OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Synthesis of Ynolates via Double Deprotonation of Nonbrominated Esters

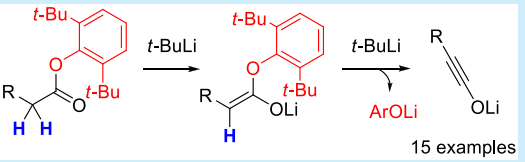
Jun Sun,[†] Toshiya Yoshiiwa,[†] Takayuki Iwata,[‡] and Mitsuru Shindo*[,‡]

[†]Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasuga-koen, Kasuga 816-8580, Japan

[‡]Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga-koen, Kasuga 816-8580, Japan

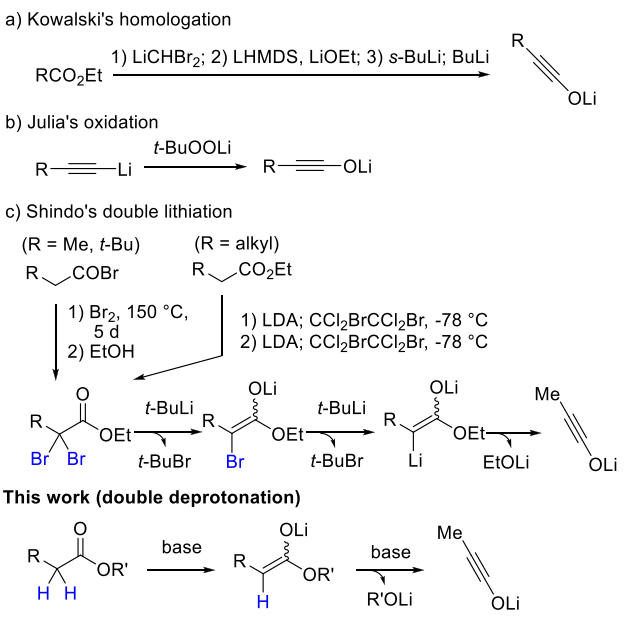
Supporting Information

ABSTRACT: Herein, we report a double deprotonation method used for the preparation of ynolates starting from nonbrominated 2,6-di-*tert*-butylphenyl esters. The current method is superior to the previously described double lithium/halogen exchange approach because easily accessible starting materials are used. This method will be especially useful for preparation of ynolates bearing functional groups in organic synthesis.



Highly reactive, stable, energy-rich reagents or species are very useful and attractive for synthetic organic chemists because they are potential key players for sequential reactions and unprecedented bond formations. Ynolates, which contain an electron-rich triple bond, are highly reactive, long-lived, less-basic, and compact nucleophiles.[1] Among several preparation methods reported so far, Kowalski's homologation[2] and Julia's oxidation[3] have been used (Scheme 1). These methods have some limitations. The former one needs excess amounts of strong bases and several operations, and the latter one requires hazardous anhydrous *tert*-butylhydroperoxide in spite of simple operation. We have developed a convenient and efficient preparation method via cleavage of ester dianions derived from α,α-dibromoesters.[4] Utilizing this method, we reported various new synthetic reactions starting from ynolates, which were used as dianion equivalents.[5] This is a convenient method starting from α,α-dibromoesters, which can be prepared via a double Hell−Volhard−Zelinsky reaction of carboxylic acids or double α-bromination of esters (Scheme 1).[6] However, these methods used to prepare α,α-dibromoesters have some drawbacks, especially on a large scale. The former method is limited to the preparation of only a few substrates, such as methyl or *tert*-butyl substituted ynolates, and require long reaction times under harsh conditions. The latter, which is more general, requires two steps from the nonbrominated ester precursor. Therefore, one may hesitate to prepare functionalized ynolates due to these preparative drawbacks. If more readily available starting materials can be directly converted into ynolates, this carbanion species will be more widely used in organic synthesis.

Scheme 1. Formation of Ynolates



A double elimination reaction is commonly used for the formation of a triple bond. Therefore, double deprotonation of nonbrominated esters to induce a double elimination step is a promising protocol for the generation of ynolates rather than a double lithium−halogen exchange approach. Herein, we report the preparation of ynolates via the double deprotonation of nonhalogenated esters.

In the first deprotonation step, to give an ester enolate, a sterically hindered non-nucleophilic lithium amide base, such as LDA, is not preferable because a secondary amine, such as diisopropylamine, is generated. This amine will be reconverted into the lithium amide base upon treatment with a strong base in the second deprotonation step. To avoid the residual amine species, alkyllithium reagents are the preferred base in the first step to form the ester enolate. However, alkyllithium reagents are also strong nucleophiles and thus undergo an addition reaction to the carbonyl group instead of deprotonation. To

Received: June 16, 2019

DOI: 10.1021/acs.orglett.9b02069
Org. Lett. XXXX, XXX, XXX−XXX

suppress the addition reaction, the ester carbonyl should be sterically blocked.

Therefore, we selected 2,6-disubstituted phenol esters as promising precursors. This class of phenol ester, where BHT esters[7,8] are representative examples, has been known to efficiently block the carbonyl group. The second deprotonation step of the resulting ester enolate requires a stronger base to generate the ynolate via the elimination of lithium phenoxide.

On the basis of this concept, we screened several 2,6-disubstituted phenol ester derivatives of propionic acid (**1**) (Figure 1). The yields of the corresponding ynolates were

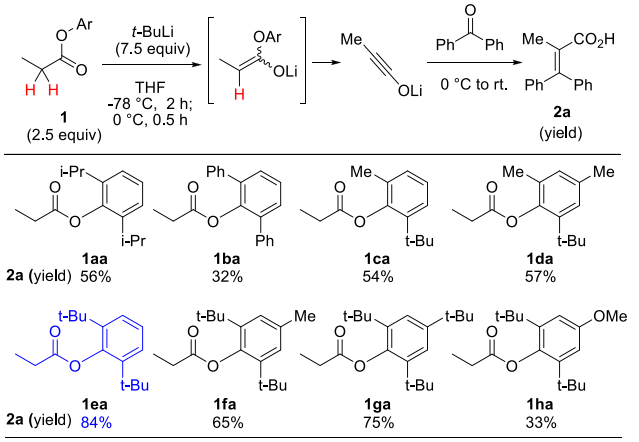
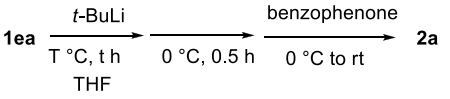


Figure 1. Screening of sterically hindered esters used as an ynolate precursor.

evaluated by those of the olefination product **2a** formed upon reaction with benzophenone, which itself is a high yielding reaction.[9] The initial screening reactions were performed at −78 °C upon treatment with an excess amount (7.5 equiv) of *tert*-butyllithium, allowing the reaction mixture to warm up to 0 °C and the addition of benzophenone. As shown in Figure 1, 2,6-di-*tert*-butylphenol ester **1ea** provided a relatively good yield of the desired olefin product (**2a**), which confirmed the generation of the ynolate using this protocol. Less sterically hindered esters (**1aa**−**1da**) gave lower yields, along with the adducts formed upon the addition reaction between the alkyllithium reagent and ester moiety. The reaction of **1fa** afforded some side products, which were attributed to the generation of the benzyl anion. In the case of **1ha**, the modest yield was attributed to the poor leaving group. Other commercially available alkyllithiums were less efficient than *t*-BuLi (not shown).

Subsequently, we optimized the reaction conditions using **1ea** as the ynolate precursor. To confirm the efficiency of the ynolate generation, an excess amount (3.0 equiv) of the trapping reagent (benzophenone) was reacted with the ynolates generated in the reaction (Table 1). The use of 3 equiv of *tert*-butyllithium, which is 1.5 times the required amount of base, provided the best yield (44%) among entries 1−3 and 9, suggesting that the efficiency of ynolate generation was approximately 40−50%. The use of lower temperatures (T = −20 to −60 °C) in the second step did not lead to an improvement in the reaction yield (entries 4−6). Ether or toluene−TMEDA, which are expected to be more stable in the presence of alkyllithium reagents,[10] were not effective (entries 7 and 8).

Table 1. Optimization of the Ynolate Generation Step

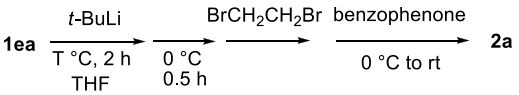


entry	*t*-BuLi (equiv)	T (°C)	t (h)	benzophenone (equiv)	yield (%)[a]
1	2.0	−78	1	3.0	24
2	2.5	−78	1	3.0	31
3	3.0	−78	1	3.0	44
4	3.0	−20	1	3.0	30
5	3.0	−50	1	3.0	44
6	3.0	−60	1	3.0	43
7[b]	3.0	−78	2	3.0	5
8[c]	3.0	−78	2	3.0	25
9	3.5	−78	2	3.0	40

[a]NMR yield based on **1ea**. [b]In ether. [c]In toluene−TMEDA (1:2).

We then tried to determine the actual amount of ester (**1**) required for benzophenone (Table 2). As shown entries 1−3,

Table 2. Optimization of the Ynolate Generation Step



entry	**1ea** (equiv)	*t*-BuLi (equiv)	T (°C)	1,2-dibromoethane (equiv)	yield (%)[a]
1	2.0	6.0	−78	none	68
2	2.5	7.5	−78	none	90 (84)[b]
3	3.0	9.0	−78	none	58
4	2.5	7.5	−78	0.5	99
5	2.5	7.5	−78	1.0	>99 (95)[b]
6	2.5	7.5	−78	2.0	>99
7	2.2	6.6	−78	1.0	>99 (97)[b]
8	2.2	5.5	−78	1.0	85
9	2.2	6.6	−50	1.0	>99
10	2.2	6.6	−30	1.0	58

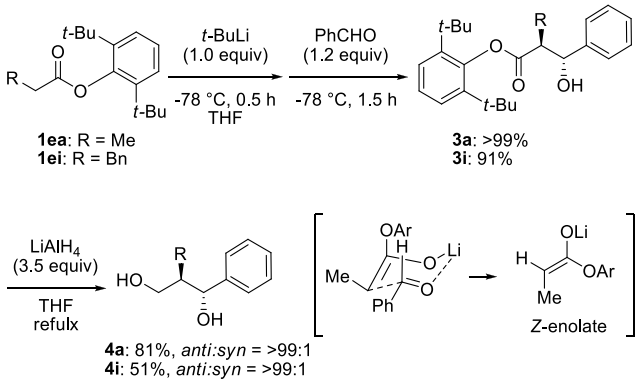
[a]NMR yield based on benzophenone. [b]Isolated yield.

when 2.5 equiv of ester were used, the best yield (84%) was obtained. As the side products included the *tert*-butyl adduct of benzophenone, an excess of *t*-BuLi was found to be present in the solution of the prepared ynolate, although *t*-BuLi should be decomposed by THF at room temperature. Therefore, we decided to add 1,2-dibromoethane to the reaction mixture after generating the ynolate in order to deactivate the excess alkyllithium reagent. As a result, the yield of the product significantly improved (up to >99%) (entries 4−6) upon the addition of 0.5−2.0 equiv of 1,2-dibromoethane. Furthermore, the amount of ester and *t*-BuLi can be reduced to 2.2 and 6.6 equiv, respectively (entry 7). Conducting the deprotonation step at temperatures lower than −50 °C worked well, but higher temperatures did not give better results (entries 9 and 10).

To check that the enolate was formed as an intermediate, the enolates derived from esters **1ea** and **1ei** were trapped with benzaldehyde to provide aldol adducts **3a** and **3i** (Scheme 2). The relative stereochemistry of the major adduct was confirmed to be *anti* upon conversion into diols **4a**[11] and **4i**[12] via $LiAlH_4$ reduction. This suggests the quantitative formation of the (*Z*)-enolate based on the Zimmerman−Traxler six-membered transition model.[13] The (*Z*)-enolate will

DOI: 10.1021/acs.orglett.9b02069
Org. Lett. XXXX, XXX, XXX−XXX

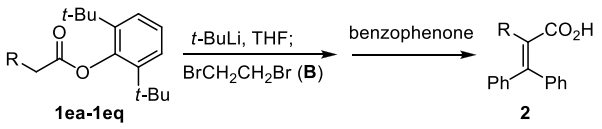
Scheme 2. Aldol Reaction of the Enolates Derived from 2,6-di-*tert*-Butylphenylesters 1ea and 1ei



easily undergo an *anti*-elimination reaction upon treatment with base.

To show the generality of this method for the preparation of ynolates, various kinds of ynolates were prepared from **1ea**–**1eq** as shown in Table 3. Ynolates containing a primary alkyl

Table 3. Synthesis of Various Ynolates



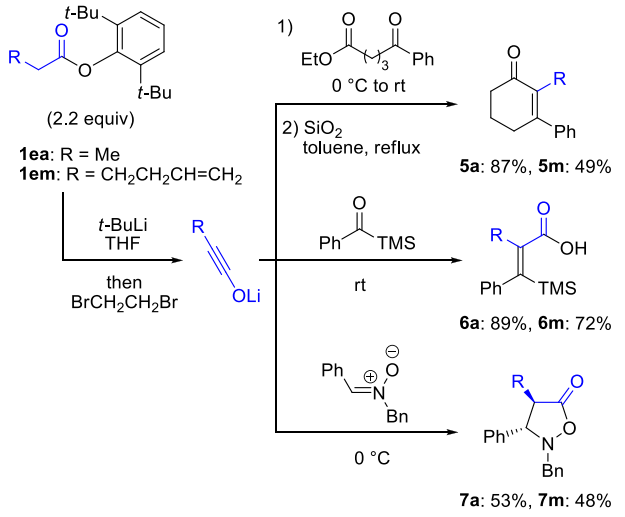
product	R	yield (%) A[b]	B[c]	product	R	yield (%) A[b]	B[c]
2a	Me-	84	97	**2j**	Ph	-[a]	57
2b	Et-	78	80	**2k**	Ph	-[a]	68
2c		44	26	**2l**		-[a]	21
2d		0	0	**2m**		71	75
2e	*n*-Bu-	80	90	**2n**		31	23
2f		-[a]	73	**2o**	TBDPSO(CH2)3	-[a]	67
2g		-[a]	49	**2p**	Ph(CH2)2CH=CH(CH2)3	-[a]	76
2h	Ph-	0	0	**2q**	(CH2)11	-[a]	75
2i	Ph	27	11				

[a]Not examined. [b]Condition A: Ester **1** (2.5 equiv), and *t*-BuLi (7.5 equiv) were used. [c]Condition B: Ester **1** (2.2 equiv), *t*-BuLi (6.6 equiv), and 1,2-dibromoethane (1.0 equiv) were used.

group (R) were generated in good yield, but secondary and tertiary alkyl groups gave poor yields (**2c** and **2d**), which may be attributed to steric hindrance inhibiting the second deprotonation step. Ynolates bearing phenylethyl (**2j**) and phenylpropyl (**2k**) groups can be prepared. We successfully synthesized a variety of functionalized ynolates bearing alkene (**2l** and **2m**), alkyne (**2n**), and siloxy (**2o**) groups. It is noteworthy that the ynolate precursors were easily prepared via reacting the acid chloride with lithium 2,6-di-*tert*-butylphenoxide, and 2,6-di-*tert*-butylphenol was recovered quantitatively after the reaction.

As synthetic applications, a tandem [2 + 2] cycloaddition-Dieckmann condensation initiated by the as-prepared ynolates[5a] was performed to give the desired cyclohex-2-enone products **5a** and **5m** in good yield (Scheme 3).

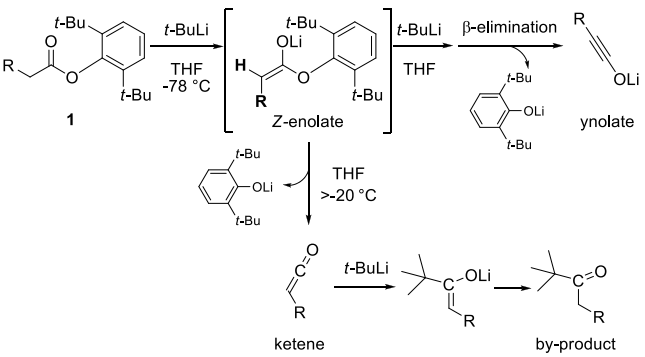
Scheme 3. Synthetic Applications of Ynolates



Torquoselective olefination using acylsilane[5c] also provided vinyl silanes **6a** and **6m** in good yield. Furthermore, 1,3-dipolar cycloaddition of the ynolates[5b] with nitrone afforded *trans*-isoxazolidinones **7a** and **7m** in satisfactory yield.

When compared with the dibromoester method, this protocol afforded several kinds of side products, which were found to be *tert*-butyl ketones formed in 5–10% yield based on the starting ester (Scheme 4). Lithium ester enolates are

Scheme 4. β-Elimination vs Ketene Formation (Side Reaction)



known to decompose via the elimination of alkoxide at higher temperatures (>−20 °C) to give a ketene intermediate,[7] which immediately reacts with a nucleophile. In this protocol, these pathways will be a critical issue to be overcome in future studies.

In conclusion, we have developed a double deprotonation method used for preparation of ynolates starting from simple and readily available nonbrominated esters. The current method is superior to the previously reported double

DOI: 10.1021/acs.orglett.9b02069
Org. Lett. XXXX, XXX, XXX−XXX

lithium−halogen exchange strategy because readily accessible starting materials bearing functional groups are used. It is noteworthy that no lithium alkoxide coexists in the reaction because the leaving group is the less basic lithium 2,6-di-*tert*-butylphenoxide. This method will be especially useful for the preparation of functionalized ynolates in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02069.

Experimental details, and ^{1}H NMR and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shindo@cm.kyushu-u.ac.jp

ORCID

Mitsuru Shindo: 0000-0002-0588-8075

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by JSPS KAKENHI (nos. JP22390002, JP24106731, JP16H01157, JP26293004, JP17K14449, JP18H04418, JP18H04624, and JP18H02557), the Asahi Glass Foundation (T.I.), and the MEXT Project of "Integrated Research Consortium on Chemical Sciences" (T.I.). This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices."

■ REFERENCES

(1) For reviews on ynolates: (a) Shindo, M. Synthetic Uses of Ynolates. *Tetrahedron* **2007**, *63*, 10−36. (b) Shindo, M.; Matsumoto, K. *Recent Advances in the Chemistry of Metal Ynolates*; Patai's Chemistry of Functional Groups; Zabicky, J., Ed.; John Wiley & Sons, Ltd: Chichester, UK, 2016; Vol. 2.

(2) Kowalski, C. J.; Haque, M. S.; Fields, K. W. Ester Homologation via.Alpha.-Bromo.Alpha.-Keto Dianion Rearrangement. *J. Am. Chem. Soc.* **1985**, *107*, 1429−1430.

(3) Julia, M.; Pfeuty Saint-Jalmes, V.; Verpeaux, J.-N. Oxidation of Carbanions with Lithium *tert*-Butyl Peroxide. *Synlett* **1993**, *1993*, 233−234.

(4) (a) Shindo, M.; Sato, Y.; Shishido, K. Novel Synthesis of Ynolates via the Cleavage of Ester Dianions: α-Bromo and α,α-Dibromo Esters as Precursors. *Tetrahedron* **1998**, *54*, 2411−2422. (b) Shindo, M.; Koretsune, R.; Yokota, W.; Itoh, K.; Shishido, K. Practical Synthesis of Ynolate Anions: Naphthalene-Catalyzed Reductive Lithiation of α,α-Dibromo Esters. *Tetrahedron Lett.* **2001**, *42*, 8357−8360.

(5) For selected examples: (a) Shindo, M.; Sato, Y.; Shishido, K. A Novel Tandem [2 + 2] Cycloaddition−Dieckmann Condensation: Facile One-Pot Process to Obtain 2,3-Disubstituted-2-Cycloalkenones from Ynolates. *J. Am. Chem. Soc.* **1999**, *121*, 6507−6508. (b) Shindo, M.; Itoh, K.; Tsuchiya, C.; Shishido, K. Anionic Inverse Electron-Demand 1,3-Dipolar Cycloaddition of Nitrones with Ynolates. Facile Stereoselective Synthesis of 5-Isoxazolidinones Leading to β-Amino Acids. *Org. Lett.* **2002**, *4*, 3119−3121. (c) Shindo, M.; Matsumoto, K.; Mori, S.; Shishido, K. The First General Method for *Z*-Selective Olefination of Acylsilanes via Ynolate Anions Providing Multi-substituted Alkenes. *J. Am. Chem. Soc.* **2002**, *124*, 6840−6841. (d) Umezu, S.; dos Passos Gomes, G.; Yoshinaga, T.; Sakae, M.; Matsumoto, K.; Iwata, T.; Alabugin, I.; Shindo, M. Regioselective One-Pot Synthesis of Triptycenes via Triple-Cycloadditions of Arynes to Ynolates. *Angew. Chem., Int. Ed.* **2017**, *56*, 1298−1302. Recent application using ynolates: (e) Winterton, S. E.; Ready, J. M. [3 + 2]-Cycloadditions of Azomethine Imines and Ynolates. *Org. Lett.* **2016**, *18*, 2608−2611. (f) Wu, J.-L.; Lu, Y.-S.; Tang, B.; Peng, X.-S. Total Syntheses of Shizukaols A and E. *Nat. Commun.* **2018**, *9*, 4040. (g) Nader, M. W.; Oberdorfer, F. [11C]Lithium Trimethylsilyl Ynolate: A New [11C] Precursor and Its Application in Heterocyclic Synthesis. *Tetrahedron Lett.* **2011**, *52*, 2309−2311.

(6) (a) Shindo, M.; Sato, Y.; Koretsune, R.; Yoshikawa, T.; Matsumoto, K.; Itoh, K.; Shishido, K. Synthesis of α,α-Dibromo Esters as Precursors of Ynolates. *Chem. Pharm. Bull.* **2003**, *51*, 477−478. (b) Shindo, M.; Matsumoto, K.; Shishido, K. Generation of Ynolate and Z-Selective Olefination of Acylsilanes: (*Z*)-2-Methyl-3-Trimethylsilyl-2-Butenoic Acid. *Org. Synth.* **2007**, *84*, 11−21.

(7) Häner, R.; Laube, T.; Seebach, D. Regio- and Diastereoselective Preparation of Aldols from α-Branched Ketone Enolates Generated from BHT Ester Enolates and Organolithium Reagents—In Situ Generation and Trapping of Ketenes from Ester Enolates. *J. Am. Chem. Soc.* **1985**, *107*, 5396−5403.

(8) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. Acyclic Stereoselection-13. Aryl Esters: Reagents for Threo-Aldolization. *Tetrahedron* **1981**, *37*, 4087−4095.

(9) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. Stereoselective Olefination of Unfunctionalized Ketones via Ynolates. *J. Org. Chem.* **2004**, *69*, 3912−3916.

(10) (a) Bates, T. F.; Clarke, M. T.; Thomas, R. D. Unusual Stability of an Alkyllithium Dimer. Preparation, Properties, and Decomposition Mechanism of *tert*-Butyllithium Dietherate Dimer. *J. Am. Chem. Soc.* **1988**, *110*, 5109−5112. (b) Stanetty, P.; Mihovilovic, M. D. Half-Lives of Organolithium Reagents in Common Ethereal Solvents. *J. Org. Chem.* **1997**, *62*, 1514−1515.

(11) Pietruszka, J.; Schöne, N. New 1,3-Disubstituted Enantiomerically Pure Allylboronic Esters by Johnson Rearrangement of Boron-Substituted Allyl Alcohols. *Eur. J. Org. Chem.* **2004**, *2004*, 5011−5019.

(12) Faunce, J. A.; Grisso, B. A.; Mackenzie, P. B. Enantioselective Aldol Chemistry via Alkyl Enol Ethers. Scope of the Lewis Acid Catalyzed Condensation of Optically Active Trimethylsilyl and Methyl 2-[(*E*)-1-Alkenyloxy]Ethanoates with Acetals. *J. Am. Chem. Soc.* **1991**, *113*, 3418−3426.

(13) Zimmerman, H. E.; Traxler, M. D. The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.

DOI: 10.1021/acs.orglett.9b02069
Org. Lett. XXXX, XXX, XXX−XXX