

Homologation of Electron-Rich Benzyl Bromide Derivatives via Diazo C–C Bond Insertion

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ABSTRACT: The ability to manipulate C–C bonds for selective chemical transformations is challenging and represents a growing area of research. Here, we report a formal insertion of diazo compounds into the “unactivated” C–C bond of benzyl bromide derivatives catalyzed by a simple Lewis acid. The homologation reaction proceeds via the intermediacy of a phenonium ion, and the products contain benzylic quaternary centers and an alkyl bromide amenable to further derivatization. Computational analysis provides critical insight into the reaction mechanism, in particular the key selectivity-determining step.

Synthetic approaches to organic compounds are grounded in the combination of nucleophiles and electrophiles.¹ For example, benzyl halide derivatives may participate in classical reactions such as nucleophilic substitution and electrophilic aromatic substitution (Figure 1A).² The advent of reactions that unlock “nonclassical” transformations of common building blocks provides opportunities to reimagine and/or streamline synthetic strategies. “Nonclassical” reactions may be described as those reacting at a traditionally inert functionality, for example, insertion into the C(sp²)–C(sp³) bond of a benzyl halide derivative (Figure 1B). Cascade reactions that effect formal C–C bond insertion reactions via skeletal rearrangements represent an appealing approach toward such a goal.^{3,4} Herein, we describe the development of a homologation reaction of electron-rich benzyl bromide derivatives involving formal insertion of diazo compounds into the C(sp²)–C(sp³) bond (Figure 1C).⁵

Cognizant of the ionic reactivity of diazo compounds with sp²-hybridized electrophiles (e.g., carbonyl derivatives),⁶ we questioned whether electron-rich benzyl bromide **A** would react with diazo **B**, via the intermediacy of a stabilized benzylic carbocation, to generate alkyl diazonium ion **C** (Figure 1C).⁷ Loss of nitrogen would then trigger neighboring group participation of the aryl ring, resulting in phenonium ion **D**.^{8,9} The bromide leaving group from the first step could then engage the putative spirocyclopropane at the less substituted position to afford the desired product **E**.¹⁰ Tertiary bromide **F** was considered a potential side product accessible via competitive intermolecular displacement of nitrogen in diazonium **C** or nucleophilic opening of phenonium ion **D** at the more substituted position. The desired product **E** contains an acyclic, benzylic tertiary or quaternary center—motifs present in many pharmaceutical and agrochemical molecules (Figure 1D)^{11,12}—while retaining the alkyl bromide as a functional handle for further derivatization.^{13,14} This method enables programmable introduction of trifluoromethyl, ester, amide, ketone, and sulfone functional groups via a unified approach. In particular, the incorporation of trifluoromethyl

groups into molecules continues to be important in medicinal chemistry,¹⁵ and the use of substituted trifluoromethyl diazo derivatives is particularly underexplored in this regard.¹⁶

4-Methoxybenzyl bromide **1** and trifluoromethyl diazo **2** were chosen as parent substrates for reaction discovery and optimization. After surveying a series of Lewis acids under different reaction conditions, it was found that SnBr₄ (50 mol %) in CH₂Cl₂ at –78 °C afforded bromide **3a** in 75% isolated yield (Figure 2A).¹⁷ With the optimized conditions in hand, the scope of the reaction was evaluated with respect to both substituents on the diazo and the benzyl bromide derivative. Several different electron-withdrawing groups worked well in this process (Figure 2A). Alkyl-substituted diazo derivatives containing an ethyl ester (**3b**), benzyl ester (**3c**), redox-active ester (**3d**), and a nitrile (**3e**) were all effective in this reaction. With ester derivatives, minor quantities of isomer **3'** are observed in the ¹H NMR spectrum of the crude reaction mixture. For completeness, the ratio of **3:3'** in the isolated material is quoted in parentheses, and the ratio in the crude reaction mixture is quoted in brackets below. The use of monosubstituted diazo derivatives to generate tertiary benzylic centers is also possible and further highlights the range of electron-withdrawing substituents amenable in this reaction (Figure 2B). An ethyl ester (**3f**), benzyl ester (**3g**), *tert*-butyl ester (**3h**), amide (**3i**), ketone (**3j**), trifluoromethyl group (**3k**), and a sulfone (**3l**) all worked well to give the requisite tertiary benzylic centers.

Trifluoromethyl-substituted diazo **2** was employed to evaluate a number of electron-rich benzyl bromide derivatives in the homologation reaction (Figure 2C). In all cases, the

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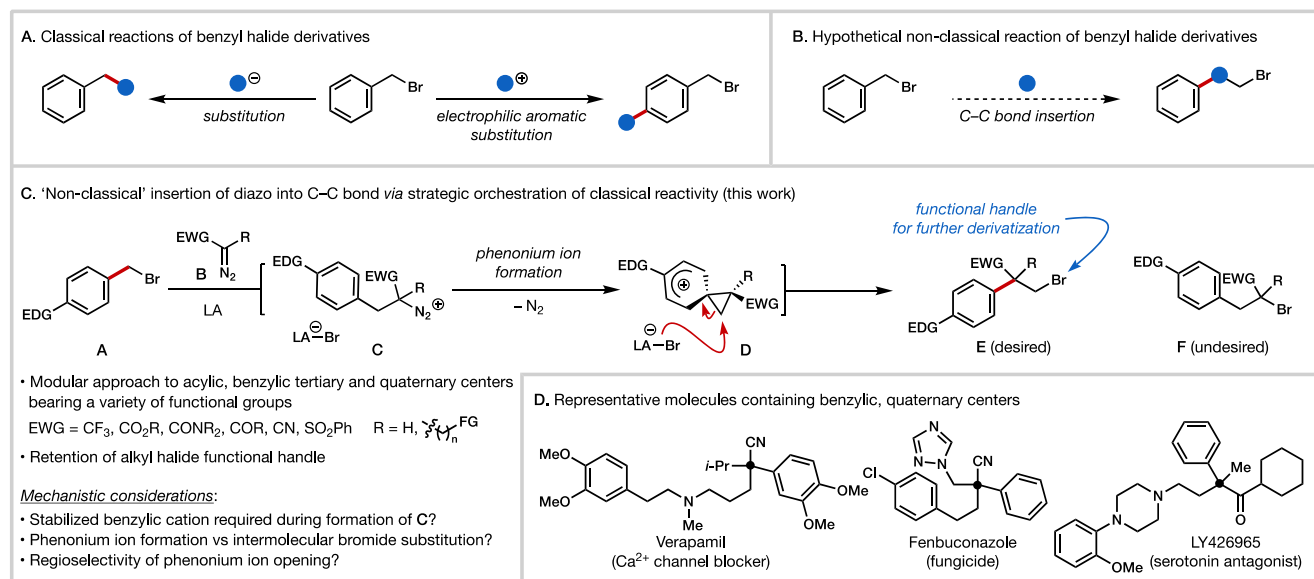


Figure 1. Nonclassical insertion of diazo compounds into C–C bond of benzyl bromide derivatives.

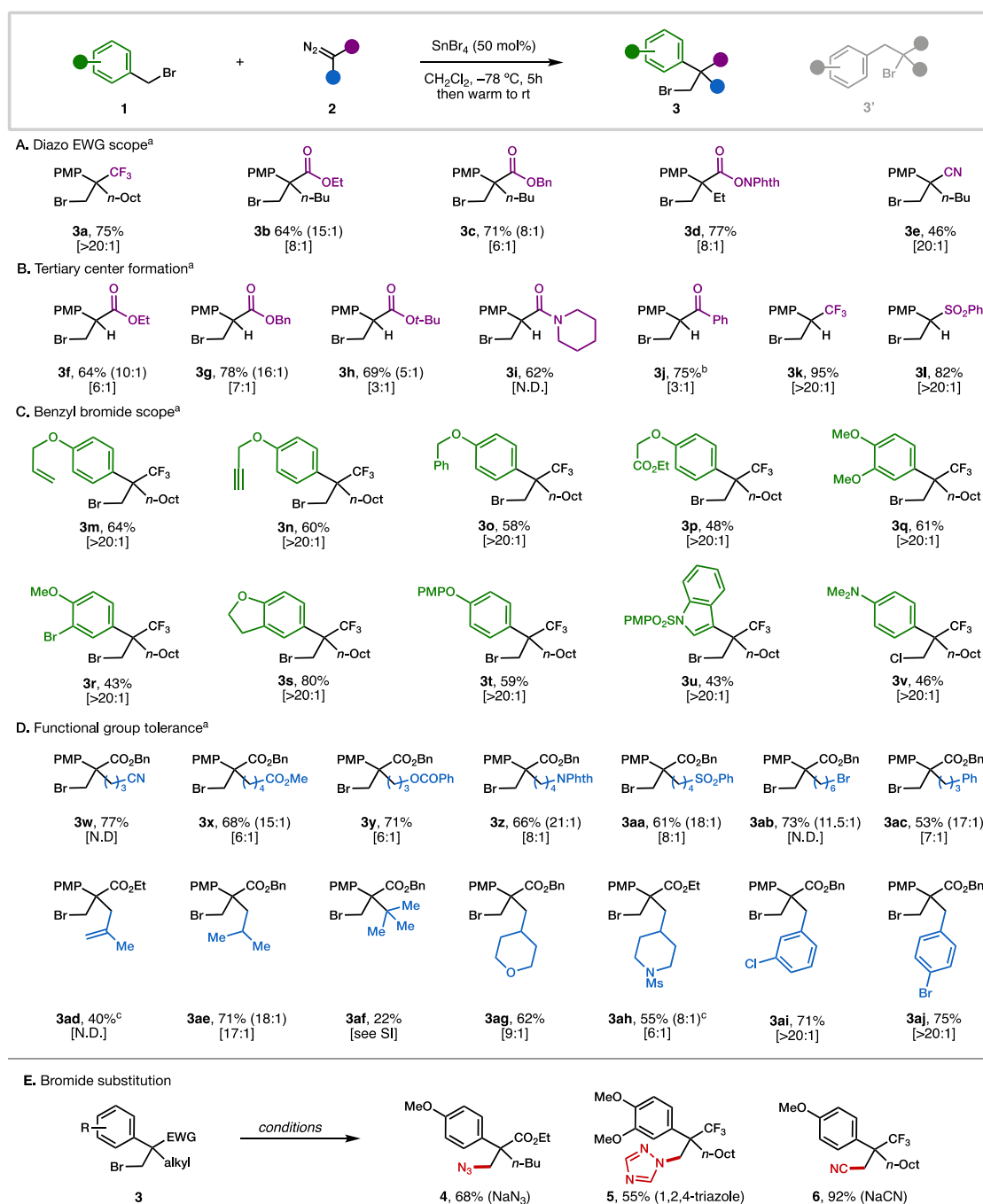
regioselectivity of phenonium ion opening was high (>20:1). Alkoxy substituents such as allyl (**3m**), propargyl (**3n**), benzyl (**3o**), and alkyl ester (**3p**) all deliver the desired products in good yields. Disubstituted arenes containing veratrole (**3q**) as well as 3-bromo and 4-methoxy (**3r**) motifs were tolerated. A dihydrobenzofuran derivative worked well (**3s**), and incorporation of an aryl ether is possible (**3t**). A rare example of an “indolyl” phenonium ion was demonstrated through use of a 3-bromomethylindole derivative (**3u**),¹⁸ and a 4-dimethylamino-substituted benzyl chloride afforded chloride **3v** in acceptable yield. Here, SnCl₄ was employed as the catalyst to avoid halogen crossover. Under these conditions, the use of benzyl bromide itself resulted in no reaction and recovered bromide (*vide infra*).¹⁹

Next, attention was turned to exploring the functional group tolerance of the reaction with respect to the alkyl substituent on the diazo derivative (**Figure 2D**).²⁰ Here, benzyl diazoacetate derivatives were employed to facilitate substrate synthesis and handling. Many different functional groups were tolerated in this reaction, including nitrile (**3w**), ester (**3x**, **3y**), phthalimide-protected amine (**3z**), sulfone (**3aa**), and bromide (**3ab**). A pendant phenyl ring was tolerated (**3ac**), and an allyl-substituted diazo afforded the desired product **3ad** in modest yield. A diazo derived from the amino acid leucine also worked well (**3ae**). Remarkably, use of a *tert*-leucine-derived diazo compound afforded **3af** which contains vicinal quaternary centers. The modest yield of this reaction (22%) results from a competitive methyl shift at the stage of phenonium ion formation (see the **Supporting Information** for details). Saturated heterocycles such as a tetrahydropyran and piperidine—commonly found in medicinally relevant compounds—could be incorporated in the diazo starting material and afforded the desired products (**3ag**, **3ah**) in good yield. Use of benzyl-substituted diazo compounds opens the possibility of competitive aryl migration at the stage of the putative alkyl diazonium **C** (see **Figure 1C**). In both cases, the reaction proceeds in high yield, and the more electron-rich arene migrated selectively (**3ai**, **3aj**).²¹

One enabling feature of this reaction is the retention of the alkyl bromide as a functional handle for further manipulation.

For example, substitution of the bromide with azide delivers $\beta^{2,2}$ -amino acid derivative **4** in 68% yield (**Figure 2E**).²² Displacement with 1,2,4-triazole gave **5** in 55% yield.²³ 1,2,4-Triazoles are emerging as privileged scaffolds in medicinal chemistry²⁴ and also represent a core component of many agrochemical compounds (e.g., fenbuconazole, **Figure 1D**). Use of cyanide as the nucleophile afforded nitrile **6** in 92% yield.

Quantum chemical calculations (ω B97X-D/def2-QZVPP// ω B97X-D/6-31+G(d,p) with an SMD description of dichloromethane) were used to study the multistep mechanism between 4-methoxybenzyl bromide and benzyl 2-diazobutanoate (as a model substrate) catalyzed by SnBr₄ (**Figure 3A**).²⁵ The initial nucleophilic displacement to form **Int-II** is computed to proceed most favorably in an S_N1 fashion, with a barrier height of 18.5 kcal mol^{−1} for **TS-II** (vs 29.7 kcal mol^{−1} for the uncatalyzed S_N2 pathway). This is the rate-determining step, for which lower barriers are obtained with electron-rich benzyl bromide derivatives (**Figure 3B**). Coordination of the bromide and Lewis acid results in a SnBr₅[−] leaving group in **TS-I**. After **TS-II** is crossed, the sequential loss of dinitrogen and phenonium ion formation proceeds through separate C–N breaking (**TS-III**) and C–C forming (**TS-IV**) TSs in a highly exergonic fashion ($G_{\text{rel}} = -32.3$ kcal mol^{−1}) to produce the phenonium **Int-IV**. The intervening intermediates, alkyl diazonium **Int-II** and tertiary carbocation **Int-III**, exist as local potential energy minima with extremely small exit barriers of just 0.3 and 2.0 kcal mol^{−1}, respectively. Compared to phenonium formation, competing 1,2-hydride shifts (**TS-VI** and **TS-VII**) have higher barriers of 3.4–3.6 kcal mol^{−1}. On the basis of these small barrier heights, we expect **Int-II** and **Int-III** to be short-lived, potentially preventing equilibration of atomic motions and the surrounding solvent, which limits the applicability of transition-state theory (TST).²⁶ We therefore initiated quasi-classical molecular dynamics trajectories²⁷ in the region of **TS-II**. Many of these trajectories evolved to phenonium **Int-IV**, passing through **Int-II** with an extremely short average lifetime (262 fs, only a few complete C–N vibrations occurred in many trajectories)²⁸ and **Int-III**, which had a longer lifetime of 439 fs, confirming the existence of



^a Isolated yield of **3** quoted. The ratio of **3**:**3'** in isolated material is given in parentheses. The ratio of **3**:**3'** in the crude reaction mixture is given in brackets.
^b *In situ* yield quoted ^c The ethyl ester was employed.

Figure 2. Reaction scope and demonstration of product utility.

dynamic intermediates. Although the potential energy surface is formally stepwise, we observed high fidelity transfer of stereochemical information from the starting material through to the phenonium configuration in MD trajectories that followed the main pathway.²⁹

Regioselectivity is determined by nucleophilic phenonium opening via **TS-V** (Figure 3A). Nucleophilic attack by the pentavalent SnBr_5^- anion is energetically favored over the free bromide anion by over 4 kcal mol⁻¹ for **TS-V-A** (see the Supporting Information, Figure S5) and C–Br formation occurs irreversibly ($\Delta G = -16.4$ or -17.3 kcal mol⁻¹). The fleeting intermediacy of acyclic **Int-III** and the much greater

stability of **Int-IV** mean that direct addition of bromide before phenonium formation is unlikely. The direct trapping of tertiary carbocation (**Int-III**) by SnBr_5^- is less favorable than phenonium formation by 1.5 kcal mol⁻¹ (see Figure S3). This minor pathway could nonetheless provide a direct route to product **B** in addition to the opening of phenonium through **TS-V-B**. We then compared DFT-computed selectivities arising from the competing TSs for seven substrate combinations with experiment. The trends and regioselectivities were well reproduced (see Figure S7). Compared to the favored ring-opening pathway **TS-V-A**, which involves nucleophilic attack at the methylene group, the less-favorable

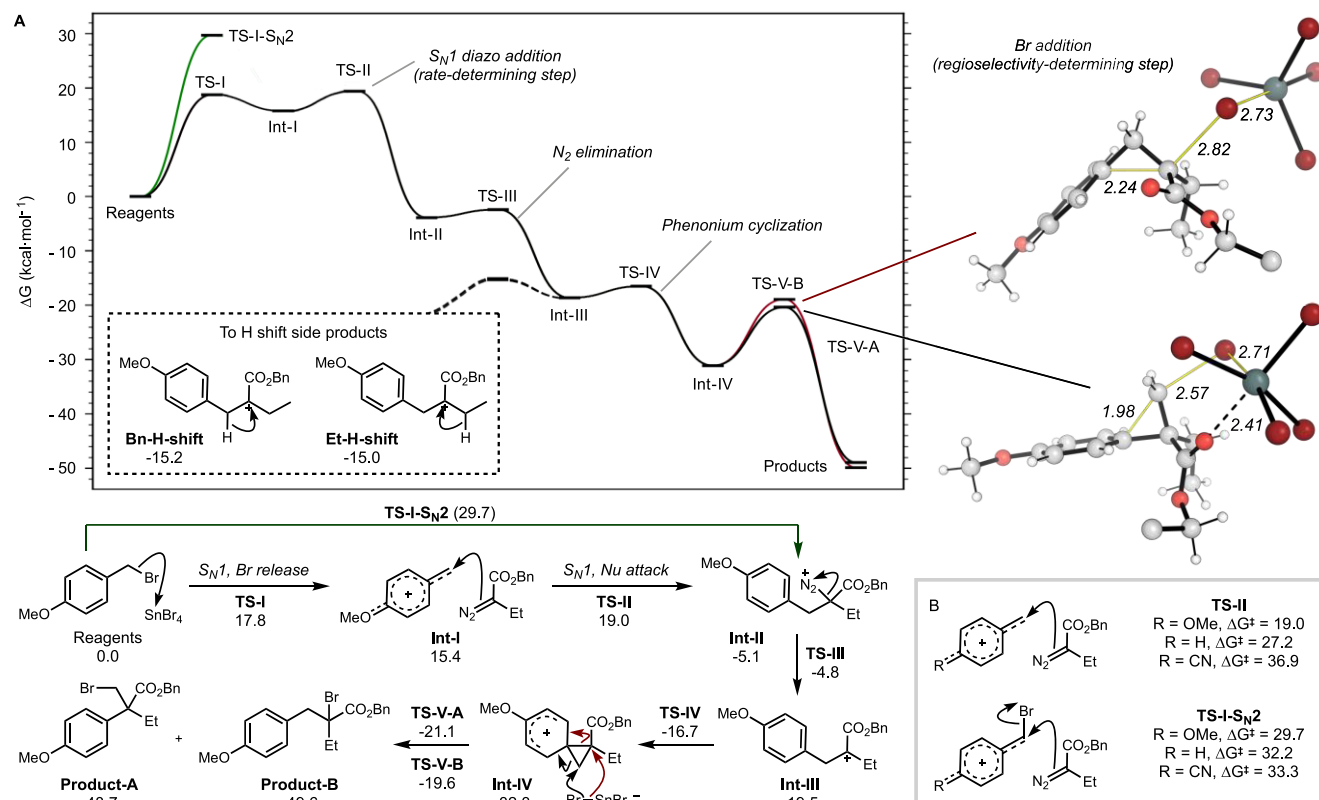


Figure 3. (A) Computed Gibbs energy profile at $-78\text{ }^{\circ}\text{C}$, 1 M standard state. DFT calculations were performed at the $\omega\text{B97X-D/def2-QZVPP//}\omega\text{B97X-D/6-31+G(d,p)}$ (def2-SVPD for Sn during optimization) level of theory. Ph groups are omitted for clarity. (B) Relative energies of diazo addition to benzyl bromide derivatives.

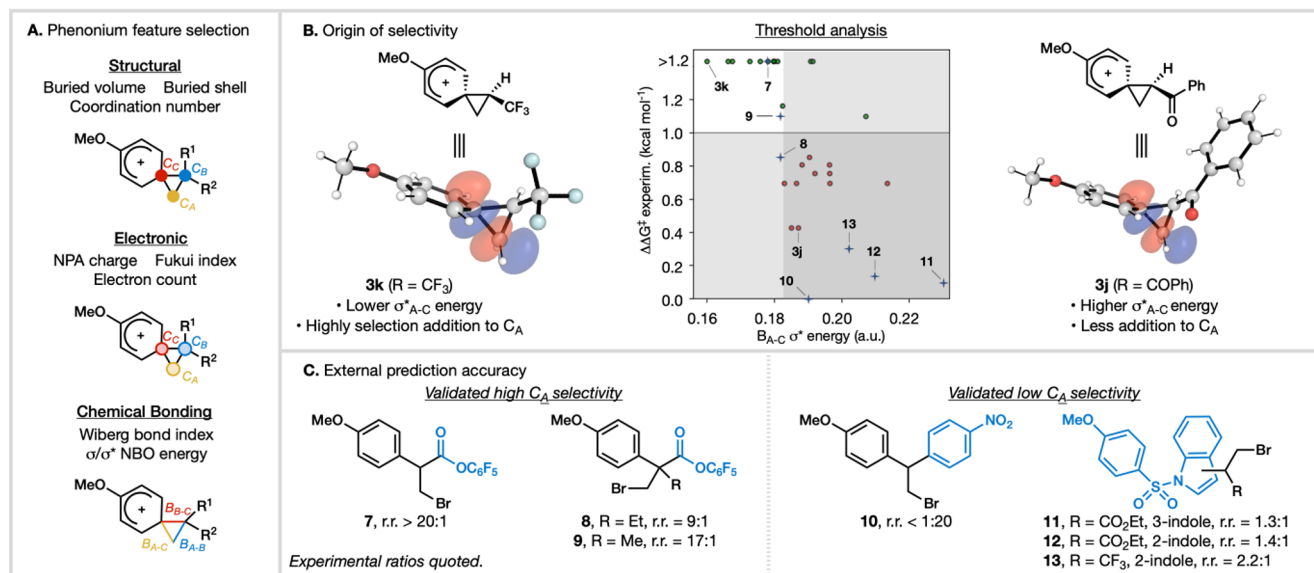


Figure 4. Selectivity of phenonium ion opening. (A) Phenonium descriptors considered. (B) Classification of selectivity using C_A–C_C antibonding energy establishing a threshold value. (C) Experimental validation of the model.

TS-V-B requires greater elongation of the cyclic C–C bond (by 0.26 Å) to reach the TS, which is looser and more “exploded” than its more stable counterpart.³⁰ Similarly, greater C–C bond breaking in the minor vs major TS was observed for all substrates considered.

To further investigate the relationship between structure of the phenonium intermediate and experimentally observed regioselectivity, we performed a statistical analysis. Structural,

electronic, and chemical bonding parameters of 25 phenonium intermediates were selected as key descriptors (Figure 4A and Figure S9). Inspired by Sigman and Doyle’s application of a single-node decision tree to infer mechanistic information, we sought to identify a single descriptor able to function as a classifier separating highly regioselective from unselective substrates.³¹ The use of a classification model, rather than (non)linear regression model, is also particularly well-suited

here since several substrates produce a single regioisomer (>20:1), preventing an exact value of $\Delta\Delta G^\ddagger$ being assigned. We therefore split the experimental data into high and low selectivity values, with an experimental r.r. of 13:1 ($\Delta\Delta G^\ddagger = 1$ kcal mol⁻¹) serving as this cutoff. We identified a chemical bonding feature, the energy of the natural C_A–C_C σ^* orbital, performed best and allowed us to identify a “threshold” energy (0.183 au) below which all substrates react with high regioselectivity (Figure 4B). Phenonium ions with C_A–C_C σ^* energies below this threshold universally give experimental selectivities >13:1, while of those with energies above this threshold 11/14 (79%) give low selectivities. This is the bond cleaved irreversibly in the transition structure, leading to the formation of the major (i.e., homologated) regioisomer.

To validate this model, seven out-of-sample substrates bearing different substituents to those used during training were designed theoretically with predicted selectivities ranging from high (7–9) to low (10–13). These predictions generated by the classifier were consistent with the experimental results (Figure 4C).

In conclusion, we report a homologation reaction of benzyl bromides with diazo derivatives. This reaction exploits the classical reactivity of benzyl halides (as electrophiles) and aromatic rings (as nucleophiles) to achieve formal insertion of a diazo into the C(sp²)–C(sp³) bond. Computational analysis of the reaction coordinate revealed a rate-determining S_N1 mechanism for the initial C–C bond formation followed by a cascading sequence of cationic intermediates leading to a phenonium ion. Insights into the regioselectivity of phenonium ion opening were gained and enabled *a priori* prediction of reaction outcomes for new substrate combinations. Overall, this work provides a modular method for constructing acyclic, benzylic quaternary centers from readily accessible starting materials which we anticipate may find utility in drug discovery programs.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c11503>.

Experimental procedures, characterization data for novel compounds, crystallographic analysis, and computational details (PDF)

Accession Codes

CCDC 2101216 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, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): N.J.R. and A.M. have filed a provisional patent on chemistry disclosed in this manuscript.

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