

Palladium-Catalyzed 1,4-Difunctionalization of Butadiene To Form Skipped Polyenes

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S Supporting Information

ABSTRACT: A palladium-catalyzed 1,4-addition across the commodity chemical 1,3-butadiene to afford skipped polyene products is reported. Through a palladium $\sigma \rightarrow \pi \rightarrow \sigma$ allyl isomerization, two new carbon–carbon bonds are formed with high regioselectivity and trans stereo-selectivity of the newly formed alkene. The utility of this method is highlighted by the successful synthesis of the ripostatin A skipped triene core.

The four-carbon feedstock 1,3-butadiene is a product of petroleum cracking on an annual scale of >10 million tons,¹ which makes it an especially attractive candidate for conversion into more complex building blocks for synthesis. In this regard, we envisioned using this simple and symmetric diene² in an approach similar to the venerable Diels–Alder reaction in which carbon–carbon bonds at both termini are formed with the preservation of a single alkene in the product. In contrast to cycloadditions of 1,3-butadiene with dienophiles, we wanted to form the carbon–carbon bonds controllably using two distinct reaction partners through a 1,4-difunctionalization process (Figure 1a). This would efficiently generate significant molecular complexity from a simple feedstock. In considering possible coupling partners, a specific goal was ultimately to form skipped diene and triene products, as these are common motifs in various natural products^{3–15} and often are challenging to prepare.^{16–19} Herein we present the development of a Pd-catalyzed 1,4-addition of vinyl electrophiles and boronic acid derivatives across 1,3-butadiene to access these important structural motifs, highlighted by the synthesis of the skipped triene core of ripostatin A.³

To accomplish a 1,4-difunctionalization of 1,3-butadiene using a three-component coupling strategy, several important selectivity issues had to be considered.^{20,21} We recently reported a three-component coupling of substituted 1,3-dienes, vinyl triflates, and boronic acids wherein selective formation of the 1,2-addition product was observed (Figure 1b).^{21d} The use of vinyl triflates was proposed to account for the high selectivity for the three-component coupling products rather than either the Heck or Suzuki products, presumably because of the cationic nature of the intermediates along the reaction path. The use of these and related reagents provided an obvious starting point for reaction development. Achieving a 1,4-addition rather than a 1,2-addition across 1,3-butadiene after oxidative addition to form **A** requires a $\sigma \rightarrow \pi \rightarrow \sigma$ isomerization of the allyl complex²² (**A** \rightarrow **B** \rightarrow **C** in Figure 1c) and subsequent cross-coupling of **C** with a boronic acid

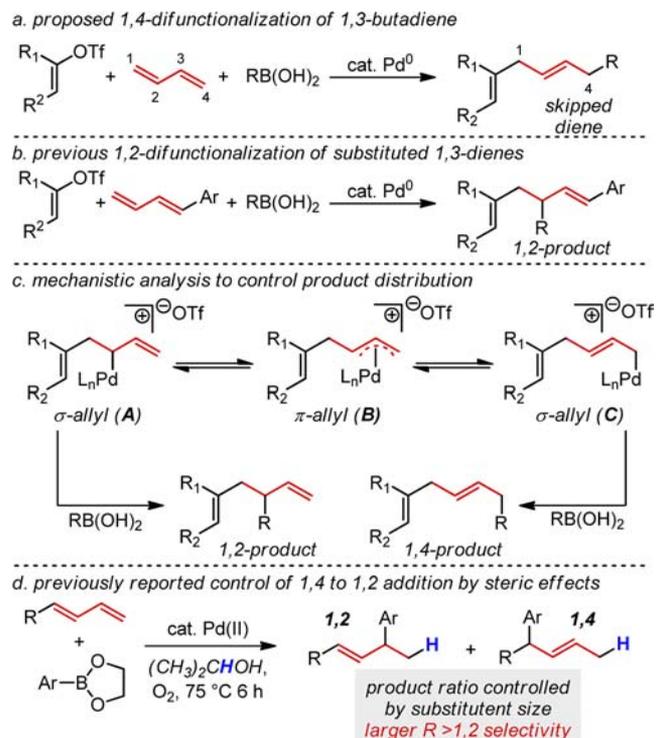


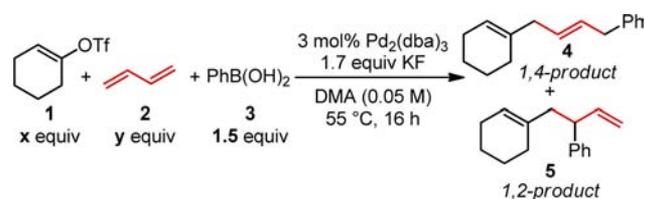
Figure 1. Proposed 1,4-difunctionalization of 1,3-butadiene with vinyl triflates and boronic acids.

derivative. A key previous report suggested that this isomerization is facile (Figure 1d). Specifically, a systematic study of substituent effects in the hydroarylation of terminal 1,3-dienes, which proceeds through a similar π -allyl species, revealed a linear free energy relationship between Charton steric parameters and the logarithm of the ratio of the yields of the 1,2- and 1,4-regioisomers.^{21e} For 1,3-butadiene, extrapolation of the Charton relationship would indicate >20:1 selectivity for the 1,4-addition reaction. However, the use of a Pd–vinyl rather than a Pd–H species to initiate the alkene functionalization and the likely requirement of different reaction conditions than those used in the hydroarylation reaction make the outcome of this reaction less predictable.

To explore the possibility of a 1,4-difunctionalization of 1,3-butadiene, vinyl triflate **1** and phenylboronic acid (**3**) were chosen for reaction optimization (Table 1). The initial reaction

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Table 1. Optimization of the Three-Component Coupling with 1,3-Butadiene

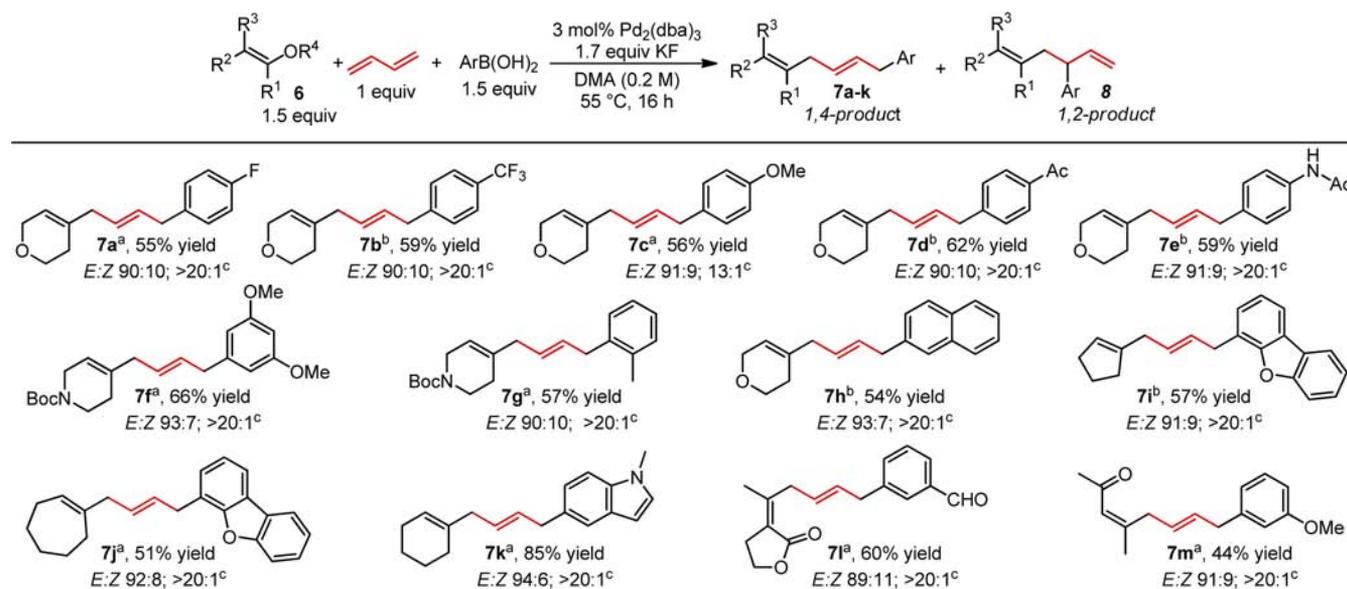
entry	conc. (M)	x	y	yield (%) ^a	4:5 ^b	E:Z ^b
1	0.05	1.0	balloon	81	2.4	88:12
2	0.05	1.0	1.0 ^c	50	12.6	91:9
3	0.2	1.0	1.0 ^c	79	15.0	91:9
4	0.05	1.5	1.0 ^c	71	16.7	90:10
5	0.2	1.5	1.0 ^c	75	>20	92:8
6 ^d	0.2	1.5	1.0 ^c	73	14.3	92:8

^aIsolated yields. ^bDetermined by ¹H NMR analysis. ^cA 15 wt % solution of 2 in *n*-hexane was used. ^dThe nonaflate (Nf) analogue of 1 was used.

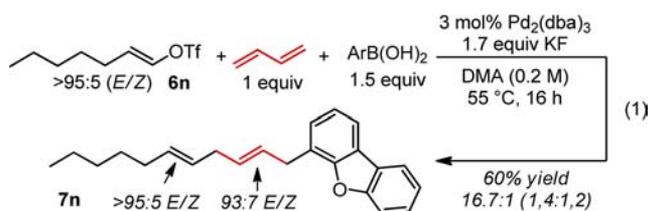
conditions tested were those found to be optimal for the previously reported three-component coupling.^{21d} While the three-component coupling products were formed in an excellent yield, the product distribution was suboptimal, as a 24:1 ratio of the desired 1,4-addition product 4 to the 1,2-addition product 5 as an inseparable mixture was obtained (entry 1). Initially, 1,3-butadiene was introduced in the gas phase via a balloon, which did not allow the stoichiometry to be easily controlled. Therefore, we moved to a standard commercial solution (15 wt % in *n*-hexane) as the source of 1,3-butadiene. This change resulted in a significant improvement in the selectivity for the 1,4-addition product, albeit at the cost of yield. An origin for this improvement may be inhibition of $\sigma \rightarrow \pi \rightarrow \sigma$ isomerization when 1,3-butadiene is in substantial molar excess, as it may act as a ligand on Pd. Modest concentration deviations of the diene had negligible effects.²³ Further improvement in both the selectivity and yield was

observed when the reaction was performed at higher overall concentration (entry 3) or an excess of the vinyl triflate was added (entry 4). Combining these changes provides an optimized procedure in which >20:1 selectivity for the 1,4-addition product and a 92:8 ratio for the desired trans alkene were observed (entry 5). It should be noted that some of the enhancement of the observed selectivity was due to consumption of the undesired terminal alkene product 5 by the reaction with the excess vinyl triflate. Therefore, the improvement in the selectivity and ease of purification came with a decrease in overall yield. Finally, the vinyl triflate could be replaced with the more economical vinyl nonaflate,²⁴ which produced nearly identical results (entry 6).

Under the optimal conditions, the scope of this 1,4-vinylarylation of 1,3-butadiene was assessed (Table 2). We initially focused on a variety of substituted arenes and heterocyclic vinyl triflates/nonaflates and observed excellent selectivity for the 1,4-addition product. Electronic effects of the arylboronic acid had little influence on the product yield (7a–f), although a lower regioselectivity was observed for the more electron-rich aryl group installed in 7c. The steric influence of *o*-tolylboronic acid (7g) resulted in good selectivity and good yield. The use of larger arenes, including several heteroaromatic groups, did not significantly influence the yield and selectivity of the process (7h–k). Unfortunately, boronic acids incorporating more Lewis basic heteroatoms (e.g., pyridine) failed to yield the three-component coupling product in an appreciable amount. Acyclic (*Z*)-vinyl triflates derived from β -dicarbonyls successfully yielded 7l and 7m without isomerization of the alkene geometry, suggesting that a wide variety of skipped dienes can be accessed using this method. Finally, the simple (*E*)-vinyl triflate 6n afforded the desired product 7n, again without the loss of stereochemical integrity originating from the vinyl triflate (eq 1). It should be noted that the internal alkene derived from 1,3-butadiene was formed in a ratio of >8:1 favoring the trans configuration in all cases, which is consistent

Table 2. Scope of 1,4-Vinylarylation of 1,3-Butadiene

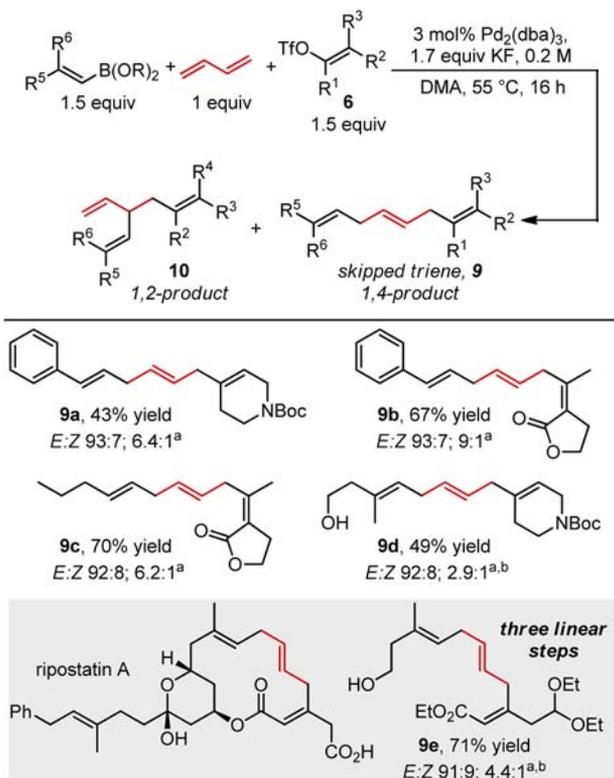
All yields and ratios are averages of two experiments on a 0.5 mmol scale. E:Z ratios were determined by ¹H NMR analysis. Yields are for mixtures of stereo- and regioisomers. ^aR³ = Tf. ^bR³ = Nf. ^c7:8 ratio as determined by ¹H NMR analysis.



with other difunctionalization reactions of this substrate.^{20k,22c,h-j}

Encouraged by the successful vinylarylations using the three-component coupling reaction, we explored a three-component vinylvinylation of 1,3-butadiene to form skipped trienes (Table 3). A styrenylboronic acid was effectively coupled with 1,3-

Table 3. Scope of 1,4-Vinylvinylation of 1,3-Butadiene



All yields and ratios are averages of two experiments on a 0.5 mmol scale. Yields are for mixtures of stereo- and regioisomers. ^a9:10 ratio and E:Z ratio determined by ¹H NMR analysis of the crude reaction mixture. ^bThe pinacol boronic ester and 6 mol % Pd₂(dba)₃ were used.

butadiene and either a cyclic or an acyclic boronic acid to form skipped triene 9a or 9b in modest to good yield. A simple acyclic vinylboronic acid was also an effective substrate in the synthesis of the skipped triene 9c. The use of a considerably more complex organometallic coupling partner required the use of a higher catalyst loading to prepare 9d. In this case and also for 9e, the pinacol boronic ester was used because it was more easily accessed. In these cases, the alkene geometries in both the vinyl triflate and the boronic ester remained intact. Additionally, the alkene derived from 1,3-butadiene was again formed in the trans configuration, suggesting a *trans*-σ-allyl intermediate (C in Figure 1c). The selectivity for 1,4-addition relative to 1,2-addition was diminished relative to the vinylarylation process, but the skipped trienes produced by 1,4-addition could be accessed by re-exposing the mixture to

the reaction conditions, which selectively consumed the terminal alkene.

To showcase the utility of this method, we targeted the skipped triene core of ripostatin A, a bacterial RNA-polymerase inhibitor.³ To our delight, the desired product 9e was formed with the appropriate display of the skipped triene core and the functional groups necessary for further manipulation. This example effectively illustrates the synthetic potential of this method in which a simple feedstock chemical is incorporated between two relatively complex fragments.

In summary, we have developed a new method that provides efficient access to skipped polyenes. This process takes advantage of the simplicity of 1,3-butadiene and the ability to functionalize its two terminal alkenes selectively and independently. Additionally, the reaction proceeds with high stereochemical integrity of the alkenes formed, as the geometries of the starting materials are relayed into the product and the alkene fashioned from 1,3-butadiene mainly has the trans geometry. The scope of the method was highlighted by the synthesis of the skipped triene core structure of ripostatin A in only three linear steps from simple starting materials. Many mechanistic questions arise when considering substituted terminal 1,3-dienes, where more highly functionalized skipped polyene products can be envisioned. Future work is focused on examining these effects and expanding the scope of the coupling partners.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures and characterization data for new substances. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) White, W. C. *Chem.-Biol. Interact.* **2007**, *166*, 10. (b) Morrow, N. L. *Environ. Health Perspect.* **1990**, *86*, 7.
- (2) For recent uses of 1,3-butadiene in precious-chemical synthesis, see: (a) Zbieg, J. R.; Yamaguchi, E. L.; McInturff, M. J.; Krische, M. J. *Science* **2012**, *336*, 324. (b) Arndt, M.; Dindaroglu, M.; Schmalz, H.-G.; Hilt, G. *Org. Lett.* **2011**, *13*, 6236.
- (3) Ripostatin: (a) Augustiniak, H.; Irschik, H.; Reichenbach, H.; Hoefle, G. *Liebigs Ann.* **1996**, 1657. (b) Irschik, H.; Augustiniak, H.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 787.
- (4) Piericidin: Kitaura, N.; Shirata, K.; Niwano, M.; Mimura, M.; Takahara, Y. Japanese Patent 05339156 A2, **1993**; *Chem. Abstr.* **1994**, *120*, 208590.
- (5) Lehaulide: Sata, N.; Abinsay, H.; Yoshida, W. Y.; Horgen, F. D.; Sitachitta, N.; Kelly, M.; Scheuer, P. J. *J. Nat. Prod.* **2005**, *68*, 1400.
- (6) Jerangolid: (a) Reichenbach, H.; Höfle, G.; Gerth, K.; Washausen, P. PCT Int. Appl. DE 19607702, 1997. (b) Gerth, K.; Washausen, P.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71.
- (7) Actinopyrone: (a) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*,

5415. (b) Taniguchi, M.; Watanabe, M.; Nagai, K.; Suzumura, K.-I.; Suzuki, K.-I.; Tanaka, A. *J. Antibiot.* **2000**, *53*, 844.

(8) Ambruticin: (a) Knauth, P.; Reichenbach, H. *J. Antibiot.* **2000**, *53*, 1182. (b) Ringel, S. M.; Greenough, R. C.; Roemer, S.; Connor, D.; Gutt, A. L.; Blair, B.; Kanter, G.; von Strandtmann, M. *J. Antibiot.* **1977**, *30*, 371.

(9) Halichlorine: (a) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861. (b) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867.

(10) Haterumalide: Ueda, K.; Hu, Y. *Tetrahedron Lett.* **1999**, *40*, 6305.

(11) Lobatamide: (a) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (b) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.

(12) Mycothiazole: Crews, P.; Kakou, Y.; Quinoa, E. *J. Am. Chem. Soc.* **1988**, *110*, 4365.

(13) Madangamine: Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007.

(14) Phorbacin: McNally, M.; Capon, R. J. *J. Nat. Prod.* **2001**, *64*, 645.

(15) Various fatty acids: Durand, S.; Parrain, J.-L.; Santelli, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 253.

(16) Julia olefination: (a) Pospíšil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516. (b) Schnermann, M. J.; Romero, A.; Hwang, I.; Nakamaru-Ogiso, E.; Yagi, T.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 11799.

(17) Cross-coupling: (a) Ye, K.-Y.; He, H.; Liu, W.-B.; Dai, L.-X.; Helmchen, G.; You, S.-L. *J. Am. Chem. Soc.* **2011**, *133*, 19006. (b) Gutierrez, A. C.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 6414. (c) Winter, P.; Vaxelaire, C.; Heinz, C.; Christmann, M. *Chem. Commun.* **2011**, 47, 394. (d) Macklin, T. K.; Micalizio, G. C. *Nat. Chem.* **2010**, *2*, 638. (e) Jeso, V.; Micalizio, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11422. (f) Diez, P. S.; Micalizio, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 9576. (g) Gu, Y.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385. (h) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317.

(18) Takai olefination: (a) Gagnepain, J.; Moulin, E.; Fürstner, A. *Chem.—Eur. J.* **2011**, *17*, 6964. (b) Macklin, T. K.; Micalizio, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 1392. (c) Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 12228. (d) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.

(19) Ring-closing metathesis: (a) Winter, P.; Hiller, W.; Christmann, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3396. (b) Tang, W.; Prusov, E. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 3401. (c) Tang, W.; Prusov, E. V. *Org. Lett.* **2012**, *14*, 4690.

(20) (a) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590. (b) Zhang, X.; Larock, R. C. *Tetrahedron* **2010**, *66*, 4265. (c) Kudirka, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (d) Shu, W.; Jia, G.; Ma, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 2788. (e) Cheng, Y.-n.; Duan, Z.; Yu, L.; Li, Z.; Zhu, Y.; Wu, Y. *Org. Lett.* **2008**, *10*, 901. (f) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921. (g) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765. (h) Oh, C. H.; Lim, Y. M. *Tetrahedron Lett.* **2003**, *44*, 267. (i) Aftab, T.; Grigg, R.; Ladlow, M.; Sridharan, V.; Thornton-Pett, M. *Chem. Commun.* **2002**, 1754. (j) Shaulis, K. M.; Hoskin, B. L.; Townsend, J. R.; Goodson, F. E.; Incarvito, C. D.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 5860. (k) Huang, T.-H.; Chang, H.-M.; Wu, M.-Y.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 99.

(21) (a) Saini, V.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11372. (b) Stokes, B. J.; Opra, S. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11408. (c) Pathak, T. P.; Sigman, M. S. *Org. Lett.* **2011**, *13*, 2774. (d) Liao, L.; Jana, R.; Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 5784. (e) Liao, L.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 10209. (f) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett.* **2010**, *12*, 2848. (g) Urkalan, K. B.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3146.

(22) (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686. (b) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem.*

Soc. **2010**, *132*, 3523. (c) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 16382. (d) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (e) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. (f) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (g) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308. (h) Bäckvall, J.-E.; Vågberg, J. O. *J. Org. Chem.* **1988**, *53*, 5695. (i) Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676. (j) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

(23) See the Supporting Information for complete table of optimization data.

(24) For a review of nonaflates, see: (a) Högermeier, J.; Reißig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747. (b) Lyapkalo, I. M.; Weibel, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015.