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# Boryl Radicals Enabled a Three-Step Sequence to Assemble All-Carbon Quaternary Centers from Activated Trichloromethyl Groups

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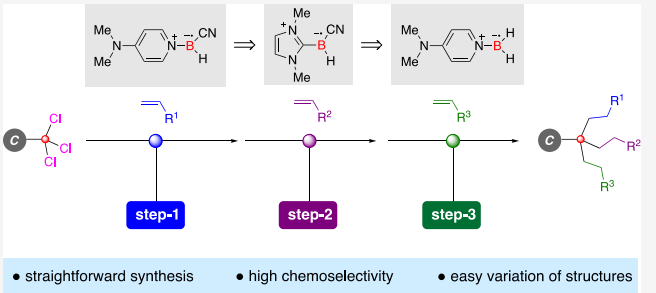
**ABSTRACT:** The construction of diversely substituted all-carbon quaternary centers has been a longstanding challenge in organic synthesis. Methods that add three alkyl substituents to a simple C($sp^3$) atom rely heavily on lengthy multiple processes, which usually involve several preactivation steps. Here, we describe a straightforward three-step sequence that uses a range of readily accessible activated trichloromethyl groups as the carbon source, the three C−Cl bonds of which are selectively functionalized to introduce three alkyl chains. In each step, only a single C−Cl bond was cleaved with the choice of an appropriate Lewis base−boryl radical as the promoter. A vast range of diversely substituted all-carbon quaternary centers could be accessed directly from these activated $CCl_3$ trichloromethyl groups or by simple derivatizations. The use of different alkene traps in each of the three steps enabled facile collections of a large library of products. The utility of this strategy was demonstrated by the synthesis of variants of two drug molecules, whose structures could be easily modulated by varying the alkene partner in each step. The results of kinetic and computational studies enabled the design of the three-step reaction and provided insights into the reaction mechanisms.




## 1. INTRODUCTION

Organic molecules containing three alkyl-substituted all-carbon quaternary centers are broadly used as pharmaceuticals and functional materials (some representative examples are shown in Figure 1a).[1,2] The structure and properties of the substituents dictate the function and utility of the products.[3] Thus, developing efficient and economical strategies to access these molecules, in particular, methods that can increase the diversity of the three alkyl substituents with ease, is an important goal of organic chemistry.[4−7] In this context, the methyl carbon atom is considered to be a simple source to introduce three distinct alkyl substituents, and the three C−H bonds are the objects for stepwise manipulations. However, due to the tremendous challenges associated with the direct activation of these three C−H bonds with high selectivity, the reaction sequence inevitably relies on lengthy multistep processes,[8] wherein several preactivation steps are required prior to the desired alkylation reactions (Figure 1b, left), thus resulting in low efficiency, high costs, and massive amounts of waste. Furthermore, although the use of other precursors to make three alkyl-substituted all-carbon quaternary centers have been reported,[9−16] the preparation of specific substrates/intermediates and the variation of each alkyl chain to enrich the product library are still rather difficult and time-consuming.

As an alternative, a straightforward three-step process that sequentially cleaves the three C−Cl bonds of trichloromethyl groups is perceived to be a particularly attractive route (Figure 1b, right) because (i) many trichloromethyl ($CCl_3$) sources (i.e., $CCl_3CO_2H$ manufactured industrially) are bulky chemicals and are also easy to insert;[17] (ii) C($sp^3$)−Cl bonds can engage in various types of C−C bond-forming reactions;[18−26] (iii) monochlorinated tertiary stereocenters resulting from two C($sp^3$)−Cl functionalizations are valuable structural motifs that can be found in a large number of bioactive molecules[27,28] and can also serve as useful synthetic intermediates;[29−41] and (iv) this streamlined sequence not only obviates any preactivation steps but also allows for convenient and facile variations of each substituent. However, this promising strategy has not yet been reported, and a main hurdle is the comparable reactivity of C−Cl bonds in chemically similar tri- and dichloroalkyl groups that induces inferior control of chemoselectivity during the dechlorination process. Furthermore, tertiary alkyl chlorides are often chemically inert, and their activation depends on transition-metal-involved oxidative addition/single electron reduction[29−38] or metal-promoted

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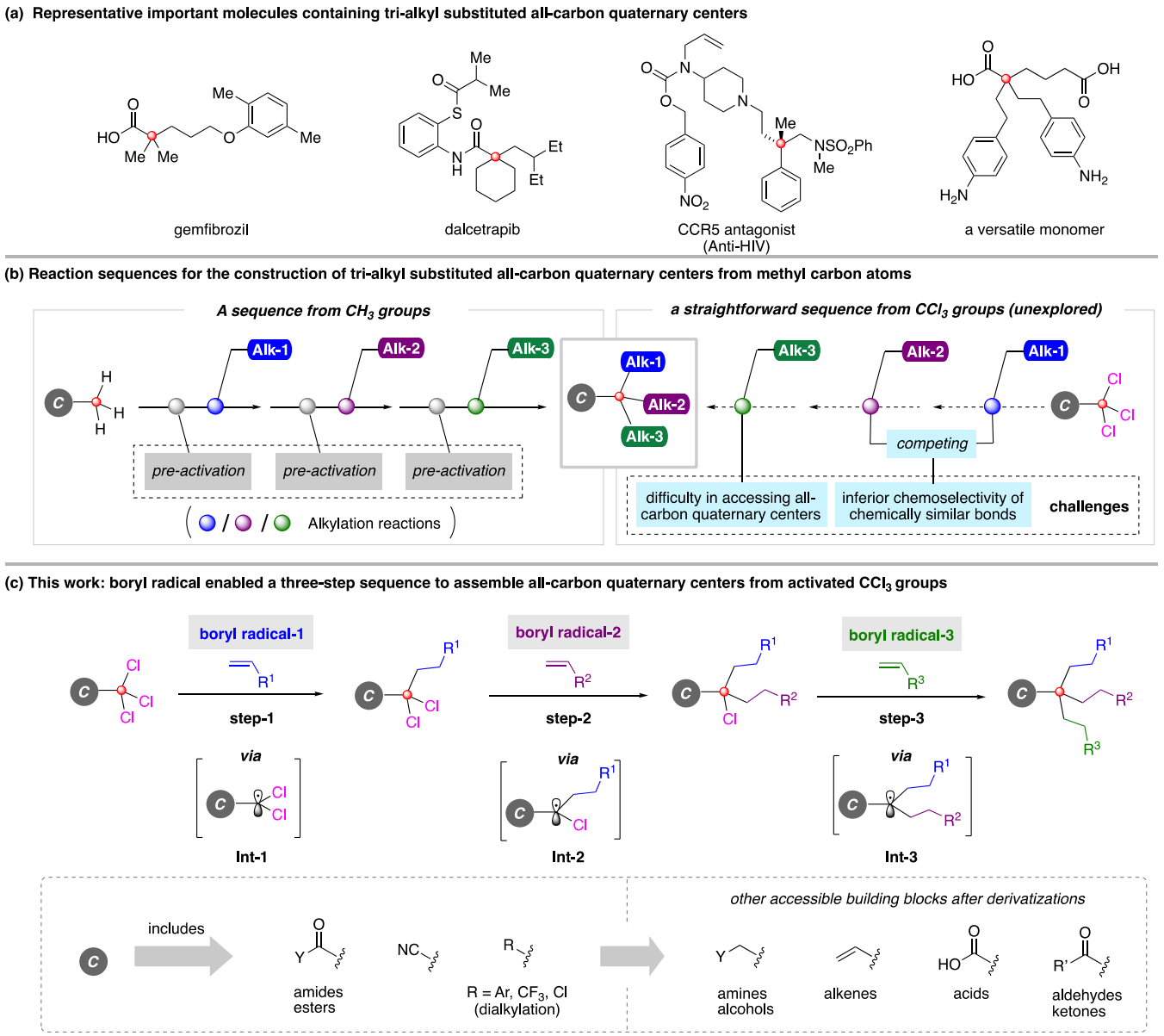


**Figure 1.** Importance and construction of all-carbon quaternary centers tethering three alkyl substituents.

Cl atom abstraction.[39−41] Thus, alkylation reactions to assemble all-carbon quaternary centers substituting three or even four different alkyl groups remain difficult.[38−40]

We speculated that the use of Lewis base−boryl radicals as promoters might meet the aforementioned challenges. These species could be generated from the readily available and inexpensive Lewis base−borane complexes through hydrogen atom abstraction under mild reaction conditions.[42,43] More importantly, their structure and reactivity could be easily modulated by modifying the Lewis base motif and the boron substituent,[44−47] thus offering ample opportunities to tune the reactivity and chemoselectivity during the dechlorination process. Although several Lewis base−boryl radicals have proven to be effective in the reduction of reactive organic iodides and bromides,[48−52] synthetically valuable reactions with chlorides, particularly for selective functionalizations of $CCl_3$ groups, are underdeveloped. Recently, we disclosed a remarkable 4-dimethylaminopyridine (DMAP) boryl radical-promoted two-stage process for sequential C−F bond functionalizations of trifluoroacetamides and acetates;[53] this strategy, however, involves relatively inert $CF_3$ groups (bond dissociation energy of 128 kcal $mol^{-1}$ for the C−F bonds in $CHF_3$) that would not be applicable to more reactive $CCl_3$ groups (bond dissociation energy of 74 kcal $mol^{-1}$ for the C−Cl bonds in $CHCl_3$).[54] Moreover, this method was only effective for the $CF_3$ groups attached to amide or ester carbonyl moieties. Therefore, to achieve selective and broadly applicable methods for stepwise functionalizations of a broad range of $CCl_3$ groups, exploring mechanistically and essentially distinct strategies is highly desirable. Herein, we report a straightforward strategy that enables a three-step sequence to consecutively and selectively alkylate the three C−Cl bonds of activated trichloromethyl groups (Figure 1c). Kinetic and computational studies were performed to guide the rational design of three sets of reaction conditions; in each one, an appropriate Lewis base−$BH_3$ complex was reasonably chosen as the boryl radical precursor to ensure both high chemoselectivity and efficiency. The mechanism of the cleavage for



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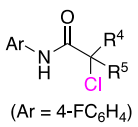
**Scheme 1. Reaction Development**[a,b,c]

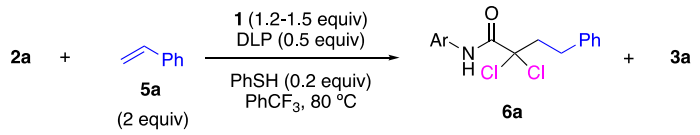
**(a) Rate constants of quenching boryl radicals I-IV by 2a and 3a**




**2a** $R^4 = R^5 = Cl$
**3a** $R^4 = H$, $R^5 = Cl$
**4a** $R^4 = R^5 = H$

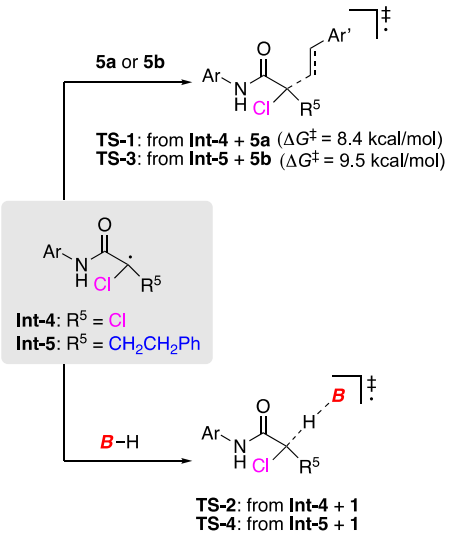
| boryl radical (B·) | 2a $k_q$ ($M^{-1}$ $s^{-1}$) at 25 °C | 3a $k_q$ ($M^{-1}$ $s^{-1}$) at 25 °C |
|---|---|---|
| DMAP-$\dot{B}H_2$ (I) | $3.9(3) \times 10^8$ | $3.7(9) \times 10^7$ |
| NHC-$\dot{B}H_2$ (II) | $2.5(5) \times 10^8$ | $4.2(8) \times 10^7$ |
| DMAP-$\dot{B}$HCN (III) | $2.9(4) \times 10^8$ | $1.3(3) \times 10^7$ |
| NHC-$\dot{B}$HCN (IV) | $8.4(13) \times 10^6$ | $2.1(6) \times 10^5$ |

**(b) Identification of boryl radical precursors for dechlorinative coupling reactions of 2a**[a]

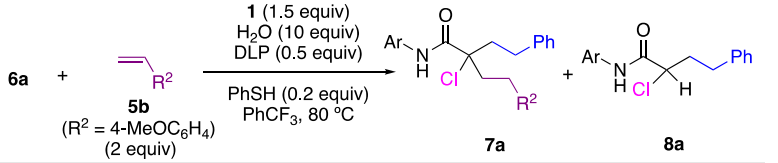



| entry | radical precursor | yield of 6a | yield of 3a | $\Delta G^{\ddagger}$ (TS-2) (kcal/mol) | $\Delta\Delta G^{\ddagger}$ (TS-2 *vs.* TS-1) (kcal/mol) |
|---|---|---|---|---|---|
| 1 | DMAP-$BH_3$ (1a) | 40% | 47% | 7.7 | -0.7 |
| 2 | NHC-$BH_3$ (1b) | 21% | 66% | 8.5 | 0.1 |
| 3 | DMAP-$BH_2CN$ (1c) | 67% (76%)[c] | trace | 12.6 | 4.2 |
| 4 | NHC-$BH_2CN$ (1d) | 63% | 10% | 9.7 | 1.3 |

**(c) Competitive reduction and coupling reactions**




**(d) Identification of boryl radical precursors for dechlorinative coupling reactions of 6a**[b]




| entry | radical precursor | yield of 7a | yield of 8a | $\Delta G^{\ddagger}$ (TS-4) (kcal/mol) | $\Delta\Delta G^{\ddagger}$ (TS-4 *vs.* TS-3) (kcal/mol) |
|---|---|---|---|---|---|
| 1 | DMAP-$BH_3$ (1a) | 61% | 19% | 9.9 | 0.4 |
| 2 | NHC-$BH_3$ (1b) | 46% | 53% | 9.6 | 0.1 |
| 3 | DMAP-$BH_2CN$ (1c) | 40% | trace (6a: 59%) | 13.6 | 4.1 |
| 4 | NHC-$BH_2CN$ (1d) | 85% | 14% | 12.0 | 2.5 |

[a]Reaction conditions: **2a** (0.3 mmol), **5a** (2 equiv), **1** (1.2−1.5 equiv), DLP (50 mol %), PhSH (20 mol %) in $PhCF_3$ (0.1 M), 80 °C, 0.5−2 h. [b]Reaction conditions: **6a** (0.1 mmol), **5b** (2 equiv), **1** (1.5 equiv), DLP (50 mol %), PhSH (20 mol %), $H_2O$ (10 equiv) in $PhCF_3$ (0.1 M), 80 °C, 0.5−10 h. [c]$H_2O$ (10 equiv) was added. NHC-$BH_3$ (**1b**), 1,3-dimethylimidazol-2-ylidene borane.

the three C−Cl bonds was also studied. Notably, a broad range of diversely substituted all-carbon quaternary centers could be accessed directly from activated $CCl_3$ groups or by simple derivatizations. The utility of this strategy was demonstrated by the synthesis of variants of two drug molecules, whose structures could be easily modulated by varying the alkene partner in each step, and the resulting diverse products are expected to be of substantial interest in medicinal studies.

## 2. RESULTS AND DISCUSSION

**2.1. Reaction Development.** Our investigation started with attempts to sequentially functionalize the three C−Cl bonds of *α,α,α*-trichloroamides. Trichloro **2a**, dichloro **3a**, and monochloro **4a** were first chosen as the model substrates to test the chemoselectivity and reactivity (Scheme 1a). A set of Lewis base−boryl radicals **I**−**IV** with different electronic properties were selected as the potential activators. To obtain more insights into the continuous dechlorination process, kinetic and computational studies were performed. The rate constants of the quenching of boryl radicals **I**−**IV** by **2a** and **3a** were measured using laser flash photolysis (LFP) experiments (Figures S1−S14).[55] The results showed that **2a** reacted with each boryl radical approximately an order of magnitude greater than **3a** (Scheme 1a), indicating a possible high chemoselectivity control during dechlorination. The calculation results also showed that the chlorine atom abstraction of **3a** had higher activation energies than that of **2a** ($\Delta\Delta G^{\ddagger}$ = 4.3, 3.8, 3.4, and 3.9 kcal $mol^{-1}$ for **I**, **II**, **III**, and **IV**, respectively; Table S8). Indeed, treatment of **2a** with boryl radical precursors **1** in the presence of a radical initiator led to the sole formation of **3a** in good yields, and the further reduction of **3a** to form **4a** was observed only to a slight extent (Table S1, entries 1−7). It should be noted that the reduction reactions of **2a** using $Bu_3SnH$,[56] $(Me_3Si)_3SiH$,[57] or $NaBH_3CN$[58] as promoters led to a mixture of **3a** and **4a** with inferior selectivity (Table S1, entries 8−11). In addition,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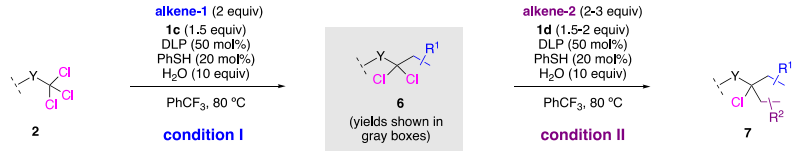
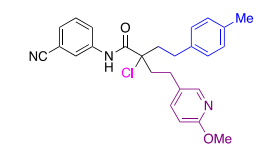
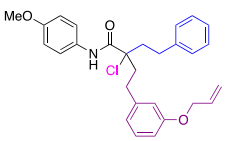
**Scheme 2. Substrate Scope of Two Consecutive Dechlorination Reactions of Trichloromethyl Groups**[a,b,c,d,e]



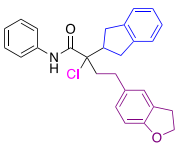

**a) Reactions of trichloroacetamides and trichloroacetates**



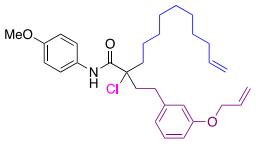
**2b→6b**, 73% **7b**, 73%



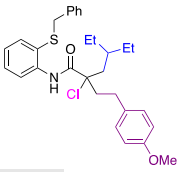
**2c→6c**, 72% **7c**, 64%



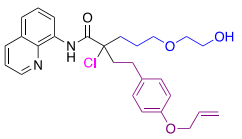
**2d→6d**, 70% (gram-scale: 65%) **7d**, 90%



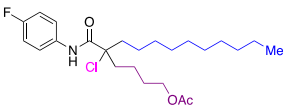
**2c→6e**, 53%[b] **7e**, 55%



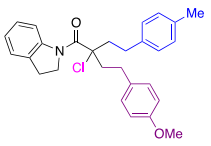
**2f→6f**, 70%[b] **7f**, 50%



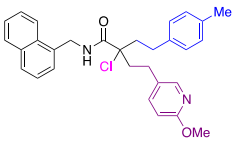
**2g→6g**, 52%[b] **7g**, 55%



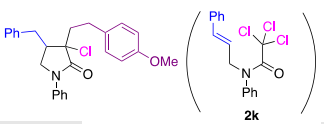
**2a→6h**, 68%[b] **7h**, 20%[b,c]



**2l→6i**, 50% **7i**, 56%

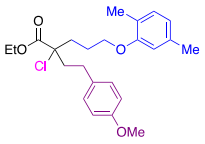


**2j→6j**, 75% **7j**, 63%

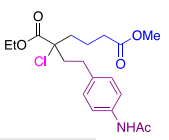


**2k→6k**, 75% **7k**, 67%

**2k**

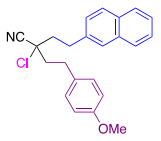


**2l→6l**, 60%[b] (gram-scale: 56%)[b] **7l**, 72%

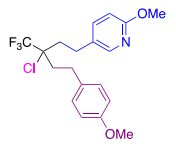


**2l→6m**, 53%[b] **7m**, 70%

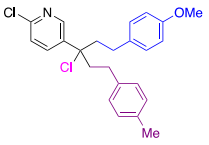
**b) Reactions of other trichloromethyl groups**



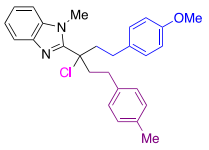
**2n→6n**, 60% **7n**, 48%



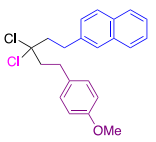
**2o→6o**, 85% **7o**, 43%[d]



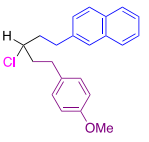
**2p→6p**, 66%[e] **7p**, 52%[d]



**2q→6q**, 57%[e] **7q**, 40%[d]

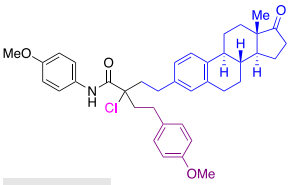


**2r→6r**, 86% **7r**, 71%

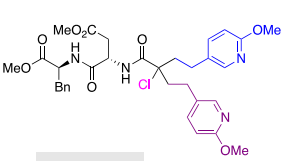


**2s→6s**, 70%[e] **7s**, trace

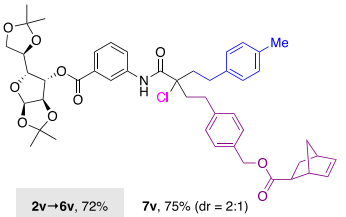
**c) Modification of bioactive molecules**



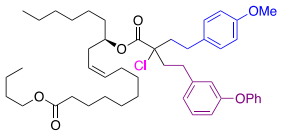
**2c→6t**, 68% **7t**, 85% (dr = 1:1)



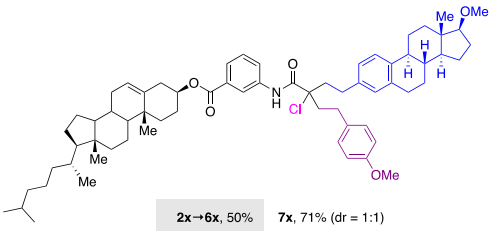
**2u→6u**, 63% **7u**, 60%



**2v→6v**, 72% **7v**, 75% (dr = 2:1)



**2w→6w**, 51% **7w**, 66% (dr = 1:1)



**2x→6x**, 50% **7x**, 71% (dr = 1:1)

[a]Reaction condition I: substrate **2** (0.2 to 0.3 mmol), alkene-1 (2 equiv), **1c** (1.5 equiv), DLP (50 mol %), PhSH (20 mol %), $H_2O$ (10 equiv) in $PhCF_3$ (0.1 M), 80 °C, 1.5−10 h (isolated yields of **6** are given in the gray boxes); reaction condition II: compound **6** (0.1 to 0.3 mmol), alkene-2 (2−3 equiv), **1d** (1.5−2 equiv), DLP (50 mol %), PhSH (20 mol %), $H_2O$ (10 equiv) in $PhCF_3$ (0.1 M), 80 °C, 2−10 h, yields were recorded relative to **6** as the starting material. [b]Alkene (8 equiv) was used. [c]The competing reduction product was formed in 70% yield. [d]**1b** was used. [e]**1d** was used.



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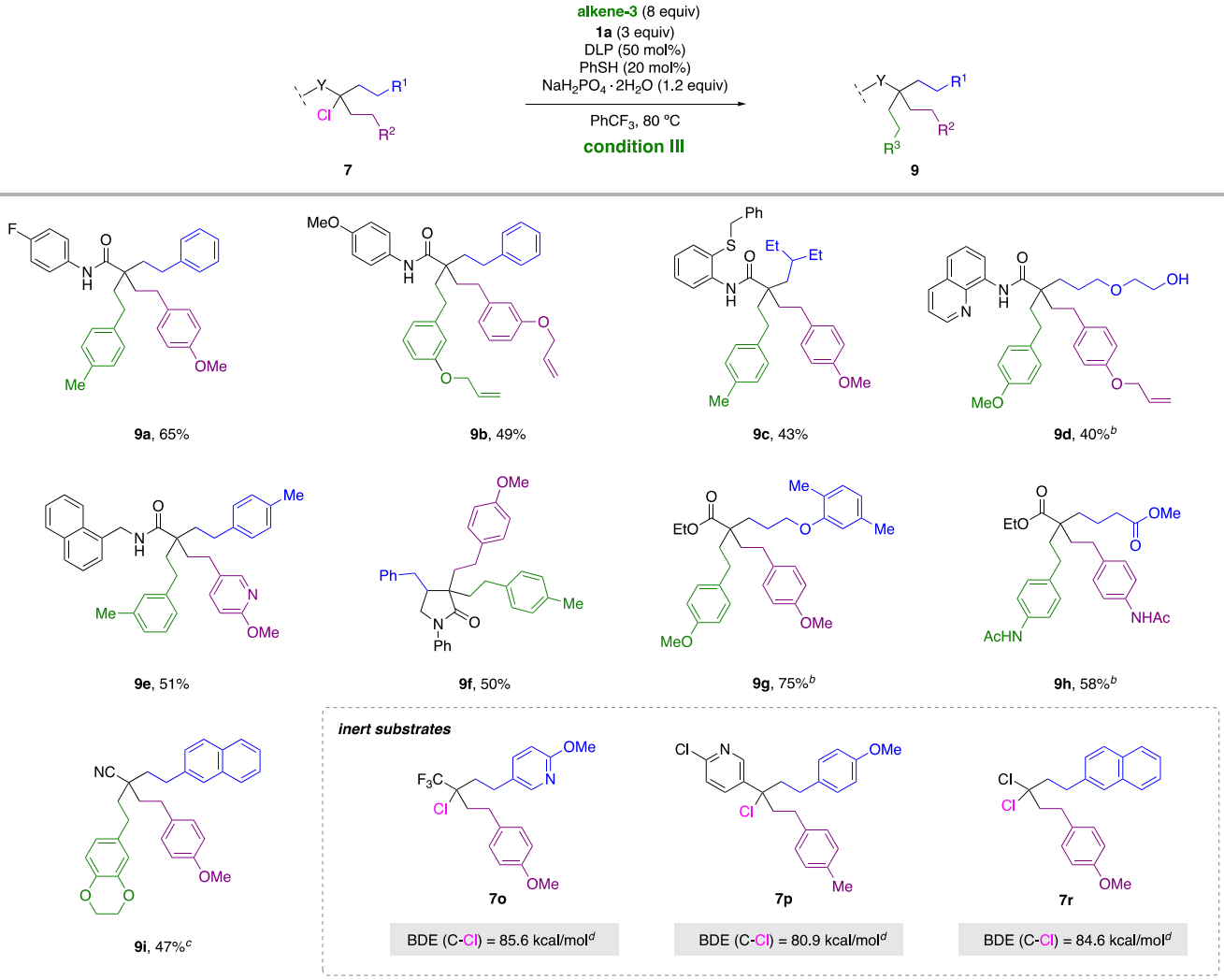
**Scheme 3. Dechlorinative Coupling of the Third C−Cl Bond**[a,b,c,d]




[a]Reaction condition III: substrate **7** (0.1 to 0.3 mmol), alkene (8 equiv), **1a** (3 equiv), DLP (50 mol %), PhSH (20 mol %), $NaH_2PO_4·2H_2O$ (1.2 equiv) in $PhCF_3$ (0.1 M), 80 °C, 4−10 h. BDE, bond dissociation energy. [b]Reactions were carried out at 120 °C using di-*tert*-butylperoxide (50 mol %) as the radical initiator. [c]**1d** was used. [d]All of the BDEs were calculated at the CBS-4M level.

the quenching of boryl radicals **I-IV** by **4a** was not detectable at 25 °C, indicating the lower reactivity of this monochloride.

After demonstrating that the selected boryl radical species exhibited high chemoselectivity, we next attempted to achieve stepwise dechlorinative coupling reactions with alkenes. Although some intramolecular trapping reactions of α,α-dichloro carbonyl radicals have been reported to form lactams,[59,60] intermolecular versions remain challenging and unexplored. Indeed, when **2a** was treated with styrene (**5a**) using **1a** or **1b** as the boryl radical precursor, the competing reduction product **3a** was formed in higher yields than the coupling product **6a** (Scheme 1b, entries 1 and 2). Additional experiments showed that **3a** was derived from hydrogen atom transfer (HAT) from electron-rich **1a** and **1b** to the electrophilic radical **Int-4** (Table S2, entries 3 and 4). This reduction reaction was calculated to proceed with an activation energy similar to that of the addition (**TS-1**, 8.4 kcal $mol^{-1}$, Scheme 1c) to **5a** ($\Delta\Delta G^{\ddagger}$ = −0.7 and 0.1 kcal $mol^{-1}$ for **1a** and **1b**, respectively, Scheme 1b, entries 1 and 2), thereby resulting in low selectivity. To suppress this competing HAT process, we reasoned that the boryl radical precursors **1c** and **1d** would be better choices, as the cyano group could decrease the electron density and cause the HAT process to be polarity-mismatched.[61] The activation energy differences ($\Delta\Delta G^{\ddagger}$) between reduction and coupling indeed increased to 4.2 (for **1c**, Scheme 1b, entry 3) and 1.3 kcal $mol^{-1}$ (for **1d**, Scheme 1b, entry 4), respectively. The experimental results demonstrated that **1c** was the optimal reactant, furnishing the coupling product **6a** in 67% yield and **3a** in only a trace amount (Scheme 1b, entry 3). The addition of 10 equiv of water could improve the product yield to 76% (Scheme 1b, entry 3). We assumed that water may quench the generated DMAP-BH(CN)Cl, thus reducing side reactions caused by this electrophilic species.[62] For dechlorinative coupling of **6a**, the reactions with **1c** and **1d** again gave superior selectivity ($\Delta\Delta G^{\ddagger}$ = 4.1 and 2.5 kcal $mol^{-1}$, respectively, Scheme 1d, entries 3 and 4) in comparison to those of **1a** and **1b** ($\Delta\Delta G^{\ddagger}$ = 0.4 and 0.1 kcal $mol^{-1}$, respectively, Scheme 1d, entries 1 and 2), and **7a** was obtained in 85% yield using **1d** as the boryl radical precursor (Scheme 1d, entry 4). The detailed optimization studies of these reactions are provided in the Supporting Information (Tables S2 and S3).



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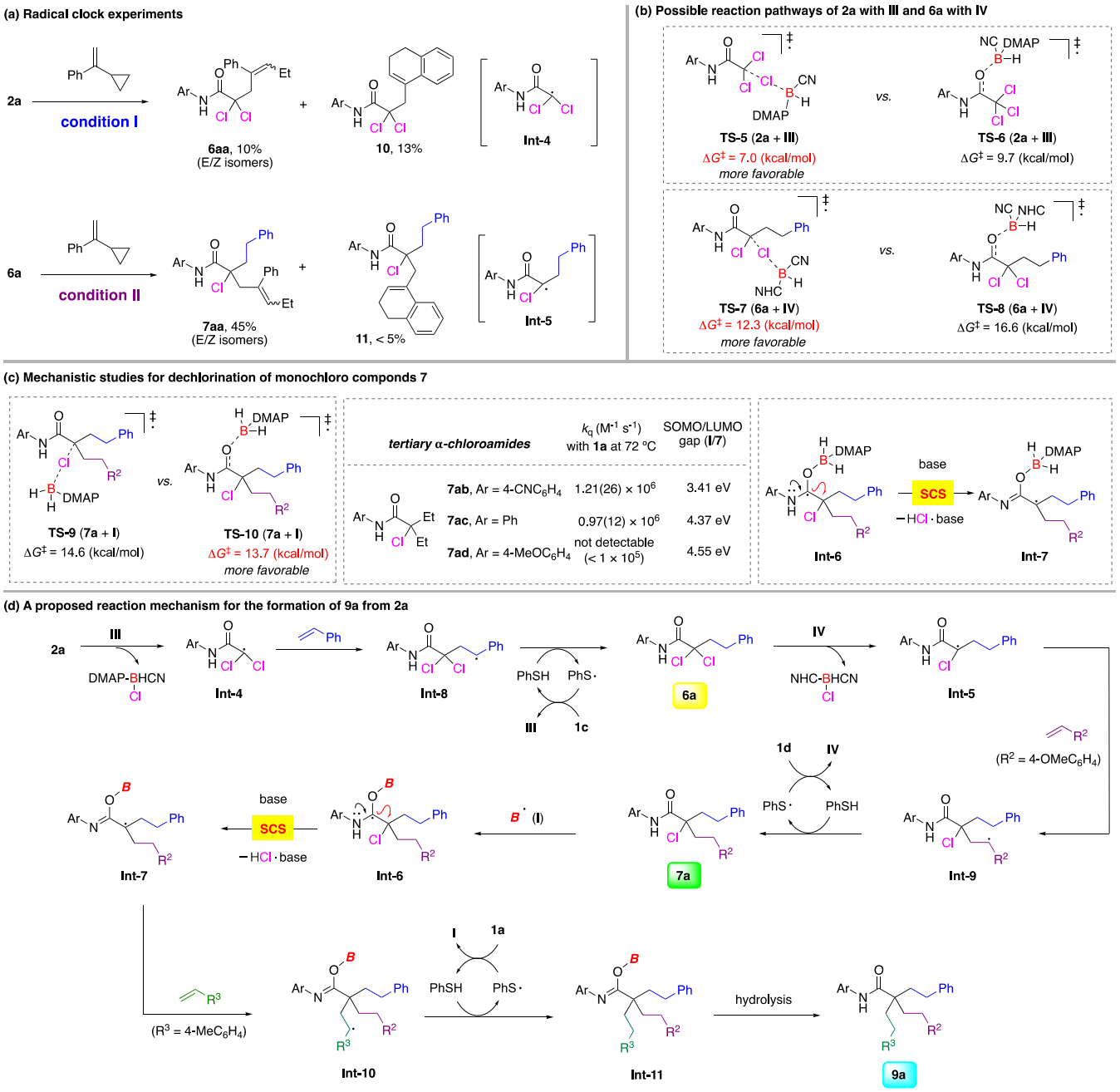
**Scheme 4. Mechanistic Studies and a Proposed Reaction Mechanism**




**2.2. Substrate Scope of Two Consecutive Dechlorination Reactions of Trichloromethyl Groups.** The dechlorinative coupling reactions of tri- and dichloro molecules showed excellent chemoselectivity and a broad substrate scope (Scheme 2). Under reaction **condition I**, only a single C−Cl bond was cleaved, giving *α*,*α*-dichloro carbonyl radicals that coupled with a wide range of alkenes to afford various dichloro products **6**. Further cleavage of the second C−Cl bond did not occur at this point, and the competing reduction reaction pathway was also not observed in most cases. After switching to **condition II**, a second C−Cl bond was selectively cleaved, and the resulting *α*-monochlorocarbonyl radicals reacted with alkenes to form a vast range of monochloro products **7**. The competing reduction reaction could be suppressed by increasing the amount of alkene. *N*-Aryl and *N*-alkyl amides bearing a variety of functional groups were converted to the corresponding di- and monochloro products (**6b**−**6j**, **7b**−**7j**) in good yields (Scheme 2a). The tertiary amide **2i** was also compatible, giving **6i**/**7i** in synthetically useful yields. Intramolecular trapping of the *α*,*α*-dichloro carbonyl radical intermediate proceeded smoothly, leading to cyclic product **6k**, which underwent a second dechlorination reaction to provide **7k** in 67% yield. Ethyl 2,2,2-trichloroacetate was also a viable substrate, affording dichloro (**6l**, **6m**) and monochloro products (**7l**, **7m**) in good yields. For aliphatic alkenes with relatively low reactivity, the first reaction with the *α*,*α*-dichloro carbonyl radical intermediates proceeded efficiently (**6e**−**6h**, **6l**−**6m**), but the second step of the reaction was sluggish (**7h**) and the competing reduction reaction was predominant. An internal alkene was a competent coupling partner as well (**6d**). Gram-scale syntheses of **6d** and **6l** were also achieved in good yields.



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The application of this stepwise dechlorination strategy was then expanded to other kinds of trichloromethyl groups (Scheme 2b). A number of trichloromethyl groups tethered to the cyano (**2n**), trifluoromethyl (**2o**), or aryl (**2p** or **2q**) groups were selectively coupled with various alkenes, producing the corresponding dichloro and monochloro products in good yields. For the reactions of **2p** and **2q**, borane **1c** was found to be ineffective, while the change to **1d** could promote efficient chlorine atom transfer. The cleavage of the C−Cl bond of dichloro products **6o**, **6p**, and **6q** was more difficult, and the use of electron-rich boryl radical **II** was required. Remarkably, subjecting carbon tetrachloride to **condition I** resulted in the functionalization of only a single C−Cl bond, and the subsequent reaction under **condition II** gave product **7r** in 71% yield. Chloroform also participated in this transformation under the **condition II**, affording dichloromethyl-substituted product **6s**, while a further reaction to cleave a second C−Cl bond was unsuccessful due to the high BDE (84.3 kcal $mol^{-1}$, Table S7, entry 4) and the high activation energy of ($\Delta G^{\ddagger}$ = 20.1 kcal $mol^{-1}$, Figure S15) of the chlorine atom transfer. Late-stage modifications of bioactive molecules were also performed (Scheme 2c). The reaction of trichloroamide **2c** with an estrone-derived alkene followed by coupling with another alkene gave monochloro-modified product **7t** in good yield. Diversification reactions of amine- or alcohol-containing bioactive molecules were carried out, and a broad array of functional groups were successively incorporated via the creation of a chloro-substituted tertiary carbon center (**7u**-**7w**). Interestingly, two bioactive molecules could be connected with an $\alpha$-monochloroamide (**7x**) linker, where an additional alkyl group was incorporated concurrently.

**2.3. Substrate Scope of Dechlorination of the Third C−Cl Bond.** After successfully functionalizing two C−Cl bonds, we next attempted to derivatize the third one, which would yield all-carbon quaternary centers, on which three different flexible and editable alkyl groups were anchored. However, when monochloro **7a** was treated with 4-methylstyrene using **1b**, **1c**, and **1d** as boryl radical precursors (Table S4, entries 2−4), almost no dechlorination occurred, presumably due to the high BDE of such a tertiary C−Cl bond (i.e., 81 kcal $mol^{-1}$ for **4a**, Table S7, entry 2), which hinders the direct chlorine atom transfer. To our delight, when **1a** was employed, the desired coupling product **9a** was obtained in 65% yield, although the competing reduction product was also formed in 28% yield (Table S4, entry 1). The dechlorinative coupling with the third alkene under **condition III** also demonstrated a broad substrate scope, allowing the construction of a wide variety of products containing an $\alpha$ all-carbon quaternary center with three alkyl chains (Scheme 3). A large amount of alkene was required to prevent the competing reduction reactions. Both *N*-aryl and *N*-alkyl amides could be converted to the corresponding products **9**. A cyclic amide product **9f** was also successfully assembled. $\alpha$-Monochloro esters **7l** and **7m** were also capable of coupling with a third alkene to access quaternary carbon centers. Notably, the reaction of $\alpha$-monochloronitrile **7n** using **1d** as the boryl radical precursor also proceeded, producing a nitrile-bound quaternary center bearing three distinct alkyl groups (**9i**). In this case, the BDE of the C−Cl bond in **7n** was computed to be 74.1 kcal $mol^{-1}$ (Table S7, entry 6), and chlorine atom transfer might take place to give the corresponding tertiary carbon radical intermediate. However, the reactions with **7o**, **7p**, and **7r** were unsuccessful because these C−Cl bonds have much higher BDE values (85.6, 80.9, and 84.6 kcal $mol^{-1}$ for **7o**, **7p**, and **7r**, respectively; Table S7, entries 8, 10, and 12) and that the chlorine atom transfer is energetically not feasible using DMAP-$BH_2$• as the promoter. The effect of other radical promoters was also tested. It was found that when $Bu_3SnH$ was used instead of DMAP-$BH_3$, hydrodechlorination of **7r** occurred, while no coupling product was detected even when excess amounts (8 equiv) of 4-methylstyrene was employed. In this case, the resulting radical intermediate was reduced by $Bu_3SnH$ very rapidly, thus impeding the radical addition to the alkene partner. It should also be mentioned that simple alkenes are not applicable, as the radical addition becomes much slower and the competing reduction product is formed predominantly.

**2.4. Mechanistic Studies.** To gain insight into the reaction mechanism, mechanistic experiments and computational studies were conducted. When an alkene bearing a radical clock was treated with **2a** or **6a** under standard **condition I** or **condition II**, respectively, cyclopropane ring-opening products were obtained, verifying the involvement of **Int-4** and **Int-5** in the reaction processes (Scheme 4a). DFT calculations revealed that boryl radicals **III** and **IV** undergo chlorine atom transfer with reasonable energy barriers (Scheme 4b, 7.0 kcal $mol^{-1}$ for **TS-5** and 12.3 kcal $mol^{-1}$ for **TS-7**). Based on our previous findings,[53,63] a pathway involving the addition of these boryl radicals to the carbonyl oxygen atoms of **2a** or **6a** was also considered. However, computational results showed that higher activation energies (9.7 kcal $mol^{-1}$ for **TS-6** and 16.6 kcal $mol^{-1}$ for **TS-8**) were required, and this pathway was thus considered to be less likely. Likewise, the chlorine atom transfer took place selectively and efficiently for **2n**-**2s** and **6n**-**6r** with the corresponding boryl radicals. On the other hand, a different mechanism was involved in the dechlorination of **7a**. In this case, the attack of boryl radical **I** to the amide oxygen atom occurred with an activation energy of 13.7 kcal $mol^{-1}$, which was lower than that of direct chlorine atom transfer (14.6 kcal $mol^{-1}$, Scheme 4c, left). Kinetic studies further revealed that the quenching constant of **I** decreased (**7ab** > **7ac** ≫ **7ad**, Scheme 4c, middle) as the $R^4$ group became more electron-donating, and it became undetectable ($<1 \times 10^5$ $M^{-1}$ $s^{-1}$) for **7ad**. This was correlated with the trend of the increasing singly occupied molecular orbital (SOMO) and lowest unoccupied molecular orbital (LUMO) gaps between **I** and the carbonyl moiety. These findings suggested that boryl radical **I** prefers to attack the carbonyl oxygen atom,[63,64] which then induces a spin-center shift (SCS) process to give **Int-7** with the elimination of HCl[38,65,66] (Scheme 4c, right). DFT calculations revealed that HCl was eliminated spontaneously after the addition of boryl radical **I**, indicating a very rapid SCS process (Figures S18 and S19). The reactions of **7a** with boryl radicals **II**, **III**, and **IV** were also computed, and the results revealed that both chlorine atom transfer and boryl radical addition were found to proceed with much higher activation energies (Table S11). These findings were correlated with the experimental results. By considering all of the above results together, we proposed the reaction mechanism shown in Scheme 4d. In brief, $\alpha,\alpha,\alpha$-trichloroacetamide **2a** and $\alpha,\alpha$-dichloroamide **6a** preferentially undergo chlorine atom transfer to boryl radicals **III** and **IV**, giving **Int-4** and **Int-5**, respectively. In this dechlroination, a resonance stabilization contributed by the adjacent functional group, such as aminocarbonyl, cyano, aryl, and trifluoromethyl groups, plays an important role in facilitating this step. On the


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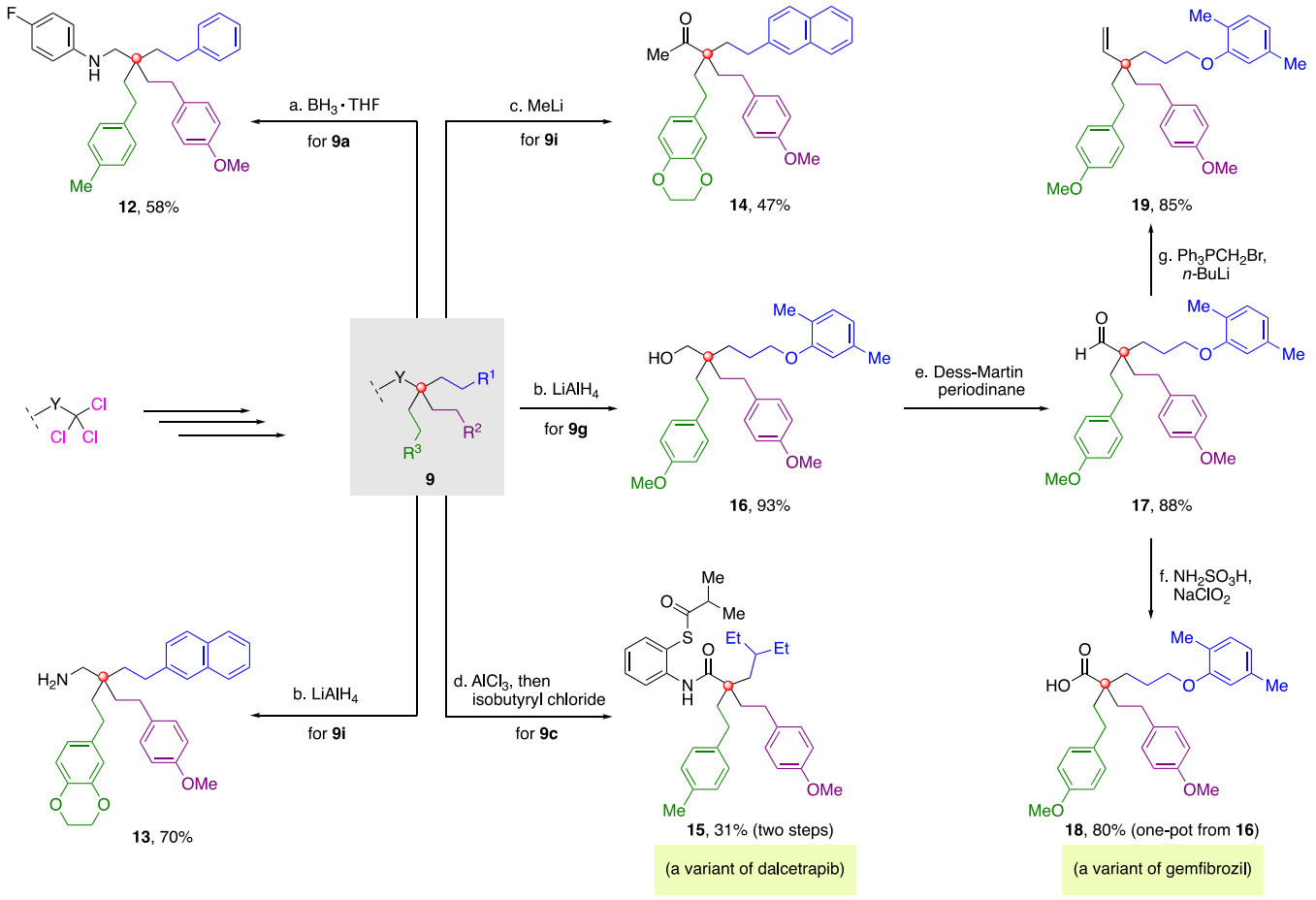
**Scheme 5. Synthetic Applications**[a]




[a]Reaction conditions: (1) $BH_3$·THF (3 equiv), THF, 0−60 °C, 12 h; (2) $LiAlH_4$ (3−5 equiv), THF, 0 °C−rt, 4−12 h; (3) MeLi (4 equiv), THF, −40 °C to rt, 2 h; (4) $AlCl_3$ (4 equiv), toluene, 35 °C, 12 h, then isobutyryl chloride (1.5 equiv), pyridine (2.5 equiv), $CH_2Cl_2$, 0 °C−rt, 12 h; (5) Dess−Martin periodinane (2.5 equiv), $CH_2Cl_2$, 0 °C−rt, 4 h; (6) $NH_2SO_3H$ (2 equiv), $NaClO_2$ (2 equiv), $CH_2Cl_2$, rt, 2 h; (7) $Ph_3PCH_2Br$ (2.5 equiv), *n*-BuLi (2.6 equiv), THF, 0 °C, 30 min, then with **17**, reflux, 12 h.

other hand, $\alpha$-monochloroamide **7a** undergoes boryl radical addition together with an SCS process to eliminate a molecule of HCl, affording **Int-7**. These radical intermediates are trapped by alkenes, followed by hydrogen atom transfer from a thiol catalyst, furnishing the corresponding coupling products and a thiyl radical. In the first dechlorinative coupling reaction, both activated and nonactivated alkenes can be used. However, the next two reactions rely mainly on styryl type alkenes, as the radical addition of these sterically more congested radical intermediates slows down and the aryl stabilization of the resulting radical intermediates is crucial to favor the reaction. Otherwise, the hydrodechlorination proceeds preferentially. Eventually, the formed thiyl radical in turn abstracts a hydrogen atom from boranes **1** to propagate the radical chain process.[61] The detailed computational studies of these reactions are provided in the Supporting information (Figures S16−S18).

**2.5. Synthetic Applications.** To amplify the synthetic utility of this straightforward dechlorination strategy, the obtained trialkyl substituted products were transformed into a variety of versatile building blocks and drug analogues, which are of great interest in synthetic and medicinal chemistry (Scheme 5). For example, the reduction reactions of **9a** and **9i** afforded $\beta$-trialkyl-substituted *N*-aryl amine **12** and free amine **13**, respectively. An $\alpha$ all-carbon quaternary-substituted ketone **14** was afforded by the nucleophilic addition of MeLi to **9i** followed by hydrolysis. The removal of the *S*-benzyl group of **9c** followed by acylation furnished a variant of dalcetrapib (**15**), which is a cholesteryl ester transfer protein inhibitor.[67] Compound **9g** tethering an $\alpha$-trialkyl-substituted quaternary center is structurally analogous to gemfibrozil,[68] which is a medication that helps with cholesterol problems. Reduction of **9g** gave an alcohol derivative **16**, which could be selectively oxidized to aldehyde **17**. Further oxidation afforded carboxylic acid **18**. Alternatively, the treatment of **17** with a Wittig reagent yielded alkene **19**. We can expect that more biologically interesting structures are accessible by changing the alkene coupling partners or further transformations of these resulting building blocks.

## 3. CONCLUSIONS

In summary, the results described here demonstrate a straightforward three-step sequence to assemble all-carbon quaternary centers from readily accessible trichloromethyl groups. The three C−Cl bonds were selectively and sequentially cleaved, and the resulting radical intermediates then coupled with alkenes to introduce three distinct alkyl chains. We expect that this strategy will be applicable to other polychlorinated molecules and show significant utility for the



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economical synthesis of various densely substituted products with broad uses. Moreover, the cooperation of the present strategy with well-developed enantioselective radical reactions, such as chiral auxiliaries, organocatalysis, and chiral transition-metal catalysis,[69] may provide a new platform to make chiral all-carbon quaternary centers.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c05798.

Experimental details, characterization data of compounds, $^{1}H$ and $^{13}C$ NMR spectral data for all new compounds, and computational results (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Ling, T.; Rivas, F. All-Carbon Quaternary Centers in Natural Products and Medicinal Chemistry: Recent Advances. *Tetrahedron* **2016**, *72*, 6729−6777.

(2) Stockdale, T. P.; Williams, C. M. Pharmaceuticals that Contain Polycyclic Hydrocarbon Scaffolds. *Chem. Soc. Rev.* **2015**, *44*, 7737−7763.

(3) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(4) Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocentres. *Nature* **2014**, *516*, 181−191.

(5) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. All-Carbon Quaternary Stereogenic Centers in Acyclic Systems through the Creation of Several C−C Bonds per Chemical Step. *J. Am. Chem. Soc.* **2014**, *136*, 2682−2694.

(6) Feng, J.; Holmes, M.; Krische, M. J. Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis. *Chem. Rev.* **2017**, *117*, 12564−12580.

(7) Xue, W.; Jia, X.; Wang, X.; Tao, X.; Yin, Z.; Gong, H. Nickel-catalyzed Formation of Quaternary Carbon Centers using Tertiary Alkyl Electrophiles. *Chem. Soc. Rev.* **2021**, *50*, 4162−4184.

(8) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2005.

(9) Wang, Z.; Yin, H.; Fu, G. C. Catalytic Enantioconvergent Coupling of Secondary and Tertiary Electrophiles with Olefins. *Nature* **2018**, *563*, 379−383.

(10) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. Asymmetric Catalytic Formation of Quaternary Carbons by Iminium Ion Trapping of Radicals. *Nature* **2016**, *532*, 218−222.

(11) Wendlandt, A. E.; Vangal, P.; Jacobsen, E. N. Quaternary Stereocentres via an Enantioconvergent Catalytic $S_N1$ Reaction. *Nature* **2018**, *556*, 447−451.

(12) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehydes. *Science* **2013**, *340*, 1065−1068.

(13) Hervieu, C.; Kirillova, M. S.; Suárez, T.; Müller, M.; Merino, E.; Nevado, C. Asymmetric, Visible Light-Mediated Radical Sulfinyl-Smiles Rearrangement to Access All-Carbon Quaternary Stereocentres. *Nat. Chem.* **2021**, *13*, 327−334.

(14) Mei, T.-S.; Patel, H. H.; Sigman, M. S. Enantioselective Construction of Remote Quaternary Stereocentres. *Nature* **2014**, *508*, 340−344.

(15) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H. Ni-Catalyzed Reductive Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2018**, *140*, 14490−14497.

(16) Lei, G.; Xu, M.; Chang, R.; Funes-Ardoiz, I.; Ye, J. Hydroalkylation of Unactivated Olefins via Visible-Light-Driven

Dual Hydrogen Atom Transfer Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 11251−11261.
(17) Liang, Y.-Y.; Lv, G.-F.; Ouyang, X.-H.; Song, R.-J.; Li, J.-H. Recent Developments in the Polychloroalkylation by Use of Simple Alkyl Chlorides. *Adv. Synth. Catal.* **2021**, *363*, 290−304.
(18) Cybularczyk-Cecotka, M.; Szczepanik, J.; Giedyk, M. Photocatalytic Strategies for the Activation of Organic Chlorides. *Nat. Catal.* **2020**, *3*, 872−886.
(19) Sharma, H. A.; Essman, J. Z.; Jacobsen, E. N. Enantioselective Catalytic 1,2-Boronate Rearrangements. *Science* **2021**, *374*, 752−757.
(20) Huang, X.; Wang, B.; Wang, Y.; Jiang, G.; Feng, J.; Zhao, H. Photoenzymatic Enantioselective Intermolecular Radical Hydroalkylation. *Nature* **2020**, *584*, 69−74.
(21) Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. Photochemical Generation of Radicals from Alkyl Electrophiles using a Nucleophilic Organic Catalyst. *Nat. Chem.* **2019**, *11*, 129−135.
(22) Giedyk, M.; Narobe, R.; Weiß, S.; Touraud, D.; Kunz, W.; König, B. Photocatalytic Activation of Alkyl Chlorides by Assembly-promoted Single Electron Transfer in Microheterogeneous Solutions. *Nat. Catal.* **2020**, *3*, 40−47.
(23) Fu, G. C. Transition-Metal Catalysis of Nucleophilic Substitution Reactions: A Radical Alternative to $S_N1$ and $S_N2$ Processes. *ACS Cent. Sci.* **2017**, *3*, 692−700.
(24) McDaniel, K. A.; Blood, A. R.; Smith, G. C.; Jui, N. T. Dearomatization of Unactivated Arenes via Catalytic Hydroalkylation. *ACS Catal.* **2021**, *11*, 4968−4972.
(25) Zhang, W.; Lu, L.; Zhang, W.; Wang, Y.; Ware, S. D.; Mondragon, J.; Rein, J.; Strotman, N.; Lehnherr, D.; See, K. A.; Lin, S. Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides. *Nature* **2022**, *604*, 292−297.
(26) Biegasiewicz, K. F.; Cooper, S. J.; Gao, X.; Oblinsky, D. G.; Kim, J. H.; Garfinkle, S. E.; Joyce, L. A.; Sandoval, B. A.; Scholes, G. D.; Hyster, T. K. Photoexcitation of Flavoenzymes Enables a Stereoselective Radical Cyclization. *Science* **2019**, *364*, 1166−1169.
(27) Gribble, G. W. Occurrence of Halogenated Alkaloids. In *The Alkaloids: Chemistry and Biology*; Knölker, H.-J., Ed.; AcademicPress: Amsterdam, 2012; pp 1−165.
(28) Gribble, G. W. Biological Activity of Recently Discovered Halogenated Marine Natural Products. *Mar. Drugs* **2015**, *13*, 4044−4136.
(29) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C-N Cross-Couplings Induced by Visible Light. *Science* **2016**, *351*, 681−684.
(30) Wang, Z.; Yang, Z.-P.; Fu, G. C. Quaternary Stereocentres via Catalytic Enantioconvergent Nucleophilic Substitution Reactions of Tertiary Alkyl Halides. *Nat. Chem.* **2021**, *13*, 236−242.
(31) Zultanski, S. L.; Fu, G. C. Nickel-Catalyzed Carbon−Carbon Bond-Forming Reactions of Unactivated Tertiary Alkyl Halides: Suzuki Arylations. *J. Am. Chem. Soc.* **2013**, *135*, 624−627.
(32) Ratani, T. S.; Bachman, S.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Carbon−Carbon Bond Formation with Alkyl Electrophiles: Cyanation of Unactivated Secondary Alkyl Chlorides at Room Temperature. *J. Am. Chem. Soc.* **2015**, *137*, 13902−13907.
(33) Börjesson, M.; Moragas, T.; Martin, R. Ni-Catalyzed Carboxylation of Unactivated Alkyl Chlorides with CO2. *J. Am. Chem. Soc.* **2016**, *138*, 7504−7507.
(34) Cho, H.; Suematsu, H.; Oyala, P. H.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Enantioconvergent Alkylations of Anilines by Racemic Tertiary Electrophiles: Synthesis and Mechanism. *J. Am. Chem. Soc.* **2022**, *144*, 4550−4558.
(35) Atack, T. C.; Cook, S. P. Manganese-Catalyzed Borylation of Unactivated Alkyl Chlorides. *J. Am. Chem. Soc.* **2016**, *138*, 6139−6142.
(36) Wang, X.; Wang, S.; Xue, W.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Bromides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 11562−11565.
(37) Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. Cross-Coupling of Non-activated Chloroalkanes with Aryl Grignard Reagents in the Presence of Iron/N-Heterocyclic Carbene Catalysts. *Org. Lett.* **2012**, *14*, 1066−1069.
(38) Deeprose, M. J.; Lowe, M.; Noble, A.; Booker-Milburn, K. I.; Aggarwal, V. K. Sequential Photocatalytic Reactions for the Diastereoselective Synthesis of Cyclobutane Scaffolds. *Org. Lett.* **2022**, *24*, 137−141.
(39) Zheng, X.; Dai, X.-J.; Yuan, H.-Q.; Ye, C.-X.; Ma, J.; Huang, P.-Q. Umpolung of Hemiaminals: Titanocene-Catalyzed Dehydroxylative Radical Coupling Reactions with Activated Alkenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3494−3498.
(40) Wu, X.; Hao, W.; Ye, K.-Y.; Jiang, B.; Pombar, G.; Song, Z.; Lin, S. Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors. *J. Am. Chem. Soc.* **2018**, *140*, 14836−14843.
(41) Wang, F.-L.; Yang, C.-J.; Liu, J.-R.; Yang, N.-Y.; Dong, X.-Y.; Jiang, R.-Q.; Chang, X.-Y.; Li, Z.-L.; Xu, G.-X.; Yuan, D.-L.; Zhang, Y.-S.; Gu, Q.-S.; Hong, X.; Liu, X.-Y. Mechanism-Based Ligand Design for Copper-Catalysed Enantioconvergent $C(sp^3)$−C(sp) Cross-Coupling of Tertiary Electrophiles with Alkynes. *Nat. Chem.* **2022**, *14*, 949−957.
(42) Ueng, S.-H.; Makhlouf Brahmi, M.; Derat, É.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. Complexes of Borane and N-Heterocyclic Carbenes: A New Class of Radical Hydrogen Atom Donor. *J. Am. Chem. Soc.* **2008**, *130*, 10082−10083.
(43) Lalevée, J.; Blanchard, N.; Tehfe, M.-A.; Chany, A.-C.; Fouassier, J.-P. New Boryl Radicals Derived from *N*-Heteroaryl Boranes: Generation and Reactivity. *Chem. - Eur. J.* **2010**, *16*, 12920−12927.
(44) Zhang, F.-L.; Wang, Y.-F. Reactions through Radical Boryl Moieties. In *Science of Synthesis: Advances in Organoboron Chemistry towards Organic Synthesis*; Fernández, E., Ed.; Thieme: Stuttgart, 2019; pp 355−392.
(45) Taniguchi, T. Advances in Chemistry of *N*-Heterocyclic Carbene Boryl Radicals. *Chem. Soc. Rev.* **2021**, *50*, 8995−9021.
(46) Lu, D.; Wu, C.; Li, P. Synergistic Effects of Lewis Bases and Substituents on the Electronic Structure and Reactivity of Boryl Radicals. *Chem. - Eur. J.* **2014**, *20*, 1630−1637.
(47) Kim, J. H.; Constantin, T.; Simonetti, M.; Llaveria, J.; Sheikh, N. S.; Leonori, D. A Radical Approach for the Selective C−H Borylation of Azines. *Nature* **2021**, *595*, 677−683.
(48) Juliá, F.; Constantin, T.; Leonori, D. Applications of Halogen-Atom Transfer (XAT) for the Generation of Carbon Radicals in Synthetic Photochemistry and Photocatalysis. *Chem. Rev.* **2022**, *122*, 2292−2352.
(49) Pan, X.; Lacôte, E.; Lalevée, J.; Curran, D. P. Polarity Reversal Catalysis in Radical Reductions of Halides by *N*-Heterocyclic Carbene Boranes. *J. Am. Chem. Soc.* **2012**, *134*, 5669−5674.
(50) Kawamoto, T.; Okada, T.; Curran, D. P.; Ryu, I. Efficient Hydroxymethylation Reactions of Iodoarenes Using CO and 1,3-Dimethylimidazol-2-ylidene Borane. *Org. Lett.* **2013**, *15*, 2144−2147.
(51) Barth, F.; Achrainer, F.; Pütz, A. M.; Zipse, H. Aminopyridine-Borane Complexes as Hydrogen Atom Donor Reagents: Reaction Mechanism and Substrate Selectivity. *Chem. - Eur. J.* **2017**, *23*, 13455−13464.
(52) Pan, X.; Lalevée, J.; Lacôte, E.; Curran, D. P. Disulfides and Boryl Sulfides Serve as both Initiators and Precatalysts in Radical Reductions of Halides by an *N*-Heterocyclic Carbene Borane. *Adv. Synth. Catal.* **2013**, *355*, 3522−3526.
(53) Yu, Y.-J.; Zhang, F.-L.; Peng, T.-Y.; Wang, C.-L.; Cheng, J.; Chen, C.; Houk, K. N.; Wang, Y.-F. Sequential C-F Bond Functionalizations of Trifluoroacetamides and Acetates via Spin-Center Shifts. *Science* **2021**, *371*, 1232−1240.
(54) Internet Bond-energy Databank (iBonD). http://ibond.nankai.edu.cn (accessed May, 2022).
(55) Lalevée, J.; Blanchard, N.; Chany, A.-C.; Tehfe, M.-A.; Allonas, X.; Fouassier, J.-P. Effect of Lewis Base Coordination on Boryl Radical

Reactivity: Investigation using Laser Flash Photolysis and Kinetic ESR. *J. Phys. Org. Chem.* **2009**, *22*, 986−993.
(56) Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, T. A New Route to Benzo[a]quinolizine Derivative by the Intramolecular Radical Cyclization. *Chem. Lett.* **1987**, *16*, 2417−2418.
(57) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. Synthesis of 2-Azabicyclo[3.3.1]nonanes by means of (Carbamoyl)dichloromethyl Radical Cyclization. *Tetrahedron* **1997**, *53*, 1391−1402.
(58) Coussanes, G.; Jakobi, H.; Lindell, S.; Bonjoch, J. Synthesis of α-Chlorolactams by Cyanoborohydride-Mediated Radical Cyclization of Trichloroacetamides. *Chem. - Eur. J.* **2018**, *24*, 8151−8156.
(59) Coussanes, G.; Vila, X.; Diaba, F.; Bonjoch, J. Radical Cyclization of Trichloroacetamides: Synthesis of Lactams. *Synthesis* **2017**, *49*, 1481−1499.
(60) Klett, J.; Wozniak, L.; Cramer, N. 1,3,2-Diazaphospholene-Catalyzed Reductive Cyclizations of Organohalides. *Angew. Chem., Int. Ed.* **2022**, No. e202202306.
(61) Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25−35.
(62) Solovyev, A.; Chu, Q.; Geib, S. J.; Fensterbank, L.; Malacria, M.; Lacôte, E.; Curran, D. P. Substitution Reactions at Tetracoordinate Boron: Synthesis of *N*-Heterocyclic Carbene Boranes with Boron−Heteroatom Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 15072−15080.
(63) Peng, T.-Y.; Xu, Z.-Y.; Zhang, F.-L.; Li, B.; Xu, W.-P.; Fu, Y.; Wang, Y.-F. Dehydroxylative Alkylation of α-Hydroxy Carboxylic Acids Derivatives via Spin-center Shift. *Angew. Chem., Int. Ed.* **2022**, No. e202201329.
(64) Walton, J. C.; Dai, W.; Curran, D. P. EPR Studies on the Addition of Ligated Boryl Radicals to Carbonyl Compounds. *J. Org. Chem.* **2020**, *85*, 4248−4255.
(65) Zhang, F.-L.; Li, B.; Houk, K. N.; Wang, Y.-F. Application of the Spin-center Shift in Organic Synthesis. *JACS Au* **2022**, *2*, 1032−1042.
(66) Wessig, P.; Muehling, O. Spin-Center Shift (SCS) − A Versatile Concept in Biological and Synthetic Chemistry. *Eur. J. Org. Chem.* **2007**, *2007*, 2219−2232.
(67) Hooper, A. J.; Burnett, J. R. Dalcetrapib, a Cholesteryl Ester Transfer Protein Modulator. *Expert Opin. Invest. Drugs* **2012**, *21*, 1427−1432.
(68) Gayler, K. M.; Quintana, J. M.; Mattke, J.; Plunk, M. A.; Kostyo, J. H.; Karunananthan, J. W.; Nguyen, H.; Shuda, M.; Ferreira, L. D.; Baker, H.; Stinchcomb, A. L.; Sharina, I.; Kane, R. R.; Martin, E. Gemfibrozil Derivatives as Activators of Soluble Guanylyl Cyclase − A Structure-Activity Study. *Eur. J. Med. Chem.* **2021**, *224*, No. 113729.
(69) Mondal, S.; Dumur, F.; Gigmes, D.; Sibi, M. P.; Bertrand, M. P.; Nechab, M. Enantioselective Radical Reactions Using Chiral Catalysts. *Chem. Rev.* **2022**, *122*, 5842−5976.




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