Article

Catalytic Remote Dihalogenation of Alkenes Induced by Transposition of Esters

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ABSTRACT: Organic halides play an indispensable role in functional molecule synthesis and pharmaceuticals, driving continuous efforts to develop efficient synthetic strategies. While direct alkene halogenation is an ideal route to halogenated products, conventional methods are typically limited to 1,2-dihalogenation. Here, we report a phosphordiamide-catalyzed strategy for remote dihalogenation of alkenes induced by transposition of esters. Without the need for preinstalled directing groups, this approach achieves 1,4-, 1,3-, and 2,3-dihalogenation of alkenes under mild and operationally simple conditions. Terminal/

internal or *cis/trans* allylic/homoallylic esters undergo remote dihalogenation smoothly with good functional group tolerance. Preliminary mechanistic studies indicate that the catalyst cooperates with NBS and SOCl₂ to form an active intermediate, which enables selective remote dihalogenation promoted by ester transposition. Moreover, the products are readily accessible via gram-scale preparations, and their diverse transformations further highlight the protocol's potential as a versatile synthetic platform.
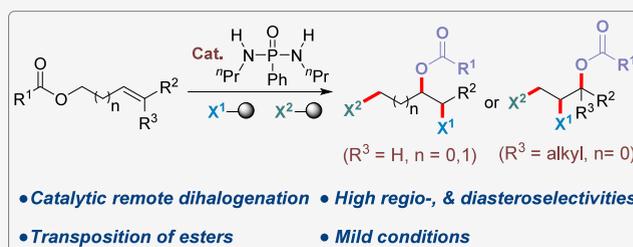
INTRODUCTION

Possessing distinct biological activities and reactivity, organic halides are indispensable in pharmaceutical development, energy materials, and functional molecule design.[1] Their critical role in molecular functionality innovation drives persistent efforts toward developing corresponding synthetic methodologies. While direct alkene halogenation is a classical, ideal route to organic halides,[2] conventional methods are confined to generating vicinal dihalides, which restrict the functional versatility of organic halides as synthetic platforms. Notably, the remote selective dihalogenation of alkenes remains underdeveloped, leaving a critical research gap that demands breakthrough strategies (Figure 1a).

Remote difunctionalization of alkenes enables precise control over functional group installation at nonadjacent carbons along carbon chains. It serves as a powerful and advanced tool to create functionalized molecules that are difficult to obtain via traditional approaches.[3] For instance, Liu and co-workers developed a palladium-catalyzed highly selective remote dioxygenation of internal alkenes with engineered pyridine-oxazoline ligands.[4] The transition-metal-catalyzed chain-walking approach operates via alkene insertion into a metal-hydride bond and β-hydrogen elimination, which drives migration of the metal center along the carbon chains to achieve remote functionalization (Figure 1b).[5] However, it is incompatible with dihalogenation due to deleterious side reactions between resulting organohalides and transition metals.[6] The use of radical intermediates provides another strategy for remote difunctionalization of alkenes (Figure 1c).[7] This process typically begins with radical addition to the alkene

to form an alkyl radical. Migration then yields a stabilized radical intermediate, which reacts with a second reagent to produce the transposed difunctionalized product. Although this approach demonstrates good compatibility with strongly coordinating groups (e.g., −NH₂, −OH, −COOH), achieving selective remote dihalogenation via halo radicals remains unreported.[8] Critically, both approaches invariably rely on preinstalled directing groups or "stopping sites" (e.g., benzylic positions of arenes, tertiary carbon centers)—to enforce regioselectivity, thereby significantly limiting substrate generality and operational simplicity.[3a,9]

As classical organic transformations, the Claisen and Cope rearrangements represent important double-bond transposition reactions of alkenes.[10] However, it is difficult to simultaneously achieve remote difunctionalizations through these traditional protocols, particularly the dihalogenation. In 2020, Jacobsen reported a 1,3-difluorination reaction of alkenes via aryl transposition.[11] In 2024, Lennox achieved 1,3-difluorination through transient oxonium intermediates.[12] Nevertheless, remote dihalogenation beyond fluorination remains a significant challenge. First, the reaction design for remote difunctionalization should ensure compatibility of introducing

a) Dihalogenation of alkenes
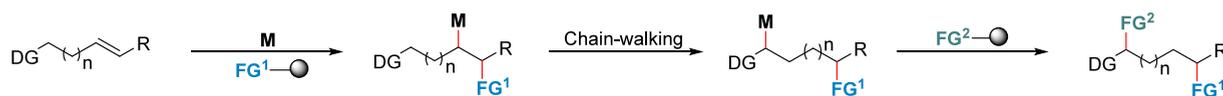

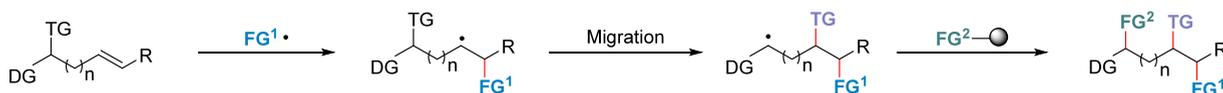*Welldeveloped*   *Underdeveloped*
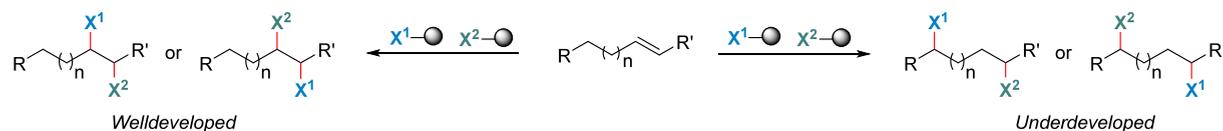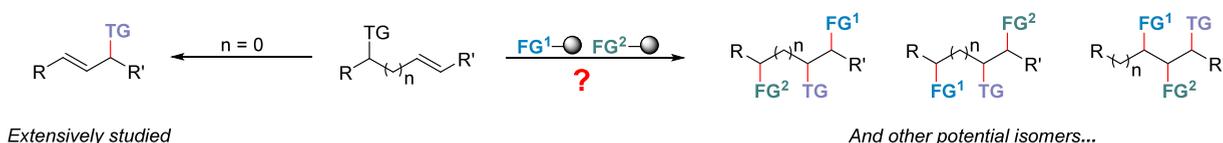
b) Chain-walking strategy for remote difunctionalization of alkenes

c) Radical-mediated strategies for remote difunctionalization of alkenes

d) Transposition of functionalization group in alkenes

Extensively studied   *And other potential isomers...*

e) This work: Catalytic remote dihalogenation of alkenes induced by transposition of esters

1,3- or 1,4-dihalogenation
(R^3 = H, n=0,1)

2,3-dihalogenation
(R^3 = alkyl, n= 0)

● *Catalytic remote dihalogenation*   ● *Transposition of esters*   ● *High chemo-, regio-, & diaseroselectivities*   ● *Mild conditions*
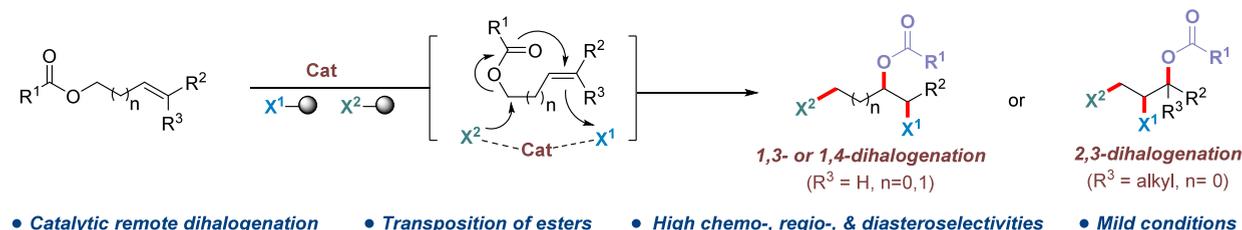
Figure 1. Catalytic functionalization and transposition in alkenes.

two distinct halogen atoms to effectively suppress side reactions.[13] Second, precise control over the transposition process is required to achieve directed migration of the transposition group to the target site, thereby preventing the formation of undesired isomers.[7e,14] Finally, multidimensional selectivity control presents challenges, requiring specific halogen installation at target positions to enable precise control over chemo- and regioselectivity (Figure 1d).[2e,f] To address the challenges of remote alkene dihalogenation, we developed a catalytic ester transposition strategy using readily available vinyl esters (Figure 1e). It demonstrated a precise 1,3-, 1,4-, and 2,3-homo/hetero-dihalogenation patterns with triple control over chemo-, regio-, and diastereoselectivity. This protocol provides a new synthetic platform for complex functional molecules.

Using compound **1a** as the model substrate, we systematically investigated the influence of key parameters, including catalyst, solvent, and halogen source, on the reaction efficiency and selectivity (Table 1). Through multidimensional condition evaluations, we identified a catalytic system delivering high activity and selectivity. Specifically, employing Ph(O)P-(NH^{n}Pr)$_2$ as the catalyst with stoichiometric *N*-bromosuccinimide (NBS)/SOCl$_2$ in DCE at room temperature, 1,4-

bromochlorination product **2a** was afforded in 83% yield and >20:1 selectivity after 1 h (entry 1). Only a small amount of product was observed without the catalyst Ph(O)P(NH^{n}Pr)$_2$ (entry 2). Owing to its weaker Lewis basicity, Ph(O)P(OMe)$_2$ struggled to activate halogenating reagents, thus affording poor yields (entry 3). In contrast, (O)P(C$_8$H$_{17}$)$_3$ delivered moderate yields but exhibited low selectivity, which is attributed to the absence of hydrogen-bonding interactions during the catalytic process (entry 4). The use of methanol as a solvent was not good for product formation (entry 5). Selectivity dropped substantially with acetonitrile as solvent (entry 6). *N, N*-dimethylformamide predominantly promoted side-product formation (entry 7). Alternative brominating reagents, such as 1,3-dibromo-5,5-dimethylhydantoin (DBH) or *N*-bromophthalimide (NBP), resulted in a decline in the selectivities (entries 8−9). The reaction failed to proceed when the inorganic chloride source LiCl was used (entry 10). Increasing halogenating reagent usage showed no significant impact on reaction outcomes (entry 11). The reaction concentration had a little impact on the reactivities (entries 12−13). Notably, the reaction could also be performed under air atmosphere (entry 14).

Table 1. Optimization for 1,4-Bromochlorination of Alkenes[a]
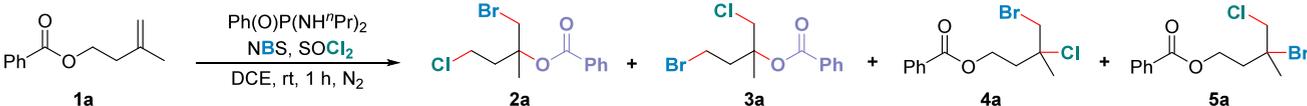
entry	variation from standard conditions	yield [%][b]			rr (2a/other)
		2a	3a	4a + 5a	
1	none	83 (80[c])	ND.	0	>20:1
2	w/o Ph(O)P(NH^{n}Pr)$_2$	6	ND.	2	3:1
3	Ph(O)P(OMe)$_2$ instead of Ph(O)P(NH^{n}Pr)$_2$	2	ND.	0	
4	(O)P(C$_8$H$_{17}$)$_3$ instead of Ph(O)P(NH^{n}Pr)$_2$	57	ND.	22	3:1
5	MeOH instead of DCE	1	ND.	3	1:3
6	MeCN instead of DCE	71	ND.	10	7:1
7	DMF instead of DCE	13	ND.	23	1:2
8[d]	DBH instead of NBS	63	ND.	6	10:1
9	NBP instead of NBS	73	ND.	4	18:1
10[e]	LiCl instead of SOCl$_2$	0	ND.	0	
11	NBS (1.5 equiv), SOCl$_2$ (0.75 equiv)	80	ND.	1	>20:1
12	1.0 mL DCE	70	ND.	3	>20:1
13	4.0 mL DCE	61	ND.	0	>20:1
14	air instead of N$_2$	81	ND.	3	>20:1

[a]Conditions: Unless otherwise noted, all reactions were performed with **1a** (0.20 mmol), NBS (0.20 mmol), SOCl$_2$ (0.10 mmol), and Ph(O)P(NH^{n}Pr)$_2$ (0.01 mmol) in DCE (2.0 mL) at room temperature for 1 h. [b]Yields were determined by GC-FID. [c]Isolated yield. [d][Br] (0.10 mmol). [e][Cl] (0.20 mmol).

■ RESULTS AND DISCUSSION

With the optimized conditions established, we evaluated the generality of substrate scope in this transformation (Figure 2). The experimental results demonstrated that aromatic esters bearing either electron-donating or electron-withdrawing groups underwent transposition smoothly to afford the corresponding 1,4-bromochlorination products (**2a**–**2i**) with excellent chemo- and regioselectivity. Dual-substituted aromatic esters were also well tolerated, delivering the desired products with high yields (**2j**–**2k**). Furthermore, esters containing heteroaromatic rings (such as pyridine, pyrimidine, quinoline, and benzofuran) exhibited good compatibility (**2l**–**2q**). Significantly, coumarin and cinnamate esters underwent ester transposition exclusively at the unactivated double bonds, leading to the corresponding products (**2r**–**2u**). Additionally, the structure of **2r** was confirmed by single-crystal X-ray diffraction analysis (CCDC 2464012). Terephthalate ester was also applicable to this transformation (**2v**). Remarkably, carbonate ester was tolerated and gave the target product **2w** in 69% yield with 12:1 regioselectivity. Besides, using a phosphonate as the transposition group could afford the corresponding remote bromochlorination product **2x** in 47% yield. Finally, this protocol could be successfully extended to substrates incorporating pharmaceutical fragments (acedoben, probenecid, and aspirin) and gave corresponding products in moderate to good yields (**2y**–**2aa**). To achieve asymmetric remote bromochlorination of in future studies, it is necessary to design new chiral catalysts, as the employment of known chiral thiourea catalyst only afforded racemic product (For details please see Figure S5, SI).

Subsequently, we proceeded to investigate the generality of this transformation with various alkenes (Figure 3). The homoallyl benzoate **1ab** was exclusively converted to the 1,4-bromochlorination product **2ab** in 59% yield. Notably, the (Z)-phytyl benzoate **1ac** afforded corresponding product **2ac** in 82% yield with >20:1 chemo-, regio-, and diastereoselectiv-

ity. The reaction could also be applied to (E)-internal alkene **1ad**, yielding **2ad** in 85% yield. The system accommodated extended carbon chains (**1ae**, **1af**), affording (**2ae**, **2af**) in 66–75% yields with retained selectivity. Bishomoallyl ester **1ag** underwent 1,4-bromochlorination to give transpositional ester **2ag** with a remaining homoallyl group in 57% yield. The 1,1-dialkyl-substituted vinyl esters (**1ah**, **1ai**) underwent transformation to deliver the corresponding products (**2ah**, **2ai**) with excellent yields and selectivities. The system also demonstrated broad compatibility with allylic esters bearing double bonds at various positions, delivering the 1,3-bromochlorination products (**2aj**–**2an**) with high selectivity. The but-3-en-2-yl benzoate **1ao** provided 1,3-bromochlorination product **2ao** in 42% yield with >20:1 chemo-, regio-, and diastereoselectivity. The penta-1,4-dien-3-yl benzoate **1ap** underwent selective 1,3-bromochlorination to give **2ap** in 40% yield with a remaining allyl group. A substrate bearing a free hydroxyl group underwent bromochlorination to afford the product **2aq** with high diastereoselectivity.

Building upon the efficacy of this remote bromochlorination strategy, we further explored halogen sources to expand the dihalogenation patterns (Figure 4). The replacement of SOCl$_2$ with SOBr$_2$ enabled highly selective 1,4-dibromination of homoallylic esters. Terminal alkenes (**1a**, **1ab**) afforded the corresponding products (**6a**, **6ab**) in 79–83% yields. The internal alkene **1ac** underwent 1,4-dibromination to give **6ac** in 76% yield with >20:1 chemo-, regio-, and diastereoselectivity. Additionally, when using 1,3-dichloro-5,5-dimethylhydantoin (DCH) as the chloronium source, substrate **1a** underwent 1,4-dichlorination smoothly to afford **7a** in 75% yield. This protocol also demonstrated good compatibility with allylic esters, providing 1,3-dibromination products (**6aj**–**6al**) in 56–81% yields and the 1,3-dichloride **7ak** in 62% yield. Remarkably, 1,1-dimethyl substituted allylic esters underwent 1,3-ester transposition due to the gem-dimethyl effect, facilitating efficient construction of 2,3-dihalides. In the presence of NBS/SOCl$_2$, 3-methylbut-2-en-1-yl benzoate **1ar**
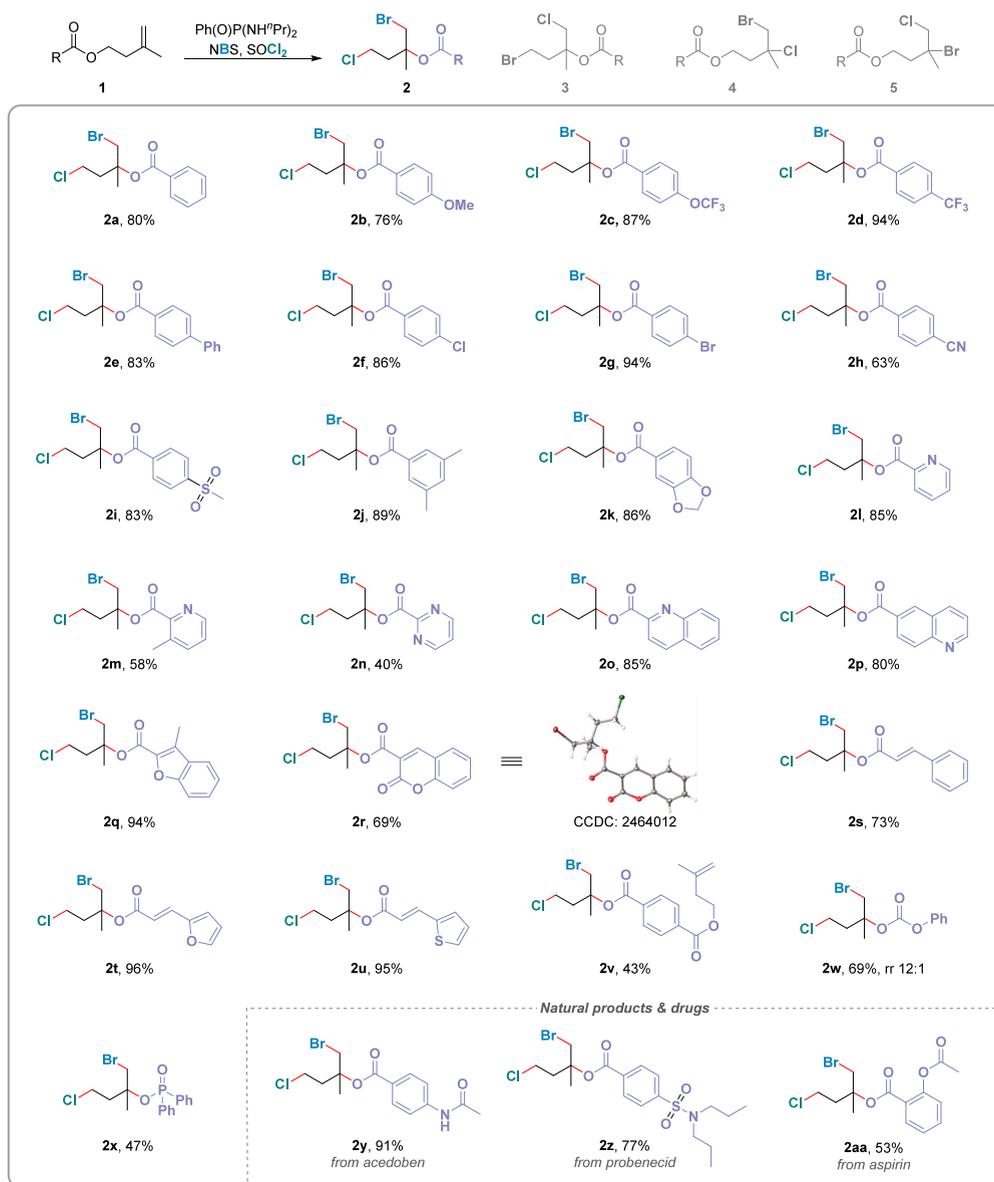
Figure 2. Substrate scope of transposition groups. [a]Conditions: Unless otherwise noted, all reactions were performed with **1** (0.20 mmol), NBS (0.20 mmol), SOCl$_2$ (0.10 mmol), and Ph(O)P(NH^{n}Pr)$_2$ (0.01 mmol) in DCE (2.0 mL) at room temperature for 1 h.

underwent efficient 2,3-bromochlorination, delivering product **2ar** in 71% yield with 10:1 regioselectivity. The methoxy-substituted analogue **1as** afforded **2as** in 91% yield with higher selectivity. The cinnamyl substrate **1at** exhibited exclusive reactivity at the more electron-rich double bond, providing **2at** in 62% yield. For a heterocyclic substrate, thiophene-containing substrate **1au** generated transpositional ester **2au** in 58% yield. The sterically congested substrate **1av** produced the desired 2,3-bromochlorination product **2av** in 74% yield with high regioselectivity. Moreover, the use of NBS/SOBr$_2$ and DCH/SOCl$_2$, respectively, delivered the corresponding 2,3-dibromides (**6as**, **6at**) and 2,3-dichlorides (**7as**, **7at**) in moderate to good yields.

Mechanistic Studies

To elucidate the reaction mechanism of this remote dihalogenation, we conducted a series of mechanistic studies. Radical inhibition experiments with butylated hydroxytoluene (BHT) showed negligible impact on the yield of **2a** (Figure

5a), implying the absence of radical intermediates in the dominant pathway.[7d,15] A mixture of potential intermediates **4a** and **5a** showed no conversion to **2a** under standard conditions (Figure 5b). It rules out the interconversion between side-products **4a** and **5a** and product **2a**. As shown in the mechanistic studies (Figure 5c), this reaction exhibited notable water sensitivity. Adding 0.5 equiv H$_2$O reduced the yield of **2a** from 83 to 38%, while 1.0 equiv H$_2$O further decreased the yield to 25% and selectivity to 5:1 (Figure 5c, entries 2−3). The water acted as a competing nucleophile and the bromohydroxylated product was obtained in 50% yield (SI, Figure S1). To identify the byproduct of this protocol, we conducted the NMR analysis in the absence of **1a** before workup and successfully observed the characteristic signals of **8**, which was further confirmed by HRMS. Subsequent scale-up experiments led to the isolation of succinimide **9** in 84% yield (Figure 5d). Given the absence of proton sources in the reaction, the obtained succinimide **9** was probably generated from the hydrolysis of byproduct **8** during workup.
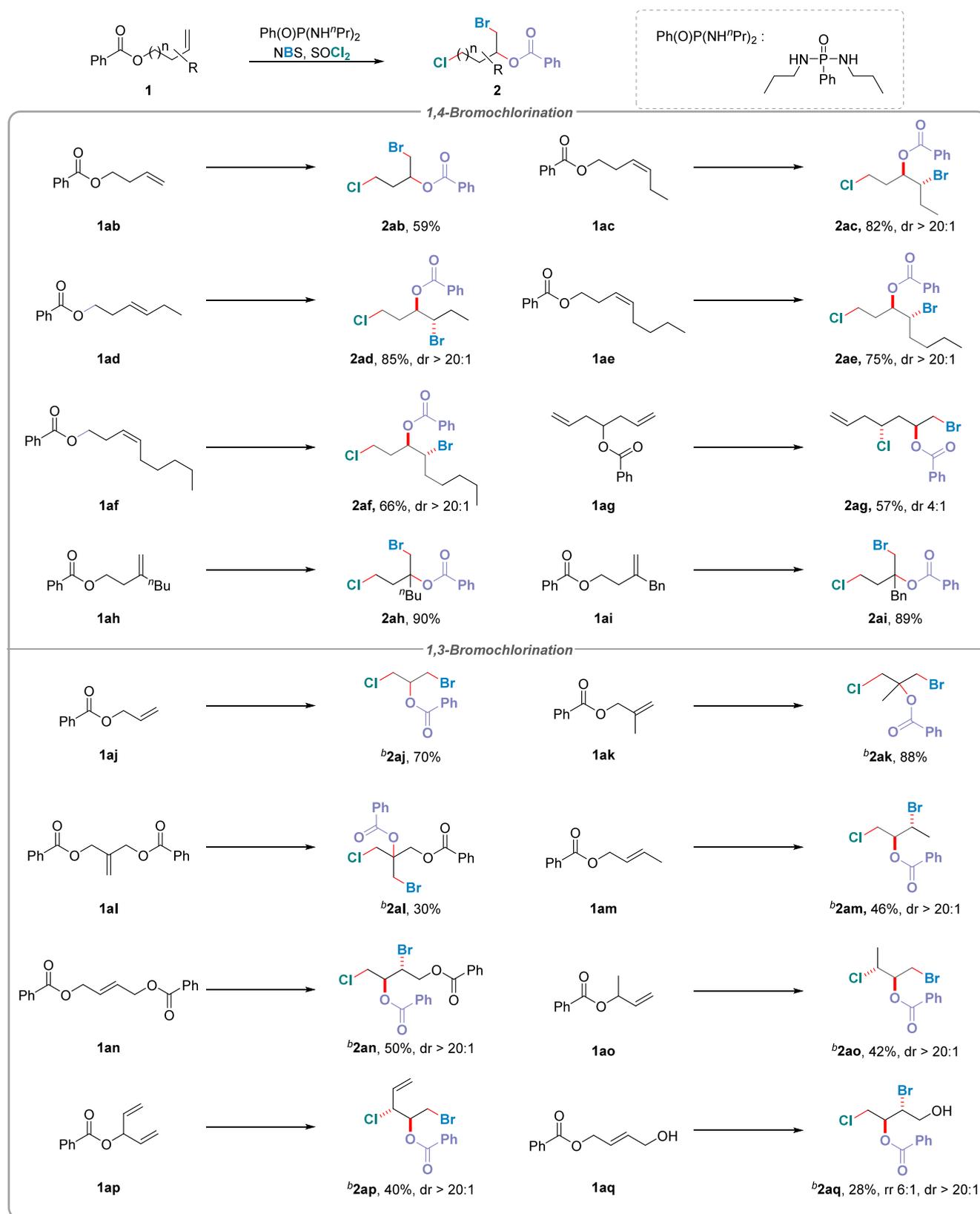
Figure 3. Substrate scope for remote bromochlorination of alkenes induced by transposition of esters. [a]Conditions: Unless otherwise noted, all reactions were performed with **1** (0.20 mmol), NBS (0.20 mmol), SOCl$_2$ (0.10 mmol), and Ph(O)P(NH^{n}Pr)$_2$ (0.01 mmol) in DCE (2.0 mL) at room temperature for 1 h. [b]Reaction with NBS (0.40 mmol) and SOCl$_2$ (0.20 mmol) for 4 h.

In the absence of the catalyst, product **2a** was obtained in only 6% yield with 3:1 regioselectivity (Figure 5f, entry 2). [1]H

NMR monitoring showed that only small amounts of succinimide **9** were generated from the reaction of NBS with
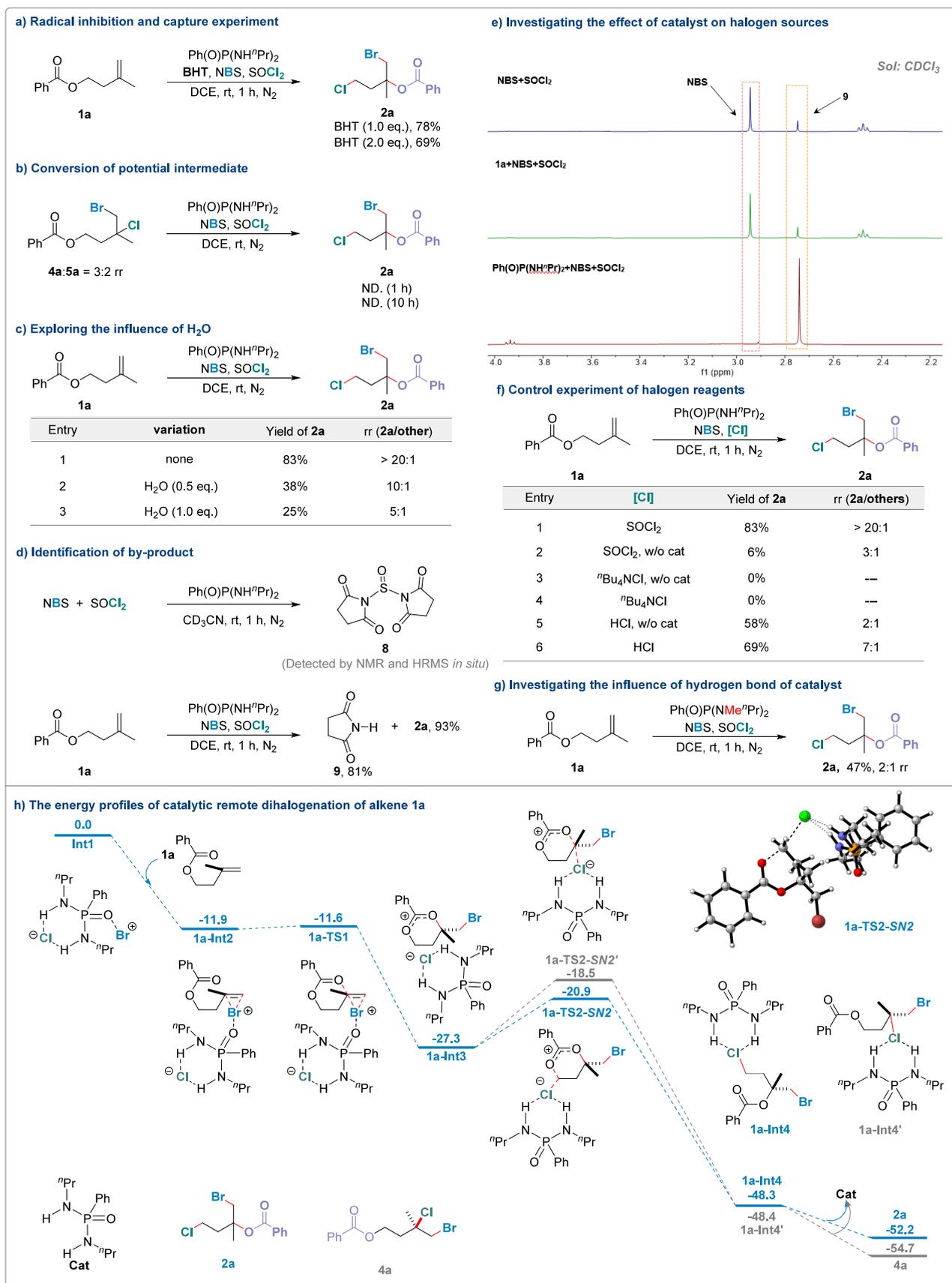
Figure 4. Substrate scope for remote dihalogenation of alkenes induced by transposition of esters. [a]Conditions: Unless otherwise noted, all reactions were performed with **1** (0.20 mmol), NBS or DCH (0.20 mmol), SOX_2 (0.10 mmol), and $Ph(O)P(NH^nPr)_2$ (0.01 mmol) in DCE (2.0 mL) at room temperature for 1 h.

$SOCl_2$. The further addition of substrate **1a** exhibited negligible influence on this outcome. Strikingly, upon introduction of the catalyst $Ph(O)P(NH^nPr)_2$, the character-

istic signals of NBS disappeared completely, accompanied by a substantial increase in the intensity of succinimide **9** (Figure 5e). These underscore the critical role of the catalyst

Figure 5. Mechanistic studies and DFT calculations.

Ph(O)P(NH^{n}Pr)$_2$ in activating SOCl$_2$ and NBS, which likely facilitates the generation of active halogenating species such as

BrCl.[2e,16] When using ^{n}Bu$_4$NCl as a chlorine source, neither **2a** nor isomers formed due to inefficient BrCl generation (Figure
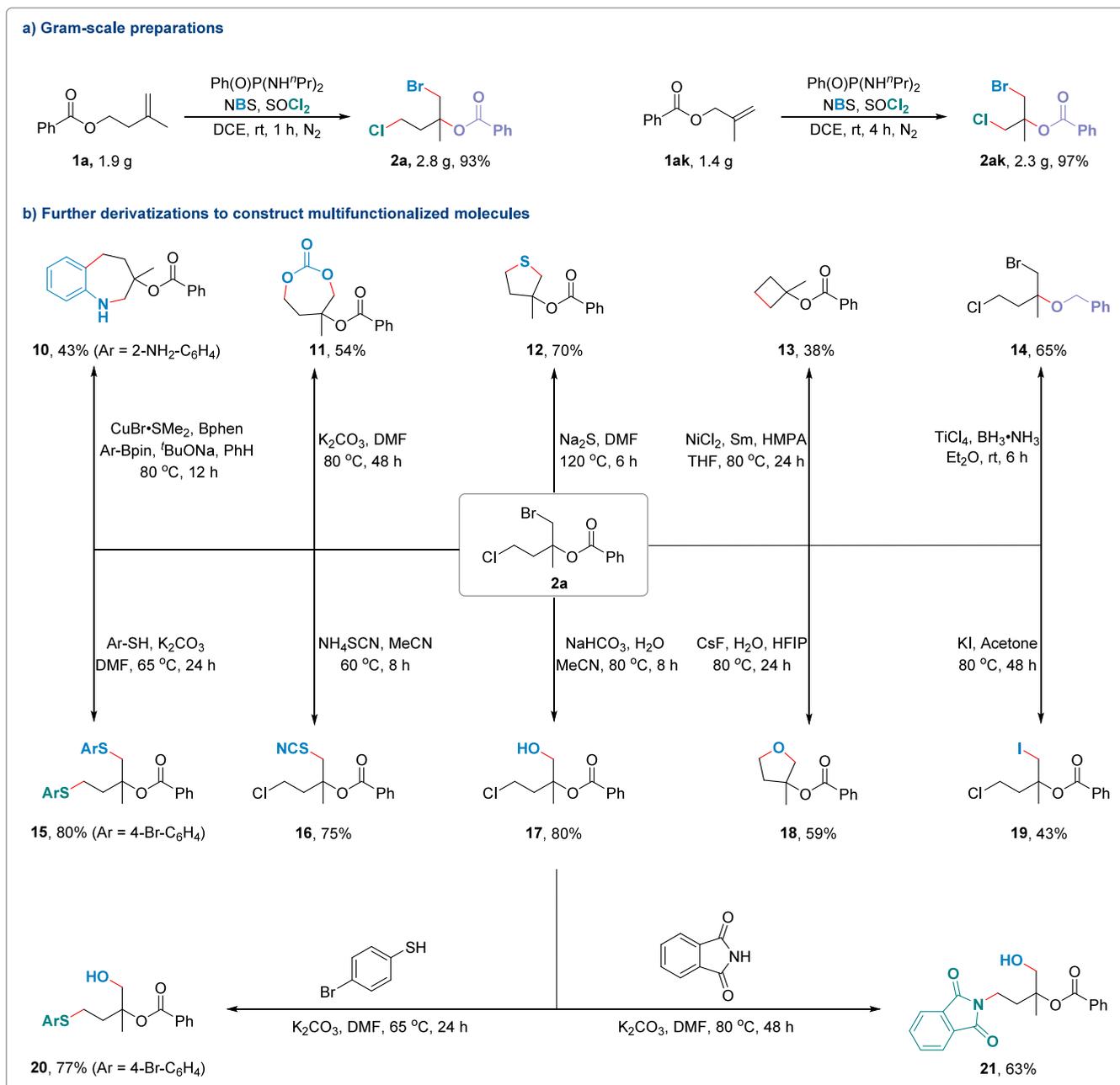
Figure 6. Gram-scale preparations and further derivatizations to construct multifunctionalized molecules.

5f, entries 3−4).[2f] HCl rapidly reacted with NBS to produce BrCl, then delivered **2a** in 58% yield with 2:1 regioselectivity without added catalyst (Figure 5f, entry 5).[17] In contrast, the yield of **2a** was increased to 69% and selectivity increased to 7:1 in the presence of the catalyst (Figure 5f, entry 6). Previous studies revealed that hydrogen bonding stabilizes halide anions, while the nucleophilic oxygen atom in the catalyst could stabilize bromonium ions.[18] After the removal of the catalyst's N−H bond via methyl protection, the yield and selectivity of **2a** significantly decreased. (Figure 5g). These experiments suggest that the catalyst cooperates with NBS and SOCl$_2$ to generate an active halogenating intermediate. Furthermore, the good diastereocontrol of substrates such as **1ac** and **1am** suggests that a bromonium intermediate is probably involved.[19] Besides, the high diastereoselectivity (>20:1 dr) of **1ao** reveals that the chloride ion is installed

via a concerted SN2 mechanism. In contrast, the lower diastereoselectivity (4:1 dr) of **1ag** suggests that chloride ion attacks through a mixture of SN2 and SN1 pathways for different substrates.

Taking the bromochlorination of alkene **1** as an example, we propose a plausible mechanism based on mechanistic investigations (SI, Figure S4). Initially, the catalyst Ph(O)P-(NH^{n}Pr)$_2$ acts as a Lewis base to activate the halogenation reagents (NBS, SOCl$_2$). Then intermediate **Int1** containing two hydrogen bonds and the byproduct **8** are obtained. Byproduct **8** readily undergoes hydrolysis to give succinimide **9** after workup. Upon interaction of the halogenating intermediate **Int1** with alkene **1**, the double bond reacts with the bromonium ion to form a bromonium intermediate. The ester group facilitates bromonium ion ring-opening via cyclic transition state **TS1**, generating the pivotal intermediate **Int3**

that controls regioselectivity. Chloride subsequently attacks **Int3** to achieve ring opening, forming a C−Cl bond while inducing ester transposition to yield the remote bromochlorination product **2**. This nucleophilic attack proceeds via competing SN1 and SN2 pathways.

Density functional theory (DFT) calculations were performed on the reaction pathways for both the 1,4-bromochlorination and 1,2-bromochlorination of substrate **1a** (Figure 5h). The computational results indicate that both halogenation pathways proceed via a common intermediate **1a-In3**. Although the 1,2-bromochlorination isomer **4a** is thermodynamically favored over the desired product **2a**, the reaction selectivity is governed by the stability difference of the transition state **TS2**. The free energy of **1a-TS2**-*SN2* is 2.4 kcal/mol lower than that of **1a-TS2**-*SN2′*. This energy advantage is consistent with the experimentally observed excellent 1,4-regioselectivity. Furthermore, computational analysis of the two ring-opening pathways for the key intermediate **1ag-Int3** in the 1,4-bromochlorination of substrate **1ag** (SI, Figure S9). It reveals an extremely small difference in the free energy barriers between the corresponding transition states **1ag-TS2**-*SN1* and **1ag-TS2**-*SN2* ($\Delta\Delta G^{\ddagger} = 0.3$ kcal/mol). This minor energy difference accounts for the observed diastereomeric ratio (4:1 dr) of product **2ag**. These DFT calculation results provide further support for the proposed mechanism.

To validate the utility of this protocol, we conducted scale-up and diversification studies (Figure 6). Gram-scale preparations delivered 2.8 g of 1,4-bromochloride **2a** and 2.3 g of 1,3-bromochloride **2ak** in good yields. Then, further derivatizations of the **2a** were performed to construct multifunctionalized molecules. Copper-catalyzed coupling-cyclization with 2-aminophenylboronic acid pinacol ester gave seven-membered *N*-heterocycle **10** in 43% yield. Treatment of **2a** with K_2CO_3 delivered seven-membered cyclic carbonate ester **11** in 54% yield. Through nucleophilic cyclization, product **2a** reacted with Na_2S to give five-membered *S*-heterocycle **12** in 70% yield. Nickel-catalyzed intramolecular reductive coupling of **2a** led to the formation of cyclobutane derivatives **13**. In the presence of $TiCl_4$, **2a** reacted with the borane-ammonia complex smoothly to furnish ether **14** in 65% yield. Using excess thiophenol, **2a** can be transformed into the 1,4-dithioether **15** in 80% yield. Treatment of **2a** with NH_4SCN or water easily provided chlorinated thiocyanate **16** or chlorinated alcohol **17** by chemoselective nucleophilic substitution. In the presence of CsF, **2a** underwent cyclization with water to afford *O*-heterocycle **18** in 59% yield. The obtained 1,4-iodochloride **19** further expanded the chemical space of this protocol. The alcohol **17** could be further derivatized to afford the mercapto-substituted alcohol **20** with thiophenol in 77% yield, while treatment with an imide reagent provided the imide-substituted alcohol **21** in 63% yield.

CONCLUSIONS

In summary, we have developed a phosphordiamide-catalyzed, directing-group-free strategy for the remote dihalogenation of alkenes via ester transposition, enabling regioselective control. Under mild conditions, the cooperative action of the catalyst with $NBS/SOCl_2$ generates an active intermediate that mediates the efficient and selective construction of 1,3-, 1,4-, and 2,3-dihalides through synergistic engagement with allylic/homoallylic esters. This transformation demonstrates broad applicability across various unactivated alkenes while exhibiting excellent functional group tolerance (e.g., cyano, hydroxyl groups). Gram-scale preparations confirm operational practicality, and the products readily undergo diverse derivatizations (e.g., cross-coupling, cyclization), highlighting the protocol's potential utility in complex molecule assembly and pharmaceutical synthesis. We envision that this strategy will serve as a general paradigm for remote difunctionalization of alkenes, facilitating the development of diverse transposition-induced remote difunctionalizations.

■ ASSOCIATED CONTENT

ⓈI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c20677.

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

Accession Codes

Deposition Number 2464012 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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