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Transition-Metal-Free C(sp^3)−H Coupling of Cycloalkanes Enabled by Single-Electron Transfer and Hydrogen Atom Transfer

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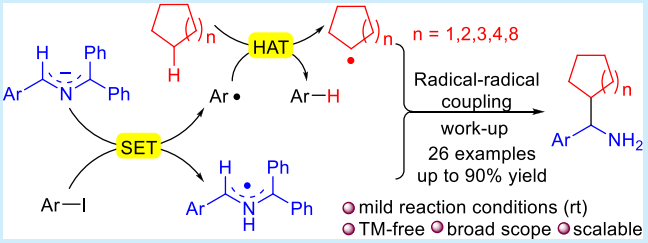
ABSTRACT: Here we report a unique transition-metal-free C(sp^3)−H/C(sp^3)−H coupling of cycloalkanes at room temperature. Unactivated cycloalkanes and 2-azaallyls underwent the combination process of single-electron transfer (SET) and hydrogen atom transfer (HAT) to deliver a wide variety of cycloalkane-functionalized products. This expedient approach enables C(sp^3)−H/C(sp^3)−H coupling of cycloalkanes under mild conditions without transition metals, initiators, and oxidants.



Cycloalkanes are among the most important, inexpensive, and readily available organic compounds extensively existing in nature. The development of efficient and straightforward approaches for C−H functionalization of cycloalkanes is in great demand from the environmental and economic perspectives.[1] However, because of the high dissociation energy (~95−100 kcal·mol^{-1})[2] and low acidity (pK_a ~ 50−60)[3] of the C(sp^3)−H bond, cycloalkanes are regarded as inert coupling partners, which are difficult to activate in organic reactions. Consequently, realizing C−H activation of cycloalkanes remains a significant challenge in the synthetic community.

For decades, traditional synthetic approaches for C−H functionalization of cycloalkanes have generally employed transition-metal-catalyzed cross-coupling methodologies, including Ru, Fe, Cu, Sc, Pd, Ag, and Ni catalysts (Scheme 1a).[4] A representative study by Li[5] described an effective Ru-catalyzed oxidative cross-coupling of chelating arenes and cycloalkanes using 2-pyridine as a directing group, which led to a mixture of both mono- and biscycloalkylation products. Later, transition-metal-free C−H bond activation of cycloalkanes to enable coupling with pyridine *N*-oxide under the influence of an oxidant was well-developed by Li,[6] despite the need for preactivated substrates and problems with regioselectivity. A representative study by Guo[7] reported a transition-metal-free C−H functionalization of cycloalkanes with heteroaromatics promoted by ^{t}BuOO^{t}Bu at high reaction temperature (140 °C) (Scheme 1b). Recently, impressive radical reactions via single-electron transfer (SET) and hydrogen atom transfer (HAT) have been achieved in C−H functionalization of cycloalkanes.[8] MacMillan's group developed an effective protocol for the direct C(sp^3) arylation of cycloalkanes through the combination of light-driven, polyoxometalate-facilitated HAT/SET and Ni catalysis.[9] Similarly, Doyle's group reported an example of C−H functionalization of cyclohexane enabled by the catalytic generation of chlorine radicals by photoredox and Ni catalysis (Scheme 1c).[10]

Despite these advances, these approaches are generally limited by high reaction temperatures (100−150 °C) and the addition of transition metal catalysts, initiators, and stoichiometric quantities of oxidants. Notably, most of these reactions focus on C(sp^2)−H/C(sp^3)−H coupling of cycloalkanes, whereas a mild and general approach for C(sp^3)−H/C(sp^3)−H dehydrogenative coupling is still relatively rare.[1,9,11]

Recently, superelectron donors (SEDs) have emerged as an effective strategy for C−C bond coupling since the pioneering studies of Murphy.[12] Walsh[13] and Chruma and co-workers[14] developed 2-azaallyl anions as SEDs for application to radical cross-coupling platforms for transition-metal-free C−C bond formation. Inspired by these elegant studies, we introduced a series of transition-metal-free radical coupling reactions enabled by 2-azaallyl anions as SED.[15] Specifically, SET between 2-azaallyl anions and alkyl/aryl iodides enables the formation of 2-azaallyl radicals and alkyl/aryl radicals. Next, the coupling process between radicals delivers several new methods for C−C bond formation. More recently, we reported a cross-dehydrogenative coupling protocol between C(sp^3)−H bonds of saturated heterocycles and *N*-benzylimines, which undergo a combination of SET and HAT processes under heating conditions.[16]

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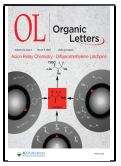
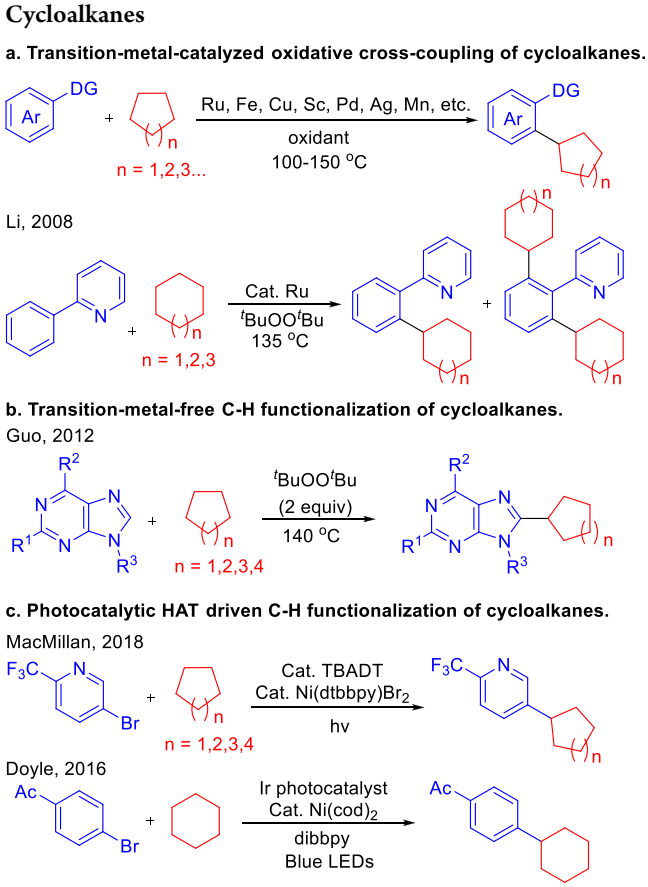
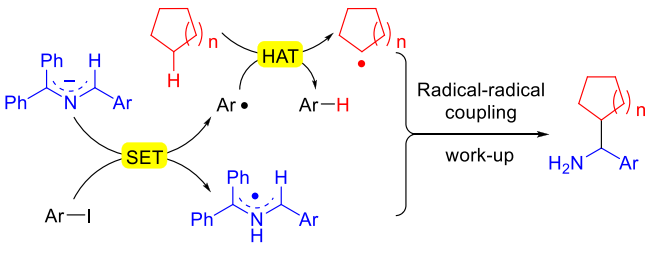


Scheme 1. General Strategy for C−H Functionalization of Cycloalkanes



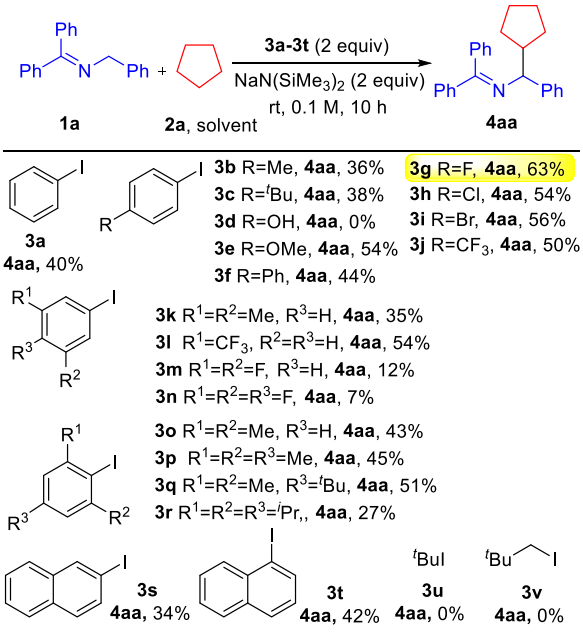
On the basis of this strategy, we hoped that such a combination of radical pathways would enable access to cycloalkane-functionalized products from abundant and cheap feedstocks. We proposed that aryl radicals generated from SET between azaallyl anions and aryl iodides would be ideally suited to act as hydrogen atom abstractors. Many of them possess high reactivity and are able to perform the desired C−H abstraction.[17] Then aryl radicals would enable HAT with unactivated cycloalkanes to give cycloalkane radicals, which would finally couple with 2-azaallyl radical to form a new $C(sp^3)-C(sp^3)$ bond (Scheme 2). Herein we describe the first transition-metal-free $C(sp^3)-H/C(sp^3)-H$ coupling of cycloalkanes with 2-azaallyls. This approach enables room-temperature C−H functionalization of cycloalkanes by the combination of SET and HAT processes (26 examples, up to 90% yield).

Scheme 2. Proposed Mechanism for $C(sp^3)-H$ Functionalization of Cycloalkanes with 2-Azaallyl Anions via the Combination of SET and HAT Process



With this mechanistic hypothesis in hand, we first explored electron acceptors for the proposed C−H functionalization of cycloalkanes. Twenty aryl/alkyl iodides (**3a−t**) were screened using *N*-benzylimine **1a** and cyclopentane (**2a**) (solvent) as the model substrates with $NaN(SiMe_3)_2$ at room temperature for 10 h. We were pleased to find that most aryl iodides delivered the cyclopentane-functionalized product **4aa**, while alkyl iodides led to no reaction (Table 1). Among them, 4-

Table 1. Effect of Aryl Iodide Electron Acceptors and Hydrogen Abstractor Precursors[a]



[a]Reactions were conducted on a 0.1 mmol scale. Assay yields were determined by ^1H NMR spectroscopy of the crude reaction mixtures using $C_2H_2Cl_4$ as an internal standard.

fluoroiodobenzene (**3g**) was the best electron acceptor, generating **4aa** in 63% assay yield (AY, as determined by ^1H NMR spectroscopy). We speculated that this may be due to the fact that the redox potential of 4-fluoroiodobenzene is lower than that of the imine.[14b] Compared with the radicals generated by other aryl iodides, the aryl radical produced by **3g** has a higher activation energy and more easily undergoes HAT with cycloalkanes.

As a model coupling reaction, we next explored the reaction optimization in the presence of aryl iodide **3g** at room temperature. Initially, a range of other bases were evaluated, including $LiN(SiMe_3)_2$, $KN(SiMe_3)_2$, LiO^{t}Bu, NaO^{t}Bu, and KO^{t}Bu (Table 2, entries 2−6). Among them, $LiN(SiMe_3)_2$ and $KN(SiMe_3)_2$ generated **4aa** only in 10% and 5% AY, while other bases (LiO^{t}Bu, NaO^{t}Bu, and KO^{t}Bu) caused no reaction. Using $NaN(SiMe_3)_2$, we further studied the concentration of cyclopentane (solvent). The concentration proved to be an important factor in this coupling reaction. Increasing the concentration from 0.1 to 0.2 M resulted in a slight decrease to 61% AY (entry 7). However, reducing the concentration to 0.05 M led to the desired product in 76% AY and 74% isolated yield (entry 8). Under otherwise identical conditions, decreasing or increasing the temperature resulted in decreased AY (45−54%; entries 9−11). Finally, the reaction time study

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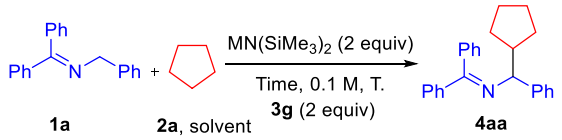
Table 2. Optimization of the Reaction Conditions[a]



entry	base	T (°C)	conc. (M)	time (h)	yield of **4aa** (%)[b]
1	$NaN(SiMe_3)_2$	rt	0.1	10	63
2	$LiN(SiMe_3)_2$	rt	0.1	10	10
3	$KN(SiMe_3)_2$	rt	0.1	10	5
4	LiO^tBu	rt	0.1	10	0
5	NaO^tBu	rt	0.1	10	0
6	KO^tBu	rt	0.1	10	0
7	$NaN(SiMe_3)_2$	rt	0.2	10	61
8	$NaN(SiMe_3)_2$	rt	0.05	10	76 (74[b])
9	$NaN(SiMe_3)_2$	0	0.1	10	49
10	$NaN(SiMe_3)_2$	40	0.1	10	54
11	$NaN(SiMe_3)_2$	80	0.1	10	45
12	$NaN(SiMe_3)_2$	rt	0.05	14	74
13	$NaN(SiMe_3)_2$	rt	0.05	6	67

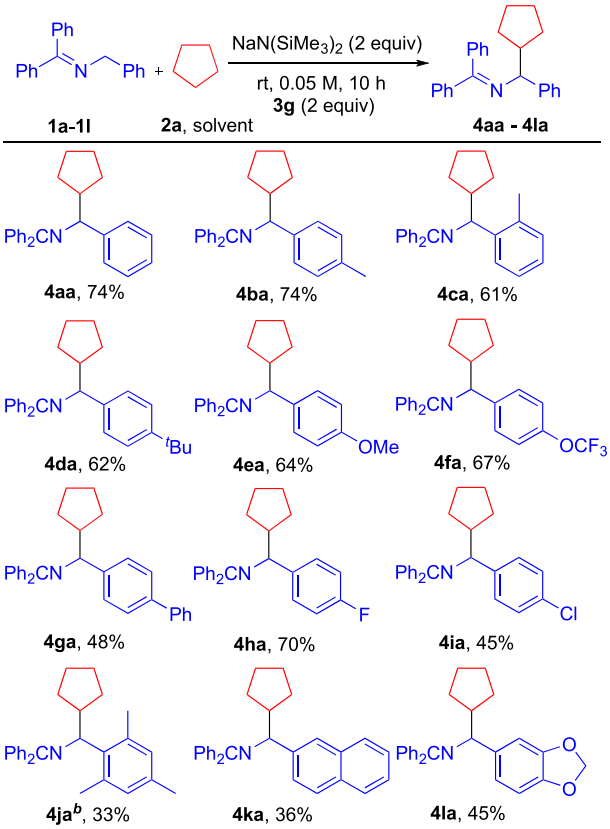
[a]Reactions were conducted on a 0.1 mmol scale. Assay yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using $C_2H_2Cl_4$ as an internal standard. [b]Yield of isolated product after chromatographic purification.

indicated that increasing or decreasing the time also led to slight lower AYs (67−74%; entries 12 and 13).

With the optimized reaction conditions (Table 2, entry 8), we next evaluated ketimine coupling partners in the C−H functionalization of **2a** (Table 3). Generally, ketimines bearing various substituted aryl groups were all suitable reaction partners in this coupling and afforded the corresponding cyclopentane-functionalized products **4aa**−**la** in moderate to good yields. The structure of compound **4aa** was confirmed by X-ray crystallography (CCDC 2022061). *N*-Benzyl groups bearing the alkyl substituents 4-Me (**1b**), 2-Me (**1c**), and 4-^{t}Bu (**1d**) generated the coupling products **4ba**, **4ca**, and **4da** in 74%, 61%, and 62% yield, respectively. Substrates with electron-donating substituents 4-OMe (**1e**) and 4-OCF_3 (**1f**) led to products **4ea** and **4fa** in 64% and 67% yield, respectively. Coupling with ketimine **1g** bearing a biphenyl group led to product **4ga** in 48% yield. *N*-Benzyl groups possessing the electron-withdrawing substituents 4-F (**1h**) and 4-Cl (**1i**) gave products **4ha** and **4ia** in 70% and 45% yield, respectively. The sterically hindered 2,4,6-trimethyl (**1j**) and 1-naphthyl (**1k**) derivatives coupled with **2a** to afford products **4ja** and **4ka** in 33% and 36% yield, respectively. Furthermore, ketimine **1l** with a piperonyl group generated product **4la** in 45% yield.

We further investigated the ability of the C−H functionalization to accommodate various cycloalkanes (Table 4). A variety of readily available saturated cycloalkanes, such as cyclohexane (**2b**), cycloheptane (**2c**), cyclooctane (**2d**), and cyclododecane (**2e**), coupled with *N*-benzyl ketimine **1a** to give cycloalkane-functionalized products **4ab**, **4ac**, **4ad**, and **4ae** in 60%, 79%, 80%, and 40% yield, respectively. Likewise, **2a**, **2b**, **2c**, and **2d** reacted with ketimine **1m** to provide the corresponding products **4ma**, **4mb**, **4mc**, and **4md** in 86%, 50%, 58%, and 61% yield, respectively. Furthermore, fused polycyclic compounds such as 9,10-dihydroanthracene (**2f**), xanthene (**2g**), and 10-methyl-9,10-dihydroacridine (**2h**) were also suitable coupling partners (see Table S1 for details of the reaction optimization), generating the coupling products **4af**, **4ag**, **4ah**, **4mf**, **4 mg**, and **4mh** in moderate to excellent yields (42−90%). Additionally, we examined the reaction of acyclic alkanes, such as diphenylmethane and *n*-pentane. Unfortunately, both of them led to no reaction.

Table 3. Scope of Ketimines[a]



[a]Reactions were conducted on a 0.5 mmol scale using 1 equiv of **1a**−**l**, 2 equiv of the electron acceptor, and 2 equiv of the base at 0.05 M. [b]$KN(SiMe_3)_2$ was used as the base.

To demonstrate the scalability and utility of the coupling process, the telescoped gram-scale experiment was performed by employing benzylamine (5 mmol) and benzophenone imine (5 mmol) in THF at 65 °C for 12 h, followed by solvent removal to give ketimine **1a**. The unpurified imine **1a** was coupled with **2a** under the standard reaction conditions. After 10 h at room temperature, 1.21 g of the desired product **4aa** was isolated in 71% yield over two steps (Scheme 3a). Furthermore, hydrolysis of the product **4aa** furnished the corresponding α-cycloalkane-functionalized benzylamine **5aa** in 91% yield (Scheme 3b), which has potential application value in medicinally relevant fields.[18]

Finally, to gain insight into the reaction mechanism, we turned our attention to finding evidence to confirm the electron transfer and HAT processes. For this, a control experiment without addition of **3g** was carried out (Scheme 4a). Indeed, this coupling reaction did not work, which proved that the electron acceptor **3g** is an essential additive in the transformation. Moreover, cyclohexane-d_{12} (**D-2b**) and **1a** were coupled under the standard conditions, and the deuterated product **D-4ab** was obtained in 51% yield. Notably, despite its volatility and low molecular weight, the key deuterated fluorobenzene in the reaction mixture was detected by high-resolution mass spectrometry (Scheme 4b). These results indicated that the coupling reaction proceeded via the

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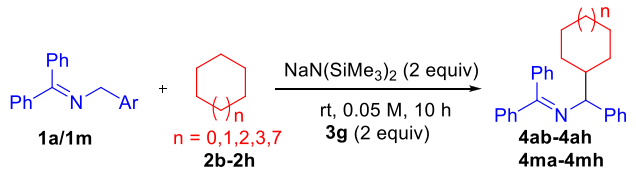
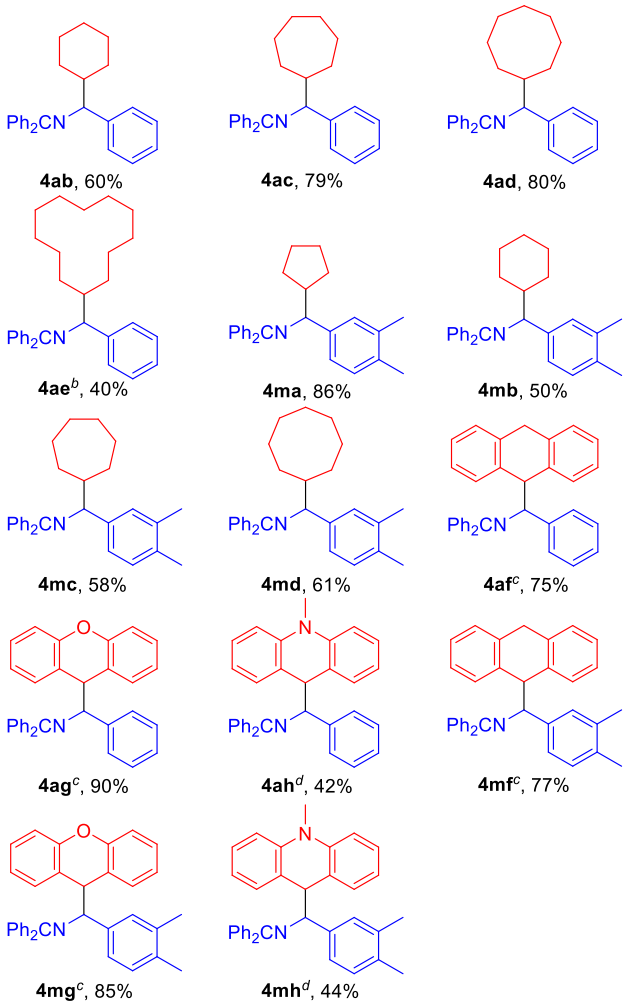
Table 4. Scope of Cycloalkanes[a]



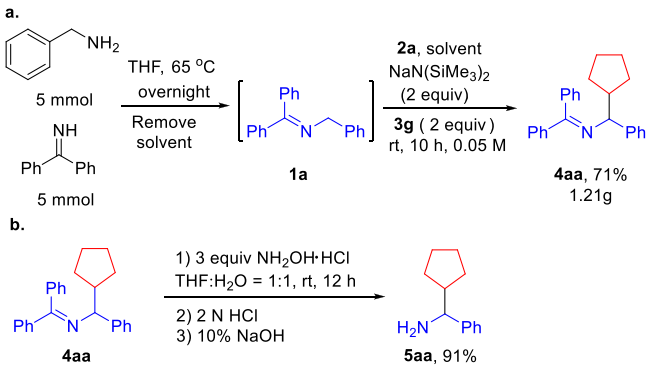


[a]Reactions were conducted on a 0.5 mmol scale using 1 equiv of **1a**, 2 equiv of the electron acceptor, and 2 equiv of the base at 0.05 M. [b]65 °C reaction temperature, 12 h reaction time. [c]Benzene was used as the solvent with 5 equiv of substrate and 3 equiv of base at 80 °C. [d]Benzene was used as the solvent with 5 equiv of substrate and 3 equiv of base at 60 °C.

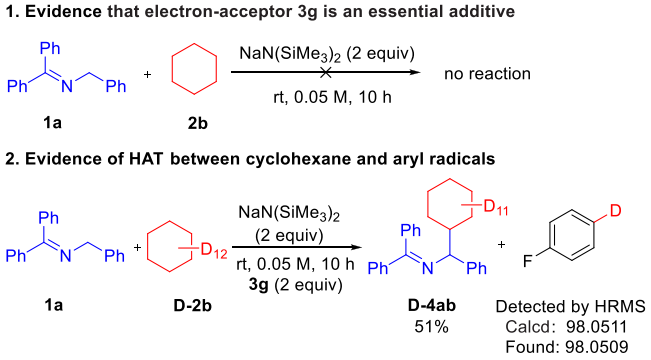
combination of SET and HAT processes, as proposed in Scheme 2.

In summary, we have developed a unique transition-metal-free C(sp^3)−H/C(sp^3)−H coupling of cycloalkanes at room temperature for the first time. In this protocol, unactivated cycloalkanes and 2-azaallyls undergo a combination of SET and HAT processes to deliver a wide variety of cycloalkane-functionalized products, in which an aryl iodide was employed as an electron acceptor and hydrogen atom abstractor precursor. Gram-scale reactions and hydrolysis demonstrate the scalability and utility of the transformation. Mechanistic studies provided insight into this C−H functionalization of cycloalkanes. It is noteworthy that this method does not require transition metals, initiators, or oxidants, enabling

Scheme 3. (a) Gram-Scale Synthesis of Compound 4aa; (b) Product Hydrolysis



Scheme 4. Mechanistic Experiments



C(sp^3)−H/C(sp^3)−H coupling of cycloalkanes under mild conditions. Furthermore, because cycloalkanes are abundant and cheap feedstocks, we anticipate that this strategy will provide an efficient approach for the synthesis of medicinally relevant cycloalkane-functionalized benzylamines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00135.

Procedures and characterization data for all new compounds (PDF)

Accession Codes

CCDC 2022061 contains 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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