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A General Method for the Dibromination of Vicinal sp^3 C–H Bonds Exploiting Weak Solvent–Substrate Noncovalent Interactions

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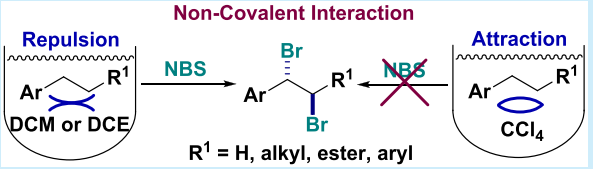
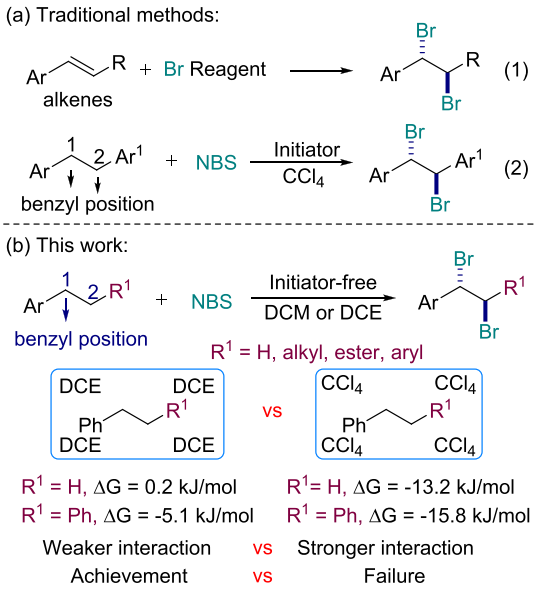
ABSTRACT: A general procedure of 1,2-dibromination of vicinal sp^3 C–H bonds of arylethanes using *N*-bromosuccinimide as the bromide reagent without an external initiator has been established. The modulation of the strength of the intermolecular noncovalent interactions between the solvent and arylethane ethanes, quantitatively evaluated via quantum chemical calculations, allows us to circumvent the fact that arylethane ethane cannot be dibrominated through traditional methods. The mechanism was explored by both experiments and quantum chemical calculations, revealing a radical chain with HAA process.



1,2-Dibromoarylethane derivatives are acknowledged as significant intermediates in the field of fine chemical synthesis; in particular, they are involved in the conversion to multiple functionalized compounds, including alkenes,[1] alkynes,[2] azirines,[3] azides,[4] alcohols,[5] ketones,[5a,6] and epoxides.[5a,b,7] A great majority of approaches for the preparation of 1,2-dibromoarylethanes through one step focus on the difunctionalization of arylalkenes (Scheme 1a, eq 1).[8] However, arylalkenes usually must be prefunctionalized from the corresponding arylalkanes, increasing the number of synthesis stages and the cost of producing 1,2-dibromoarylethanes. For instance, styrene is industrially produced by the oxidative dehydrogenation of phenylethane, which is more expensive than phenylethane ($1277 per ton vs $638 per ton). To save a reaction step and production costs, the direct 1,2-dibromation of phenylethane is the ideal transformation. Nevertheless, a few examples report the synchronous introduction of two bromine atoms into vicinal sp^3 C–H bonds in one pot. The reactions are limited to the dibromination reaction of 1,2-diarylethane with *N*-bromosuccinimide (NBS) in the presence of an external initiator, like peroxide or azodiisobutyronitrile, in carbon tetrachloride (CCl_4) during heating (Scheme 1a, eq 2).[9] In these transformations, two benzyl radicals are indispensable for the formation of 1,2-dibromoethane compounds by quenching of two bromine radicals. To the best of our knowledge, the 1,2-dibromination reaction of ethanes separately bearing one aryl group and one non-aryl group (e.g., proton, alkyl, or ester) at vicinal positions has not been demonstrated to date. We initially considered this may be due to the higher stability of the radical in position 2 compared to that of the benzyl radical in the 1-aryl-2-non-aryl-substituted ethanes (Scheme 1b). 1,2-Dibromination of phenylethane with NBS performed by our group under the literature reaction conditions gave no 1,2-dibromoethane product (Table S5, entry 9). However, when DCE (1,2-dichloroethane), DCM (dichloromethane), TCE (1,1,2,2-tetrachloroethane), or chloroform was employed as the solvent in place of CCl_4, in the absence of any external initiator, unexpectedly, 60–65%

Scheme 1. Traditional Method versus Our Method for Synthesis of 1,2-Dibromoarylethane



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yields of 1,2-dibromoethane product were successfully attained in the transformation (Table S5). This finding suggests that not only the stability of radicals but also the interaction between the arylethane and solvent molecules may represent significant a reaction factor.

To reveal the type of interactions of phenylethane and 1,2-diphenylethane with the solvent (CCl_4, DCM, DCE, and TCE), a series of quantum chemical calculations were performed, accounting for several possible interaction geometries (Scheme 1b; details in Table S11). The average values of the Gibbs free energy of interaction between phenylethane and a solvent molecule decrease in the following order: DCM (~0 kJ/mol) > DCE (−0.2 kJ/mol) > TCE (−6.3 kJ/mol) > CCl_4 (−13.2 kJ/mol). In the latter two environments, the phenylethane molecules are therefore less available for the 1,2-dibromination reaction because of strong interactions with the solvation shell. A similar thing happens to 1,2-diphenylethane, whose average ΔG values of interaction are −3.2 kJ/mol (DCM), −5.1 kJ/mol (DCE), −6.7 kJ/mol (TCE), and −15.8 kJ/mol (CCl_4); this may be why the introduction of an external initiator is necessary in the 1,2-dibromination process of 1,2-diphenylethane in CCl_4. The computed values of substrate−solvent interaction are consistent with the experimentally determined reaction yields. The strength of the intermolecular noncovalent interactions (NCIs) established between the reactant and the solvent is also depicted in Figure S9, where in the case of CCl_4 strongly attractive NCIs are shown between the Cl atoms of the solvent and the C atoms of the reactant molecule. TCE also shows extended positive NCI regions but less strongly attractive ones. In the case of DCM and DCE, the NCIs are weakly attractive or even repulsive in nature.

To further establish an available synthesis method for the dibromination of vicinal sp^3 C−H bonds, a new radical initiator free 1,2-dibromination transformation of 1-arylethane derivatives with NBS as the bromine source has been developed, affording various 1,2-dibromo products with efficiencies ranging from moderate to high. In this dibromination reaction, chloroalkanes other than CCl_4 were used as the solvent, and the reactivity was obviously enhanced under thermal conditions. The high-value-added compounds (e.g., azides, alcohols, ketones, and epoxides) were readily synthesized from 1,2-dibromophenylethane. A preliminary mechanistic study was attempted, involving a set of possible reactions, explored by means of quantum chemical calculations, and revealed feasible radical chain pathways with hydrogen atom abstraction (HAA).

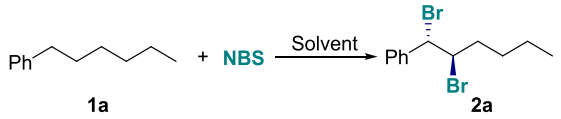
To refine the dibromination reaction, the treatment of hexylbenzene **1a** with NBS was performed at 100 °C for 6 h (Table 1). CCl_4 was initially employed as the solvent, and a trace of dibromination product **2a** was detected (entry 1). On the contrary, when CCl_4 was replaced with DCE, chloroform ($CHCl_3$), or dichloromethane (DCM), **2a** was effortlessly formed (entries 2−4). Solvent screening demonstrated that DCM is the optimum, producing the highest yield (82%, entry 4). When the amount of NBS was decreased from 3.5 to 2.5 equiv, the conversion efficiency did not vary significantly (entries 5 and 6). To further increase the yield, temperature and time effects were also investigated, finally confirming 100 °C and 6 h as the optimized conditions (entries 7−11).

Exploiting the optimal reaction conditions to broaden the scope of the investigated reaction, we tested a variety of substrates, allowing the synthesis of arylethane derivatives **2a**−**2u** (Table 2). Benzenes with long chain alkyls **1a**−**1f** readily reacted with NBS to yield vicinal dibromoethanes **2a**−**2f** with high efficiencies. Interestingly, 1,2,3-tribromination product **2g** instead of a dibrominated or monobrominated compound[10] was isolated via conversion of cyclopropylbenzene **1g**. Dibrominated compounds **2h**−**2j** were easily obtained with excellent diastereoselectivities by using 1-ester-2-phenylethanes as the substrate. In particular, *trans*-**2i** was isolated and characterized by X-ray single-crystal diffractometry, which uncontroversially revealed the position of the two bromine atoms lying almost on the same plane (Figure S8). Product **2k** was obtained in 54% yield by decreasing the reaction temperature to 80 °C without any additive. **1l** was successfully transformed into the corresponding product **2l** in modest yield and high diastereoselectivity. For products **2a**−**2j** and **2l**, the *trans* structure is primarily synthesized due to the higher stability with respect to the other isomers, as shown by quantum chemical calculations. The optimal reaction conditions of 1,2-dibromination of phenylethane **1m** were also identified, with synthesis of **2m** in 85% yield (Tables S5−S8). The effects due to the presence of electron-withdrawing groups in the aryl ring of phenylethanes were also inspected; upon 1,2-dibromination, the desired products **2m**−**2r** were effortlessly obtained in 34−81% yields. The treatment of 4-methylphenylethane **1r** with NBS provided 1,2-dibromo product **2r** under the standard reaction conditions.

With an increase in the amount of NBS to 3.5 equiv, tribromination compound **2s** could be isolated in moderate yield. In addition to the methyl group, 2-methoxy and 2-acetoxy groups in the aromatic ring were also compatible with the investigated reaction, straightforwardly forming products **2t** and **2u**, respectively.

To show the broadness of the synthetic applicability of 1,2-dibromoethane derivatives, various compounds were formed when **2m** was used as a reactant (Scheme 2a). 1,2-Dibromophenylethane **2m** facilely reacted with NaN_3 to provide azides **4** and **5** in DMSO and DMF, respectively.[4] 1,2-Dihydroxyphenylethane **6** was produced from **2m** under basic conditions. When **2m** was heated in acetone and H_2O,

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	yield and dr[b]
1	CCl_4	trace
2	DCE	78%, dr = 69:31
3	$CHCl_3$	81%, dr = 74:26
4	DCM	82%, dr = 75:25
5	DCM	62%,[c] dr = 80:20
6	DCM	82%[d] (79%),[e] dr = 75:25
7	DCM	trace[d,f]
8	DCM	76%,[d,g] dr = 75:25
9	DCM	77%,[d,h] dr = 75:25
10	DCM	67%,[d,i] dr = 75:25
11	DCM	82%,[d,j] dr = 75:25

[a]Reaction conditions: **1a** (0.5 mmol, 1 equiv), NBS (1.75 mmol, 3.5 equiv), solvent (2.0 mL), 100 °C, 6 h, N_2. [b]Yield and dr value determined by ^1H NMR using the crude reaction. [c]NBS (1.0 mmol, 2.0 equiv). [d]NBS (1.25 mmol, 2.5 equiv). [e]Isolated yield. [f]At 60 °C. [g]At 80 °C. [h]At 120 °C. [i]For 3 h. [j]For 12 h.

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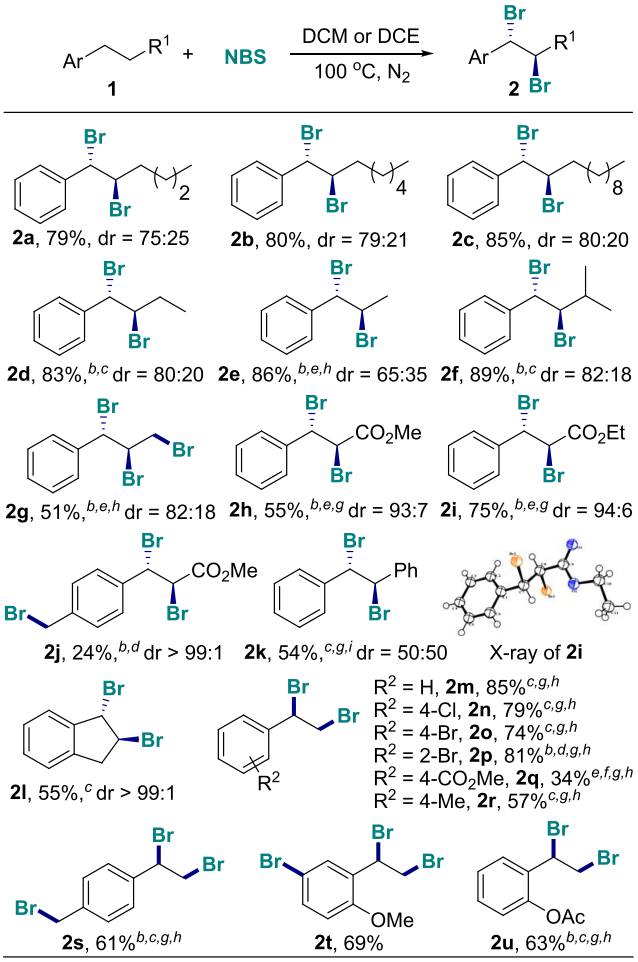
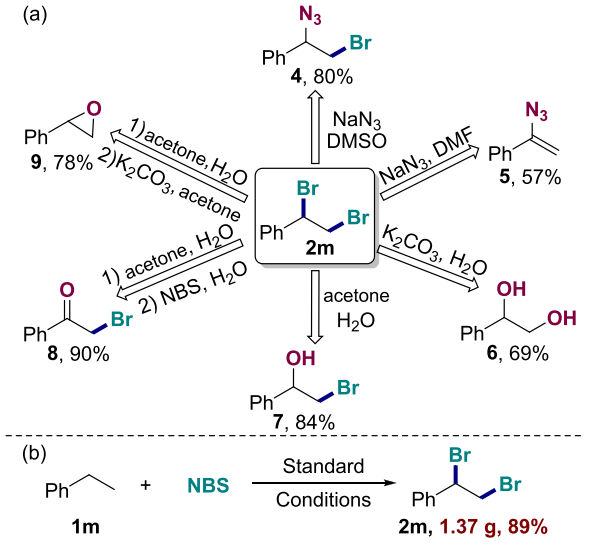
Table 2. Substrate Scope of Arylethane Derivatives[a]



[a]Reaction conditions: **1** (0.5 mmol, 1 equiv), NBS (1.25 mmol, 2.5 equiv), DCM (2.0 mL), 100 °C, 6 h, N_2, isolated yield, dr value determined by ^{1}H NMR using the crude reaction. [b]NBS (1.75 mmol, 3.5 equiv). [c]For 12 h. [d]For 24 h. [e]For 48 h. [f]NBS (2.5 mmol, 5 equiv). [g]DCE (2.0 mL). [h]$Me_4N^+I^-$ (10 mol %). [i]At 80 °C.

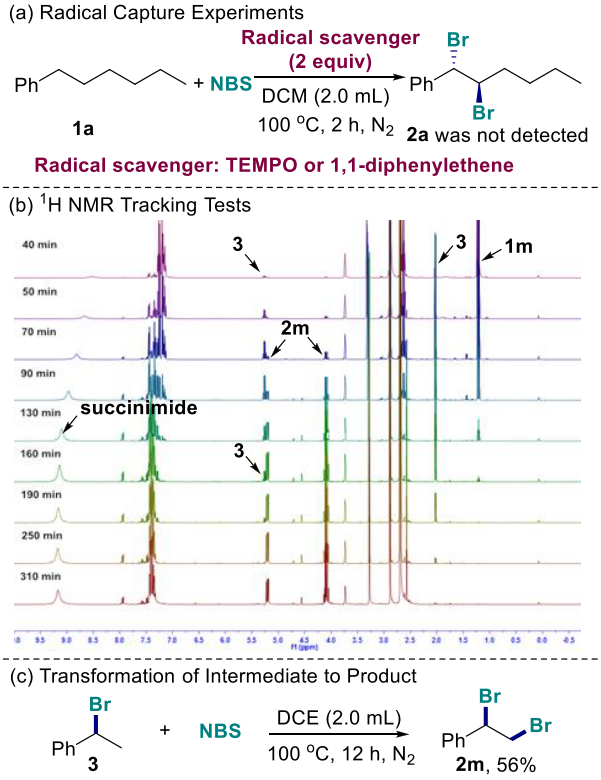
Scheme 2. Synthetic Application of 1,2-Dibromophenylethane



alcohol **7** could be easily obtained.[5] Ketone **8** and epoxide **9** could be derived from **2m** by a two-step procedure.[6,7] In particular, **9** was also readily synthesized from **2m** via a successive step (see the Supporting Information). Finally, a gram-scale transformation was successfully subjected to the optimal reaction conditions, forming **2m** in 89% yield (1.37 g) (Scheme 2b; details in the Supporting Information).

Furthermore, a series of preliminary experiments were carried out to shed light on still unclarified aspects of the mechanism of the dibromination reaction of arylethane derivatives (Scheme 3). Product **2a** was not detected with

Scheme 3. Preliminary Mechanistic Research



the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) or 1,1-diphenylethene in the reaction of **1a** with NBS under the standard reaction conditions. These results indicate that this reaction includes a radical process (Scheme 3a). To capture the intermediates in the dibromination process of **2m** with NBS, the reaction was tracked by *in situ* ^{1}H NMR experiments (Scheme 3b). The characteristic peak of (1-bromoethyl)benzene **3** arises at 40 min, its intensity increasing with a decrease in the amount of **1m**. Simultaneously, the increase in the amount of product **2m** accompanies the decreases in the amounts of **1m** and **3**. Furthermore, **3** could react with NBS to give **2m** in 56% yield using the optimal conditions (Scheme 3c). Compound **3** may therefore be one of the intermediates in the transformation. On the contrary, HBr and Br_2 could be detected by means of classical methods (e.g., $AgNO_3$ and KI in a starch solution), which reveal that both HBr and Br_2 are intermediates (details in the Supporting Information). The intermolecular kinetic isotope effect (KIE) experiment was examined, giving a k_H/k_D value of 2.7. This result implies that the C−H bond cleavage is possibly involved in the rate-determining step (Figure S6). Hammett's analysis provided a ρ slope value of −0.219 through the competition

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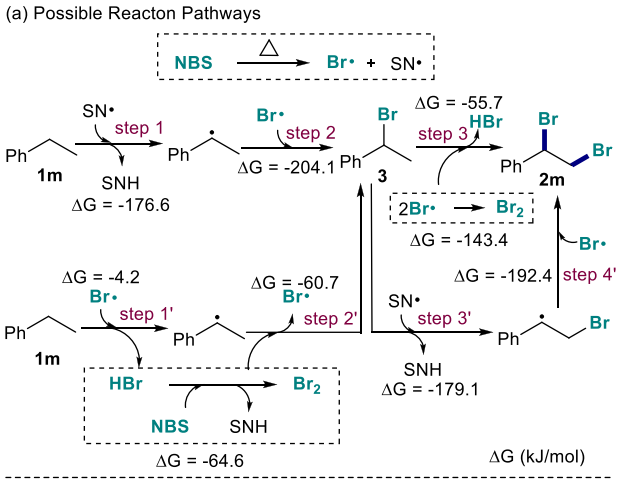
experiments of NBS with *para*-substituted phenylethanes (Figure S7). Although this result suggests that cationic species are probably contained in the transition state, the radical approach is still dominating, because the radical species were shown to be largely more stable than the cationic ones on the basis of quantum chemical calculations. Both the KIE and a Hammett plot show that a HAA procedure is part of the 1,2-dibromination reaction.

On the basis of both the experimental evidence and the computed thermochemical data (Table S12), possible reaction pathways for the 1,2-dibromination of aryl alkanes with NBS were proposed (Scheme 4a). First, bromine and succinimide

Scheme 4. Possible Reaction Mechanism



radicals are rapidly achieved by thermal dissociation of NBS. One way consists of steps 1−3, which starts with the extraction of hydrogen from **1m** by the succinimide radical (step 1). Subsequently, a newly formed benzyl radical couples with the bromine radical to form intermediate **3**, which is successively brominated by bromine to deliver product **2m** via a radical pathway (steps 2 and 3).[9,11] We consider that step 3 is a radical process because the radical capture experiment of **3** with TEMPO was carried out under the standard reaction conditions, and a detailed probable pathway also was presented (see the Supporting Information). In addition, other pathways cannot be totally excluded according to the literature.[12] Alternatively, a benzyl radical may be produced by the single-electron transfer of the bromine radical with **1m**, generating HBr that then reacts with NBS to give Br_2 by an ionic reaction (step 1′). Br_2 then reacts with a benzyl radical to afford **3** (step 2′), which is oxidized by the succinimide radical to provide a benzyl radical that can react with the bromine radical to give **2m** (steps 3′ and 4′). Quantum chemical calculations were also conducted to compare the reaction pathways, including steps 1−3 and 1′−4′. The process including stages 1−3 was established as the most probable way on the basis of the thermochemical data (Scheme 4b). For the two pathways, the most probable structures of transient states were also determined (see the Supporting Information). The activation Gibbs free energies for 1,2-dibromination reaction of 1,2-diphenylethane were shown to be slightly higher than that of phenylethane. Furthermore, with regard to the impact of the solvent interactions on the mechanism, we are inclined to suppose that the reaction requires the substrate to get free from the first solvation shell, especially in the molecular fragment involved in the reaction; if the substrate−solvent specific interactions are strong (as in the case of CCl_4), then the substrate does not get free and it is highly unlikely that the reaction would occur. Weak interactions guarantee the success of the reaction.

In conclusion, a simple method for 1,2-dibromination of arylethane compounds was described for the first time under heating conditions, in the absence of any external radical initiator. Diverse 1,2-dibromoarylethane compounds were easily derived in moderate to high yields when employing chloroalkanes such as DCM, DCE, TCE, etc., except CCl_4 as a solvent. Additionally, highly valuable chemicals such as azides, alcohols, ketones, and epoxides were facilely synthesized from 1,2-dibromophenylethane. A radical chain with HAA process could be hypothesized through preliminary mechanistic reactions and quantum chemical calculations. Furthermore, calculations were employed to verify the intermolecular weak noncovalent interactions between arylethane with chloroalkanes, which are responsible for the different reactivity of reactants in different solvents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04235.

Experimental procedures, characterization data, and NMR spectra of products (PDF)

Accession Codes

CCDC 1955811 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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Author Contributions

Z.Q. and W.L. contributed equally to this work. The design of this protocol was carried out by B.Q. The manuscript was written through contributions of B.Q. and E.B. The empirical data were acquired by Z.Q. and W.L. The quantum chemical calculations were finished by E.B. Y.N. participated in the modification of the manuscript. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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