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

Stereocontrolled Synthesis of Triols Containing Four Asymmetric Centers: Application of *C,O*-Chelated Germyl Enolates to a Diastereoselective Aldol Reaction

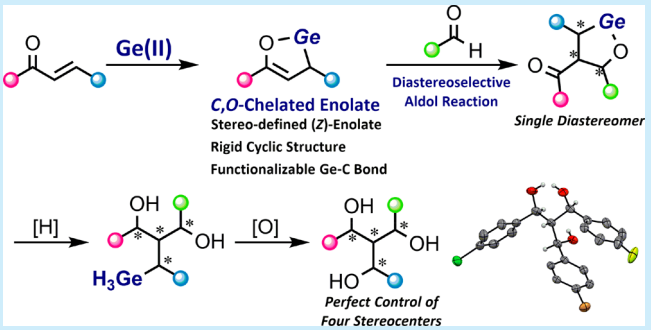
Yohei Minami,[†] Akihito Konishi,*[,†,‡] and Makoto Yasuda*[,†]

[†]Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

[‡]Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

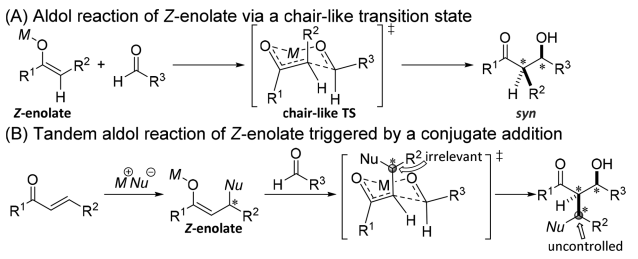
Supporting Information

ABSTRACT: The treatment of α,β-unsaturated ketones with divalent germanium salts cleanly generated *C,O*-chelated germyl enolates. The aldol reactions of the chelated enolates with the aldehydes achieved a high diastereoselectivity in the construction of the five-membered aldol adducts. Furthermore, the subsequent transformation of the Ge−C bond in the aldol adduct enabled the stereocontrolled synthesis of triols bearing four asymmetric centers.



Aldol reactions using organometallic enolates are the most important reactions for the stereoselective construction of carbon−carbon bonds.[1−6] The significant transfer of enolate stereochemistry to the product has improved in the area of asymmetric synthesis, enabling the formation of new bonds in a stereocontrolled manner. In an aldol reaction, a six-membered chairlike cyclic transition state determines the stereochemistry of the aldol adduct; the reaction of a (*Z*)-enolate with an aldehyde provides a *syn*-aldol adduct, whereas an *anti*-aldol adduct is generated from an (*E*)-enolate (Scheme 1A).[7] Despite broad explorations of stereocontrolled and enantiocontrolled synthetic methods involving an aldol reaction, including auxiliary[8]-, substrate[9]-, and ligand[10,11]-mediated aldol reactions, synthetic control over the relative configurations of multiple (>2) stereocenters in an acyclic enolate and the derived products continues to be an important subject of study.[12,13]

Scheme 1. Control over the Relative Configurations of (A) Usual and (B) Tandem Aldol Reactions of (*Z*)-Enolate



The tandem aldol reaction, which was triggered by a conjugate addition to α,β-unsaturated carbonyls, offers a promising method for synthesizing aldols with multiple stereocenters. Although a stereodefined enolate is generated through this process, the relative configurations of the three stereocenters in the aldol cannot be controlled. In the absence of external stereocenter sources, one stereocenter generated by the addition of a nucleophile is irrelevant to the formation of the chairlike structure in the transition state (Scheme 1B). In an aldol reaction, structural rigidification in the transition state is required for controlling the relative configurations of the multiple stereocenters in the product.

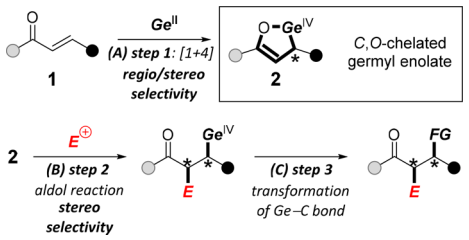
Previously, Saigo[14,15] and our group[16−19] reported the reductive generation of germyl enolates from α-halo carbonyl compounds and Ge(II) salts, based on the mild reducing capacity of the Ge(II) salts. The addition of ligands to the germyl enolate changed the coordination number of the germanium center flexibly from a tetracoordinated to a pentacoordinated center or hexacoordinated center.[20] The application of Ge(II) salts, which combine chemical stability and good reduction potential, to the generation of germyl enolates is useful for the stereoselective and regioselective preparation of organometallic enolates. Herein, we focused on the *C,O*-chelated germyl enolates **2** derived from the [1 + 4] cycloaddition of Ge(II) salts to the α,β-unsaturated ketones **1**. This protocol was originally employed to trap the reactive

Received: June 7, 2018

DOI: 10.1021/acs.orglett.8b01778
Org. Lett. XXXX, XXX, XXX−XXX

Ge(II) species, but the reactivity of the generated *C,O*-chelated germyl enolates **2** has not been investigated previously.[21] The rigid chelated structure of the *C,O*-chelated germyl enolates **2** provided the following advantages, which ameliorate the synthetic drawbacks of conventional organometallic enolates (see Scheme 2).

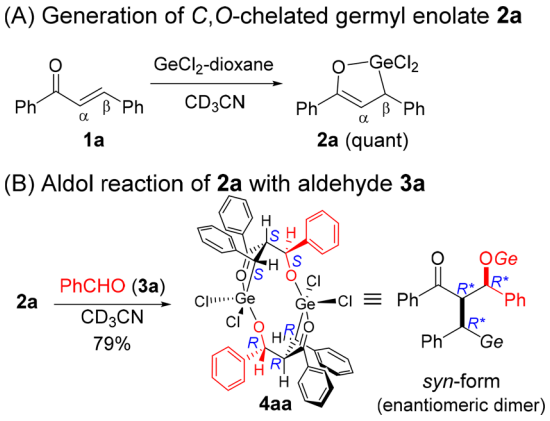
Scheme 2. *C,O*-Chelated Germyl Enolate (2): (A) [1 + 4] Cycloaddition of Ge(II) Salts Using a *α,β*-Unsaturated Carbonyl (1), (B) an Aldol Reaction, and (C) Further Transformation



First, the cycloaddition of a Ge(II) salt to the *α,β*-unsaturated ketones **1** unambiguously gave the (*Z*)-enolate, ensuring the regioselectivity and stereoselectivity of the enolate (Scheme 2, step 1). Second, the rigid cyclic structure[22,23] of the *C,O*-chelated enolate facilitated the high diastereoselective aldol reactions (step 2).[24−28] Finally, the Ge−C bond in the aldol adduct could be transformed to a new functional group (step 3). In this study, we reported the diastereoselective aldol reaction of the *C,O*-chelated germyl enolates with aldehydes. The subsequent derivatization of the obtained aldol adducts accomplished the perfectly stereocontrolled triol syntheses with multiple asymmetric carbon atoms, up to a total of four.

The *C,O*-chelated enolates were prepared by reducing *α,β*-unsaturated carbonyls with Ge(II) salts. As a model study, we first examined the reaction of a chalcone with a $GeCl_2$-dioxane complex according to Mazières' procedure (see Scheme 3A).[21]

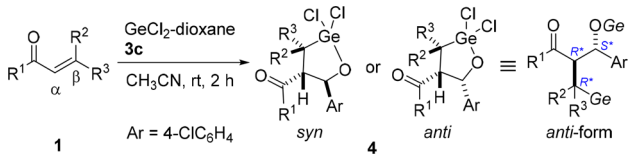
Scheme 3. (A) Preparation of the *C,O*-Chelated Germyl Enolate 2a, and (B) Aldol Reaction of 2a with 3a

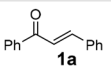


Monitoring the reaction in CD_3CN revealed upfield shifts in the signals of the *α*- and *β*-protons of the chalcone (5.96 and 4.50 ppm, respectively) in the ^1H NMR spectrum, strongly suggesting the quantitative generation of the corresponding *C,O*-chelated germyl enolate **2a**. Next, we examined the nucleophilic reactivity of the *C,O*-chelated germyl enolate **2a** with benzaldehyde **3a** (see Scheme 3B). The addition of benzaldehyde **3a** to a solution of the chelated enolate **2a** in CD_3CN immediately produced an insoluble colorless solid precipitate. Although its poor solubility hampered characterization via NMR measurements, gradual crystallization from the reaction mixture gave a single crystal suitable for X-ray analysis. This analysis revealed that the aldol adduct **4aa** was selectively generated in a *syn*-form and was solely present as a dimer of the enantiomeric pair (see Figure S1 in the Supporting Information).[29,30] Notably, the obtained aldol adduct **4aa** was found to be a single diastereomer, despite the presence of three stereocenters in its skeleton. The *C,O*-chelated germyl enolate **2a** reacted with various aldehydes (**3a**−**3h**) and gave the corresponding aldol adducts **4aa**−**ah** (see Table S1 in the Supporting Information). All aldol adducts were diastereoselectively obtained as enantiomeric pairs in the solid states, as confirmed by the X-ray crystallographic analyses. (In the manuscript, all aldol products are represented as the monomer, for clarity; see also Figures S1−S8 in the Supporting Information.)

In testing the scope of the reaction with *α,β*-unsaturated ketones, we determined that the diastereoselectivity of the aldol adducts was deeply dependent on the substituents at the *β*-position of the ketones **1**. The substituents at the *β*-position (R^2 and R^3) of **1** were used to classify the obtained aldol adducts into two types (see Table 1). In Class A (entries 1 and

Table 1. Scope of the Aldol Addition with *α,β*-Unsaturated Ketones of 1a−1d and Aldehyde 3c[a]



entry	α,β-unsaturated ketone **1**	product	yield/%	*syn* or *anti*	dimer or monomer	class
1	 **1a**	**4ac**	82	*syn*	dimer	A
2	 **1b**	**4bc**	85	*syn*	dimer	A
3	 **1c**	**4cc**	34	*anti*	monomer	B
4	 **1d**	**4dc**	82	*anti*	monomer	B

[a]Isolated yield. All structures of **4aa**−**4ah** were determined by X-ray analysis.

2 in Table 1), which included the *β*-monosubstituted ketones (R^2 = H), the aldol adducts **4ac** (Figure S3 in the Supporting Information) and **4bc** (Figure S9 in the Supporting Information) assumed the *syn*-forms as dimers of the enantiomeric pairs. On the other hand, the *β,β′*-disubstituted ketones (R^2 = Me and R^3 = Me or Ph; Class B) gave the monomeric *anti*-aldol adducts **4cc** and **4dc** (entries 3 and 4 in Table 1). The X-ray analysis revealed that **4cc** was present as a monomeric adduct and diastereoselectively assumed an *anti*-form (see Figure S11 in the Supporting Information). The O atom of the carbonyl group intramolecularly interacted with the Ge center, and its interaction slightly distorted the five-

DOI: 10.1021/acs.orglett.8b01778
Org. Lett. XXXX, XXX, XXX−XXX

membered ring. The ^{1}H NMR measurements of **4cc** and **4dc** supported the maintenance of the *anti*-form in the solution phase, in which the coupling (J) constants (4.4 Hz) between the two methine protons in the pentagonal ring agreed well with those estimated using the Karplus equation,[31] based on the dihedral angle. Considering that the *C*,*O*-chelated enolate was a type of (*Z*)-enolate, the observed *anti*-selectivity under the aldol reactions appeared to be quite unusual. (*Z*)-enolates are expected to preferably afford the *syn*-adduct via a six-membered chairlike cyclic structure. The departure from this expectation suggested that our reaction might proceed via a different reaction mechanism.

The *syn*-/*anti*-selectivity of the obtained aldol adducts (Table 1) may have been achieved through a reaction mechanism involving a boatlike cyclic transition state, as proposed in Figure 1.[32−36] It was impossible for the chelated

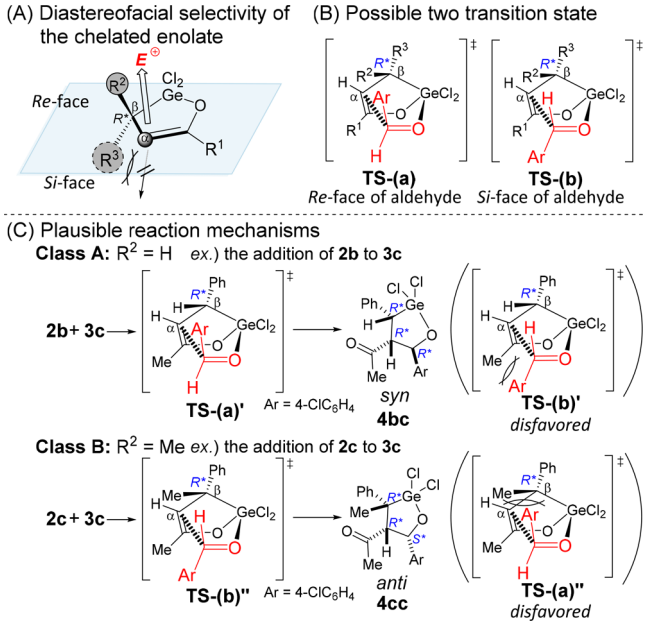
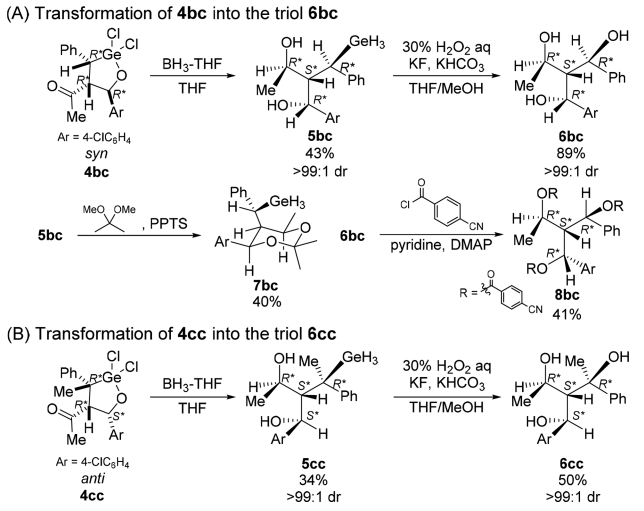


Figure 1. Origin of the diastereoselectivity of the aldol reactions. (A) Diastereofacial selectivity of the *C*,*O*-chelated germyl enolate, (B) two possible structures of the boatlike cyclic transition state, and (C) plausible reaction mechanism underlying the production of Class A and Class B.

enolates to assume a chairlike transition state, because of the presence of fixed cyclic structures around the Ge−C bond. Therefore, the aldol reaction was expected to proceed via a boatlike cyclic transition state, in which the substitution patterns at the β-position (R^2 and R^3) of the ketones led to differences in the stabilities of the transition states. The reaction of one enantiomer (herein, the relative absolute configuration was considered to be *R**) of the chelated germyl enolate with the arylaldehyde involved two diastereofacial selective steps. One involved the facial selectivity of the chelated enolate. The *Si*-face of the chelated enolate was blocked by the larger substituent ($R^3 > R^2$); therefore, the *Re*-face of the chelated enolate preferably attacked electrophiles in our study (Figure 1A). The second step involved the facial selectivity of the carbonyl carbon of the arylaldehydes, which was dependent on the steric demands between the aryl groups of the aldehyde and the R^2 group of the chelated enolate (Figure 1B). Among the Class A compounds (R^2 = H), the nucleophilic attack on the *Re*-face of the carbonyl carbon was much less hindered, as shown in TS-(a)′ in Figure 1C, to provide the *syn*-aldol adduct **4bc**. The *Si*-face of the carbonyl carbon was disfavored due to steric repulsion between the methyl group and the Ar group of the aldehyde (TS-(b)′ in Figure 1C). The dimerization of the aldol adducts, which immediately precipitated from the reaction solution, could shift the reversible reaction to the *syn*-selective aldol adduct. On the other hand, in the case of the Class B compounds (R^2 = Me), the methyl group at the β-position of the enolate hampered the nucleophilic attack on the *Re*-face of the carbonyl carbon (TS-(a)″ in Figure 1C), leading to an attack on the *Si*-face of the carbonyl carbon and affording the *anti*-aldol adduct **4cc** (TS-(b)″ in Figure 1C).

The accessibility of the stereocontrolled aldol adducts from the *C*,*O*-chelated germanium enolates prompted us to diastereoselectively transform the aldol adducts into the triols containing multiple asymmetric centers (see Scheme 4). The

Scheme 4. Diastereocontrolled Transformations of 4bc and 4cc into the Triols 6bc and 6cc[a]



[a]PPTS = pyridinium *p*-toluenesulfonate, DMAP = *N*,*N*-dimethyl-4-aminopyridine.

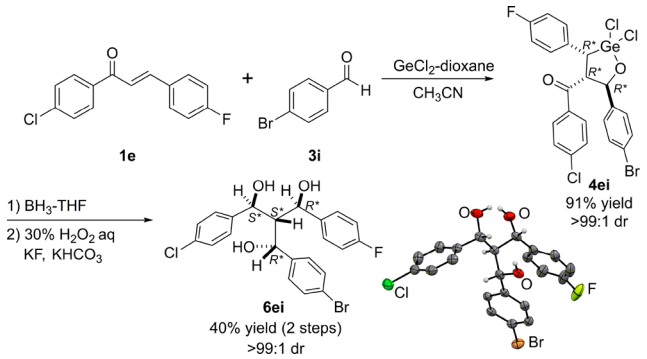
reduction of the carbonyl group was initially performed by a BH_3-THF complex to give the diol **5** bearing a germyl ($-GeH_3$) group. Both the *syn*- and *anti*-aldol adducts of **4bc** and **4cc** were successfully transformed to the diols **5bc** and **5cc** with high diastereoselectivity. The X-ray analyses of **7bc** (Figure S16 in the Supporting Information), which is the acetalized derivative of **5bc**, and **5cc** (Figure S13 in the Supporting Information) demonstrated that the relative configurations of the aldol adducts **4bc** and **4cc** were preserved, and the reduction of the carbonyl groups of **4bc** and **4cc** diastereoselectively proceeded. The relative configurations of **5bc** and **5cc** revealed that the facial selectivity of the carbonyl group was irrelevant to the *syn*-/*anti*-configuration of the aldol adducts of **4bc** and **4cc**. A borane group would approach the carbonyl group from the aldehyde side of the substituent (*Si*-face in Scheme S2 in the Supporting Information). The simultaneous hydrogenation of a germanium moiety led to the corresponding products. The residual germyl groups in **5bc** and **5cc** were hydroxylated under the oxidative conditions[37] to give the diaryl triols **6**. An X-ray analysis of **8bc** (Figure S17 in the Supporting Information),

DOI: 10.1021/acs.orglett.8b01778
Org. Lett. XXXX, XXX, XXX−XXX

which is the 3-fold esterified derivative of **6bc**, and **6cc** (Figure S14 in the Supporting Information) revealed that the oxidation of the Ge−C bonds in **5bc** and **5cc** proceeded with stereoretention. Note that all stereocenters, up to four, were perfectly controlled under our conditions.[38−40]

Our procedure was applicable to the synthesis of the triaryl triol **6ei**, which includes a unique substitution pattern (Scheme 5). The total yield of **6ei** was 36% in three steps, and a single diastereomer was generated, as confirmed by X-ray analysis.

Scheme 5. Diastereocontrolled Synthesis of 6ei



In conclusion, we examined the aldol reaction of the *C,O*-chelated germyl enolates. The high diastereoselectivity was deeply dependent on the substituent patterns at the β-position of α,β-unsaturated ketones. The transformation of the obtained aldol adducts into triols bearing four stereocenters was accomplished with perfect stereoretention. The highly diastereocontrolled triols may potentially be exploited in building blocks for natural products and organometallic ligands. Further studies of other transformations of the Ge−C bond in the aldol adduct are underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01778.

Experimental procedures, characterization of products, and spectroscopic data (PDF)

Accession Codes

CCDC 1837677−1837693 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 e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: a-koni@chem.eng.osaka-u.ac.jp (A. Konishi).
*E-mail: yasuda@chem.eng.osaka-u.ac.jp (M. Yasuda).

ORCID

Akihito Konishi: 0000-0002-3438-786X
Makoto Yasuda: 0000-0002-6618-2893

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI (Grant Nos. JP15H05848 in Middle Molecular Strategy, JP18H01977, and JP18K14201). A.K. would like to thank the Tonen General Sekiyu Research & Development Encouragement Foundation for financial support. We thank Dr. N. Kanehisa (Osaka University) for valuable advice regarding X-ray crystallography. Thanks are due to the Analytical Instrumentation Facility, Graduate School of Engineering, Osaka University.

■ REFERENCES

(1) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.
(2) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917.
(3) Gati, W.; Yamamoto, H. *Acc. Chem. Res.* **2016**, *49*, 1757.
(4) Matsuo, J.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9109.
(5) Beutner, G. L.; Denmark, S. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 9086.
(6) Braun, M. *Modern Enolate Chemistry: From Preparation to Applications in Asymmetric Synthesis*; Wiley−VCH: Weinheim, Germany, 2016.
(7) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 7260.
(8) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(9) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
(10) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, *11*, 1441.
(11) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, *19*, 1455.
(12) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.
(13) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175.
(14) Hashimoto, Y.; Kagoshima, H.; Saigo, K. *Tetrahedron Lett.* **1994**, *35*, 4805.
(15) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691.
(16) Yasuda, M.; Tanaka, S.; Baba, A. *Org. Lett.* **2005**, *7*, 1845.
(17) Tanaka, S.; Yasuda, M.; Baba, A. *Synlett* **2007**, *2007*, 1720.
(18) Tanaka, S.; Tagashira, N.; Chiba, K.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6620.
(19) Tanaka, S.; Tagashira, N.; Chiba, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2008**, *73*, 6312.
(20) Konishi, A.; Minami, Y.; Hosoi, T.; Chiba, K.; Yasuda, M. *Chem.—Eur. J.* **2016**, *22*, 12688.
(21) Mazières, S.; Lavayssière, H.; Dousse, G.; Satgé, J. *Inorg. Chim. Acta* **1996**, *252*, 25.
(22) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046.
(23) Okamoto, K.; Hayashi, T. *Org. Lett.* **2007**, *9*, 5067.
(24) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, *2000*, 1523.
(25) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802.
(26) McClure, C. K.; Jung, K. Y. *J. Org. Chem.* **1991**, *56*, 867.
(27) Mukaiyama, T.; Ichikawa, J.; Toba, M.; Hayashi, M. *Chem. Lett.* **1985**, *14*, 1539.
(28) Iwata, S.; Shoda, S.; Kobayashi, S. *Organometallics* **1995**, *14*, 5533.
(29) Goel, S. C.; Chiang, M. Y.; Buhro, W. E. *J. Am. Chem. Soc.* **1991**, *113*, 7069.
(30) Allan, J. F.; Henderson, K. W.; Kennedy, A. R. *Chem. Commun.* **1999**, *6*, 1325.
(31) Hoch, J. C.; Dobson, C. M.; Karplus, M. *Biochemistry* **1985**, *24*, 3831.
(32) Annunziata, R.; Cinquini, M.; Cozzi, F.; Lombardi Borgia, A. *J. Org. Chem.* **1992**, *57*, 6339.
(33) Mukai, C.; Jong Kim, I.; Hanaoka, M. *Tetrahedron: Asymmetry* **1992**, *3*, 1007.
(34) Adrian, J. C.; Barkin, J. L.; Fox, R. J.; Chick, J. E.; Hunter, A. D.; Nicklow, R. A. *J. Org. Chem.* **2000**, *65*, 6264.

DOI: 10.1021/acs.orglett.8b01778
Org. Lett. XXXX, XXX, XXX−XXX

(35) Mangelinckx, S.; De Sterck, B.; Colpaert, F.; Catak, S.; Jacobs, J.; Rooryck, S.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N. *J. Org. Chem.* **2012**, *77*, 3415.
(36) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174.
(37) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.
(38) Zhang, P.; Han, Z.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 11054.
(39) Abiko, A.; Liu, J.-F.; Buske, D. C.; Moriyama, S.; Masamune, S. *J. Am. Chem. Soc.* **1999**, *121*, 7168.
(40) Mukaiyama, T.; Pudhom, K.; Yamane, K.; Arai, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 413.

DOI: 10.1021/acs.orglett.8b01778
Org. Lett. XXXX, XXX, XXX−XXX