allyl alcohols was also successful. Toleration of pyridyl moiety is noteworthy and serves as a complement for transition-metal based protocols wherein the strong coordination of pyridine is often problematic. Both cinnamaldehyde-derived secondary alcohols (**1m**) and benzylidene acetone derived tertiary alcohol substrates (**1n**) underwent the rearrangement uneventfully, despite of the lower yield of the metastable product **3m**. This problem can be solved by *in-situ* reduction with $NaBH_4$. When both aryl and styrenyl are available, aryl migration product was obtained as the sole product (**3o**). The substrate derived from dibenzylideneacetone (dba) also reacted smoothly, delivering the expected product **3p** in 57% yield. Aliphatic alkenyl group could also migrate, despite with diminished efficiency (**3q'**). Notwithstanding, trisubstituted alkene displayed higher migration aptitude, giving the target product in relatively high yield (**3r**). Migration of C_{sp} moiety was also realized (**3s** and **3t**). Cyclopropenyl carbinols derived from cyclic stocks such as 1-indanone, 3-coumaranone and 1-benzosuberone facilely delivered the ring-enlarged products **3u**, **3v** and **3w** in moderate to high yields. Notably, product **3u** shares a common tricyclic skeleton with the natural product (−)-cycloclavine. The more rigid benzocycloheptatrienone derived substrate also succumbed to facile ring-enlargement to the cyclooctenone with a spiro cyclopropane (obtained as its oxidized form **4x**). The ring-enlarged products **3y**-**3z** were also successfully obtained from aliphatic cycloalkenone derived substrates. Saturated cyclic alkenone derived substrates, as expected, are less reactive, and while **3aa** was obtained in a decent yield due to strain release, **3ab** was formed with decreased efficiency.

Variation on the cyclopropene was then scrutinized. Migration of phenyl substituents can also be easily achieved with spirocyclic substrates (**3ac**, **3ad**). 3,3-Diphenyl substituted cyclopropene is not compatible, leading to the ring-opening products, likely due to the very facile selenium-mediated deoxygenation to form the cyclopropenyl cation intermediate [40]. Nonetheless, 3-aryl-3-alkyl pattern is tolerated, and product **3ae** was obtained in a 46% yield. In addition, a linear alkyl substitution at the 3-position turned out promising (**3af**). Finally, medium ring fused cyclopropane is a frequent subunit in many natural products such as the neuroprotective preschisanartane [41]. The product **3ag** bearing a 7/3 bicyclic skeleton can be efficiently accessed. With respect to limitations, migration of $C(sp^3)$-moieties or hydride without enough strain release turned out challenging, as is also the case for SPR with a few representative substrates (**3ah**-**3aj**).

The facile cyclopropane incorporation can be used in late-stage ring-reorganization (Fig. 2). As such, flavanone was readily converted by the same 2-step sequence to a bicyclic product **3ak** as a single diastereoisomer in 75% yield, whose structure and configuration were determined by NOESY spectrum (Fig. S11 in Supporting information) and single crystal X-ray diffraction of its oxidation product **4ak** (Figs. S3 and S4 in Supporting information). The high diastereoselectivity control arises from the high



Scheme 2. Scope of electrophilic selenium reagent induced SPR of cyclopropenyl carbinol. Reactions conditions: **1** (0.2 mmol), **2** (2 equiv.) and DTBP (2 equiv.) in anhydrous THF (4 mL) at −40 °C for 1~3 h. [a] Na_2CO_3 as base, H_2O (2 equiv.); [b] at 0 °C; [c] overnight; [d] at −30 °C; [e] gram scale yields are shown in parentheses; [f] at −20 °C; [g] MeOH (4 mL) as the solvent; [h] at −10 °C; [i] treated with 2.4 equiv. $NaBH_4$ and methanol (0.3 mL) after full conversion; [j] 2,6-lutidine as base; [k] at −15 °C; [l] at −50 °C; [m] 3 equiv. of **2**; [n] $BF_3{\cdot}Et_2O$ (4 equiv.) was used; [o] 4 equiv. of **2**.

1,3-diastereocontrol by the phenyl group in the addition of cyclopeopenyl moiety to the ketone, and subsequent face-selective approaching of the electrophile in the most stable conformation of the carbinol substrate, as revealed by density functional theory (DFT) calculations with Orca 5.0 (for details, see Fig. S12 in Supporting information) [42]. In a similar manner, D-(−)-carvone can be readily converted to **3al** in a good yield as a single diastereomer. The substrate derived from safranal, the main ingredient of crocus sativus, reacted smoothly under standard conditions, affording the desired product **3am** in 64% yield. Finally, TBS-protected testosterone was converted to separable pentacyclic derivatives **3an** and **3an'** in 1.5:1 *dr*, with their A rings being efficiently edited to cyclopropyl spired cyclopentenone (Figs. S5–S8 in Supporting information).

We then set out to investigate the compatibility of other electrophiles in this reaction (Scheme 3). Initially, we chose *N*–bromo succinimide (NBS) as the electrophile. Treatment of **1a** under condition A afforded the phenyl migrated product **5a** in 83% yield.

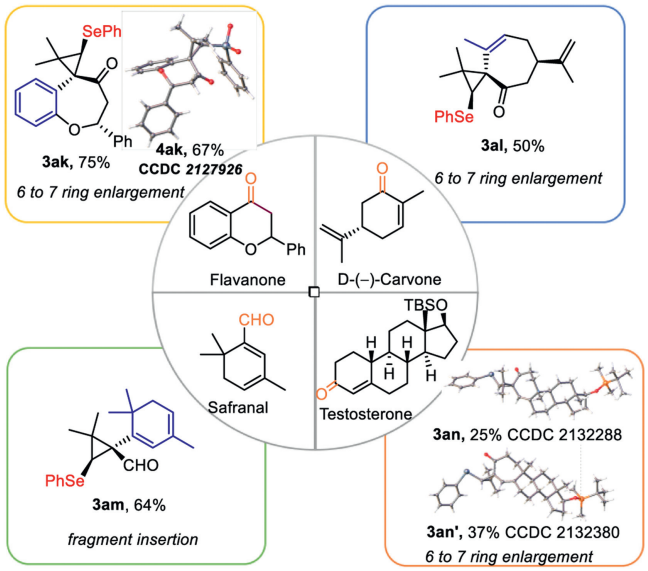
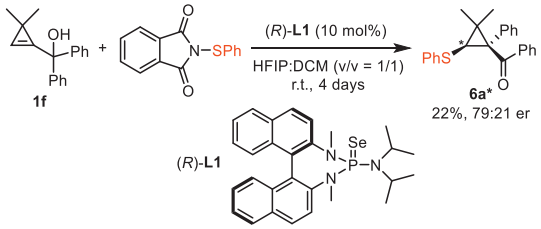


Fig. 2. Cyclopropane incorporating valorization of natural compounds.



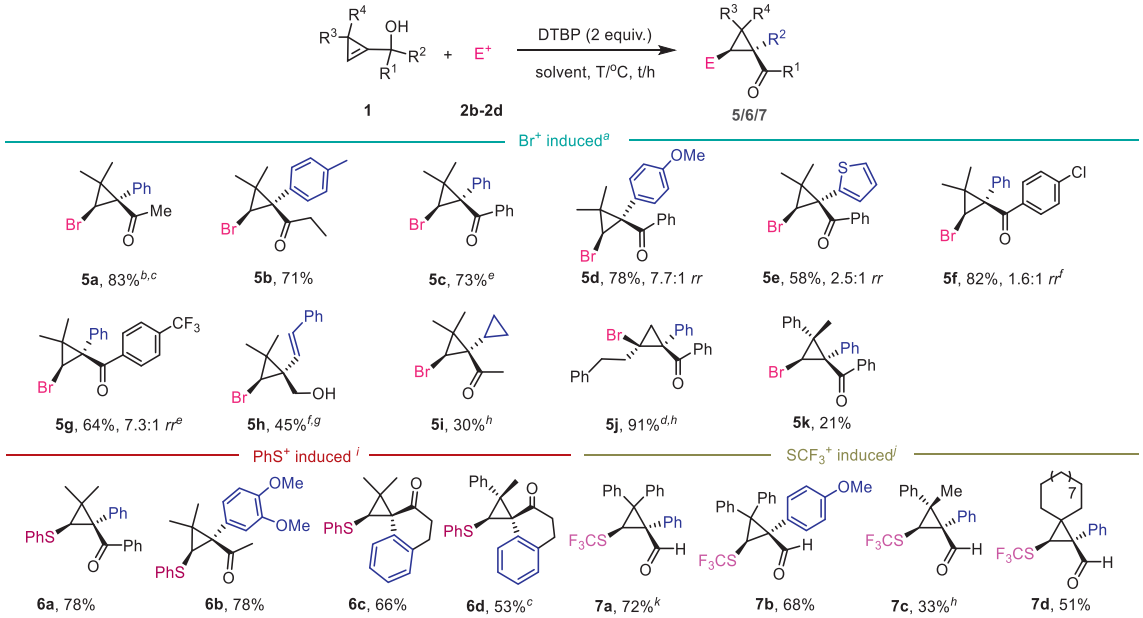
Scheme 4. Preliminary studies on asymmetric catalysis of SPR.

Acetophenone and benzophenone derived cyclopropenyl carbinol substrates delivered the corresponding rearranged products **5b**-**5g** in moderate to good yields. Styryl migration is also nicely realized (**5h**). Cyclopropyl migration, failed in the selenylation conditions above, is feasible and the product **5i** was obtained in 30% yield. Non-substitution at the 3-position of the cyclopropene ring turned out to be beneficial, as product **5j** was obtained in a high yield of 91%. 3-Aryl-3-alkyl substitution pattern is also accommodated (**5k**), albeit with a poor yield likely due to competing ring-opening side processes.

The reaction of phenylsulfenyl chloride as the electrophile with benzophenone derived substrate delivered the target product **6a** in a yield of 78% (Scheme 3). Acetophenone derivatives with electron-donating methoxy substituents at the phenyl ring was also produced in good yields (**6b**). Furthermore, dimethyl or aryl/alkyl substitution at the 3-position of the cyclopropene ring were both obtained in moderate yields (**6c**, **6d**).

Finally, the SPR triggered by trifluorothiomethylation reagent could incorporate SCF_3^+ into cyclopropane efficiently, enabling direct and diversified decoration of the cyclopropane without laborious preparation of trifluorothiomethylated olefins (Scheme 3) [43]. We found that cyclopropenyl carbinols bearing a secondary alcohol are amenable to the trifluorothiomethylation promoted SPR, as demonstrated by the moderate to good yields of products **7a**-**7d**, which feature different substitution patterns at the 3-position.

Although catalytic asymmetric SPR [44–46] and electrophilic sulfenylation [47] has witnessed much progress recently, successful catalytic asymmetric SPR protocols all feature a styrene-type olefin moiety, which involves a benzylic cationic center whose enantiocontrol is relatively easier. Realizing high enantiocontrol in catalytic SPR reactions involving nonstabilized cationic centers, especially bulky tertiary ones remain a well-known challenge. Using the readily available cyclopropene substrate to construct polysubstituted cyclopropane with two chiral centers would be highly fascinating. After some initial attempts, we found that up to 79:21 *er* and exclusive diastereoselectivity can be obtained using the chiral P=Se type chiral Lewis base catalyst (*R*)-**L1**, indicating its potential use in asymmetric synthesis (Scheme 4).



Scheme 3. SPR of cyclopropenyl carbinol induced by other electrophiles. [a] Reaction condition A for Br^+: **1** (0.2 mmol), NBS (**2b**) (2 equiv.) and DTBP (2 equiv.) in anhydrous CH_3CN (4 mL) at – 40 °C for 1~6 h; [b] Na_2CO_3 as base, H_2O (2 equiv.), *i*-PrOH as solvent; [c] at 0 °C; [d] overnight; [e] at –20 °C; [f] at –30 °C; [g] treated with 2.4 equiv. $NaBH_4$ and methanol (0.3 mL) after full conversion; [h] at –10 °C; [i] reaction condition B for PhS^+: **1** (0.1 mmol), PhSCl (**2c**) (3 equiv.) and DTBP (2 equiv.) in anhydrous THF (4 mL) at –20 °C for overnight; [j] reaction condition C for CF_3S^+: **1** (0.2 mmol), 2-[(*trifluoromethyl*)*thio*]-1,1-dioxide-1,2-benzisothiazol-3(2*H*)-one (**2d**) (1.5 equiv.), TMSCl (2 equiv.) and DTBP (10 mol%) in anhydrous CH_3CN (4 mL) at –20 °C overnight; [k] at r.t.

In summary, we disclosed an unprecedented SPR on the strained cyclopropene ring for the facile synthesis of stereo-defined carbonylated cyclopropanes. The readily availability of the cyclopropene α-carbinols, tolerance of various hetero-atom based electrophiles and migrating groups of various hybridization characters, ready scalability, latestage cyclopropane-implementation and scaffold editing are all notable features of this reaction. Preliminary studies on the catalytic asymmetric version of the reaction also reveals the potential for developing more challenging, non-benzylic and/or tertiary center based asymmetric SPRs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109447.

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