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[4 + 2]-Cycloaddition and 1,4-Addition of *ortho*-Quinone Methides by a Chiral Crotyl Silane

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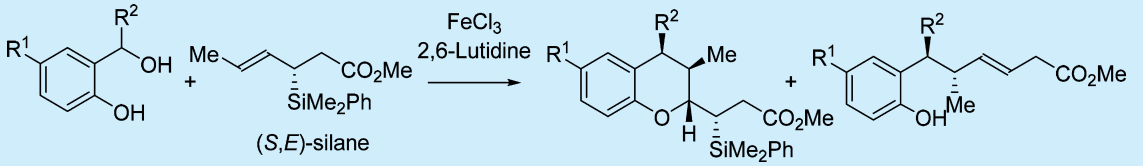
Supporting Information



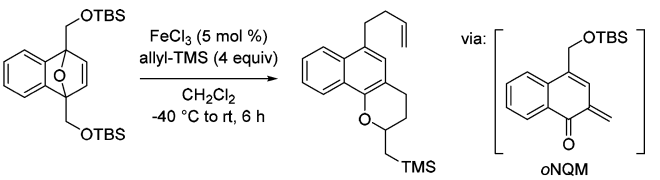
ABSTRACT: Anhydrous $FeCl_3$ in the presence of 2,6-lutidine promotes the substrate-controlled enantioselective [4 + 2]-cycloaddition and crotylation reaction between an enantioenriched (*S*,*E*)-crotyl silane and *in situ* generated *ortho*-quinone methides (*o*QMs). The reaction produces both the chiral chroman and crotylation products in a ratio reflective of the electronic nature of the parent *o*QM with overall combined yields up to 96%. A ring-opening and elimination sequence was subsequently developed to provide direct access to the crotylation products, containing two contiguous tertiary carbon stereocenters, in good yields and enantioselectivities.

ortho-Quinone Methides (*o*QMs) are transient, reactive intermediates that have demonstrated wide usage in organic synthesis and pharmaceuticals.[1] In light of their elusive nature, significant efforts have been made toward selective reactions of *o*QMs formed *in situ*, generating a 1,3-cyclohexadiene core substituted with a carbonyl and an exocyclic methylene group that can be represented by two canonical forms: a zwitterionic or biradical species.[2] This highly polarized structure renders *o*QMs highly susceptible to reaction with nucleophiles in 1,4-addition reactions as well as dienophiles in inverse electron-demand [4 + 2] cycloaddition reactions, providing two unique pathways toward rearomatization.[3] Since the first demonstration of an asymmetric reaction of an *o*QM by Pettus, notable advances have been made toward utilizing *o*QM intermediates in asymmetric synthesis.[4]

Herein, we report an enantioselective $FeCl_3$-promoted [4 + 2]-cycloaddition and 1,4-addition reaction between a chiral crotyl silane and *in situ* generated *o*QMs to give the corresponding stereochemically well-defined benzopyran and 1,4-addition products with useful levels of enantioselectivity. In the process of our initial studies, key observations were made that led to the development of a cycloaddition and subsequent ring-opening reaction sequence that selectively yielded the 1,4-addition product with two contiguous tertiary carbon stereocenters, which remains an important and challenging bond construction to access selectively.[5] Formally, this reaction sequence can be considered an asymmetric crotylation of an *o*QM, and to our knowledge, is the first example of such a transformation.[6]

Recent work by the Sajiki laboratory has demonstrated the potential for an allyl silane to utilize both of the aforementioned *o*QM reaction pathways in their $FeCl_3$-catalyzed reaction between the related 1-naphthoquinone-2-methide and allyl-TMS (Scheme 1).[6b] In their proposed two-step sequence, an initial cycloaddition reaction between the

Scheme 1. Sajiki $FeCl_3$ Catalyzed Sequential Cycloaddition and 1,4-Addition of *o*-Naphthoquinone by Allyl-TMS



generated *ortho*-naphthoquinone methide (*o*NQM) and allyl-TMS is followed by the formation of a *para*-naphthoquinone methide that undergoes nucleophilic attack by a second equivalent of allyl-TMS. The dual reactivity exhibited by allyl-TMS highlights the ability of allyl silane reagents to function as both nucleophiles in 1,4-conjugate addition reactions[7] and dienophiles in inverse electron-demand hetero-Diels−Alder reactions.[8] We have had a longstanding interest in developing and utilizing related chiral silane reagents in asymmetric reactions with a variety of reaction partners.[9] In that context, we intended to expand the use of these chiral silane reagents in asymmetric reactions with *o*QMs.

The present work was inspired by studies reported by the Schaus laboratory in which Fe(III) chloride salts were utilized to promote the *in situ* formation and reaction of *o*QMs.[10] The reactivity of the *o*QM generated from *o*-hydroxybenzyl alcohol, or diol, **1a**, and allyl-TMS was initially examined (Table 1).

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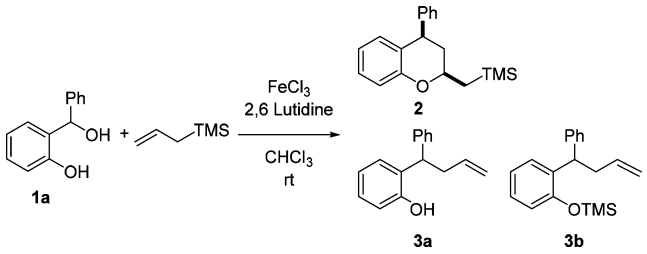
Table 1. [4 + 2] Cycloaddition and 1,4-Addition of *o*-Quinone Methide by Allyl-TMS[a]



entry	concn (M)	time (h)	yield **2** (%)[b]	yield **3a** (%)	yield **3b** (%)
1	0.5	18	0	42	22
2	0.25	18	0	61	17
3	0.1	18	36	33	1
4	0.1	1	49	35	1
5	0.05	18	72	20	0
6	0.05	1	72	21	0

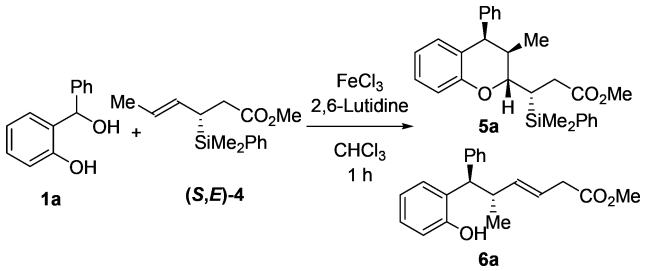
[a]Reaction conditions: diol (0.25 mmol, 1 equiv), allyl-TMS (3 equiv), $FeCl_3$ (0.8 equiv with respect to diol), and 2,6-lutidine (0.4 equiv with respect to diol). Diastereomeric ratio determined by ^{1}H NMR. [b]Isolated dr 1:1.

Anhydrous $FeCl_3$ (0.8 equivalent) in the presence of 2,6-lutidine (0.4 equivalent) at an initial concentration of 0.5 M at room temperature afforded the 1,4-addition product in 42% yield as the free phenol **3a** and 22% yield as the silylated phenol **3b**, but no cycloaddition product **2** was observed (Table 1, entry 1). Encouraged by this result, the reaction concentration was lowered to 0.25 M, resulting in a small increase in overall yield (Table 1, entry 2). Upon lowering the reaction concentration further, mixtures of the cycloaddition product **2** in addition to the allylation product **3a** were obtained (Table 1, entries 3−6). Decreasing the reaction time to 1 h at 0.05 M ultimately gave an optimal overall yield of 93% combined for **2** and **3a** (Table 1, entry 6).

We next sought to extend this [4 + 2]-cycloaddition and 1,4-addition reaction of diol **1a** to the chiral crotyl (*S,E*)-silane **4** (Table 2).[11] Studies were initiated using the optimized reaction conditions for allyl-TMS (Table 2, entry 1), which gave a mixture of 51% of the cycloaddition product **5a** and 16% of the 1,4-addition, or crotylation, product **6a**. Lowering the temperature to 0 °C (Table 2, entry 2) gave a markedly cleaner reaction and an increase in overall yield to 71% of **5a**, in 59% yield as a single diastereomer, and **6a** in 12% yield with a 22:1 dr. Increasing the concentration (Table 2, entry 3) and lowering the $FeCl_3$ and 2,6-lutidine loading (Table 2, entries 5−7) all led to diminished overall yields. It was also noted that the omission of 2,6-lutidine (Table 2, entry 4) resulted in a lower yield with observed baseline byproducts, which indicated the importance of the base as an acid scavenger to minimize potential side reactions.

The optimized reaction conditions for (*S,E*)-silane **4** were used to explore the substrate scope of the cycloaddition and 1,4-addition (Figure 1). A variety of diols bearing electron-rich and electron-deficient substituents were evaluated and found to be tolerated under the reaction conditions. Electron-donating groups *meta* to the *o*QM methylene (**1b**, **1c**) gave only modest increases in overall yield for the corresponding products relative to **1a**. Interestingly though for substrate **1c**, it was noted that the relative ratio of cycloaddition **5c** to crotylation product **6c** (10:1 ratio) increased almost 2-fold

Table 2. [4 + 2] Cycloaddition and 1,4-Addition of *o*-Quinone Methide by (*S*)-Crotyl Silane 4[a]



entry	$FeCl_3$ (equiv)	lutidine (equiv)	temp (°C)	yield **5a** (%)[b]	yield **6a** (%)[c]
1	0.8	0.4	rt	51	16
2	0.8	0.4	0	59	12
3[d]	0.8	0.4	0	53	16
4	0.4	0	0	51	16
5	0.6	0.3	0	57	10
6	0.4	0.2	0	21	14
7	0.6	0.6	0	33	32

[a]Reaction conditions: diol (0.25 mmol, 1 equiv), (*S*)-crotyl silane (2 equiv), and 0.05 M with respect to **1a**. Diastereromeric ratio determined by ^{1}H NMR. [b]Single diastereomer. [c]dr ranged from 3:1 to 22:1. [d]Run at 0.1 M.

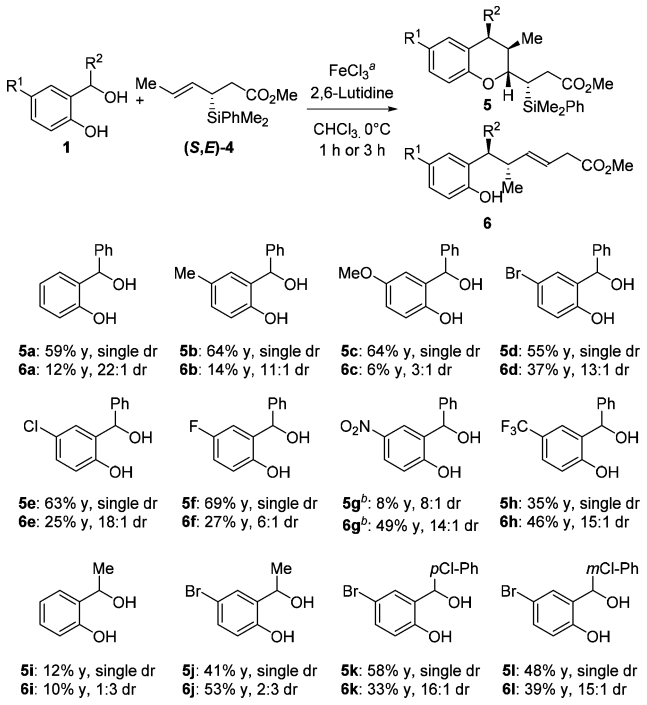


Figure 1. $FeCl_3$ and 2,6-lutidine mediated cycloaddition and crotylation of diols by (S)-crotyl silane.[a] [a] Reaction conditions (unless otherwise noted): **1** (0.25 mmol), **2** (2 equiv), $FeCl_3$ (0.8 equiv), 2,6-lutidine (0.4 equiv), and 0.05 M with respect to diol. Diastereromeric ratios determined by ^{1}H NMR. [b] $FeCl_3$ (2.5 equiv) and 2,6-lutidine (1.25 equiv). Detailed experimental conditions are provided in the Supporting Information.

compared to the relative product ratios obtained for **1a** and **1b** (5:1 ratio for each), which is consistent with a decrease in electrophilicity and reactivity of a more electron-rich *o*QM toward nucleophilic addition.[12] Conversely, very strongly electron-withdrawing substituents such as trifluoro (**1g**) and

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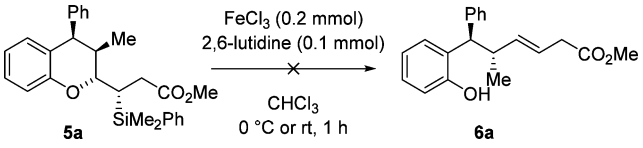
nitro (**1h**) favored the crotylation over the cycloaddition product and gave comparable overall yields. Notably, substitution with a halide onto the phenol of the diphenyl diol substrates (**1d–f**) gave excellent overall yields with product ratios slightly favoring the cycloaddition product. Substitution on the R^2 aryl ring (**1k** and **1l**) was also well tolerated, while substitution with a methyl group at that position (**1i**, **1j**) necessitated the stabilizing Br-substitution on the phenol ring in order to achieve an appreciable overall yield.

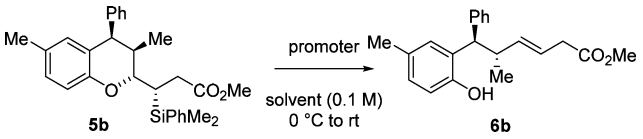
Given the possibility that the crotylation products could have arisen from an in situ ring opening of the pyran and silane elimination (ring-opening reaction) of the generated cycloaddition products, **5a** was isolated and resubjected to the corresponding $FeCl_3$/2,6-lutidine reaction conditions as well as at room temperature (Scheme 2). However, conversion to **6a** was not observed in either case, which indicated the existence of two potentially distinct reaction pathways to generate products **5** and **6**.

Scheme 2. Resubjection of 5a to Reaction Conditions



To further probe access to the crotylation products from the corresponding cycloaddition products, conditions were screened to promote a concomitant pyran ring opening and silicon elimination of **5b** (Table 3). Use of the fluoride ion source TBAF while stirring at room temperature gave incomplete conversion, even with substoichiometric amounts (Table 3, entries 1 and 2). Interestingly, a significant portion of the product obtained was the isomerized α,β-unsaturated isomer of **6b**. Other fluoride sources such as NH_4F and CsF (Table 3, entries 3 and 4) as well the Lewis acid $BF_3{\cdot}OEt_2$ (Table 3, entries 5 and 6) gave no reaction at room temperature. The lack of reactivity observed suggested that more forcing conditions were required to promote the reaction. Upon changing the solvent to DCE and refluxing overnight in the presence of $BF_3{\cdot}OEt_2$, **6b** was isolated in a 70% yield (Table 3, entry 7). A minor product from this reaction was isolated and identified as the *Z*-isomer of **6b**, which was proposed to form from a potential E1-type elimination of the silane moiety. When utilizing the strong Lewis acid $TiCl_4$, an optimal yield was achieved after only 3 h at room temperature (Table 3, entry 8) as a mixture of 3:1 *E*/*Z* isomers.

Table 3. Ring-Opening and Silicon Elimination of 5b[a]



entry	promoter	promoter equiv	solvent	time (h)	yield (%)
1	TBAF	8	THF	43	37[b,c]
2	TBAF	20	THF	46	31[b,d]
3[e]	NH_4F	20	THF	44	nr
4[f]	CsF	20	DMF	18	nr
5	$BF_3{\cdot}OEt_2$	6	DCM	22	nr
6	$BF_3{\cdot}OEt_2$	30	DCM	19	nr
7[g]	$BF_3{\cdot}OEt_2$	5	DCE	22	70[h]
8	$TiCl_4$	3	DCM	3	75[i]

[a]Reaction conditions: **5b** dissolved in given solvent, and reagent added at 0 °C and stirred at rt unless otherwise stated. [b]Reaction not to completion. [c]Isolated mix of **6b** β,γ- and α,β-unsaturated isomers in 1:7 ratio. [d]Ratio of 1:5 mix of **6b**-β,γ/**6b**-α,β isomers. [e]Reaction ran at 0.06 M. [f]Reaction ran at 100 °C. [g]Reaction ran at 70 °C. [h]Ratio of 21:1 *E*/*Z* isomers and >30:1 dr. [i]Ratio of 3:1 *E*/*Z* isomers and >30:1 dr.

With the optimized conditions in hand, we then extended this ring-opening reaction to utilize the crude product mixture obtained from the $FeCl_3$ promoted reaction between **1** and **4** (Figure 2). Gratifyingly, when subjecting the crude reaction product mixture of **1a** and **4** to the $TiCl_4$ mediated ring-opening reaction conditions, **6a** was obtained in 61% yield over two steps. Good overall yields were obtained for substrates containing electron-donating substituents (**1b** and **1c**) and demonstrated a unique approach to formally obtain 1,4-addition products, despite the tendency for an electron-rich parent *o*QM to discourage 1,4-addition. Substrates bearing halide substituents in the diphenyl diol series (**1d**, **1e**, **1f**) performed well under the ring-opening reaction conditions, in accordance with the high overall yields observed in the initial $FeCl_3$-promoted reactions. Reactions of **1i** and **1j** also

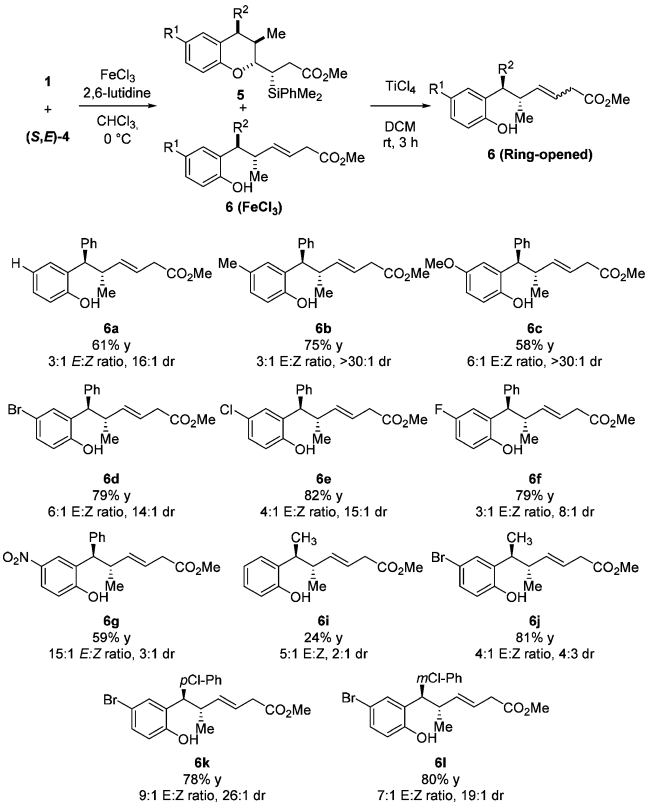


Figure 2. $TiCl_4$-promoted ring opening and silicon elimination of the crude product mixture of **1** and **4**.[a] [a]Reaction conditions (unless otherwise noted): Ran general procedure for the $FeCl_3$ and 2,6-lutidine reaction to obtain crude product mixture of **5** and **6**. To the crude product mixture at 0 °C $TiCl_4$ solution (1 M in DCM, 3 equiv) was added, which was warmed to rt and stirred for 3 h. *E*/*Z* ratio and dr determined by ^1H NMR. Detailed experimental conditions are provided in the Supporting Information.

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demonstrated the importance of the initial $FeCl_3$-promoted reaction for the success of the subsequent ring-opening process and provided a method to selectively access vicinal, methyl tertiary stereocenters. Crotylation products containing two aryl halide moieties (**6k** and **6l**) were obtained in excellent yield and were envisioned to enable future elaboration of the crotylation products in a divergent fashion.

In conclusion, we have developed an enantioselective cycloaddition and crotylation reaction of *ortho*-quinone methides with a chiral (*S*,*E*)-crotyl silane reagent **4** in the presence of the readily available and inexpensive promoter $FeCl_3$. The transformation provides access to both the chiral pyran product **5** as well as the crotylation product **6** with two contiguous tertiary carbon stereocenters. A $TiCl_4$-mediated ring opening of the pyran with concomitant elimination of silicon, or formally a crotylation of the *o*QM, reaction sequence was developed in the process to achieve the crotylation product **6** in good to excellent yields. Studies focused on the further elaboration and application of this methodology are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03395.

Experimental procedures and spectroscopy data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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