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Fe-Catalyzed Structurally Divergent γ-Polyhaloalkylation of Siloxydienes

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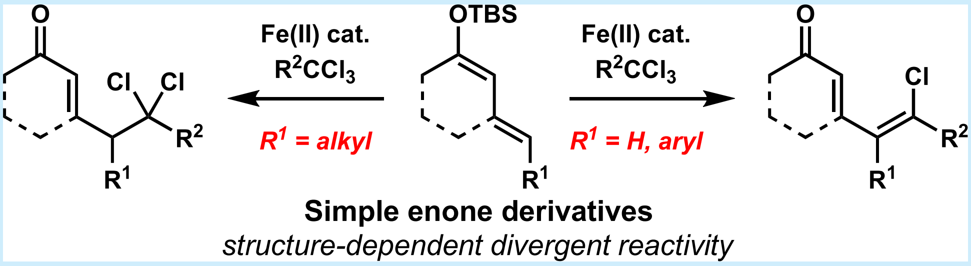

ABSTRACT: Regioselective γ-polyhaloalkylation is achieved using tetrahalomethanes or α,α,α-trihaloalkyl compounds and siloxydienes via Fe(II) catalysis. A range of siloxydienes are functionalized in good yields with high stereoselectivity under mild reaction conditions. Structural divergence is observed as either haloalkylated or haloalkenylated products are formed on the basis of the substitution pattern of the siloxydiene. The halogenated products show utility in further synthetic transformations, selective reduction, and cross-coupling reactions.

Carbon−carbon bond formation reactions are the bedrock of organic synthesis, and functionalization of unsaturated carbonyl systems is among the most versatile transformations in organic synthesis.[1] However, these composite functional groups also present challenges in site selectivity owing to the multiple sites possessing similar electronic properties. Solutions for site selective α-, α'-, and β-functionalization of enone systems via enolate or conjugate addition transformations are well-known, but efficient and general protocols for γ-functionalization remain limited.

Our laboratory has developed a radical-based strategy for bond formation at enone γ-sites via easily accessible siloxydiene derivatives of unsaturated carbonyl compounds.[2] In one prior example,[2d] we presented a Cu(II)-catalyzed γ-alkylation reaction utilizing siloxydienes and α-halocarbonyl compounds (Scheme 1a). A limitation of this transformation is the necessity of an electron-withdrawing group neighboring the radical precursor, presumably facilitating the reaction due to radical stabilization. To address this limitation, we have sought alternative radical precursors lacking a carbonyl group and took inspiration from the pioneering science of Kharasch and co-workers, who discovered polyhaloalkanes that are capable of addition to π-systems (Scheme 1b).[3] Significant expansions of this approach have appeared in recent years,[4] although regioselectivity in polarized alkene systems remains underdeveloped. Given our own interest in regioselective radical additions and redox-active first-row transition metals,[2,5] we set out to examine the compatibility of a Kharasch-type transformation for the synthesis of substituted enones bearing versatile halogenation patterns for further synthetic applications including approaches to halogenated natural products.[6] The Mitani group demonstrated the viability of haloradical addition to a silyl dienol ether in 2002, describing a single example of γ-dibromomethylenation of trimethylsiloxybutadiene via photoirradiation (Scheme 1c).[7] A related transformation disclosed by Sun and co-workers successfully accessed α,β-unsaturated γ,γ-dihalogenated dienoates via N-heterocyclic carbene catalysis, although the mechanism requires both aldehyde substrates and a preinstalled carboxylate leaving group at the γ-position (Scheme 1d).[8] Jiang and co-workers developed an approach to γ-dihalomethylene compounds embedded in naphthalones through photoredox catalysis with specially designed 1,7-diynes (Scheme 1e).[9] We envisioned an approach to the synthetically valuable halomethylenated enones that would encompass a wider range of carbonyl-containing substrates and avoid the need for preinstalled functional groups by employing radical-based site selective addition (Scheme 1f). In this report, we disclose an efficient Fe-catalyzed coupling of siloxydienes and

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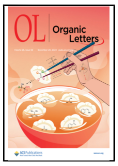

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Scheme 1. Methods of Haloalkylation and Alkenylation

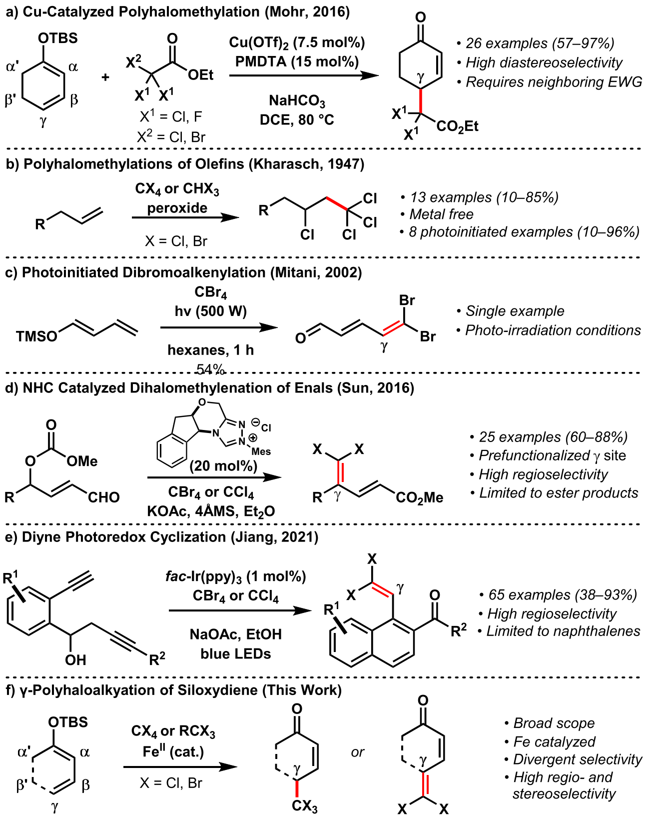
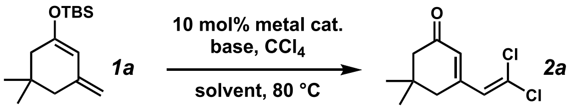


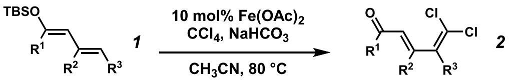
Table 1. Optimization of γ-Polyhalomethylenation[a]

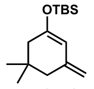
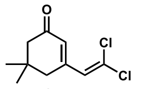
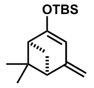
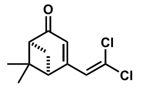
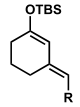
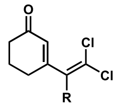
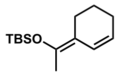
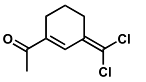
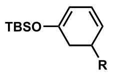
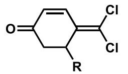
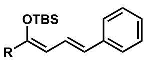
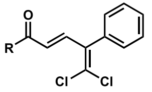
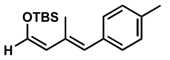
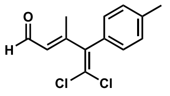


Entry	Metal catalyst	Solvent	Base	% Yield[a]
1	$Fe(OAc)_2$	CH_3CN	None	60
2	$Fe(OAc)_2$	CH_3CN	$(i\text{-}Pr)_2NEt$	61
3	$Fe(OAc)_2$	CH_3CN	2,6-lutidine	45
4	$Fe(OAc)_2$	CH_3CN	DBN	17
5	$Fe(OAc)_2$	CH_3CN	K_2CO_3	14
6	$Fe(OAc)_2$	CH_3CN	Na_2CO_3	74
7	$Fe(OAc)_2$	CH_3CN	$NaHCO_3$	94 (92)[b]
8	$Fe(OAc)_2$	i-PrCN	$NaHCO_3$	43
9	$Fe(OAc)_2$	toluene	$NaHCO_3$	0
10	$Fe(OAc)_2$	THF	$NaHCO_3$	39
11	$Fe(OAc)_2$	EtOH	$NaHCO_3$	32
12	none	CH_3CN	$NaHCO_3$	0
13	$FeCl_3$	CH_3CN	$NaHCO_3$	52
14	$FeCl_2$	CH_3CN	$NaHCO_3$	60
15	$Fe(OTf)_2$	CH_3CN	$NaHCO_3$	23
16	$Cu(OAc)_2•H_2O$	CH_3CN	$NaHCO_3$	22
17	$Mn(acac)_3$	CH_3CN	$NaHCO_3$	0

[a] NMR yield (using CH_2Br_2 as an internal standard) for the reaction of siloxydiene **1a** (0.25 mmol), a metal (10 mol %), a base (2.0 equiv), and CCl_4 (10.0 equiv) in a solvent (2.5 mL) at 80 °C for 12 h. [b] Isolated yield in parentheses.

Table 2. Scope of Siloxydiene Coupling Partners[a]



Entry	Siloxydiene		Product		% Yield
1		*1a*		*2a*	92
2		*1b*		*2b*	68
3		*1c*, R = H		*2c*	42
4		*1d*, R = Ph		*2d*	69
5		*1e*		*2e*	15
6		*1f*, R = H		*2f*	44
7		*1g*, R = Me		*2g*	34
8		*1h*, R = p-Tol		*2h*	84
9		*1i*, R = t-Bu		*2i*	75
10		*1j*		*2j*	57

[a] Isolated yield (average of two runs) from the reaction of dienol ether (0.25 mmol), CCl_4 (10.0 equiv), $NaHCO_3$ (2.0 equiv), and 10 mol % $Fe(OAc)_2$ in 2.5 mL of MeCN at 80 °C for 12 h.

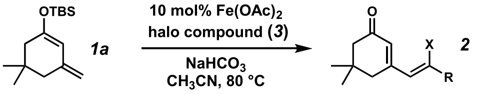
haloalkanes that is regio- and stereoselective and furnishes either γ-polyhaloalkylated or γ-haloalkenylated enones.

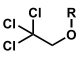
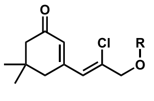
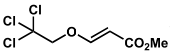
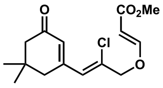
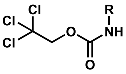
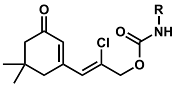
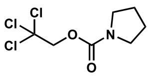
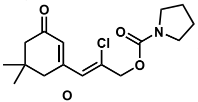
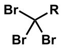
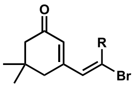
We selected readily available, isophorone-derived siloxydiene **1a** and commercially available carbon tetrachloride to examine the halofunctionalization conditions (Table 1). The initial reaction using $Fe(OAc)_2$ as a catalyst in an acetonitrile solvent furnished dihalomethylenated product **2a** in a fair yield (entry 1). A screen of basic additives found that although organic bases did little to improve efficiency, inorganic bases had a stronger effect (entries 2–7). The counterion had an effect, with sodium salts performing significantly better than potassium salts. Ultimately, $NaHCO_3$ proved to be the best base investigated, providing the dihalomethylenated enone in 94% yield. The precise role of the additive is uncertain; one possible role is scavenging the trace acid produced from silyl chloride byproducts reacting with adventitious water, which might cause siloxydiene hydrolysis. Examining solvents revealed acetonitrile to be particularly effective for this transformation (entries 7–11). Investigation of metal sources showed that the metal is required for a productive reaction, and Fe salts were more effective than Cu or Mn, with $Fe(OAc)_2$ performing best (entries 7 and 12–17).[10] On the basis of these results, we proceeded to examine the scope of the coupling.

To understand the scope of our reaction, we began by testing a multitude of cyclic and acyclic siloxydienes (Table 2). Dihalomethylenation at exocyclic γ-sites provided derivatives of isophorone or verbenone in good yields (entry 1 or 2, respectively). The unsubstituted analogue derived from 3-methylcyclohexenone (**1c**) proceeded in moderate yield, principally due to competing hydrolysis of the starting material (entry 3). γ-Arylated exocyclic siloxydiene **1d** proceeded in 69% yield (entry 4). Dienol ether **1e**, formed from 1-acetyl-1-cyclohexene, afforded γ-dichloromethylene 1-acetyl-1-cyclohexene **2e** in 15% yield (entry 5). Endocyclic siloxydienes **1f** and **1g** were successfully alkylated in moderate yields (entries 6 and 7, respectively). Acyclic γ-arylated siloxydienes produced dichlorodienones in high yields (entries 8 and 9). Siloxydiene **1j**, formed from a γ-aryl aldehyde, was transformed into dihalomethylenated congener **2j** in 57% yield, demonstrating the compatibility of our conditions with a sensitive aldehyde functionality (entry 10).

To expand beyond one-carbon additions, we investigated a variety of substituted α,α,α-trichloro coupling partners with isophorone-derived siloxydiene **1a** (Table 3). Initial tests using trichloroethanol (**3a**) and benzyl ether **3b** found that coupling products could indeed form with these more complex haloalkanes, leading to halomethylenation products in 23% and 21% yields, respectively (entries 1 and 2, respectively). Transforming the benzyl ether into a benzoate ester (**3c**) led to substantial improvement, and chlorinated dienone (Z)-**2m** was isolated in 75% yield (entry 3). Ethyl (2,2,2-trichloroethyl) carbonate (**3d**) and vinylogous carbonate **3e** displayed moderate reactivity with siloxydienes under our conditions (entries 4 and 5, respectively). Carbamate-containing substrates coupled more efficiently, demonstrating tolerance of both acidic N-containing functional groups and highly polar carbonyl moieties (entries 6−9). The reaction between siloxydiene **1a** and either tetrabromomethane or bromoform led to the halomethylene product in 52% or 15% yield, respectively (entry 10 or 11, respectively). On a 2.5 mmol scale, the yield of dienone **2t** improved to 58%. In all cases, the Z isomer predominated, with the exception of monobromoenone **2u** generated through coupling with bromoform. The stereochemical preference was most pronounced when the coupling partner contained an electron-withdrawing group.

Table 3. Scope of Polyhalo Coupling Partners[a]

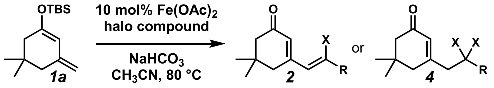


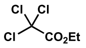
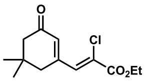
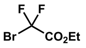
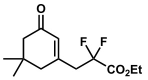
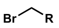
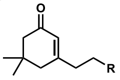
Entry	Halo Compound	Product	Z/E[b]	% Yield
1	 **3a**, R = H	 **2k**	8.2:1	23
2	**3b**, R = Bn	**2l**	4.2:1	21
3	**3c**, R = Bz	**2m**	Z only	75
4	**3d**, R = CO$_2$Et	**2n**	Z only	43
5	 **3e**	 **2o**	37.1:1	46
6	 **3f**, R = n-Pr	 **2p**	Z only	77
7	**3g**, R = Cy	**2q**	11.4:1	53
8	**3h**, R = allyl	**2r**	14.1:1	69
9	 **3i**	 **2s**	12.6:1	53
10	 **3k**, R = Br	 **2t**		52 (58)[c]
11	**3l**, R = H	**2u**	E only	15

[a] Isolated yield (average of two runs). See Table 2 for reaction conditions. [b] Z/E ratios were determined via NOESY NMR analysis. [c] In parentheses is the isolated yield from the reaction of dienol ether **1a** (2.5 mmol), CBr$_4$ (5.0 equiv), NaHCO$_3$ (2.0 equiv), and 10 mol % Fe(OAc)$_2$ in 25 mL of MeCN at 80 °C for 12 h.

We surveyed haloalkanes containing proximal electron-withdrawing moieties that might produce stabilized radical intermediates (Table 4). Employing trichloroacetate **3m** with isophorone-derived dienol ether **1a**, we observed coupling that furnished α-chloroenoate **2v** in 39% yield (entry 1). Ethyl bromodifluoroacetate (**3n**) also coupled successfully, but the elimination step did not occur; difluorinated ester **4a** was isolated in 28% yield (entry 2). Attempts to couple ethyl bromoacetate (**3o**) and bromoacetonitrile (**3p**) revealed that electron-withdrawing groups alone are capable of activation, although the yields were moderate (entries 3 and 4, respectively). This observation differs from our previously described Cu-catalyzed alkylation in which primary α-halides were found to be unreactive.[2d,11]

Table 4. Scope of α-Halo Ester and Nitrile Coupling Partners[a]

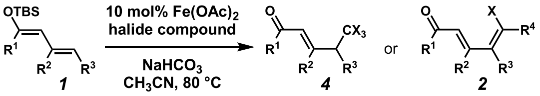


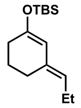
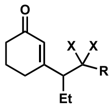
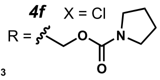
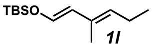
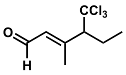
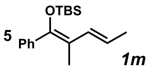
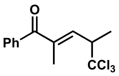
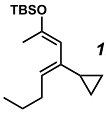
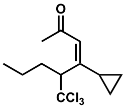
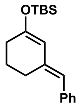
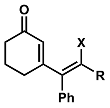
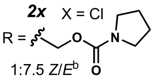
Entry	Halo Compound	Product	% Yield
1	 **3m**	 **2v** 9.3:1 Z/E	39
2	 **3n**	 **4a**	28
3	 **3o**, R = CO$_2$Et	 **4b**	29
4	**3p**, R = CN	**4c**	35

[a] Isolated yield (average of two runs). See Table 2 for reaction conditions.

In our examination of the scope of the transformation, we noted a departure in the reaction pathway for enones bearing a γ-alkyl substituent, where we observed the γ-trichloromethylated products were predominant (Table 5). Exocyclic γ-alkyl siloxydiene **1k** was converted into trichloromethyl cyclohexenone **4d** or tribromomethyl cyclohexenone **4e** in 48% or 41% yield, respectively, with no detectable dihalomethylene product (entry 1 or 2, respectively). Similarly, carbamate **4f**

Table 5. Scope of γ-Alkyl Siloxydiene Coupling Partners[a]

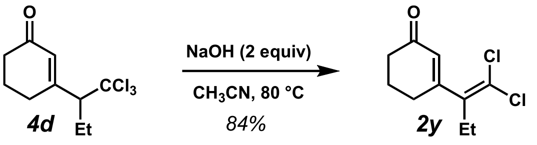


Entry	Siloxydiene	Halide	Product	% Yield
1	 **1k**	CCl$_4$	 **4d** X = R = Cl	48
2		CBr$_4$	**4e** X = R = Br	41
3		**3i**	**4f** X = Cl R = 	44
4	 **1l**	CCl$_4$	 **4g**	70
5	 **1m**	CCl$_4$	 **4h**	75
6	 **1n**	CCl$_4$	 **4i**	21
7	 **1d**	CBr$_4$	 **2w** X = R = Br	44
8		**3i**	**2x** X = Cl R =  1:7.5 Z/E[b]	40

[a] Isolated yield (average of two runs). See Table 2 for reaction conditions. [b] Z/E ratios were determined via NOESY NMR analysis.

was formed through coupling with trichloride **3i** (entry 3). Aldehyde-derived acyclic dienol silane **1l** produced trichloromethylated product **4g** in 70% yield, and aryl-containing siloxydiene **1m** generated enone **4h** in 75% yield (entries 4 and 5, respectively). Siloxydiene **1n**, containing a β-cyclopropyl substituent, afforded trichloromethylation product **4i** in 21% yield with no evidence of ring fission side products (entry 6). In a direct comparison of the divergent reactivity, we utilized siloxydienes **1k** and **1d**, bearing aliphatic and aryl γ-substituents, respectively (entries 1−3, 7, and 8). A stark selectivity difference was observed, with γ-alkyl dienol **1k** generating the haloalkylated products and γ-aryl dienol ether **1d** forming the halomethylated products, all with nearly identical yields.

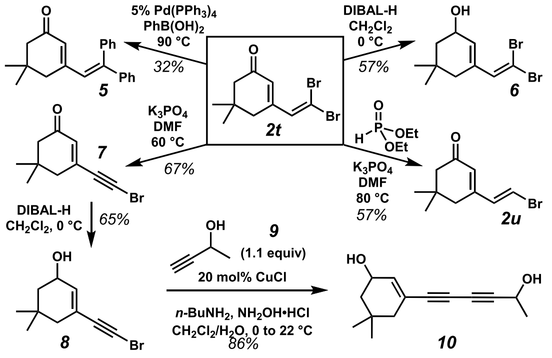
The observed structural divergence as a function of the γ-substituent is suggestive of a reaction pathway involving initial polyhaloalkylation and a varying propensity to undergo subsequent elimination to form the halomethylene moiety. This disparity could be explained by the differing acidities of the aliphatic or benzylic γ-proton after C−C bond formation. Derivatives with an unsubstituted γ-site (e.g., **1a**) undergo rapid elimination, although electronically similar γ-alkyl substrates (e.g., **1k**) undergo elimination very slowly. This disparity is perhaps due to the introduction of allylic strain[12] involving the γ-alkyl substituent that hinders favorable bond alignment. For trihaloalkylated enones including γ-aryl groups (e.g., **1d**), the benzylic nature of the γ-site likely increases acidity, and the corresponding elimination products benefit from a thermodynamic driving force from additional conjugation with the arene. To examine these ideas, isolated γ-alkyl trichloromethylation product **4d** was exposed to the base at higher temperatures. Although the bicarbonate base utilized in the coupling reaction was ineffective even over a prolonged period of time, the stronger base NaOH facilitated the elimination with high efficiency. As a result, previously inaccessible dihalomethylene product **2y** was isolated in 84% yield from the trichloromethylation product (eq 1).



(Eq. 1)

Turning to the synthetic utility of the γ-haloalkenylated products, we examined dibrominated isophorone derivative **2t** in Suzuki cross-coupling, which afforded diarylated product **5** in 32% yield (Scheme 2).[8] Chemoselective carbonyl reduction with DIBAL-H furnished allylic alcohol **6** in 57% yield. Selective hydrodehalogenation was achieved using the Hirao protocol,[13] delivering mono-brominated alkene (E)-**2u** in 57% yield. Notably, this hydrodehalogenation provides a viable alternative to the direct coupling with bromoform (Table 3, entry 11). Elimination with tribasic potassium phosphate was found to efficiently convert the dihalomethylene into bromine enyne **7**. The efficiency of a mild, relatively weak base to access β-bromoenynes presents many potential further applications by virtue of the reactivity of the haloalkyne. Despite the sensitivity of the bromoenyne, DIBAL-H reduction was achieved to form alcohol **8**, which subsequently underwent Cadiot−Chodkiewicz coupling[14] to produce diyne **10** in 86% yield.

Scheme 2. Synthetic Applications of Coupling Products



To conclude, we have developed a robust, general, Fe-catalyzed methodology for accessing halogenated γ-alkylated enones via readily available siloxydienes and halogenated compounds. Depending on the nature of the γ-site, divergent reactivity is observed, leading to polyhaloalkenylation or polyhaloalkylation products. The transformation proceeds in good yields, exhibits complete regiocontrol, and tolerates sterically demanding coupling partners. The introduction of a halogenated functional group with regio- and stereocontrol facilitates further site selective transformations such as cross-couplings. The incorporation of this technology in target-directed synthesis, including toward halogenated natural products, along with mechanistic analysis, is a future direction of our research.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03689.

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

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Notes

The authors declare no competing financial interest.

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