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Mild Darzens Annulations for the Assembly of Trifluoromethylthiolated (SCF_3) Aziridine and Cyclopropane Structures

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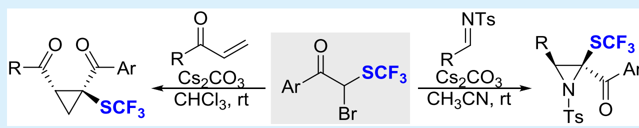
ABSTRACT: We report mild new annulation approaches to trisubstituted trifluoromethylthiolated (SCF_3) aziridines and cyclopropanes via Darzens inspired protocols. The products of these anionic annulations, rarely studied previously, possess attractive features rendering them valuable building blocks for synthesis platforms. In this study, trisubstituted acetophenone nucleophiles bearing SCF_3 and bromine substituents in their α position were shown to undergo [2 + 1] annulations with vinyl ketones and tosyl-protected imines under mild reaction conditions.



With continued usage and development for well over a century, the Darzens reaction has cemented itself as a premier workhorse in the synthesis of 3-membered rings, most notably oxiranes and aziridines.[1] Cyclopropanes can be similarly assembled by reacting Michael acceptors with alpha-halo-esters or ketones. The Johnson−Corey−Chaykovsky reaction,[2,3] which is conceptually related to Darzens reactions, offers a complementary approach to these strained rings. Both these important [2 + 1] annulation canvases have been successfully employed in obtaining 3-membered ring systems. The success of fluorinated substituents in pharmaceutical[4,5] and agrochemical products has catalyzed interest in new reactions for synthesis of fluorinated strained rings. For example, Xiao disclosed routes toward trifluoromethylated oxiranes, aziridines and cyclopropanes though utilization of 2,2,2-(trifluoroethyl)diphenylsulfonium triflate.[6] Koenigs later expanded upon this approach with nitro-styrene electrophiles.[7] More recently, Pace reported homologation strategies to access fluorinated epoxides and aziridines[8] and trifluoromethylated aziridines.[9] The juxtaposition of the trifluoromethylthiol (SCF_3) group, a moiety of modern importance,[10−13] with our interest in the Darzens reaction[14−16] led us to ponder whether a useful marriage could be forged between these?

There are very few reported methods to access SCF_3-containing aziridines and cyclopropanes. Only a single example to access a disubstituted SCF_3-containing aziridine has been reported (Figure 1a), which involved direct aziridination of a vinyl ketone containing an α-SCF_3 group.[17] No trisubstituted routes have been reported to date. With regards to SCF_3-cyclopropanes, Haas and Hinsken introduced the first route in 1985 (Figure 1b).[18] Their carbenoid approach utilized aryl-mercury-halogen carbenes in conjunction with vinyl-SCF_3 moieties. An alternative approach to access SCF_3-cyclopropanes was developed by Stroech (Figure 1c),[19] which relies on trifluoromethanesulfenyl chloride (SCF_3Cl) to install

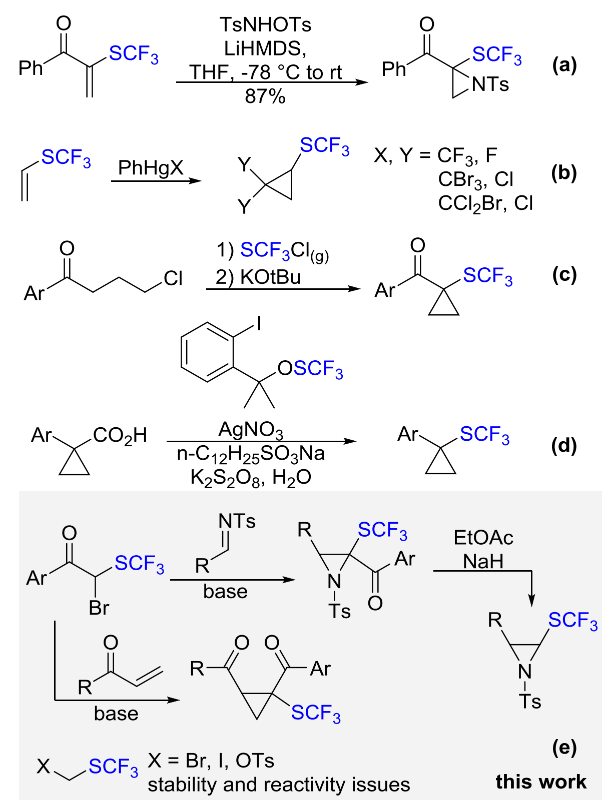


Figure 1. Prior art and proposed studies for the synthesis of trifluorothiomethylated aziridines and cyclopropanes.

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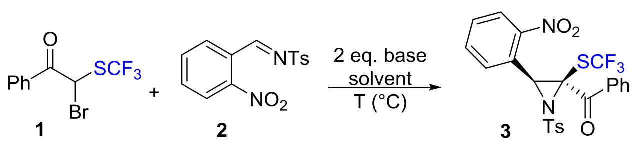
the SCF_3 group followed by a base-mediated cyclization. A major drawback of this route are toxicity concerns and handling of SCF_3Cl gas.[20] Shen reported a silver-mediated decarboxylative trifluoromethylthiolation, including two cyclopropane examples (Figure 1d).[21] In this study, we describe the development and investigations of mild annulation routes to trisubstituted SCF_3-containing aziridines and cyclopropanes and an intriguing deacylation reaction to access disubstituted SCF_3-aziridines (Figure 1e).

Our preliminary investigations commenced with the synthesis of CF_3SCH_2X (where X = I, Br, and OTs) unsubstituted nucleophiles. We were unable to reliably synthesize CF_3SCH_2I and CF_3SCH_2Br, which we attribute to product stability issues. CF_3SCH_2OTs on the other hand we did synthesize, but this nucleophile did not possess the desired reactivity when reacted with tosyl-imines and enones. We therefore turned our attention to a nucleophile bearing an electron-withdrawing group in lieu of a hydrogen, reasoning that deprotonation could occur with a mild base. A ketone was chosen as the electron-withdrawing group, as the pK_a of its alpha-proton is substantially lower than esters, amides, and sulfones. To that end, we chose to synthesize and evaluate SCF_3-substituted bromo-acetophenone **1** (Table 1).[22,23] The highly electrophilic

Table 1. SCF_3-Aziridine Synthesis Optimization



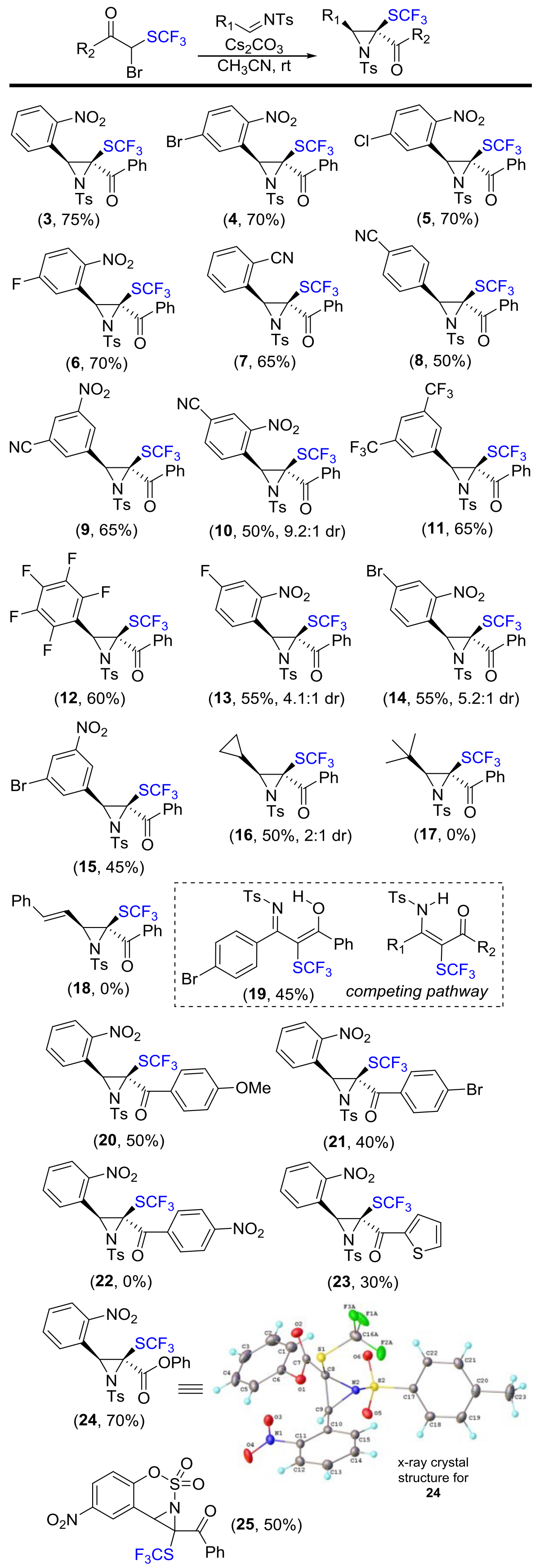
entry	base	solvent, temp	yield (%)
1	LiHMDS[b]	THF, 0 °C to rt	0
2	DBU[d]	THF, 0 °C to rt	15
3	KOtBu[a]	THF, 0 °C to rt	50
4	NaH[a]	THF, 0 °C to rt	50
5	Cs_2CO_3[c]	DMSO, rt	0
6	Cs_2CO_3[c]	$CHCl_3$, rt	10
7	Cs_2CO_3[a]	DMF, rt	30
8	Cs_2CO_3[a]	CH_2Cl_2, rt	40
9	Cs_2CO_3[a]	CH_3CN, rt	75

[a] **1** (1 equiv) and **2** (1 equiv) added together over 30 min to base (2 equiv) and solvent. [b] Base added last over 30 min. [c] **1** and **2** added together quickly. [d] Base added last quickly.

2-nitro tosyl imine **2** was chosen for the optimization studies, due to its enhanced reactivity in the first addition step and decreased likelihood of the resulting Mannich adduct undergoing undesirable isomerization and hydride shift events,[24,25] leading to enamines instead of aziridines. During our optimizations we learned that base, solvent, and order of addition were all determined to be critical for success. Strong bases (Table 1, entries 1−4) did work, with yields as high as 50% when both substrates were added together last and slowly. Cesium carbonate (entries 5−9) was shown to be the best performing base for this anionic reaction cascade. Solvent choice and the aforementioned addition order are decisive, with acetonitrile along with slow addition of substrate resulting in the target aziridine **3** being isolated in 75% yield and as a single diastereomer.

The scope and limitations for our new synthesis of trisubstituted SCF_3-aziridines is presented in Scheme 1. Optimized reaction conditions from Table 1 were used and

Scheme 1. Scope of SCF_3-Aziridine Synthesis



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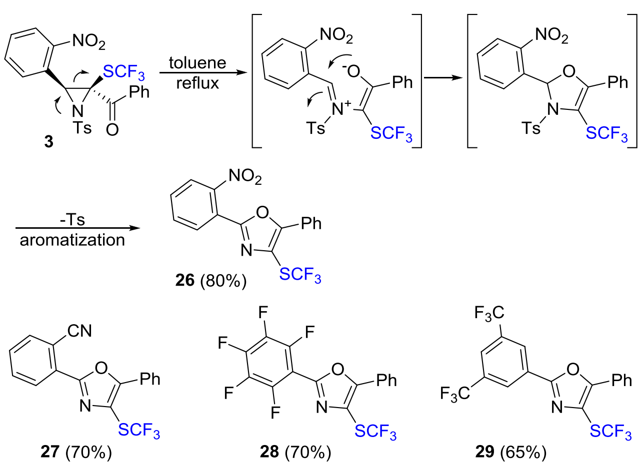
diastereoselectivities (dr) were determined from integration of ^{1}H NMR from crude reaction mixtures. All yields are isolated yields. Highly reactive electron-poor sulfonyl imines have been identified as the best reaction partners (3−15, Table 1), with aryl-substituted nitro, cyano, fluoro, and trifluoromethyl groups being performing best. Ortho-substitution has been shown to produce slightly higher yields in these cases. The main competing reaction pathway is a hydride shift to form an enamide, which becomes the major product when appropriate aryl deactivation is not present as exemplified by 4-bromo product **19**. Interestingly, a cyclopropyl imine is compatible for the reaction cascade affording aziridine product **16**. Beyond phenyl, we have learned that electronics of the nucleophile substituents are critical as well with the parent phenyl performing the best (**3**) followed by 4-OMe (**20**), then 4-Br (**21**) with 4-NO_2 (**22**) failing to react.

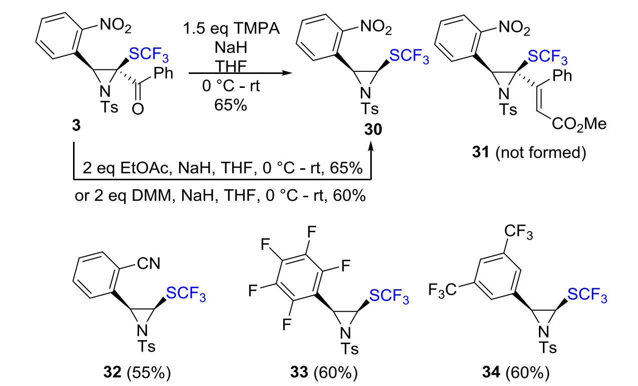
Excitingly, a phenyl ester nucleophile works as well as the phenyl ketone nucleophile (**24**). We were able to secure a crystal structure of **24**, which confirmed that the SCF_3- and aryl substituents are syn to each other. This ester product opens the door significantly for expanded synthetic applications. Finally, an intriguing cyclic sulfamate aldimine has been shown to form aziridine product **25**.

We have identified two attractive applications for these SCF_3-aziridine products (Scheme 2 and Scheme 3). Aziridine

Scheme 2. SCF_3-Aziridine Ring Expansion to Oxazoles



Scheme 3. Synthesis of Disubstituted SCF_3-Aziridines via an Unexpected Anionic Deacylation Process

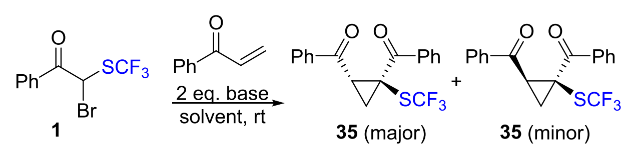


3 undergoes a facile ring expansion under mild thermal conditions to form SCF_3-substituted oxazole **26** in 80% yield. Presumably, following aziridine ring opening the resulting dipole undergoes a cyclization followed by loss of the N-tosyl protecting group driven by aromatization and formation of the oxazole product. Padwa first demonstrated this type of rearrangement for N-alkyl and N-aryl aziridines using forcing conditions (220 °C).[26] The three reported N-sulfonyl examples proceed under higher temperature and lower yield.[27] This is the first example of an SCF_3-substituted ring expansion case affording a rare example of an SCF_3-substituted oxazole. We have further demonstrated this ring expansion for the synthesis of SCF_3-oxazoles **27**, **28**, and **29**. It is worth noting that oxazoles are a prominent motif in pharmaceutical architectures and our two-step route represents a novel entry for their assembly.[28,29]

Unexpectedly, when we attempted a Horner−Wadsworth−Emmons olefination of ketone **3** with trimethyl phosphonoacetate (TMPA) none of the expected enoate (**31**) was observed, but instead all *cis*-SCF_3 disubstituted aziridine **30** was formed as the only product in 65% yield. Presumably, the phosphonate anion adds to the ketone, which then undergoes a deacylation to form an SCF_3-stabilized aziridine carbanion and then the product upon protonation. This is the first example of a 1,2-disubstituted SCF_3-aziridine being synthesized and a rare example of a mild anion-mediated aziridine deacylation reaction. We were eager to learn if we could replace the phosphonate anion with a more affordable and readily available carbanion for this anionic deacylation process. Our investigations have identified both ethyl acetate and dimethyl malonate (DMM) as excellent replacements for TMPA. Disubstituted SCF_3-aziridines **32**, **33**, and **34** were also synthesized as single syn-diastereomers employing ethyl acetate as deacylation nucleophile.

We next turned our attention to using this class of nucleophiles for the synthesis of SCF_3-substituted cyclopropanes. We rationalized that highly reactive enones with limited stability would provide the best opportunity for the tandem Michael-S_N2 displacement to occur. To that end, we chose phenyl vinyl ketone as our electrophile (Table 2). For

Table 2. SCF_3-Cyclopropane Synthesis Optimization



entry	base	solvent	yield (%), major:minor
1	Cs_2CO_3[a]	CH_3CN	70, 1:25:1
2	Cs_2CO_3[a]	$CHCl_3$	65, 12.7:1
3	Cs_2CO_3[a]	CH_2Cl_2	50, 5.3:1
4	K_2CO_3[a]	$CHCl_3$	60, 4.7:1
5	Na_2CO_3[a]	$CHCl_3$	0
6	Li_2CO_3[a]	$CHCl_3$	0
7	Et_3N[a]	CH_2Cl_2	trace
8	LiHMDS[b,c]	THF	0
9	Proton sponge[a]	CH_3CN	0
10	DBU[a]	THF	10, 1.5:1
11	KOtBu[a]	*t*-BuOH	40, 6:1
12	NaH[b,c]	THF	20, 5.9:1

[a]Both substrates added together over 30 min to base and solvent. [b]Base added last over 30 min. [c]0 °C to rt. Diastereomeric ratio was based on integration of ^{1}H NMR crude mixtures.

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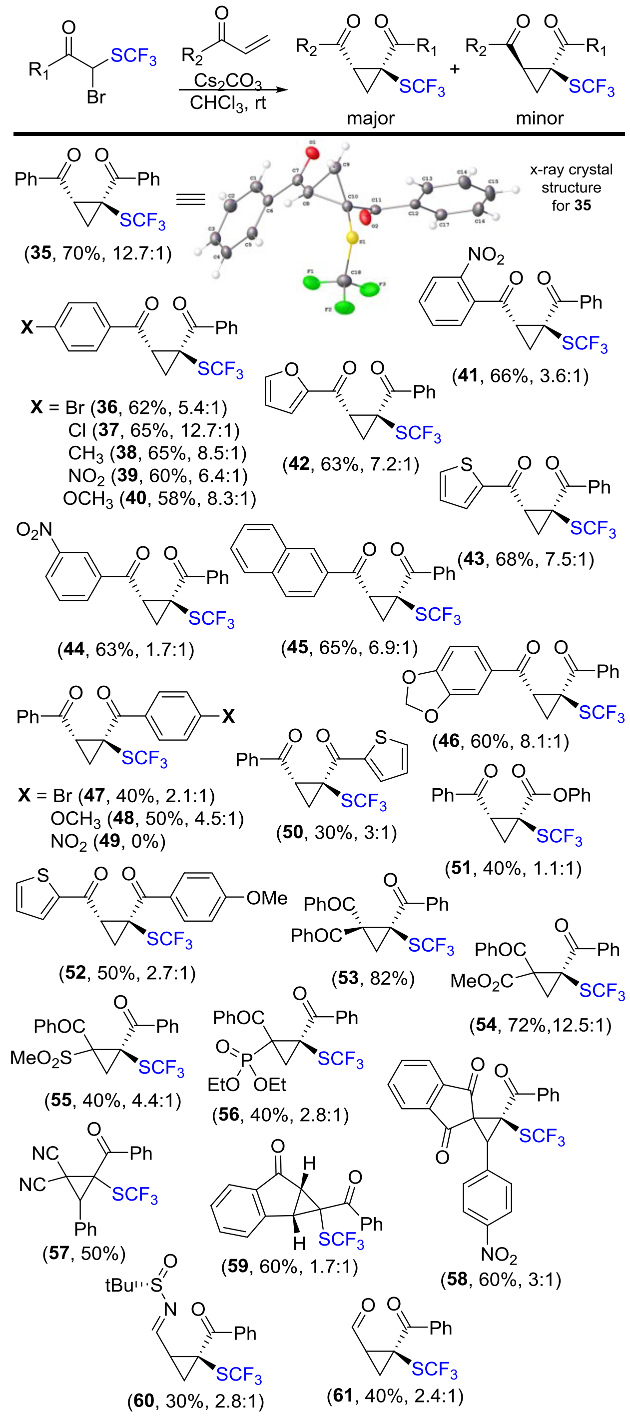
our first attempt, we ran the reaction under the same optimized conditions developed for SCF_3-aziridine synthesis. We were exhilarated to learn that the desired cyclopropane target product (**35**) was formed in 60% yield as a 1.25:1 mixture of diastereomers (Table 2, entry 1). Switching the solvent from acetonitrile for chloroform ($CHCl_3$), a more nonpolar solvent, further increased the yield while more importantly drastically increasing diastereoselectivity to 12.7:1 favoring major isomer of **35** (entry 2). Perhaps unsurprisingly, the activated Cs_2CO_3 followed by K_2CO_3 (entry 4) were the only carbonate bases which provided the cyclopropane with both Na_2CO_3 and Li_2CO_3 (entries 5−6), failing to facilitate formation of any cyclopropane products. This is attributed to the enhanced solubility in organic solvents which Cs_2CO_3 provides.[30] Of the other reaction conditions tested, only potassium *tert*-butoxide (KO*t*-Bu) in *tert*-butanol (*t*-BuOH) and NaH in THF provided any remnants of cyclopropane formation. All other reaction conditions led to recovered starting materials and complex mixtures of degradations pathways.

A variety of aryl vinyl ketones were evaluated with nucleophile **1** (**35**−**46**, Scheme 4), employing the optimized reaction conditions from Table 2. We were able to secure an X-ray crystal structure analysis for cyclopropane **35**, which confirmed the syn-relationship between the two phenacyl groups in the major diastereomer. Isolated yields were remarkably uniform (58−70%) for these products with diastereoselectivity ranging from 1.7:1 to 12.7:1. Interestingly, when the phenyl group of the nucleophile was substituted in the 4-position with bromide, methoxy, or nitro group, product yields and diastereoselectivity were reduced in the case of bromide (**47**) and methoxy (**48**) with no product formed for the 4-nitro substituted nucleophile (**49**). Cyclopropane product **51** is notable as it demonstrates that an ester nucleophile is also compatible with this cascade, thus greatly expanding synthetic application possibilities.

We have also evaluated the cyclopropane synthesis scope for a variety of other Michael acceptors, affording tri- to pentasubstituted cyclopropane products (Scheme 4). Doubly activated Michael acceptors bearing one or two benzoyl group performed well (**53**−**56**), with the 1,1-bis-acyl and 1,1-acyl-ester acceptors affording the cyclopropanes in 82% (**53**) and 72% (**54**) yield, respectively, with lower yields observed for the analogous sulfonate (**55**) and phosphonate (**56**) acceptors. By using highly reactive acceptors, we were able to access pentasubstituted cyclopropane products **57** and **58** as well as fused cyclopropane **59** from an indanone precursor. Cyclopropane products **60** and **61** are particularly noteworthy, as they are accessed from acrolein and its Ellman-imine analogue, both of which are far less reactive Michael acceptors, to afford intriguing cyclopropanes with useful functional group handles.

In conclusion, we have developed mild new approaches for synthesizing trisubstituted SCF_3-substituted aziridine and cyclopropanes from the anionic union of SCF_3-bearing bromo-nucleophiles and imines and Michael acceptors, respectively. We have expanded the cyclopropane scope and demonstrated compatibility for other nucleophiles and the Michael acceptors to deliver tetra- and pentasubstituted cyclopropanes as well as fused ones. In the case of SCF_3-substituted aziridine we report a new synthesis of SCF_3-substituted oxazoles via a mild thermally promoted aziridine ring expansion reaction. Finally, we designed the first synthesis of disubstituted SCF_3-aziridines via a deacylation protocol.

Scheme 4. Scope of SCF_3-Cyclopropane Synthesis



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02204.

Experimental procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 2087417 and 2092036 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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