JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

A Practical Solution to Stereodefined Tetrasubstituted Olefins

Jianxin Dai, Minyan Wang, Guobi Chai, Chunling Fu, and Shengming Ma*

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China

Supporting Information

ABSTRACT: Olefins, compounds with a carbon−carbon double bond, are of fundamental importance, and stereodefined construction of tetrasubstituted carbon−carbon double bond is a significant challenge. Here we show a unique and practical method for the preparation of stereodefined, fully substituted olefins via conjugate addition of organozinc reagents to readily available 2,3-allenals. Through mechanistic studies, it is confirmed that the geometry of the newly formed double bond is controlled by unique regiospecific oxygen-protonation of the enolate intermediates, generating 1,3-alkadienols. Such alkadienols would undergo a concerted 1,5-H-transfer reaction via a six-membered transition state to ensure the configuration of the carbon−carbon double bond in the final products. Using the readily available organozinc reagents and 2,3-allenals provides a very rapid access to a wide range of tetrasubstituted olefins with defined stereochemistry, bearing an extremely versatile aldehyde functionality.

Stereodefined compounds play a vital role in life science, medicine, and chemistry. Besides the widely studied chiral compounds, another critical class of stereodefined compounds is olefins. Similar to chiral compounds, stereodefined olefins are indispensable in nature, medicinal development laboratories, and industry.[1−3] For example, it has been noted that the *cis* and *trans* isomers of olefins may show very different biological activities (Figure 1).[4]

It has been demonstrated that stereoselective synthesis of 1,2-disubstituted or trisubstituted olefins has been addressed by hydrogenation[1,5] or hydro-/carbometalation of alkynes.[2] However, efficient stereoselective synthesis of tetrasubstituted olefins remains a grand challenge, since existing approaches involving the olefination of ketones, metathesis of 1,1-disubstituted olefins, elimination of appropriate alkanes, insertive coupling of alkynes, and C−H functionalization of olefins would afford a *E*/*Z*- or regio-isomeric mixtures (Scheme 1a).[3]

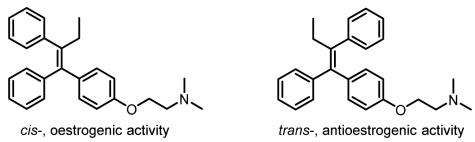
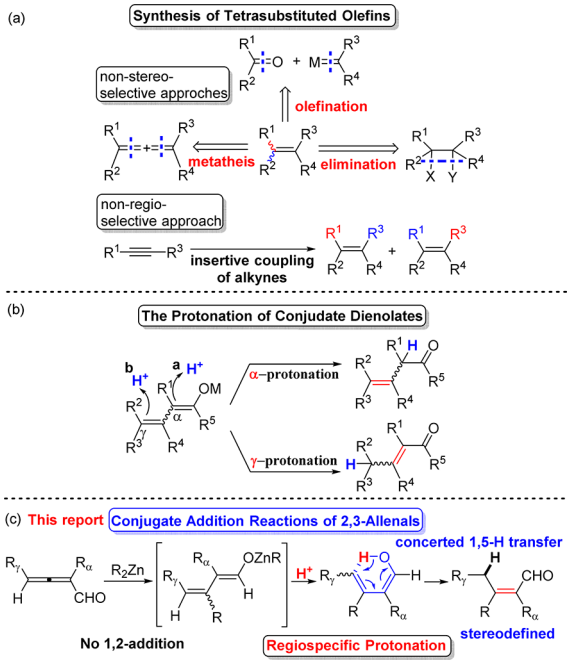


Figure 1. A typical example of *Z*/*E*-isomers of olefins with different bioactivities.

Scheme 1. (a) Known Approaches for Synthesis of Tetrasubstituted Olefins, (b) Protonations of Conjugated Dienolates, and (c) Stereodefined Tetrasubstituted Olefins from Conjugate Additions of 2,3-Allenals with Organozinc Reagents Followed by Protonation



On the other hand, the chemistry of alkenolate-type anions[6] has been well established for efficient formations of covalent chemical bonds, while that of conjugated alkadienolate-type anions has not been well developed[7] due to the intrinsic issues of regio- and stereoselectivity: the reaction with a proton may yield the α- [M = Sm,[8] Li,[9−12] Mg,[12,13] CuLi[14]], γ- [M = *n*-Bu_4N[10]], or α-/γ-mixed [M = Li[11]] protonated products (Scheme 1b). In all these reported cases except for the conjugate addition of 2,3-alkadienoates with Grignard reagents affording the α-protonation products,[12,13] the issue of stereoselectivity referring to the carbon−carbon double bonds in the products has not been addressed. Here we show that the conjugate addition of readily available 2,3-allenals[15,16] with organozincs (R_2Zn), which have been produced in large scales in industry, upon deliberate tuning of protonation surprisingly delivered, via formal γ-protonation, stereodefined tetrasubsti-

Received: January 4, 2016
Published: February 8, 2016

DOI: 10.1021/jacs.6b00051
J. Am. Chem. Soc. 2016, 138, 2532−2535

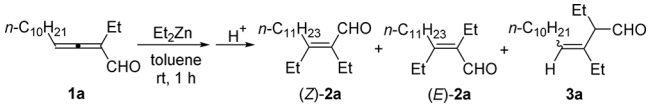
tuted olefins with a very versatile conjugated aldehyde functionality (Scheme 1c). This functionality provides ready elaboration for the efficient synthesis of different types of compounds with a stereodefined, tetrasubstituted C=C bond with the group from the organozincs (R) *trans* to the aldehyde functionality.

The initial study was started using 2-ethyltetradeca-2,3-dienal (**1a**) and Et_2Zn as the substrates, employing different Brønsted acids as the proton sources for the targeted protonation (Table 1). As expected, low yields as well as poor regio- and stereoselectivities for the γ-protonation product, tetrasubstituted 2-enal **2a** (19% and 14% yields of (*Z*)-**2a** and (*E*)-**2a**, respectively), and the α-protonation product, 2,3-diethyltetradec-3-enal (**3a**) (69% and 7% yield of (*Z*)-**3a** and (*E*)-**3a**, respectively), were observed when hydrochloric acid was applied (entry 1). It is interesting to observe that no product of the 1,2-addition to the reactive aldehyde functionality was detected.[17] The results were also unsatisfied with TFA or MeOH. However, excellent stereoselectivity and moderate yield of (*Z*)-**2a** were realized with ammonium chloride as the proton source, although a poor regioselectivity was observed, with the α-protonation product **3a** also being formed in 28% yield (entry 4). It is exciting to notice that tetrasubstituted enal was obtained as the single product in 28% yield exclusively when trifluoromethanesulfonic acid was applied as the proton source (entry 5). Fortunately, not only were the yields improved, but also excellent regio- and stereoselectivites were observed with carboxylic acids such as propanoic acid and acetic acid as the proton source (entries 4–10). Therefore, acetic acid was selected for further optimization. After a careful screening of the loading of diethylzinc, concentration, and temperature, the exclusive formation of tetrasubstituted enal (*Z*)-**2a** was realized, with 2.4 equiv of Et_2Zn in toluene (0.05 M) at −10 °C upon protonation with acetic acid affording it in 95% yield (entry 10).

With the above optimized reaction conditions in hand, we explored the scope of different 2,3-allenals (Table 2, entries 1–16). Various substituents on the 2,3-allenals were well tolerated, efficiently providing the desired stereodefined tetrasubstituted 2-alkenals **2** in fairly high yields: R^1 may be alkyl, benzyl, or allyl; the length of the carbon chain of the R^2 group may be increased from methyl to *n*-decyl. R^2 may also be cyclohexyl, benzyl or aryl; furthermore, the functional groups, such as halide and C=C bond, may also be accommodated to afford the desired 2-alkenals. In addition to diethylzinc, dibutylzinc as well as secondary alkyl organozinc reagent such as *i*-Pr_2Zn may also be applied affording the products **2p**-**2u** in satisfactory yields (Table 2, entries 17–22). Furthermore, even diphenyl zinc could also be applied affording the stereodefined tetrasubstituted 2-alkenals (*E*)-**2v** and (*E*)-**2w** in decent yields (Table 2, entries 23 and 24). Multigram scale synthesis may also be conducted easily affording 5.45 g of (*Z*)-**2f** in 93% yield (Table 2, entry 7). The configuration of the C=C bond was determined by NOESY analysis of (*E*)-**2w** and (*E*)-**2v**, and X-ray single crystal diffraction study of (*E*)-**4** (Figure S1), which was afforded by the reaction of (*E*)-**2w** with (2,4-dinitrophenyl)hydrazine, confirming the R group is *trans* to the formyl group.

Several carboxylic acids with different pK_a values were employed as the proton sources under the optimized conditions (Table S1). These results in Table 1 and Table S1

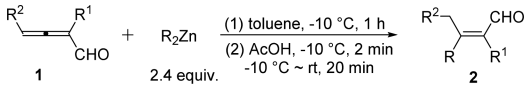
Table 1. Optimization of the Reaction Conditions for Complete Control of Regio- and Stereoselectivity[a]



entry	Et_2Zn (equiv)	proton source	NMR yield[b] (%) (*Z*)-**2a**	(*E*)-**2a**	(*Z*)-**3a**	(*E*)-**3a**
1	3.0	HCl	~19	~14	62	7
2	3.0	TFA	~44	~24	12	2
3	3.0	MeOH	~49	~4	32	2
4	3.0	NH_4Cl	61	n.d.	18	10
5	3.0	TfOH	28	n.d.	n.d.	n.d.
6	3.0	$EtCO_2H$	86	n.d.	0.9	n.d.
7	3.0	HOAc	96	n.d.	1.6	0.4
8[c]	2.4	HOAc	96	n.d.	1.6	0.4
9[c,d]	2.4	HOAc	96	n.d.	0.7	n.d.
10[c–e]	**2.4**	HOAc	**95**	**n.d.**	**n.d.**	**n.d.**

[a]Reagents and conditions: **1a** (0.4 mmol), Et_2Zn (*x* equiv), toluene (4 mL), and proton source (0.8 mL) at room temperature. [b]Yields were determined by ^1H NMR using dibromomethane as the internal standard. [c]Reaction was performed on 1.0 mmol scale. [d]Reaction was performed in toluene (20 mL). [e]Reaction was performed at −10 °C.

Table 2. Reaction of Different 2,3-Allenals (1) with Organozinc Reagents[a]

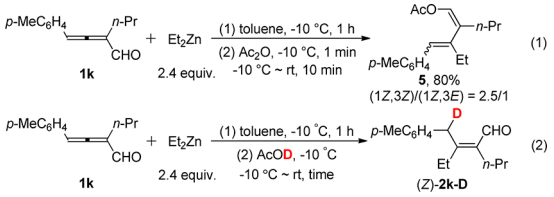


entry	1: R^1	1: R^2	R	yield[b] of **2** (%)	ratio[c]
1	Et	*n*-$C_{10}H_{21}$ (**1a**)	Et	88 (*Z*)-**2a**	>99:1
2	Et	*n*-C_9H_{19} (**1b**)	Et	90 (*Z*)-**2b**	>99:1
3	Me	*n*-C_9H_{19} (**1c**)	Et	92 (*Z*)-**2c**	>99:1
4	*n*-Pr	*n*-C_7H_{15} (**1d**)	Et	88 (*Z*)-**2d**	>99:1
5	*n*-Pr	*n*-C_9H_{19} (**1e**)	Et	87 (*Z*)-**2e**	>99:1
6	*n*-Pr	*n*-$C_{10}H_{21}$ (**1f**)	Et	90 (*Z*)-**2f**	>99:1
7[d]	*n*-Pr	*n*-$C_{10}H_{21}$ (**1f**)	Et	93 (*Z*)-**2f**	>99:1
8	*n*-Pr	Cy (**1g**)	Et	86 (*Z*)-**2g**	>99:1
9	*n*-Pr	Bn (**1h**)	Et	90 (*Z*)-**2h**	>99:1
10	*n*-Pr	$Cl(CH_2)_3$ (**1i**)	Et	87 (*Z*)-**2i**	>99:1
11	*n*-Pr	CH_2=$CH(CH_2)_7$ (**1j**)	Et	90 (*Z*)-**2j**	>99:1
12	*n*-Pr	*p*-MeC_6H_4 (**1k**)	Et	85 (*Z*)-**2k**	>99:1
13	*n*-Bu	Ph (**1l**)	Et	90 (*Z*)-**2l**	>99:1
14	*n*-Bu	*p*-MeC_6H_4 (**1m**)	Et	86 (*Z*)-**2m**	>99:1
15	allyl	*n*-C_9H_{19} (**1n**)	Et	88 (*Z*)-**2n**	>99:1
16	Bn	Me (**1o**)	Et	88 **2o**	–
17	*n*-Pr	*n*-C_7H_{15} (**1d**)	*n*-Bu	90 (*Z*)-**2p**	>99:1
18	*n*-Pr	*n*-$C_{10}H_{21}$ (**1f**)	*n*-Bu	88 (*Z*)-**2q**	>99:1
19	*n*-Pr	Bn (**1h**)	*n*-Bu	89 (*Z*)-**2r**	>99:1
20	*n*-Pr	$Cl(CH_2)_3$ (**1i**)	*n*-Bu	86 (*Z*)-**2s**	>99:1
21	allyl	*n*-C_9H_{19} (**1n**)	*n*-Bu	89 (*Z*)-**2t**	>99:1
22	*n*-Pr	Cy (**1g**)	*i*-Pr	84 (*E*)-**2u**	>99:1
23[e]	*n*-Pr	$Cl(CH_2)_3$ (**1i**)	Ph	75 (*E*)-**2v**	>99:1
24[e]	*n*-Bu	*p*-MeC_6H_4 (**1m**)	Ph	80 (*E*)-**2w**	>99:1

[a]The reaction was carried out on a 1.0 mmol scale of 2,3-allenal. [b]Isolated yield. [c]The ratios were determined by ^1H NMR analysis of the crude reaction mixtures. [d]The reaction was conducted on 5 g scale. [e]Reaction was performed at −30 °C for 11 h, then AcOH, −30 °C, 2 min, −30 °C to ~rt, 30 min.

DOI: 10.1021/jacs.6b00051
J. Am. Chem. Soc. 2016, 138, 2532–2535

indicate that the selectivity is affected by whether the pK_a of the carboxylic acid matches that of the organometallic intermediate involved. In order to further unveil the nature of such in situ formed zinc dienolate intermediate, acetic anhydride was used to capture any intermediate(s) in the reaction of **1k** with Et_2Zn (eq 1). The reaction afforded *O*-acetoxylated product **5** as an *E*/*Z* mixture referring to the C=C at the 3-position [(1*Z*,3*Z*)/(1*Z*,3*E*) = 2.5/1]. Thus, the regio- and stereoselectivity control must be accomplished during the protonation stage. A deuterium-labeling experiment applying DOAc confirmed the deuterium incorporation at the C4 position of (*Z*)-**2k-D** and the level of D incorporation increased with the reaction time, indicating that the protonation is slow as the rate-determining step (eq 2 and Figure 2). The treatment of the α-protonated



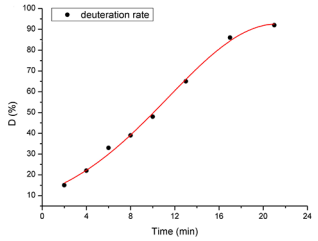
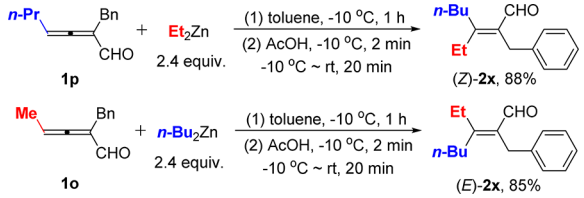


Figure 2. Protonation: D incorporation vs reaction time.

product **3a** (prepared according to entry 1 in Table 1) with $Zn(OAc)_2$ and acetic acid under the standard workup procedure failed to afford γ-protonated product **2a** excluding the possibility of forming **2a** via α-protonation (see SI). However, when **3a** was deprotonated with diethylzinc and subsequently quenched with acetic acid, (*Z*)-**2a** was formed exclusively in 60% yield (see SI).

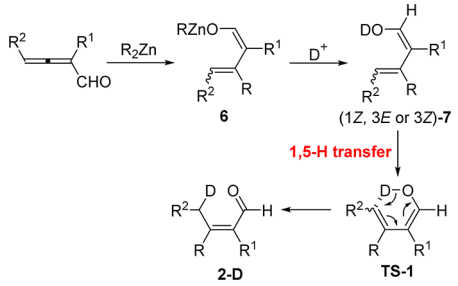
By simply switching the substituents in the related reactants, both (*Z*)-**2x** and (*E*)-**2x** were prepared exclusively (Scheme 2).

Scheme 2. Synthesis of Two Stereoisomers of 2x



Based on these results, we proposed that conjugate addition of R_2Zn with 2,3-allenals[18] would form the zinc dienolate intermediate **6** as a *Z* and *E* mixture referring to the C=C bond at the 3-position. Consequently the dienol **7** was formed also as a *Z* and *E* mixture referring to the C=C bond at the 3-position based on the results shown in eq 1 by delivering the proton regiospecifically to the anionic oxygen atom, which is a very slow process based on the results shown in Figure 2. The final product **2** was then formed exclusively via the concerted intramolecular 1,5-hydride transfer of (1*Z*,3*E*)-**7** or (1*Z*,3*Z*)-**7** (Scheme 3). It is interesting to note that in the literature it has

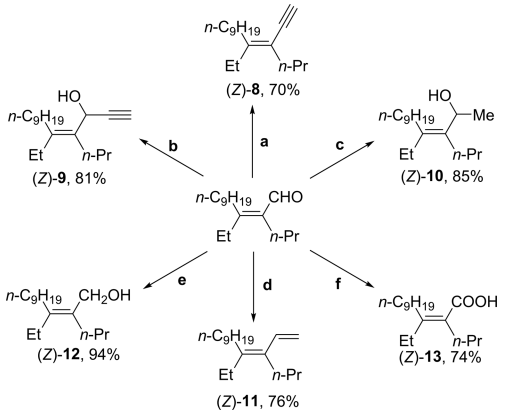
Scheme 3. Proposed Mechanism for the Selectivity



been noted that the rate of α-protonation is much faster than that of γ-protonation,[19] so that the reaction quenched with proton yields mostly the α-protonated products.[13]

These tetrasubstituted alkenals are very useful building blocks for the synthesis of compounds with a stereodefined tetrasubstituted C=C bond (Scheme 4). For example, treatment with trimethylsilyldiazomethane has been shown to give enyne (*Z*)-**8** in 70% yield;[20] 1,2-addition with organic magnesium or lithium reagents afforded propargylic alcohol (*Z*)-**9** or secondary allylic alcohol (*Z*)-**10** in 81% yield or 85% yield, respectively;[21,22] the conjugated dienes (*Z*)-**11** could be prepared by a Wittig reaction in 76% yield;[23] reduction with $NaBH_4$ or oxidation with $NaClO_2/H_2O_2$ afforded primary allylic alcohol (*Z*)-**12** or α,β-unsaturated carboxylic acid (*Z*)-**13** in 94% yield or 74% yield, respectively.[24,25]

Scheme 4. Transformations of Tetrasubstituted Alkenals to Other Functionalized Tetrasubstituted Olefins



Reagents and conditions: (a) $TMSCHN_2$ (1.5 equiv), *n*-BuLi (1.4 equiv), THF, −78 °C ~ rt, 12 h; (b) HC≡CMgBr (3 equiv), THF −40 °C, 11 h; (c) MeLi (1.2 equiv), Et_2O, −78 °C, 4 h; (d) PPh_3=CH_2·HBr (2 equiv), *n*-BuLi (2 equiv), THF, 0 °C ~ rt, 11 h; (e) $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 3 h; (f) NaH_2PO_4 (0.25 equiv), H_2O_2 (1.04 equiv), $NaClO_2$ (1.4 equiv), CH_3CN/H_2O, rt, 11 h.

In summary, we have observed a regiospecific conjugate addition of 2,3-allenals with organozinc reagents, which, upon protonation, introduces the R group of R_2Zn to the center carbon atom of the 2,3-allenals, providing stereodefined tetrasubstituted 2-alkenals with the R group *trans* to the formyl group in high yields with a very broad scope. The mechanistic study revealed that the highly stereoselectivity was realized by regiospecific delivery of the proton to the anionic oxygen of the

DOI: 10.1021/jacs.6b00051
J. Am. Chem. Soc. 2016, 138, 2532−2535

dienolate intermediate, forming the alkadienol intermediates, which underwent concerted 1,5-H transfer to afford the stereodefined conjugated enals. As we know, stereodefined tetrasubstituted olefins are important units in many biologically active molecules and natural products as well as key synthetic intermediates for organic synthesis, and their synthesis is challenging. Thus, this methodology, with an interesting mechanism, provides a promising platform for further study in stereodefined synthesis of C=C bonds. Further studies in this area are being actively pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00051.

Experimental procedures and compound characterization data (PDF)

X-ray crystallographic data for **4** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*masm@sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (21232006) and National Basic Research Program (2015CB856600) is greatly appreciated. S.M. is a Qiu Shi Adjunct Professor at Zhejiang University. We thank Mr. Yulin Han and Xin Huang in our group for reproducing the results presented in entries 14, 17, and 23 in Table 2.

■ REFERENCES

(1) Oger, C.; Balas, L.; Durand, T.; Galano, J.-M. *Chem. Rev.* **2013**, *113*, 1313−1350.

(2) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474−1485.

(3) (a) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698−4745. (b) Mori, M. *Eur. J. Org. Chem.* **2007**, *2007*, 4981−4993. (c) Shindo, M.; Matsumoto, K. *Top. Curr. Chem.* **2012**, *327*, 1−32. (d) Paek, S.-M. *Molecules* **2012**, *17*, 3348−3358. (e) He, Z.; Kirchberg, S.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3699−3702. (f) Barczak, N. T.; Rooke, D. A.; Menard, Z. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7579−7582.

(4) Harper, M. J. K.; Walpole, A. L. *Nature* **1966**, *212*, 87.

(5) Shen, R.; Chen, T.; Zhao, Y.; Qiu, R.; Zhou, Y.; Yin, S.; Wang, X.; Goto, M.; Han, L. *J. Am. Chem. Soc.* **2011**, *133*, 17037−17044.

(6) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366−2447.

(7) (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566−2587. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2011**, *111*, 3076−3154.

(8) (a) Molander, G. A.; La Belle, B. E.; Hahn, L. G. *J. Org. Chem.* **1986**, *51*, 5259−5264. (b) Otaka, A.; Yukimasa, A.; Watanabe, J.; Sasaki, Y.; Oishi, S.; Tamamura, H.; Fujii, N. *Chem. Commun.* **2003**, 1834−1835. (c) Reutrakul, V.; Jaratjaroonphong, J.; Tuchinda, P.; Kuhakarn, C.; Kongsaeree, P.; Prabpai, S.; Pohmakotr, M. *Tetrahedron Lett.* **2006**, *47*, 4753−4757.

(9) (a) Bunnell, C. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1977**, *99*, 5184−5187. (b) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1042−1044.

(10) Najafi, M. R.; Wang, M. L.; Zweifel, G. *J. Org. Chem.* **1991**, *56*, 2468−2476.

(11) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1995**, *78*, 539−552.

(12) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603−606.

(13) (a) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546−14547. (b) Chai, G.; Lu, Z.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2009**, *351*, 1946−1954.

(14) (a) Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715−8724. (b) Dieter, R. K.; Lu, K. *Tetrahedron Lett.* **1999**, *40*, 4011−4014.

(15) Yin, S.; Ma, S.; Jiao, N.; Tao, F. *Chin. J. Chem.* **2002**, *20*, 707−710.

(16) Ma, S.; Liu, J.; Li, S.; Chen, B.; Cheng, J.; Kuang, J.; Liu, Y.; Wan, B.; Wang, Y.; Ye, J.; Yu, Q.; Yuan, W.; Yu, S. *Adv. Synth. Catal.* **2011**, *353*, 1005−1017.

(17) Chen, B.; Lu, Z.; Chai, G.; Fu, C.; Ma, S. *J. Org. Chem.* **2008**, *73*, 9486−9489.

(18) Chai, G.; Wu, S.; Fu, C.; Ma, S. *J. Am. Chem. Soc.* **2011**, *133*, 3740−3743.

(19) (a) Duhaime, R. M.; Weedon, A. C. *J. Am. Chem. Soc.* **1987**, *109*, 2479−2483. (b) Duhaime, R. M.; Lombardo, D. A.; Skinner, I. A.; Weedon, A. C. *J. Org. Chem.* **1985**, *50*, 873−879.

(20) Sibilska, K.; Sicinski, R. R.; Ochalek, J. T.; Plum, L. A.; DeLuca, H. F. *J. Med. Chem.* **2014**, *57*, 8319−8331.

(21) Spencer, W. T.; Frontier, A. J. *J. Org. Chem.* **2012**, *77*, 7730−7736.

(22) Mao, G.; Wang, C.; Chen, J.; Muramatsu, A.; Xi, Z. *Tetrahedron Lett.* **2005**, *46*, 5369−5372.

(23) Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7304−7311.

(24) Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 1996−2003.

(25) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.

DOI: 10.1021/jacs.6b00051
J. Am. Chem. Soc. 2016, 138, 2532−2535