Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

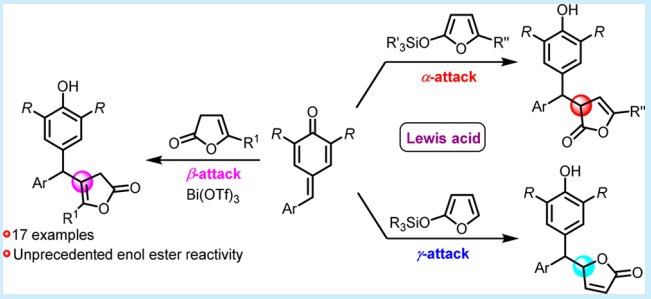
Unravelling the Nucleophilicity of Butenolides for 1,6-Conjugate Addition to *p*-Quinone Methides: A Direct Access to Diversely Substituted Butenolide-Derived Diarylmethanes

Brijesh M. Sharma,[†] Dinesh R. Shinde,[#] Ruchi Jain,[†] Eeshwaraiah Begari,[†] Shruti Satbhaiya,[†] Rajesh G. Gonnade,[§] and Pradeep Kumar*[,†]

[†]Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India
Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India
[#]Central NMR Facility, CSIR-National Chemical Laboratory, Pune 411008, India
[§]Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India

Supporting Information

ABSTRACT: A Lewis acid catalyzed regioselective C−C bond is constructed through β-addition of deconjugated butenolides with *p*-quinone methides in a 1,6-conjugate addition manner. Interestingly, Lewis acid catalyzed vinylogous Mukaiyama−Michael reaction of silyloxyfurans with *p*-QMs proceeds selectively through the α or γ position exclusively. The reaction is mild with broad substrate scope, thus allowing easy access to a wide range of bis-arylated α-/β-/γ-substituted butenolides.



Butenolides are structurally important scaffolds in various biologically active molecules, natural products, and synthetic intermediates.[1] Among various unsaturated γ-lactone derivatives, the butenolide-derived diarylmethane unit appears as a privileged structural motif in various complex lignans and secolignans.[2] The regioselectively functionalized sites of butenolide-derived diarylmethane constitutes an important structural feature of a diverse range of natural and unnatural products, exhibiting a wide spectrum of biological activities (Figure 1). Owing to the prevalence and significance of butenolides and its congeners, the development of streamlined strategies to exploit the nucleophilicity of all the positions (α, β, γ) of butenolide regioselectively remains an active area in the realm of exploratory synthetic research.[3]

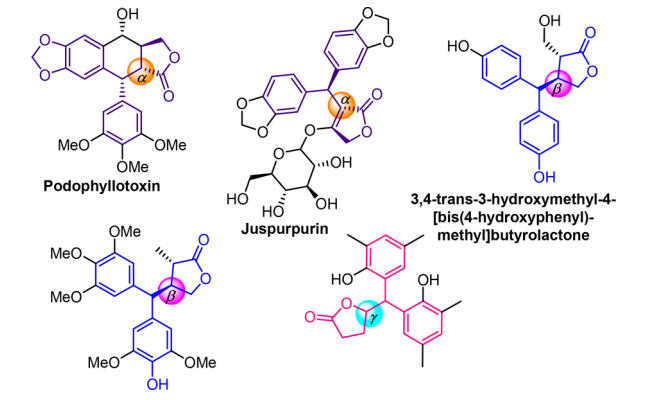
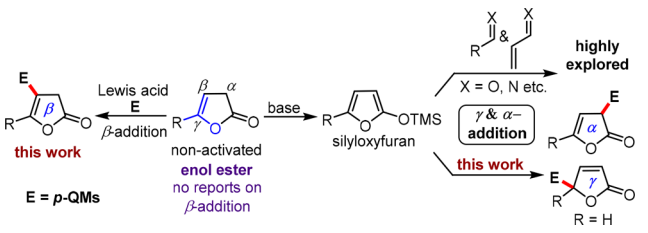


Figure 1. Natural and unnatural products containing γ-butenolide-/γ-butyrolactone-derived diarylmethane scaffolds.

A deconjugated butenolide, α-angelica lactone, has emerged as a valuable building block for the construction of butenolide derivatives.[4] It has been synthetically exploited through in situ conversion to dienolate intermediates and silyloxyfurans for the electrophilic attack at the γ-position. A few reports for α-attack of silyloxyfurans are also available in the literature. However, the nucleophilicity of the β-position has not been explored rigorously (Scheme 1).

In contrast to the well explored γ-attack of deconjugated butenolides or silyloxyfurans, only two reports by Mukaiyama[5] and Lavilla[6] were found for nucleophilic attack of α-angelica

Scheme 1. Regioselectivity of Deconjugated Butenolides and Silyloxyfurans toward 1,6-Conjugate Addition Reaction



Received: March 6, 2018

DOI: 10.1021/acs.orglett.8b00745
Org. Lett. XXXX, XXX, XXX−XXX

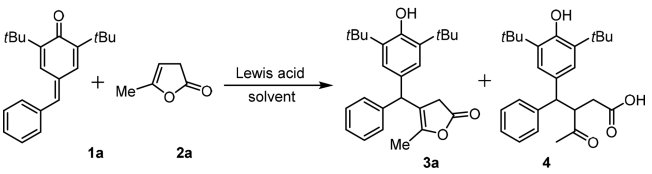
lactone from the β-position. However, the initial attack from the β-position in both reports led to skeletal rearrangements of the butenolide framework in a reaction cascade. With our ongoing interest and endeavors in butenolide chemistry,[7] we envisioned a regioselective β-attack of deconjugated butenolides in an enol ester-type reactivity (unexplored).

Among various reports on α-addition,[8] only a few were based on Lewis acid catalyzed α-addition with retention of a double bond without isomerization toward more stable α,β-unsaturated butenolide. Toward this goal, Boukouvalas et al.[9] have successfully achieved the α-addition of 2-furanolates regioselectively using an Sn-enolate-based chelation-controlled strategy. Recently, Hartwig and co-workers exquisitely demonstrated Ir-catalyzed regio- and enantioselective α-allylation of trimethylsilyloxyfuran.[10] In fact, in a few synthetic methodologies, α-addition with silyloxyfurans was reported as a minor product but not explored to a large extent.[11] Recently, Zhou and co-workers reported an enantioselective α-addition/transesterification of deconjugated butenolides with *o*-quinone methides.[12] To the best of our knowledge, there is no report of Lewis acid catalyzed nucleophilic addition from the α,β,γ-positions of butenolides on a *p*-QMs as a single substrate.

In recent years, *p*-quinone methides have been explored extensively due to their unique ability as powerful Michael acceptors with a variety of nucleophiles.[13] In 2004, Eklund and co-workers[14] elegantly showed the oxidative metabolism of plant lignan hydroxymatairesinol to its corresponding butyrolactone lignins, isohydroxymatairesinol and *epi*-isohydroxymatairesinol, via a *p*-QMs intermediate. Recently, our group also reported a Tf_2NH-catalyzed 1,6-conjugate addition reaction of *p*-QMs with vinyl azide.[15] In continuation herein, we report a highly efficient and regioselective 1,6-conjugate addition of deconjugated butenolides and silyloxyfurans to *p*-QMs catalyzed by Lewis acid, leading to a diversely substituted butenolide-derived diarylmethane scaffold.

To investigate our hypothesis, we started our exploration of an β-addition reaction using α-angelica lactone **2a** and *p*-QMs **1a** as a model substrate. Table 1 summarizes the effect of several parameters on this reaction. Initially, when 20 mol % of $BF_3{\cdot}OEt_2$ was used to catalyze the reaction between **1a** and **2a** in CH_2Cl_2 at 0 °C, it resulted in the formation of undesired hydrolyzed product **4** exclusively in 5 min only via β-attack (entry 1). The formation of product **4** gave us the idea about the reaction proceeding via an enol ester-type reactivity. The intermediate oxonium ion thus formed was quenched due to the presence of traces of moisture, thus accounting for the formation of hydrolyzed product **4**. To rationalize our concept and to minimize the side product, we attempted the reaction using activated molecular sieves (entry 2). Though this has resulted in the formation of desired product **3a** in 33% yield along with product **3a′**[16] having an isomerized *exo*-double bond in 11% yield, the formation of hydrolyzed product **4** in 37% yield could not be suppressed. Use of other Lewis acids seemed to be the best alternative for improving yields and selectivity of product **3a**. Interestingly, 20 mol % of $Bi(OTf)_3$ afforded 74% yield of product **3a** with the formation of a trace amount of **4** (entry 3). Screening of other Lewis acids such as $Cu(OTf)_2$, $Sc(OTf)_3$, AgOTf, and $La(OTf)_3$ was ineffective in terms of product selectivity and yields (entries 4–7). With the promising result of $Bi(OTf)_3$, we further screened its efficacy in other solvents such as THF and CH_3CN but ended with unsatisfactory results (entries 8 and 9). As this reaction led to the formation of product **3a** in a nearly racemic form, we

Table 1. Optimization Studies[a]



					yield[b]	
entry	catalyst	solvent	temp (°C)	time (min)	**3a**	**4**
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	5		83
2[c,d]	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	15	33	37
3[e]	$Bi(OTf)_3$	CH_2Cl_2	0	5	74	<5
4	$Cu(OTf)_2$	CH_2Cl_2	0	15	45	28
5	$Sc(OTf)_3$	CH_2Cl_2	0	5	–	67
6	AgOTf	CH_2Cl_2	0	10	8	78
7[f]	$La(OTf)_3$	CH_2Cl_2	0	15	6	14
8	$Bi(OTf)_3$	THF	0	15	12	69
9	$Bi(OTf)_3$	CH_3CN	0	5		86
10	BH*a	toluene	25	24 h	NR	
11	BH*a	toluene	60	24 h	NR	
12	BH*b	toluene	25	24 h	NR	

[a]Unless otherwise stated, the reaction was performed with *p*-QMs **1a** (0.17 mmol, 50 mg), α-angelica lactone **2a** (0.17 mmol, 15 μL), and Lewis acid/BH* (20 mol %) in 2 mL of solvent at the specified temperature. [b]Isolated yields. [c]4 Å molecular sieves (50 mg). [d]Formation of **3a′** was observed in 11% yield. [e]No reaction when performed in the presence of 4 Å molecular sieves, and the yield of **3a** with 10 mol % of $Bi(OTf)_3$ was 55%. [f]Yields brsm **1a**. NR = no reaction. BH* = Appropriate chiral phosphoric acid (for the structure of BH*, see the SI).

considered attempting the asymmetric version of same β-addition reaction. To this end, we tested chiral phosphoric acids containing bulky groups on the BINOL backbone such as (*S*)-TRIP catalyst, but unfortunately, the reaction did not work (entries 10 and 11).

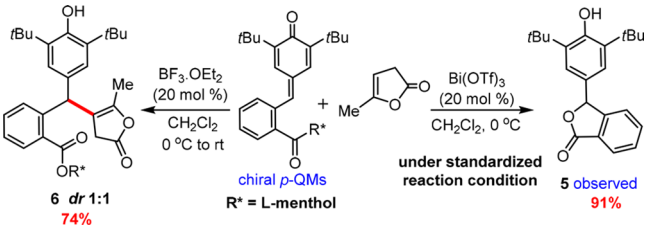
This could probably be attributed to the inefficiency of the catalyst to activate *p*-QMs toward nucleophilic attack. A similar set of disappointing results was obtained on switching to chiral metal phosphates with a view to activate *p*-QMs through the interaction of its lone pair with the Lewis acidic metal (entry 12).

After having attempted the chiral catalysts in triggering the β-addition, we considered inducing chirality employing a chiral auxiliary. Accordingly, we prepared (−)-menthol-incorporated *p*-QMs[17] and subjected it to the standardized reaction conditions, but to our dismay, we ended up obtaining the undesired auxiliary-cleaved product **5** in 91% yield. The formation of **5** may be attributed to steric crowding toward the incoming nucleophile, thus facilitating intramolecular 1,6-conjugate addition by ester carbonyl followed by elimination of the menthol moiety (Scheme 2). On the other hand, $BF_3{\cdot}OEt_2$ worked well in the case of chiral *p*-QMs to deliver the required product **6** in 74% yield with dr ∼ 1:1 (^{1}H NMR analysis).

The effect of temperature on 1,6-conjugate addition reactions was also studied. To our surprise, the reaction did not work at lower temperature (−78 °C). Interestingly, though the reaction failed to proceed at 0 °C for more than 2 days, as soon as it was brought to room temperature the formation of product **6** was observed within 5 min. Thus, we observed that the influence of chiral auxiliary on the reactive site is minimal, which can be attributed not only to the presence of spacer ($-CO_2-$), thus

DOI: 10.1021/acs.orglett.8b00745
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Attempts for Chiral Induction

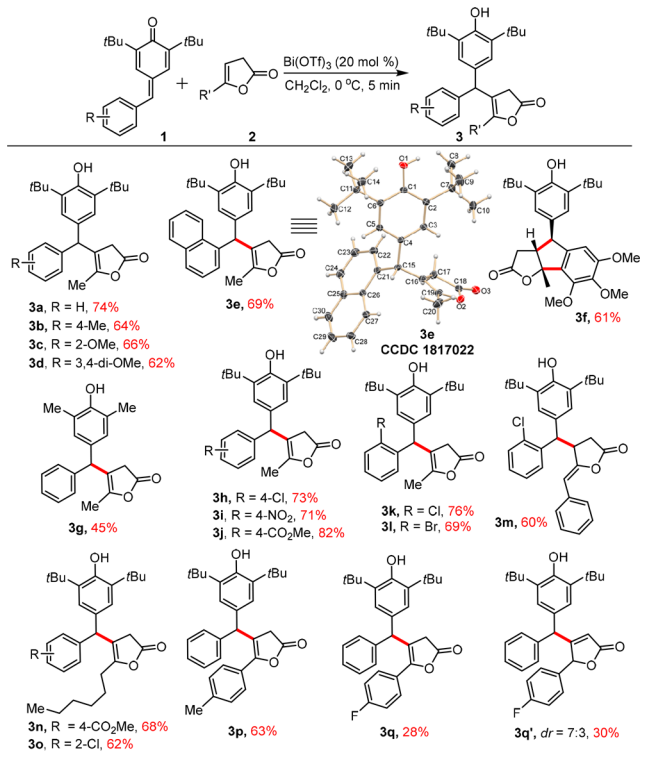


orienting the auxiliary away from the reactive site, but also to the short reaction time giving no scope for chiral induction.

The reaction of butenolides with diversely substituted *p*-QMs **1a−l** was examined for both compatibility and wide substrate applicability under the reaction conditions. The reaction was found to be very facile with *α*-angelica lactone and its derivatives.

Interestingly, *p*-QMs with electron-withdrawing substituents **1h−l** furnished the desired products **3h−l** in good yields (69−82%), in comparison with electron-donating substituents, which gave only moderate yields (45−74%) of the products **3a−g** (Scheme 3). In the case of 3,4,5-trimethoxy-substituted *p*-

Scheme 3. Substrate Scope for *β*-Addition



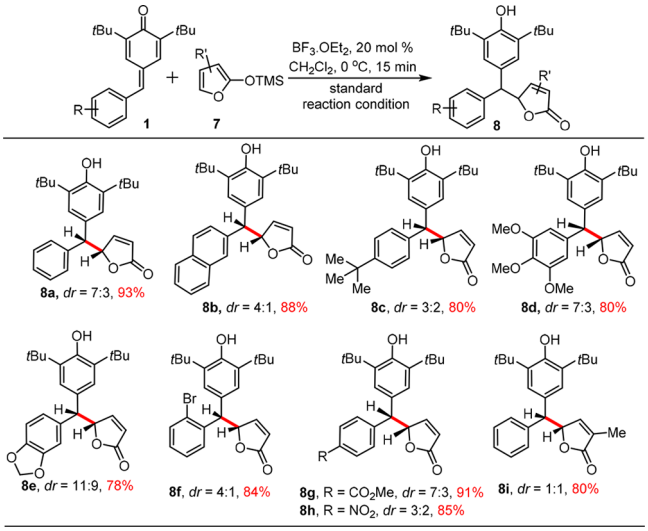
QMs **1f**, product with tricyclic core **3f** was obtained in 61% yield, and the structure was further confirmed by single-crystal X-ray analysis. The formation of tricyclic product can be attributed to [3 + 2] cycloaddition of the oxonium ion formed after an initial *β*-attack. The characterization of this product validates the enol ester-type reactivity of the butenolide. Surprisingly, when the *tert*-butyl groups at the 2- and 6-positions of phenol were replaced with a methyl group to give *p*-QMs **1q**, yields of product **3g** reduced drastically to 45%, suggesting that bulky substituents are crucial for the stability of *p*-QM. The scope of the reaction was further investigated with *α*-angelica lactones bearing different substituents at the *γ*-position. Both electron-donating and electron-withdrawing groups on the aryl ring attached to *α*-angelica lactone, as well as alkyl substituents, were well suited to furnish the products **3m−q** in 58−68% yields. It is noteworthy that $-CH_2Ph$-substituted lactone resulted in the formation of product **3m** with an *exo* double bond in 60% yield due to the elimination of competing acidic proton at the benzylic position. Moreover, lactone **2e** having −F group gave **3q** in a crude yield of 66%. However, attempts to purify **3q** on a column gave two fractions of **3q** and **3q′** in 28% and 30% yields, respectively. This was probably due to epimerization of acidic proton at the *α*-position of the product during silica gel column chromatography due to the −ve inductive effect of the −F group. The structure of products **3e** and **3m** was further confirmed by single-crystal X-ray analysis (see the Supporting Information (SI).

On the basis of the experimental results, a plausible mechanism for the formation of various products during *β*-addition is proposed. $Bi(OTf)_3$-catalyzed activation of *p*-QMs followed by 1,6-conjugate addition by deconjugated butenolides, when R, R^1 = H, leads to the formation of **oxonium intermediate A** (see SI), which undergoes deprotonation affording product **3** (*endo* double bond) and **3′** (*exo*). On the other hand, if **oxonium intermediate A** is quenched by moisture it leads to the formation of undesired hydrolyzed product **4**. Finally, the [3 + 2]-cycloaddition on deconjugated butenolides takes place when the oxonium ion of **intermediate B** is intercepted with a highly electron-donating aromatic ring of *p*-QMs.

After having explored the *β*-attack, we sought to access the *γ*-position of butenolides via Lewis acid catalyzed vinylogous Mukaiyama−Michael reaction[18] of *γ*-unsubstituted silyloxyfurans on *p*-QMs. After having standardized the reaction conditions (see SI optimization Table), we studied the substrate scope of the *p*-QMs and silyloxyfurans (Scheme 4).

The presence of electron-donating and electron-withdrawing substituents on *p*-QMs and silyloxyfurans has very little impact on the product **8a−i** yields (78−93%) and diastereoselectivity. The structure of product **8b** was further confirmed by single-crystal X-ray analysis.

Scheme 4. Substrate Scope for *γ*-Addition[a]

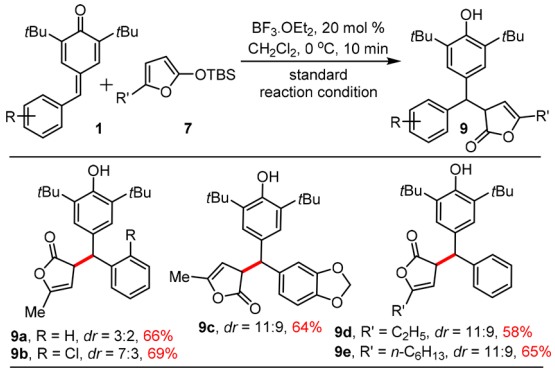


[a]*tert*-Butyldimethylsilylfuran **7b** was used in the case of **8i**.

DOI: 10.1021/acs.orglett.8b00745
Org. Lett. XXXX, XXX, XXX−XXX

Structural variation in the silyloxyfuran system at the γ-position gave surprising results with exclusive α-attack (Scheme 5), which has not been observed with other electrophiles, with

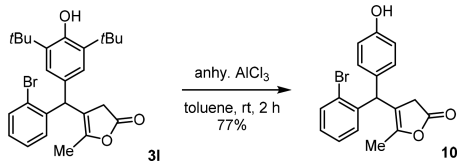
Scheme 5. Substrate Scope for α-Addition



γ being the preferred site of the attack. Thus, it gives us deeper insights and the need for better understanding of the reactivity and substrate selectivity of *p*-QMs. A series of substrates having linear alkyl groups attached to the γ-position of the silyloxyfuran moiety readily underwent efficient Mukaiyama–Michael reaction under the optimized reaction conditions to furnish the product **9a–e** in good yields (58–69%).

The synthetic utility of this method was further explored by carrying out de-*tert*-butylation of **3l** using anhydrous $AlCl_3$ to deliver product **10** in 77% yield, which represents the important structural motifs of various butenolide-derived natural products (Scheme 6).

Scheme 6. De-*tert*-butylation of Butenolide-Derived Diarylmethane Unit



In spite of the above advantages, this method has some defined limitations (see SI). For example, *p*-QMs **1f** underwent homodimerization[19] under the reaction conditions to give product **11** in 88% yield. These results were consistent, even in the presence of other Lewis acids such as $BF_3{\cdot}OEt_2$ and Tf_2NH. Highly reactive butenolides such as furan-2(3*H*)-one **2f** and furan-2(5*H*)-one **2g** underwent decomposition under the reaction conditions.

In conclusion, we have explored the electrophile-driven selectivity of *p*-QMs toward nucleophilic reactivity of the α-, β-, γ-positions of butenolides. This protocol allows synthesis of diversely substituted butenolide-derived diarylmethane units embedded in various natural products belonging to the lignan and secolignan families. The enol ester reactivity of butenolide was one of the key findings of this work. Further efforts toward asymmetric induction in the unexplored β-attack and [3 + 2]-cycloaddition reactions of deconjugated butenolides and their applications in organic synthesis are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00745.

General procedures, X-ray crystallographic data, and ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1817022–1817027 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pk.tripathi@ncl.res.in.

ORCID

Rajesh G. Gonnade: 0000-0002-2841-0197
Pradeep Kumar: 0000-0002-3077-4408

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

B.M.S. thanks the Council of Scientific and Industrial Research (CSIR) for the award of a Senior Research Fellowship. Financial support in the form of an INSA Senior Scientist award to P.K. from INSA, New Delhi, is gratefully acknowledged.

■ REFERENCES

(1) For selected examples, see: (a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. (b) Bandichhor, R.; Nosse, B.; Reiser, O. In *Natural Product Synthesis I: Targets, Methods, Concepts*; Springer: Berlin, 2005; p 43. (c) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426. (d) Guo, F.; Li, Z.; Xu, X.; Wang, K.; Shao, M.; Zhao, F.; Wang, H.; Hua, H.; Pei, Y.; Bai, J. *Fitoterapia* **2016**, *113*, 44.

(2) (a) Kavitha, J.; Gopalaiah, K.; Rajasekhar, D.; Subbaraju, G. V. *J. Nat. Prod.* **2003**, *66*, 1113. (b) Wu, J.-l.; Li, N.; Hasegawa, T.; Sakai, J.-i.; Mitsui, T.; Ogura, H.; Kataoka, T.; Oka, S.; Kiuchi, M.; Tomida, A.; Turuo, T.; Li, M.; Tang, W.; Ando, M. *J. Nat. Prod.* **2006**, *69*, 790. (c) Feng, W.-S.; Chen, H.; Zheng, X.-K.; Wang, Y.-Z.; Gao, L.; Li, H.-W. *J. Asian Nat. Prod. Res.* **2009**, *11*, 658. (d) Yu, X.; Che, Z.; Xu, H. *Chem. - Eur. J.* **2017**, *23*, 4467.

(3) (a) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (c) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502.

(4) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056.

(5) Sato, T.; Hanna, J.; Nakamura, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1055.

(6) Isambert, N.; Cruz, M.; Arévalo, M. J.; Gomez, E.; Lavilla, R. *Org. Lett.* **2007**, *9*, 4199.

(7) (a) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843. (b) Show, K.; Kumar, P. *Eur. J. Org. Chem.* **2016**, *2016*, 4696.

(8) (a) Egorova, A. Y.; Timofeeva, Z. Y. *Russ. J. Gen. Chem.* **2003**, *73*, 655. (b) Mao, B.; Ji, Y.; Fañanás-Mastral, M.; Caroli, G.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3168.

(9) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1988**, 1595.

DOI: 10.1021/acs.orglett.8b00745
Org. Lett. XXXX, XXX, XXX–XXX

(10) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 15249.
(11) (a) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703. (b) Takahashi, A.; Yanai, H.; Zhang, M.; Sonoda, T.; Mishima, M.; Taguchi, T. *J. Org. Chem.* **2010**, *75*, 1259. (c) Woyciechowska, M.; Forcher, G.; Buda, S.; Mlynarski, J. *Chem. Commun.* **2012**, *48*, 11029.
(12) Wu, B.; Yu, Z.; Gao, X.; Lan, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2017**, *56*, 4006.
(13) For Lewis acid mediated reaction with *p*-QMs, see: (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136. (b) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1990**, *55*, 3708. (c) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 12134. (d) Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. *Eur. J. Org. Chem.* **2016**, *2016*, 3006. (e) Mahesh, S.; Kant, G.; Anand, R. V. *RSC Adv.* **2016**, *6*, 80718. (f) Huang, B.; Shen, Y.; Mao, Z.; Liu, Y.; Cui, S. *Org. Lett.* **2016**, *18*, 4888. (g) Xie, K.-X.; Zhang, Z.-P.; Li, X. *Org. Lett.* **2017**, *19*, 6708.
(14) Eklund, P. C.; Willför, S. M.; Smeds, A. I.; Sundell, F. J.; Sjöholm, R. E.; Holmbom, B. R. *J. Nat. Prod.* **2004**, *67*, 927.
(15) Rathod, J.; Sharma, B. M.; Mali, P. S.; Kumar, P. *Synthesis* **2017**, *49*, 5224.
(16) The structure of **3a′** (see SI), dr ∼ 4:1 was determined by ^{1}H NMR.
(17) Oertling, H.; Reckziegel, A.; Surburg, H.; Bertram, H.-J. *Chem. Rev.* **2007**, *107*, 2136.
(18) (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (b) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595. (c) Jadhav, A. P.; Rao, V. B.; Singh, P.; Gonnade, R.; Singh, R. P. *Chem. Commun.* **2015**, *51*, 13941.
(19) Snyder, S. A.; ElSohly, A. M.; Kontes, F. *Nat. Prod. Rep.* **2011**, *28*, 897.

DOI: 10.1021/acs.orglett.8b00745
Org. Lett. XXXX, XXX, XXX−XXX