Organic LETTERS
Letter
pubs.acs.org/OrgLett

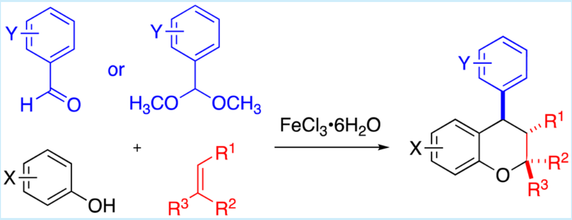
Multicomponent Condensation Reactions via *ortho*-Quinone Methides

Emily E. Allen, Calvin Zhu, James S. Panek, and Scott E. Schaus*

Department of Chemistry, Center for Molecular Discovery (BU-CMD), Life Science and Engineering Building, Boston University, 24 Cummington Mall, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: Iron(III) salts promote the condensation of aldehydes or acetals with electron-rich phenols to generate *ortho*-quinone methides that undergo Diels—Alder condensations with alkenes. The reaction sequence occurs in a single vessel to afford benzopyrans in up to 95% yield. The reaction was discovered while investigating a two-component strategy using 2-(hydroxy(phenyl)methyl)phenols to access the desired *ortho*-quinone methide in a Diels—Alder condensation. The two-component condensation also afforded the corresponding benzopyran products in yields up to 97%. Taken together, the two- and three-component strategies using *ortho*-quinone methide intermediates provide efficient access to benzopyrans in good yields and selectivities.



ortho-Quinone Methides (*o*QMs) are reactive synthetic building blocks useful for the synthesis of natural products and pharmaceutical compounds (Figure 1).[1] They are short-lived intermediates, and their reactivity is understood by two canonical forms: a biradical species or a polarized zwitterion.[2] These resonance structures highlight the susceptibility of *o*QMs to undergo nucleophilic attack at the methide carbon, with rearomatization as the thermodynamic driving force.[3] In addition, *o*QMs react with electron-rich dienophiles in inverse-electron demand hetero-Diels—Alder reactions.[4] We reported a Diels—Alder reaction of *o*QMs and dienophiles promoted by Fe salts.[5] We postulated that we would be able to develop a multicomponent approach using *o*QMs as reactive intermediates in Diels—Alder reactions using phenols and aldehydes as *o*QM precursors. Herein we report a one-pot, multicomponent reaction (MCR) strategy, enabling convergent approaches in the synthesis of benzopyrans using *o*QMs as reactive intermediates.[6]

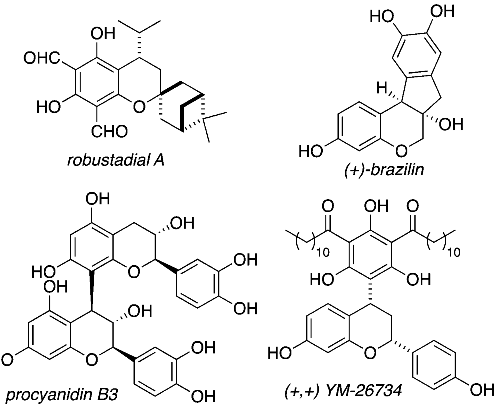


Figure 1. Representative natural products and pharmaceuticals bearing substituted benzopyrans.

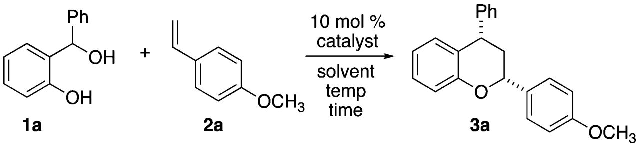
Condensation reactions between hydroxybenzyl alcohols and olefins affording benzopyrans have featured specific dienophile reaction partners catalyzed by chiral phosphoric acid (PA) catalysts.[7] Schneider reported the chiral PA-catalyzed reactions with electron-rich enamines and diones,[8] and Rueping described the asymmetric synthesis of chromans in the reaction of hydroxybenzyl alcohols with diones and styrene derivatives.[9] Similarly, Shi examined reactions with vinyl indoles and enamides catalyzed by chiral PA catalysts.[10] These two-component approaches are advantageous when the *o*-hydroxybenzyl alcohols are easily prepared and react well in the cycloaddition reaction. However, we wished to determine if metals could promote the reaction of hydroxybenzyl alcohols with olefins and investigated the multicomponent strategy to access *o*QMs in situ.

We initially designed experiments to evaluate the reactivity of *o*-hydroxybenzyl alcohols and *p*-methoxy styrene with Lewis acids (Table 1). Magnesium chloride led to a trace amount of product after 1 h (Table 1, entry 1), and Pd(TFA)$_2$ (entry 2) resulted in a 22% yield. The reaction promoted by FeCl$_3$·6H$_2$O (Table 1, entry 3) afforded a 36% yield of the desired product in a 6:1 dr. Anhydrous FeCl$_3$ afforded a 57% yield and 4:1 dr (Table 1, entry 4) after 1 h in CH$_2$Cl$_2$. The addition of molecular sieves slowed the reaction; FeCl$_3$ with 4 Å MS (200 mg) in CH$_2$Cl$_2$ gave a 28% yield and 1:1 dr (Table 1, entry 5). Dry HCl was generated from TMSCl and MeOH and promoted the reaction in 26% yield and 4:1 dr (Table 1,

Received: March 2, 2017

DOI: 10.1021/acs.orglett.7b00647
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Catalyzed Hetero-Diels–Alder of *o*-Quinone Methides[a]



entry	catalyst	solvent	time (h)	yield (%)[b]	dr[c]
1	$MgCl_2$	CH_2Cl_2	1	<5	—
2	$Pd(TFA)_2$	CH_2Cl_2	5	22	2:1
3	$FeCl_3 \cdot 6H_2O$	CH_2Cl_2	6	36	6:1
4	$FeCl_3$	CH_2Cl_2	1	57	4:1
5[d]	$FeCl_3$, 4 Å MS	CH_2Cl_2	1	28	1:1
6	TMSCl/MeOH	CH_2Cl_2	1	26	4:1
7[e]	$FeCl_3$	$CHCl_3$	1.3	82	4:1

[a]Reaction conditions: diol (0.5 mmol, 1 equiv), *p*-methoxystyrene (2 equiv), catalyst (10 mol % with respect to diol) and 0.5 M with respect to diol, 0 °C to rt. [b]Isolated yields. [c]diastereomeric ratio determined by ^{1}H NMR [d]4 Å MS (200 mg), [e]$CHCl_3$ stabilized with amylenes.

entry 6). Anhydrous $FeCl_3$ proved the most efficient at mediating the reaction, and after evaluating additional solvents, $CHCl_3$ afforded a higher yield than CH_2Cl_2 (82% yield, entry 7).

The optimized reaction conditions were used to explore the scope of the two-component hetero-Diels–Alder reaction (Figure 2). We evaluated diols featuring both electron-rich and -deficient substituents. Diols with pendant aryl rings at the methide carbon performed better than those with alkyl groups, likely due to the increased stability of the *o*QM from conjugation (**3b** vs **3l**). Styrene worked well in the reaction (**3g**). The reaction conditions also tolerated geminal methyl substituents at the methide carbon (**3m**). Indene was effective, and although it does not bear electron-donating substituents, the rigidity of the fused bicycle and ring strain may have contributed to its reactivity (**3d–f**, **3h**, **3k**, **3m**). 1,1′-Disubstituted olefins underwent the cycloaddition condensation reaction in good yields (**3i**, **3j**, **3n**, **3o**). The geminal substitution renders the dienophile more electron-rich, which is represented in the higher isolated yields. Additionally, *α*-pinene underwent the condensation and was determined to proceed with exo selectivity (**3n**, **3o**). The use of this dienophile affords a trisubstituted benzopyran with the cyclobutane intact.

We sought to expand the type of condensation reaction that could undergo the Fe salt catalyzed process by using stabilized enolates (Scheme 1). Wang and co-workers described the reaction of *o*QM precursors with *β*-ketoesters and diones under reflux conditions to afford the corresponding 4*H*-chromenes in high yields.[11] Under $FeCl_3$ catalyzed conditions, the reaction between *o*-hydroxybenzyl alcohol **1a** and methyl acetoacetate **4a** afforded the trisubstituted benzopyran **5** featuring an adjacent hemiketal and ester. The hemiketal can be isolated and further functionalized. Reduction of the chroman hemiketal with a triethylsilane and $BF_3 \cdot OEt_2$ reduction to afford benzopyran **6** in 67% yield as a single diastereomer.[12] In addition, 4*H*-chromene **8** was accessed by an acid catalyzed dehydration of hemiketal **7** in 91% yield in two steps from the *o*-hydroxybenzyl alcohol **1a** and 2,4-pentanedione **4c**.

There are a limited number of stable *o*QMs; most reactions that use *o*QMs employ precursors that undergo in situ formation of the reactive *o*QM.[13,14] We sought to test the limits of *o*QM generation and reactivity and postulated a multicomponent condensation to generate *o*QM *in situ* from aldehydes and phenols. We envisaged a metal-mediated

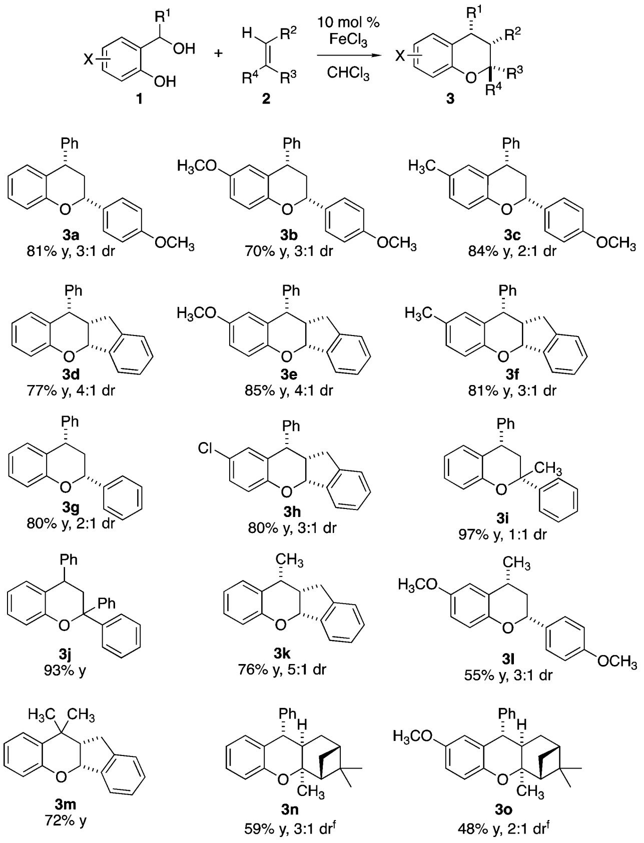
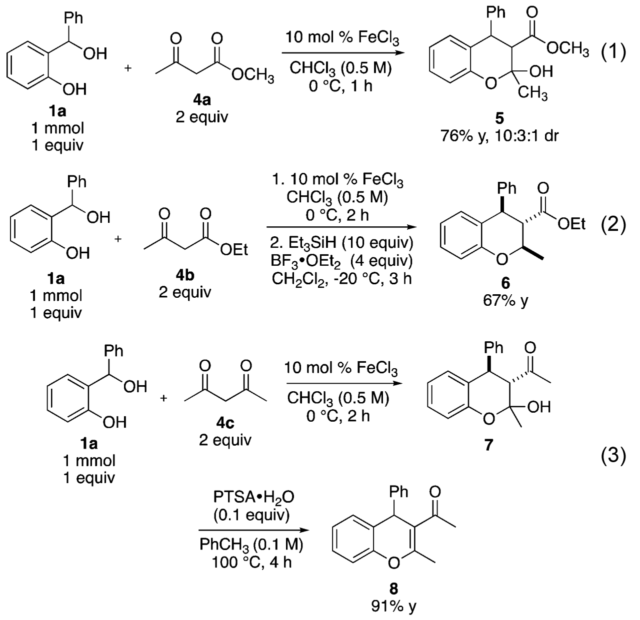


Figure 2. $FeCl_3$ mediated cycloaddition of *o*-hydroxybenzyl alcohols and olefins.[a] [a]Reaction conditions: **1** (1.0 mmol), **2** (2 equiv), $FeCl_3$ (10 mol % with respect to diol) and 0.5 M with respect to diol; diastereomeric ratio determined by ^{1}H NMR. [b]Diol (0.5 mmol, 1 equiv), *p*-methoxystyrene (2 equiv), $FeCl_3$ (20 mol % with respect to diol). Detailed experimental conditions are provided in the Supporting Information.

Scheme 1. $FeCl_3$ Mediated Cycloaddition of Diones and *β*-Ketoesters To Afford Benzopyrans and 4*H*-Chromenes



condensation reaction as a route to an *o*QM that would undergo a subsequent HDA reaction (Figure 3).

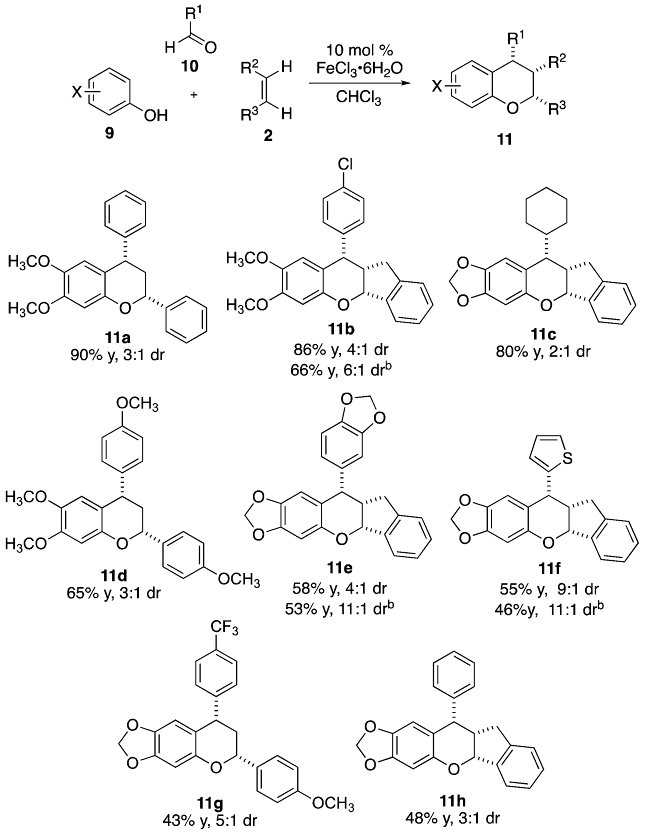


Figure 3. Multicomponent condensation reaction with aldehydes, phenols, and olefins.[a] [a] Reaction conditions: 2.0 mmol of phenol, 2.0 mmol of aldehdye, and 1.0 mmol of dienophile, 0.5 M with respect to dienophile and 10 mol % $FeCl_3{\cdot}6H_2O$ with respect to phenol; isolated yields; diastereomeric ratio determined by ^1H NMR; detailed experimental conditions are provided in the Supporting Information. [b] Yield and dr after trituration with hot hexanes.

The reaction of 3,4-dimethoxyphenol with benzaldehyde and styrene afforded **11a** in 90% yield and 3:1 dr. *p*-Chlorobenzaldehyde was used to afford **11b** in good yields and diastereoselectivities. Cyclohexanecarboxaldehyde also underwent condensation to afford chroman **11c** in good yields but in only 2:1 dr. Heteroatom-containing aldehydes underwent the transformation, albeit in modest yields (**11d**–**f**). The electron-deficient aryl aldehyde, *p*-(trifluoromethyl)benzaldehyde, afforded **11g** in 43% yield, 5:1 dr. The reaction of sesamol with benzaldehyde and indene afforded **11h** in 48% yield and 3:1 dr.

While the multicomponent reaction proceeded with aldehydes, the yields tended to be less than 70%. We hypothesized that acetals may be better electrophiles for the Friedel–Crafts reaction. Acetals react through an oxonium ion which has a lower π^* than that of an aldehyde. For comparison, the reaction of benzaldehyde dimethyl acetal with sesamol and indene afforded the corresponding product **13a** in 86% yield and 6:1 dr. The same product was isolated from the reaction of benzaldehyde in 48% yield and 3:1 dr (**11h**), providing evidence that the electrophilicity of the second component has a significant outcome on the reaction yield (Figure 4).

Sesamol and benzaldehdye dimethyl acetal were excellent reaction partners for generating the reactive *o*QM to be used in

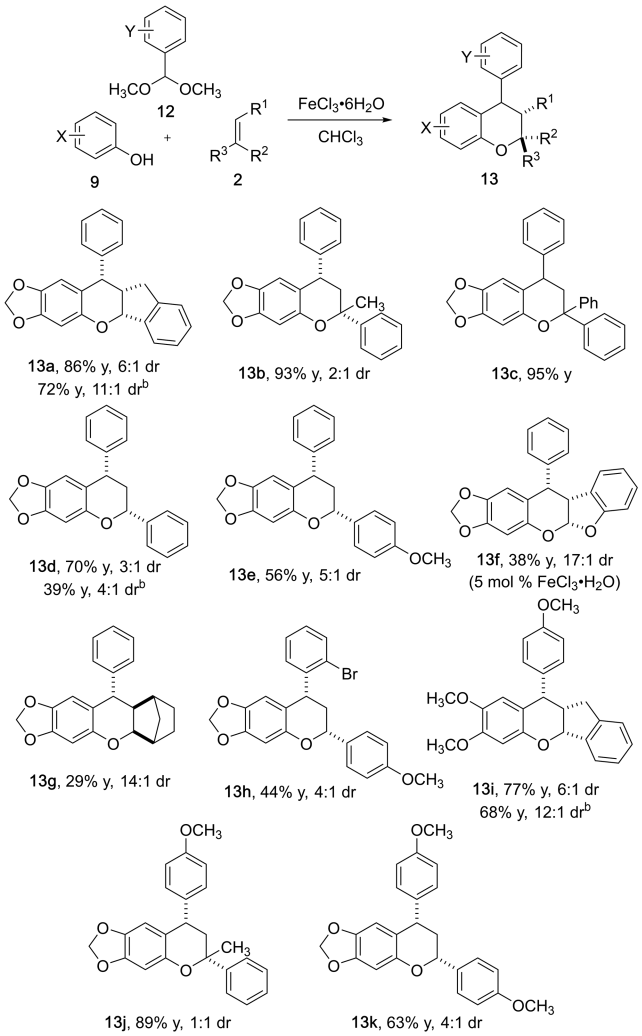


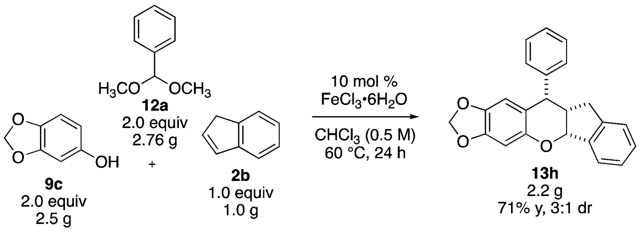
Figure 4. Multicomponent condensation reaction with acetals, phenols, and olefins.[a] [a] Reaction conditions: 2.0 mmol of phenol, 2.0 mmol of acetal, and 1.0 mmol of dienophile, 0.5 M with respect to and 10 mol % $FeCl_3{\cdot}6H_2O$ with respect to phenol unless otherwise stated; isolated yields; diastereomeric ratio determined by ^1H NMR; detailed experimental conditions are provided in the Supporting Information. [b] Yield and dr after trituration with hot hexanes.

the MCR. 1,1-Disubstituted dieneophiles were effective at trapping the *o*QM and generating a benzopyran. 1,1′-Diphenylethylene and α-methylstyrene were high yielding (**13b, 13c, 13j**). Indene proceeded with good diastereoselectivity, most likely due to the rigidity of the fused bicycle (**13a, 13i**). Styrene performed better than *p*-methoxy styrene, despite being less electron-rich (**13d**).

Interestingly, benzofuran afforded a fused pentacycle **13f** in good diastereoselectivity (17:1 dr) but low yields. The best yields were obtained with 5 mol % $FeCl_3$; the product undergoes further decomposition under the reaction conditions. Norborene afforded the corresponding condensation product **13g** in low yield and selectivity (29% yield, 14:1 dr). The reaction conditions also tolerated substituted benzaldehyde acetals. 2-Bromobenzaldehyde dimethyl acetal proceeded in lower yield, likely due to the steric hindrance of the *ortho*-Br, but still afforded **13h** in 44% yield and 4:1 dr. *p*-Methoxybenzaldehyde dimethyl acetal performed well under the general reaction conditions (**13i**–**k**); the acetal is less electrophilic than benzaldehyde dimethyl acetal, but can facilitate the formation of the *o*QM. 3,4-Dimethoxyphenol also performed well in the condensation reaction with *p*-methoxybenzaldehyde dimethyl acetal and indene to afford chroman **13i**.

Scalability of the reaction was demonstrated with 1.0 g of dienophile. The reaction of sesamol, benzaldehyde dimethyl acetal, and indene afforded 2.2 g of the desired product **13h** in 71% yield, 3:1 dr (Scheme 2). Trituration of the isolated product with boiling hexanes afforded a 64% yield and 5:1 dr.

Scheme 2. Multicomponent Reaction Scale Up



In conclusion, we have developed two strategies to access benzopyrans using Fe(III) salts as catalysts. The two-component approach to access benzopyrans and 4*H*-chromenes from *o*-hydroxybenzyl alcohols and olefins proceeds well under Fe-catalysis. Moreover, Fe(III) salts will also mediate the one-pot MCR via an in situ generated *o*QM from the condensation of a phenol and an aldehyde or acetal. The MCR features the use of readily available starting materials and performs well on gram scale. Future studies will focus on the development of an asymmetric catalytic approach and use in natural product syntheses.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00647.

Optimization, experimental procedures, compound characterization, and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seschaus@bu.edu.

ORCID

Scott E. Schaus: 0000-0002-5877-6587

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the NIH (R01 GM078240 and P50 GM067041).

■ REFERENCES

(1) (a) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757−4778. (b) Rokita, S. E. *Quinone Methides*; Wiley: 2009. (c) Willis, N. J.; Bray, C. D. *Chem. - Eur. J.* **2012**, *18*, 9160−9173. (d) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655−3664.

(2) (a) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210−9215.

(3) 1,4-Addition: Zhang, Y.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 5557−5560. Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074−17075. Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870−7871. Pathak, T. P.; Sigman, M. S. *Org. Lett.* **2011**, *13* (10), 2774−2777. Jana, R.; Pathak, T. P.; Jensen, K. H.; Sigman, M. S. *Org. Lett.* **2012**, *14* (16), 4074−4077. Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965−199678. Barbato, K. S.; Luan, Y.; Ramella, D.; Panek, J. S.; Schaus, S. E. *Org. Lett.* **2015**, *17* (23), 5812−5815.

(4) [4 + 2]-Cycloaddition: Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2004**, *69*, 9196−9203. Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10* (21), 4951−4953. Wenderski, T. A.; Marsini, M. A.; Pettus, T. R. R. *Org. Lett.* **2011**, *13* (1), 118−121. Green, J. C.; Brown, E. R.; Pettus, T. R R. *Org. Lett.* **2012**, *14*, 2929−2931.

(5) Luan, Y.; Sun, H.; Schaus, S. E. *Org. Lett.* **2011**, *13* (24), 6480−6483.

(6) Robustadial: (a) Xu, R.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734−736. (b) Salomon, R. G.; Lal, K.; Mazza, S. M.; Zarate, E. A.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 5213−5214. (c) Bharate, S. B.; Bhutani, K. K.; Khan, S. I.; Tekwani, B. L.; Jacob, M. R.; Khan, I. A.; Singh, I. P. *Bioorg. Med. Chem.* **2006**, *14*, 1750−1760. Bharate, S. B.; Singh, I. P. *Tetrahedron Lett.* **2006**, *47*, 7021−7024. (+)-Brazilin: (e) Craig, J. C.; Naik, A. R.; Pratt, R.; Johnson, E.; Bhacca, N. S. *J. Org. Chem.* **1965**, *30*, 1573−1576. (f) Huang, Y.; Zhang, J.; Pettus, T. R. R. *Org. Lett.* **2005**, *7* (26), 5841−5844. (g) Jung, Y.; Kim, I. *J. Org. Chem.* **2015**, *80* (3), 2001−2005. Procyanidin B3: (h) Oizumi, Y.; Mohri, Y.; Hirota, M.; Makabe, H. *J. Org. Chem.* **2010**, *75* (14), 4884−4886. YM-26734: (i) Oslund, R. C.; Cermak, N.; Verlinde, C. L. M. J.; Gelb, M. H. *Bioorg. Med. Chem. Lett.* **2008**, *18* (20), 5415−5419.

(7) (a) Gharpure, S. J.; Sathiyanarayanan, A. M.; Vuram, P. K. *RSC Adv.* **2013**, *3*, 18279−18282. (b) Tan, W.; Du, B.-X.; Li, X.; Zhu, Xu; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2014**, *79*, 4635−4643. (c) Zhao, J. J.; Zhang, Y. C.; Xu, M.-M.; Tang, M.; Shi, F. *J. Org. Chem.* **2015**, *80*, 10016−10024.

(8) (a) El-Sepelgy, O.; Haseloff, S.; Alamsetti, S. K.; Schneider, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 7923−7927. (b) Saha, S.; Schneider, C. *Org. Lett.* **2015**, *17*, 648−651.

(9) (a) Hsiao, C.-C.; Liao, H.-H.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13258−13263. (b) Hsiao, C.-C.; Raja, S.; Liao, H.-H.; Atodiresei, J.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 5762−5765.

(10) Zhao, J. J.; Sun, S.-B.; He, S.-H.; Wu, Q.; Shi, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 5460−5464.

(11) Fan, J.; Wang, Z. *Chem. Commun.* **2008**, 5381−5383.

(12) Triethyl silane reduction: (a) Zhu, Y.-H.; Zhang, M.; Li, Q.-Y.; Liu, Q.; Zhang, J.; Yuan, Y.-Y.; Nan, F.-J.; Wang, M.-W. *Chin. Chem. Lett.* **2014**, *25*, 693−698. (b) Bai, W.-J.; Green, J. C.; Pettus, T. R. R. *J. Org. Chem.* **2012**, *77*, 379−387.

(13) Stable: (a) Jurd, L. *Tetrahedron* **1977**, *33*, 163. (b) Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 6581−6592. (c) Amouri, H.; Vaissermann, J. *Organometallics* **2000**, *19*, 1740−1748. (d) Amouri, H.; Le Bras, J. *Acc. Chem. Res.* **2002**, *35*, 501−510. (e) MacIntosh, A. D.; Yang, H.; Pike, R. D.; Sweigart, D. A. *J. Organomet. Chem.* **2012**, *719*, 14−17.

(14) Robust leaving groups: (a) Chambers, J. D.; Crawford, J.; Williams, H. W. R.; Dufresne, C.; Scheigetz, J.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1992**, *70* (6), 1717−1732. (b) Huang, Y.; Pettus, T. R. R. *Synlett* **2008**, *2008*, 1353−1356. (b) Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.-L.; Pettus, T. R. R. *Org. Lett.* **2008**, *10*, 1477−1480.