*Organic* **LETTERS**

Letter

pubs.acs.org/OrgLett

Formal (4 + 1)-Addition of Allenoates to *o*-Quinone Methides

Katharina Zielke and Mario Waser*[ID]

Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria

S *Supporting Information*

ABSTRACT: The first (4 + 1)-annulation of *o*-quinone methides with α-branched allenoates as C1 synthons has been developed. This operationally simple protocol gives access to highly functionalized dihydrobenzofurans in an unprecedented fashion with excellent diastereoselectivities and high yields.
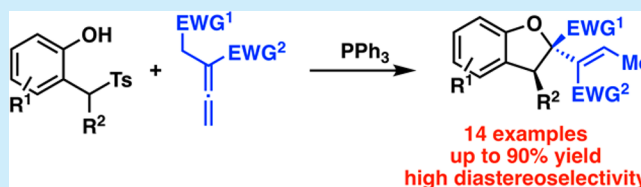
Quinone methides (QMs), either preformed or generated in situ, have emerged as a versatile class of building blocks for (asymmetric) transformations over recent years.[1] While (usually preformed) *p*-quinone methides (*p*-QMs) have been employed for vinylogous (enantioselective) 1,6-addition reactions,[2] *o*-quinone methides (*o*-QMs, **1**) were very successfully used for a variety of (4 + *n*)-type cyclization reactions.[3−7] Recently, some very inspiring reports describing formal (4 + 2) annulations between *o*-QMs (either generated in situ from precursors **2** or **3**, or preformed) and allenoate esters **4** or allene ketones **5** under chiral *tertiary* amine or phosphine catalysis have been reported (Scheme 1A).[4] Cyclization reactions of allenoates with various acceptors have been very heavily investigated recently. Depending on the nature of the reagents and the catalysts (classically either *tert*-amines or *tert*-phosphines are used) a broad variety of different (asymmetric) annulation strategies are feasible.[8,9] α-Branched allenoates **7** have also frequently been exploited as C_4-synthons for (asymmetric) (4 + 1)-cyclization reactions.[10] In sharp contrast, the use of allenoates as C_1-synthons for (4 + 1)-annulation has so far received significantly less attention.[11] These recently reported approaches either employ the γ- or the β-position of allenes as the reactive site, whereas the β'-position of allenoates **7** has, so far, to the best of our knowledge, not been exploited as the C_1-synthon site for (4 + 1)-annulations of allenoates.

Our group has very recently developed a highly enantioselective (4 + 1)-annulation protocol by reacting in situ generated chiral ammonium ylides with in situ generated *o*-QMs **1**.[5e] In ongoing investigations aimed at the introduction of new synthesis methodologies that use *o*-QMs as easily available acceptors for cyclization reactions, we have now tested the use of simple α-substituted allenoates **7** for the reaction with quinone methide precursors **3** (Scheme 1B).

We initially reasoned that this reaction should give the highly functionalized (4 + 2)-cyclization products **6**. Surprisingly, however, literally the first reaction of *o*-QM-precursor **3a** with allenoate **7a** in the presence of PPh₃ led to the exclusive formation of the unprecedented formal (4 + 1)-product **8a** as a single diastereomer (Table 1, entry 1). This unexpected outcome, which is totally in contrast to the observations made in the past with seemingly analogous systems (as shown

Scheme 1. Recent (4 + 2)-Cyclization Reports Using *o*-QMs 1 and Allenes 4 and 5 and the Herein Reported (4 + 1)-Annulation Using α-Branched Allenoates 7
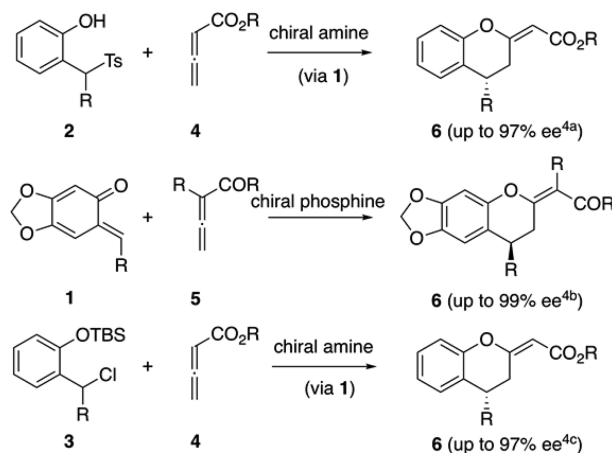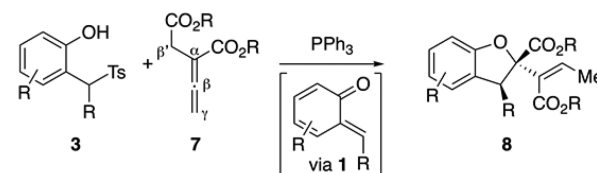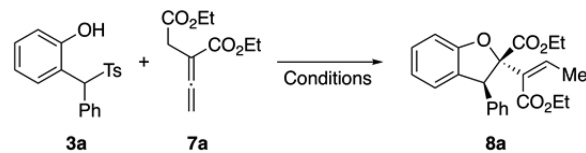

in Scheme 1),[4] prompted us to screen a variety of different conditions and activators for this reaction (Table 1 gives an overview of the most significant results).

Note that this reaction only occurs when using triarylphosphines (i.e., PPh₃) but not with trialkylphosphines or *tert*-amines (compare entries 1−3). In the latter cases, also no (4 + 2)- or other cyclization products were observed. Among the different solvents, CH₂Cl₂ turned out to be the best-suited one.

Table 1. Identification of the Optimum Conditions.[a]

entry	3a/ 7a	activator[c] (equiv)	base (equiv)	solvent[a]	yield[b] (%)
1	1:2	Ph₃P (0.2×)	Cs₂CO₃ (5×)	CH₂Cl₂	30
2	1:2	Bu₃P (0.2×)	Cs₂CO₃ (5×)	CH₂Cl₂	nr
3	1:2	DABCO (0.2×)	Cs₂CO₃ (5×)	CH₂Cl₂	nr
4	1:2	Ph₃P (0.2×)	Cs₂CO₃ (5×)	THF	8
5	1:2	Ph₃P (0.2×)	Cs₂CO₃ (5×)	toluene	10
6	1:2	Ph₃P (0.2×)		CH₂Cl₂	20
7	2:1	Ph₃P (0.2×)	Cs₂CO₃ (5×)	CH₂Cl₂	47
8	2:1	Ph₃P (0.5×)	Cs₂CO₃ (5×)	CH₂Cl₂	72
9	**2:1**	**Ph₃P (1×)**	**Cs₂CO₃ (2×)**	**CH₂Cl₂**	**86 (84)**[d]
10	2:1	Ph₃P (1×)	K₂CO₃ (2×)	CH₂Cl₂	49
11	2:1	Ph₃P (1×)	t-BuOK (2×)	CH₂Cl₂	37

[a]All reactions were carried out using 0.1 mmol of **7a** at room temperature for 20 h in dry and degassed solvents. [b]Isolated yields. [c]Based on the limiting reagent. [d]1 mmol scale experiment.

It was also found that the reaction proceeds better in the presence of an inorganic base than without (entries 1 and 6). Interestingly, when using an excess of QM-precursor **3a** we observed a higher yield compared to using an excess of allenoates **7a** (entries 1 and 7). Unfortunately, the catalytic turnover of the phosphine is rather limited, as the highest yield we could obtain with 20 mol % of PPh₃ was 47% only (entry 7), and this could not be overcome by longer reaction times or different reaction temperatures. Unfortunately, other triaryl-phosphines also did not perform better; e.g., tritolylphosphine gave a lower yield and trifur-2yl-phosphine gave no product at all. Surprisingly also, ³¹P NMR measurements during and after the reaction clearly showed the presence of PPh₃ but no Ph₃PO. Accordingly, oxidative degradation of the phosphine is not the reason for the limited turnover, but it seems more likely that elimination of PPh₃ (compare with Scheme 3) is a rather slow step. By using a larger amount of PPh₃, we were however able to increase the isolated yield significantly, and in parallel it was also possible to reduce the required amount of Cs₂CO₃ (which turned out to be the best suited inorganic base as shown in entries 9−11) to 2 equiv. It should also be highlighted that in no experiment was any other cyclization product or diastereomer detected.

With the optimum and scalable conditions in hand (entry 9), we next investigated the application scope for this reaction (Scheme 2). We first tested a few differently substituted allenoates **7** and realized that the products **8b−d** could only be isolated in lower yields of 30−40%. This can mainly be attributed to the pronounced decomposition of the used allenoates **7b−d** under the reaction conditions (compared to the seemingly more stable parent **7a**). Unfortunately, use of the γ-substituted allenoate **7e** did not yield any product **8e**. Variations of the acceptor **3** were much better tolerated. Different benzyl substituents did not affect the outcome significantly and gave the products **8f−i** in good yields and with very high diastereoselectivities (only in a few cases trace quantities of a second diastereomer were detected). Also, when introducing different aryl substituents, the products **8j−o** were obtained in similarly high yields. The most surprising

Scheme 2. Application Scope
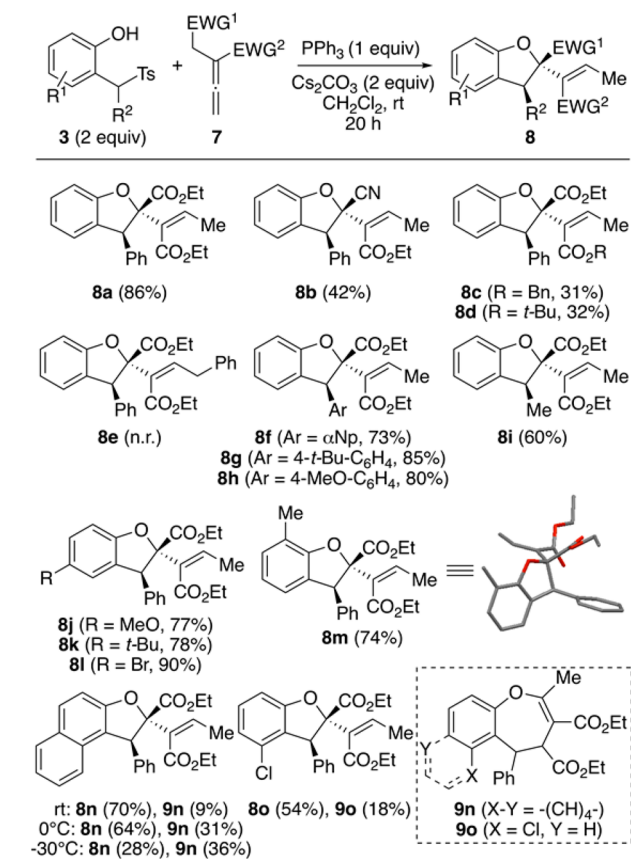
observation, however, was made in the synthesis of the naphthyl- and chloro-substituted targets **8n** and **8o**. In both cases, we observed small amounts of the formal (4 + 3)-annulation products **9** under the standard conditions. This product was never observed in any of the other cases before and must therefore be a direct consequence of the additional *ortho*-substituents in the quinone methides **1**.[12] Formation of **9** becomes more favored at lower temperatures, as demonstrated for **8n** and **9n**, which hints toward a slight kinetic preference of the (4 + 3)-annulation in these cases, but we were not able to identify conditions that solely yield these interesting products.

Concerning the relative configuration of products **8**, our initial NMR analysis of **8a** suggested the configuration depicted in Scheme 2, and luckily, we were able to carry out single-crystal X-ray analysis of the derivative **8m**, which unambiguously proved this proposed relative configuration. Accordingly, the other products were assigned in analogy.

This unprecedented (4 + 1)-annulation of allenoates may be explained by the mechanism proposed in Scheme 3. It is well-established that the phosphine adds to the β-position of the allenoates first, giving the intermediate **A**.[9] To render the β′-position nucleophilic, we then propose a proton transfer on the resonance structure **A′** to give the β′-carbanionic zwitterion **B** next.[13] Addition of **B** to the in situ formed o-QM **1** then gives the betaine **C** as the primary addition product. This intermediate could either undergo a ring-closure to access the (4 + 3)-annulation product **9** (dashed blue pathway) or, alternatively, undergo rapid proton-transfer/double-bond migration reactions[5e] toward the intermediate **D**, which can undergo a 5-*exo*-trig cyclization to yield product **8** then. This is, of course, just a proposed mechanism, but to get some further

Scheme 3. Proposed Mechanism and Reaction Outcome Using γ-Deuterated Allenoates 7a
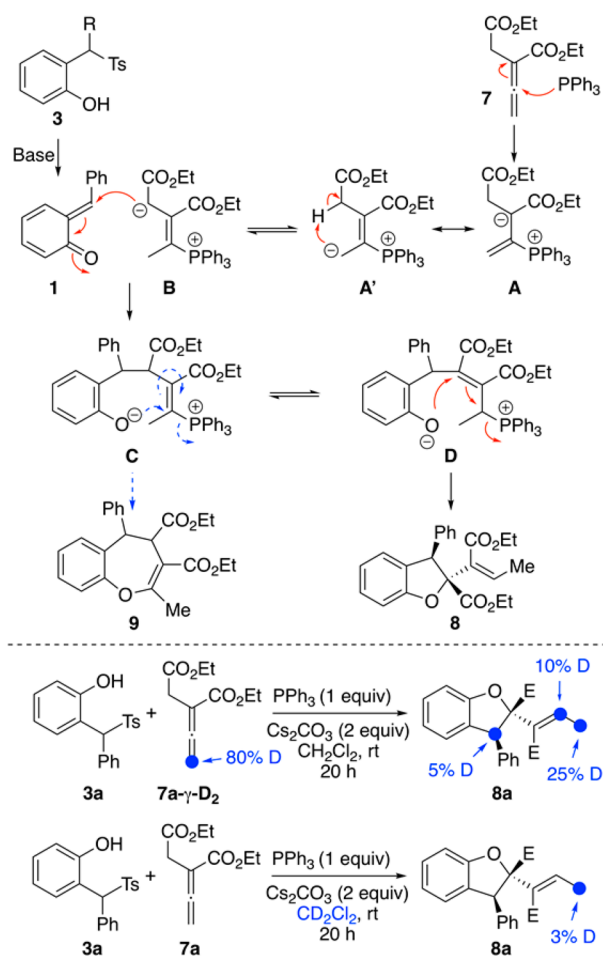
understanding we also carried out this reaction with the γ-dideuterated allenoate **7a** (Scheme 3). Upon analysis of product **8a**, we observed a significant D−H exchange in the methyl group (the former γ-position) accompanied by partial D-incorporation in the newly formed double bond (former β-position) and also in the benzylic stereogenic center. On the other hand, when we carried out the reaction with non-deuterated **7a** in CD_2Cl_2 we also observed a small amount of D-incorporation in the methyl group of product **8a** (detected by ^{2}H NMR spectroscopy). All these results therefore clearly show that intra- and intermolecular proton transfers are very easily possible on these targets/intermediates, thus making the proposed isomerizations from **A/A′** to **B** and **C** to **D** very likely.

In conclusion, we have been able to demonstrate that α-branched allenoates **7** can serve as C1 synthons for highly diastereoselective formal (4 + 1)-annulation with in situ formed *o*-quinone methides in the presence of PPh₃. Some first insights into the mechanism of this unprecedented transformation were obtained by using D-labeled allenoates, suggesting a series of fast proton transfers and double bond migrations on the intermediate zwitterions. First attempts to render this reaction enantioselective unfortunately have failed because of very little turnover and low enantioselectivities when using known chiral phosphines,[14] but this will be subject of future studies, accompanied by more detailed (computational) mechanistic investigations.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mario.waser@jku.at.

ORCID Ⓞ

Mario Waser: 0000-0002-8421-8642

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For recent reviews of *o*- and *p*-quinone methides, see: (a) Willis, N. J.; Bray, C. D. *Chem. - Eur. J.* **2012**, *18*, 9160−9173. (b) Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv.* **2014**, *4*, 55924−55959. (c) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015**, *20*, 11733−11764. (d) Parra, A.; Tortosa, M. *ChemCatChem* **2015**, *7*, 1524−1526. (e) Osipov, D. V.; Osyanin, V. A.; Klimochkin, Y. N. *Russ. Chem. Rev.* **2017**, *86*, 625−687.

(2) Selected recent examples: (a) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 12134−12138. (b) Yuan, Z.; Fang, X.; Li, X.; Wu, J.; Yao, H.; Lin, A. *J. Org. Chem.* **2015**, *80*, 11123−11130. (c) Arde, P.; Anand, R. V. *Org. Biomol. Chem.* **2016**, *14*, 5550−5554. (d) Deng, Y.-H.; Zhang, X.-Z.; Yu, K.-Y.; Yan, X.; Du, J.-Y.; Huang, H.; Fan, C.-A. *Chem. Commun.* **2016**, *52*, 4183−4186. (e) Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, K.; Enders, D. *Angew. Chem., Int. Ed.* **2016**, *55*, 12104−12108. (f) Zhang, X.-Z.; Deng, Y.-H.; Yan, X.; Yu, K.-Y.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *J. Org. Chem.* **2016**, *81*, 5655−5662. (g) Zhang, X.-Z.; Du, J.-Y.; Deng, Y.-H.; Chu, W.-D.; Yan, X.; Yu, K.-Y.; Fan, C.-A. *J. Org. Chem.* **2016**, *81*, 2598−2606. (h) Roiser, L.; Waser, M. *Org. Lett.* **2017**, *19*, 2338−2341. (i) Zhang, X.-Z.; Gan, K.-J.; Liu, X.-X.; Deng, Y.-H.; Wang, F.-X.; Yu, K.-Y.; Zhang, J.; Fan, C.-A. *Org. Lett.* **2017**, *19*, 3207−3210. (j) Xie, K.-X.; Zhang, Z.-P.; Li, X. *Org. Lett.* **2017**, *19*, 6708−6711. (k) Yuan, Z.; Pan, R.; Zhang, H.; Liu, L.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2017**, *359*, 4244−4249. (l) Liu, L.; Yuan, Z.; Pan, R.; Zeng, Y.; Lin, A.; Yao, H.; Huang, Y. *Org. Chem. Front.* **2018**, DOI: 10.1039/C7QO00846E.

(3) Selected pioneering and more recent (4 + 2)-approaches: (a) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*,

4951−4953. (b) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal.* **2009**, *351*, 2822−2826. (c) Hsiao, C.-C.; Raja, S.; Liao, H.-H.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 5762−5765. (d) Caruana, L.; Mondator, M.; Corti, V.; Morales, S.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Chem. - Eur. J.* **2015**, *21*, 6037−6041. (e) Adili, A.; Tao, Z.-L.; Chen, D.-F.; Han, Z.-Y. *Org. Biomol. Chem.* **2015**, *13*, 2247−2250. (f) Alamsetti, S. K.; Spanka, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2392−2396. (g) Wu, B.; Yu, Z.; Gao, X.; Lan, Y.; Zhou, Y. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 4006−4010. (h) Zhou, J.; Wang, M.-L.; Gao, X.; Jiang, F.-F.; Zhou, Y.-G. *Chem. Commun.* **2017**, *53*, 3531−3534. (i) Gebauer, K.; Reuß, F.; Spanka, M.; Schneider, C. *Org. Lett.* **2017**, *19*, 4588−4591.

(4) (4 + 2)-Reactions of allenoates with *o*-QMs: (a) Chen, P.; Wang, K.; Guo, W.; Liu, X.; Liu, Y.; Li, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 3689−3693. (b) Wang, Z.; Wang, T.; Yao, W.; Lu, Y. *Org. Lett.* **2017**, *19*, 4126−4129. (c) Deng, Y.-H.; Chu, W.-D.; Zhang, X.-Z.; Yan, X.; Yu, K.-Y.; Yang, L.-L.; Huang, H.; Fan, C.-A. *J. Org. Chem.* **2017**, *82*, 5433−5440.

(5) Recent (4 + 1)-approaches: (a) Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun.* **2013**, *49*, 1660−1662. (b) Lei, X.; Jiang, C.-H.; Wen, X.; Xu, Q.-L.; Sun, H. *RSC Adv.* **2015**, *5*, 14953−14957. (c) Rodriguez, K. X.; Vail, J. D.; Ashfeld, B. L. *Org. Lett.* **2016**, *18*, 4514−4517. (d) Yang, Q.-Q.; Xiao, W.-J. *Eur. J. Org. Chem.* **2017**, *2017*, 233−236. (e) Meisinger, N.; Roiser, L.; Monkowius, U.; Himmelsbach, M.; Robiette, R.; Waser, M. *Chem. - Eur. J.* **2017**, *23*, 5137−5142. (f) Jiang, X.-L.; Liu, S.-J.; Gu, Y.-Q.; Mei, G.-J.; Shi, F. *Adv. Synth. Catal.* **2017**, *359*, 3341−3346. (g) Lian, X.-L.; Adili, A.; Liu, B.; Tao, Z.-L.; Han, Z.-Y. *Org. Biomol. Chem.* **2017**, *15*, 3670−3673.

(6) (4 + 3)-cyclizations: (a) Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607−8610. (b) Izquierdo, J.; Orue, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 10634−10637. (c) Xu, J.; Yuan, S.; Peng, J.; Miao, M.; Chen, Z.; Ren, H. *Org. Biomol. Chem.* **2017**, *15*, 7513−7517.

(7) (4 + 4)-example: Samarakoon, T. B.; Hur, M. Y.; Kurtz, R. D.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 2182−2185.

(8) For illustrative overviews, see: (a) Ma, S. *Chem. Rev.* **2005**, *105*, 2829−2872. (b) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102−3116. (c) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074−3112. (d) Pei, C.-K.; Shi, M. *Chem. - Eur. J.* **2012**, *18*, 6712−6716. (e) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089−2121. (f) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927−2940.

(9) For studies illustrating the difference between phosphine and amine catalysis in allenoate cyclizations: (a) Huang, G.-T.; Lankau, T.; Yu, C.-H. *J. Org. Chem.* **2014**, *79*, 1700−1711. (b) Yang, L.-J.; Li, S.; Wang, S.; Nie, J.; Ma, J.-A. *J. Org. Chem.* **2014**, *79*, 3547−3558.

(10) (a) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550−2551. (b) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643−5647. (c) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183−13187. (d) Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803−3806.

(11) (a) Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2009**, *11*, 137−140. (b) Szeto, J.; Sriramurthy, V.; Kwon, O. *Org. Lett.* **2011**, *13*, 5420−5423. (c) Gao, Z.; Wang, C.; Yuan, C.; Zhou, L.; Xiao, Y.; Guo, H. *Chem. Commun.* **2015**, *51*, 12653−12656.

(12) A noteworthy influence of such *ortho*-substituents on the reactivity of *o*-QMs **1** was also observed in our recent ammonium ylide mediated (4 + 1)-annulation (see ref 5e).

(13) Simple DFT calculations have shown that **B** is actually slightly more stable than **A**.

(14) See the Supporting Information for some results with known chiral *tertiary* phosphines.