Organic LETTERS

Letter

pubs.acs.org/OrgLett

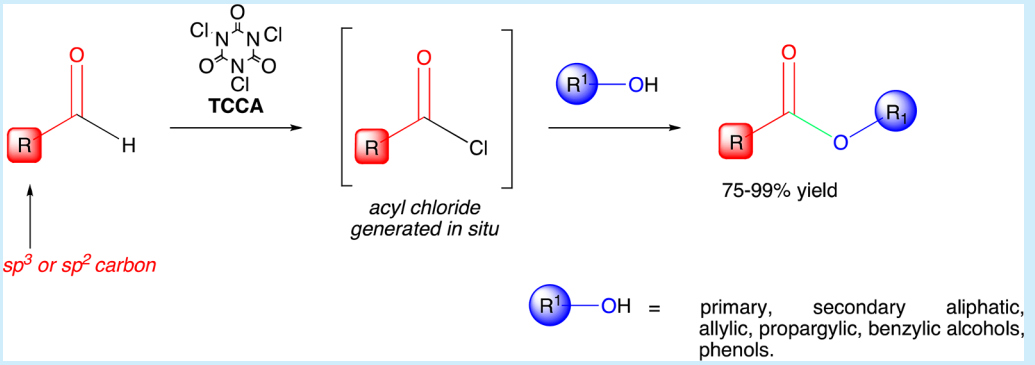
Metal-Free Direct Oxidation of Aldehydes to Esters Using TCCA

Silvia Gaspa,[†] Andrea Porcheddu,[‡] and Lidia De Luca*[,†]

[†]Dipartimento di Chimica e Farmacia, Università degli Studi di Sassari, Via Vienna 2, 07100 Sassari, Italy

[‡]Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, 09042 Monserrato, Italy

Supporting Information



ABSTRACT: Aromatic and aliphatic aldehydes are simply converted into esters by an efficient oxidative esterification carried out under mild conditions. The aldehydes are converted in situ into their corresponding acyl chlorides, which are then reacted with primary and secondary aliphatic, benzylic, allylic, and propargylic alcohols and phenols. A variety of esters are obtained in high yields.

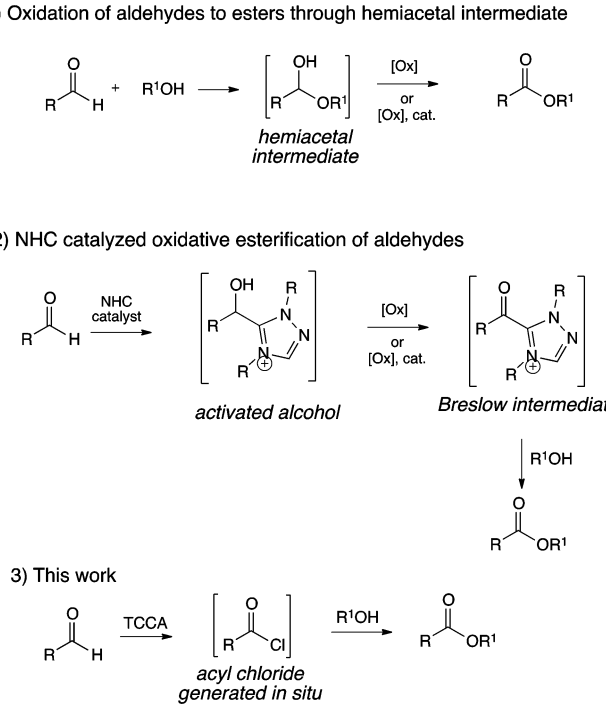
Esters are one of the most significant functional groups encountered in organic synthesis. They are abundant in various natural products, polymers, pharmaceuticals, and synthetic intermediates.[1] Classical methods for ester synthesis are based on nucleophilic substitution of carboxylic acid derivatives (carboxylic halides, anhydrides, and activated esters) with alcohols.[2] An elegant alternative approach is the oxidative esterification of aldehydes with alcohols. Common methods for oxidative esterification of the aldehydes[3] consist of the formation of a hemiacetal intermediate, which is subsequently oxidized to the ester. Over the past few decades, many transition-metal-free direct esterifications of aldehydes through the oxidation of hemiacetals have been reported (Scheme 1, method 1) with several organic and inorganic oxidants such as iodine,[4] oxone,[5] iodine and diacetoxyiodobenzene (PhI-$(OAc)_2$),[6] *N*-iodosuccinimide,[7] sodium hypochlorite,[8] pyridinium hydrobromide perbromide,[9] and hydrogen peroxide.[10] However, most of the reagents outlined above suffer from drawbacks due to steric attributes of the aldehydes and/or the alcohols and instability of the hemiacetal intermediate. Most of the methods provide only methyl esters or work only with more reactive aromatic aldehydes. Oxidative esterifications of aldehydes catalyzed by TM catalysts have also been investigated (Scheme 1, method 1). Effective conversion of aldehydes to esters was achieved by using rhodium-,[11] vanadium-,[12] palladium-,[13] gold-,[14] iron-,[15] and copper-based[16] catalysts. The main restrictions of these procedures are related to the limited substrate scope, the unfavorable stoichiometric ratios of the reagents, and the harsh and sensitive reaction conditions used. In addition, catalyst cost presents an impractical aspect for large-scale use. An interesting alternative approach to the esterification of aldehydes, not involving the formation of hemiacetals, is the N-heterocyclic carbene (NHC) catalyzed oxidative esterification of aldehydes (Scheme 1, method 2). Examples of both metal-free NHC-catalyzed[17] and NHC transition-metal-catalyzed[18] esterifications were reported. However, these methods work only with either aromatic or aliphatic aldehydes, coupled with primary alcohols when used in large excess.

For these reasons, we have investigated the possibility of developing a more general method that is suitable for the conversion of both aliphatic and aromatic aldehydes. We have envisioned use of an alternative method bypassing the hemiacetal formation in order to circumvent the steric drawbacks mentioned previously. We have searched for an alternative to organocatalyzed oxidative esterification of aldehydes such as NHC-, cyanide-,[19] or 3,4,5-trimethylthiazolium-catalyzed[20] esterifications to avoid the use of large excess of oxidants and alcohols. Our goal was to carry out a general method that would be able form acyl chlorides from both aliphatic and aromatic aldehydes, which would then react with all classes of alcohols to subsequently provide the corresponding esters (Scheme 1, method 3). Due to our interest in using TCCA as an oxidant[21] and chlorinating reagent,[22] we checked the viability of this reagent in the conversion of aldehydes to

Received: May 29, 2015

DOI: 10.1021/acs.orglett.5b01579
Org. Lett. XXXX, XXX, XXX−XXX

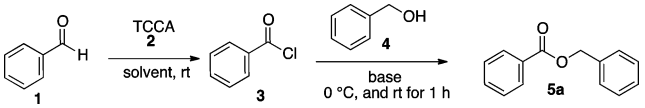
Scheme 1. Strategies To Form Esters from Aldehydes



acyl chloride[23] for ester formation.[24] TCCA is an inexpensive, commercially available sanitizing agent used as a disinfectant and preservative.[25]

We started our investigation by treating benzaldehyde (Table 1, **1**, 3.0 mmol) with TCCA (Table 1, **2**, 4.5 mmol) in dichloromethane (3.25 mL) at room temperature. The reaction was monitored by TLC until the disappearance of aldehyde, and after 5 days, the corresponding benzoyl chloride (Table 1, **3**) was quantitatively formed. This reaction mixture, containing the acyl chloride generated in situ, was treated with benzyl alcohol (Table 1, **4**, 1.0 mmol) and pyridine (3.0 mmol) at 0 °C, and after 1 h at room temperature the desired ester (Table 1, **5a**) was formed in 70% yield (Table 1, entry1).

Table 1. Screening of Reaction Conditions



entry	mmol (**1**)	mmol (TCCA)	base	solvent	yield[a] (%)
1[b]	3.0	4.5	pyridine	DCM	70
2[b]	2.0	4.5	pyridine	DCM	64
3[b]	1.1	4.5	pyridine	DCM	30
4[b]	1.1	1.1	pyridine	DCM	5
5[b]	1.1	1.1	DBU	DCM	
6[b]	1.1	1.1	DABCO	DCM	
7[b]	1.1	1.1	Cs_2CO_3	DCM	
8[b]	1.1	1.1	NEt_3	DCM	35
9[b]	1.1	1.1	NEt_3/DMAP	DCM	90

[a]Yield refers to isolated product. [b]Reaction conditions: benzaldehyde **1**, TCCA **2** in solvent (3.25 mL) at room temperature for 5 days. To this reaction mixture were added benzyl alcohol **4** (1.0 mmol) and a base at 0 °C, and after 1 h at room temperature the desired ester **5a** was obtained.

The method did not appear to be valuable due to the large excess of reagents used. In order to find the optimum reaction conditions, the same reaction was carried out with decreasing amounts of aldehyde. When 2.0 mmol of benzaldehyde was used the product **5a** was obtained in 64% yield (Table 1, entry 2). Further decreasing the amount of aldehyde to 1.1 mmol provided **5a** in 30% yield (Table 1, entry 3). The reduction of the TCCA amount to 1.1 mmol delivered the product **5a** in only trace amounts (Table 1, entry 4). Different bases were also screened, including DBU (Table 1, entry 5, 3.0 mmol), DABCO (Table 1, entry 6, 3.0 mmol), and Cs_2CO_3 (Table 1, entry 7, 3.0 mmol), but they did not furnish the desired product, NEt_3 (Table 1, entry 8, 3.0 mmol) gave the product in 35% yield, whereas NEt_3 with catalytic DMAP (2.0 mmol/10% mol) (Table 1, entry 9) proved to be effective in providing **5a** in 90% yield. A screening of solvents was carried out; acetonitrile, Et_2O, CPME, THF, and acetone were tested, but no benzoyl chloride **3** formation was detected.

After the reaction conditions were optimized, the scope of the reaction was tested (Figure 1). In general, all reactions

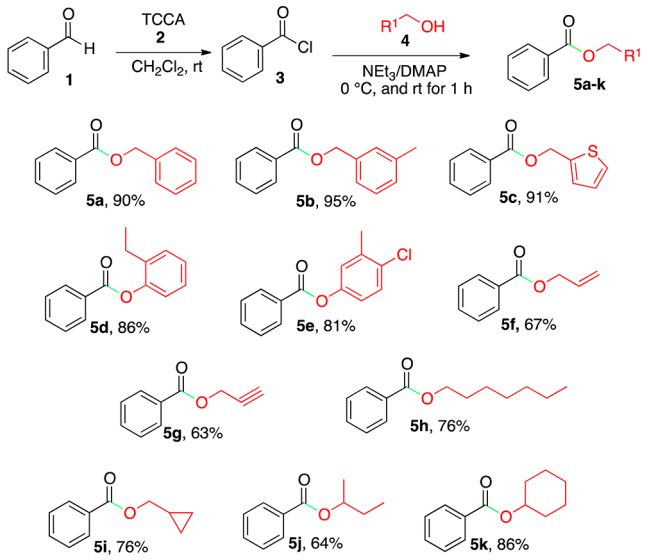


Figure 1. Evaluation of alcohol substrate scope.

proceeded without any significant side products, and the corresponding esters **5a**–**k** were obtained in high yields. Benzylic alcohols are known to readily oxidize to the corresponding aldehydes; however, we did not detect these byproducts (Figure 1, **5a**–**c**). We were delighted to observe that phenols, which are weak nucleophiles, reacted successfully (Figure 1, **5d**,**e**). Allylic and propargylic alcohols were also effectively employed in this oxidative esterification (Figure 1, **5f**–**g**). Primary aliphatic alcohols such as heptanol and cyclopropylmethanol furnished the corresponding esters also in satisfactory yields (Figure 1, **5h**,**i**). Notably, more sterically hindered secondary alcohols, such as *s*-BuOH and cyclohexyl alcohol, were also suitable for delivering the corresponding esters (Figure 1, **5j**,**k**).

We tested the method further with an array of aromatic and aliphatic aldehydes. Neither the electronic nor the steric effects of substituents on the aromatic aldehydes were found to have any influence on the reaction. Both electron-donating (methyl Figure 2, **6a**,**b**; phenyl Figure 2, **6c**) and electron-withdrawing groups (halides Figure 2, **6d**–**e**; carbonyl Figure 2, **6f**; NO_2

DOI: 10.1021/acs.orglett.5b01579
Org. Lett. XXXX, XXX, XXX–XXX

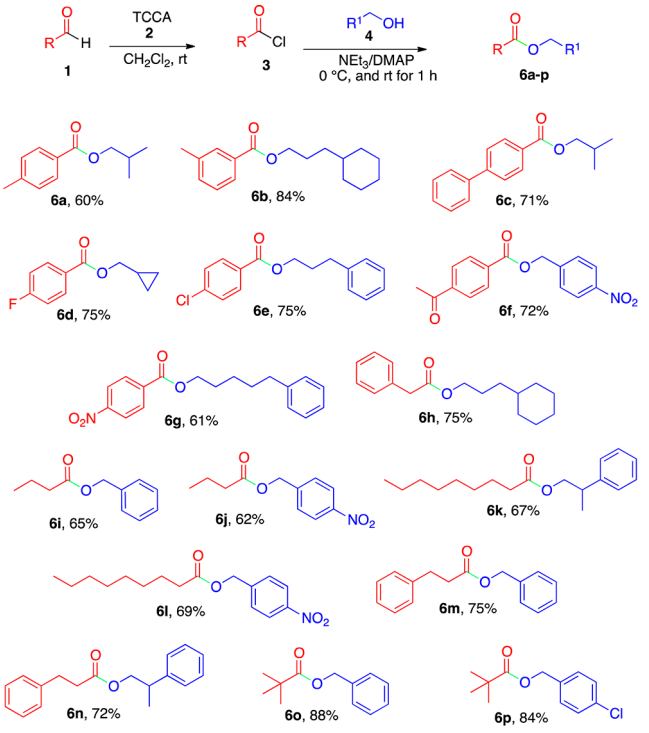


Figure 2. Evaluation of aldehyde substrate scope.

Figure 2, **6g**) were well tolerated. Aliphatic aldehydes, which typically cannot survive under strong oxidative conditions, were converted to the corresponding esters in very good yields. Unactivated aldehydes such as linear and branched aliphatic aldehydes were found to be suitable substrates (Figure 2, **6h–n**). Even very sterically hindered aliphatic aldehydes, such as pivalaldehyde, reacted well (Figure 2, **6o,p**). It is well-known that aliphatic aldehydes in the presence of chlorinating reagents undergo polychlorination at the alkyl chain. This side reaction was not observed under our optimized conditions.[24]

The method was performed with chirally pure alcohols (Figure 3), and the optically pure (*S*)-*sec*-butyl benzoate (Figure 3, **7a**) and (*S*)-2-phenylpropyl nonanoate (Figure 3, **7b**) were recovered without significant racemization of the chiral center.

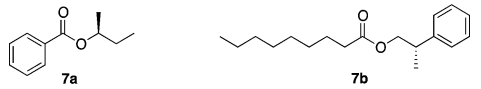
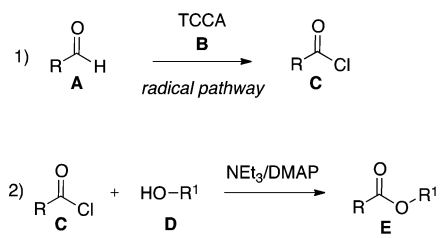


Figure 3. Evaluation of chiral alcohol scope.

A plausible reaction sequence is reported in Scheme 2. Aldehyde **A** reacts with TCCA **B** (Scheme 2, eq 1), probably via a radical pathway on the basis of previous published papers,[24,26] generating acyl chloride **C**. Then acyl chloride **C** reacts with alcohol **D** in the presence of NEt_3/DMAP to give the corresponding ester **E** (Scheme 2, eq 2).

Scheme 2. Proposed Reaction Sequence of Ester Formation



In conclusion, a one-pot protocol to oxidize aldehydes to the esters has been demonstrated. The method was employed to prepare esters directly from aliphatic and aromatic aldehydes with an array of alcohols. Primary and secondary aliphatic, benzylic, allylic, and propargylic alcohols and phenols are tolerated. The method appears to be very general and selective, has an optimal stoichiometric molar ratio of reactants, and makes use of green reagents and mild reaction conditions. Additional studies on the mechanistic details and expansion of the scope of the reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of products, and copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01579.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ldeluca@uniss.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Regione Autonoma della Sardegna (Grant No. F71J1100124002) and Fondazione Banco di Sardegna (Prot. U640.2013/AI.564.MGB, prat.2013.1194)

■ REFERENCES

(1) (a) Ishuhara, K. *Tetrahedron* **2009**, *65*, 1085. (b) Otera, J.; Nishikido, J. *Esterification: Methods, Reactions,and Applications*; Wiley-VCH: Weinheim, 2003.
(2) Otera, J.; Nishikido, J *Esterification: Methods, Reactions,and Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2010.
(3) (a) Ekoue-Kovi, K.; Wolf, C. *Chem. - Eur. J.* **2008**, *14*, 6302. (b) Tang, S.; Yuan, J.; Liu, C.; Lei, A. *Dalton Trans.* **2014**, *43*, 13460.
(4) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915.
(5) (a) Nishihara, A.; Kubota, I. *J. Org. Chem.* **1968**, *33*, 2525. (b) Travis, B. R.; Sivakumar, M.; Hollist, O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.
(6) Karade, N. N.; Budhewar, V. H.; Katkar, A. N.; Tiwari, G. B. *ARKIVOC* **2006**, *2006*, 162.
(7) (a) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213. (b) Minato, D.; Nagasue, Y.; Demizu, Y.; Onomura, O. *Angew. Chem., Int. Ed.* **2008**, *47*, 9458. (c) Newman, M. S.; Kumar, S. *J. Org. Chem.* **1978**, *43*, 370. (d) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087. (e) Chenung, Y.-F. *Tetrahedron Lett.* **1979**, *20*, 3809. (f) Markó, I. E.; Mekhalfia, A.; Ollis, W. D. *Synlett* **1990**, *1990*, 347.
(8) (a) Stevens, R. V.; Chapman, K. T. *Tetrahedron Lett.* **1982**, *23*, 4647. (b) Hiegel, G. A.; Bayne, C. D.; Donde, Y.; Tamashiro, G. S.; Hilberath, L. A. *Synth. Commun.* **1996**, *26*, 2633.
(9) Sayama, S.; Onami, T. *Synlett* **2004**, 2739.
(10) Tank, R.; Pathak, U.; Vimal, M.; Bhattacharyya, S.; Pandey, L. K. *Green Chem.* **2011**, *13*, 3350.
(11) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrahedron* **1981**, *37*, 4313.

DOI: 10.1021/acs.orglett.5b01579
Org. Lett. XXXX, XXX, XXX–XXX

(12) (a) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577. (b) Gopinath, R.; Barkakaty, B.; Talukdar, B.; Patel, B. K. *J. Org. Chem.* **2003**, *68*, 2944. (c) Talukdar, D.; Sharma, K.; Bharadwaj, S. K.; Thakur, A. J. *Synlett* **2013**, *24*, 963.
(13) (a) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052. (b) Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J. *Org. Lett.* **2008**, *10*, 1537. (c) Liu, C.; Zheng, L.; Liu, D.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5662. (d) Taschaen, B. A.; Schmink, J. R.; Molander, G. A. *Org. Lett.* **2013**, *15*, 500.
(14) (a) Marsden, C.; Taarning, E.; Hansen, D.; Johansen, L.; Klitgaard, S. K.; Egeblad, K.; Christensen, C. H. *Green Chem.* **2008**, *10*, 168. (b) Suzuki, K.; Yamaguchi, T.; Matsushita, K.; Iitsuka, C.; Miura, J.; Akaogi, T.; Ishida, H. *ACS Catal.* **2013**, *3*, 1845.
(15) Wu, X.-F.; Darcel, C. *Eur. J. Org. Chem.* **2009**, *2009*, 1144.
(16) (a) Yoo, W.-J.; Li, C.-J. *Tetrahedron Lett.* **2007**, *48*, 1033. (b) Zhu, Y.; Wei, Y. *RSC Adv.* **2013**, *3*, 13668.
(17) (a) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331. (b) De Sarkar, S.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190. (c) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 12374.
(18) (a) Zhang, M.; Zhang, S.; Zhang, G.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2011**, *52*, 2480. (b) Zhao, J.; Much-Lichtenfeld, C.; Studer, A. *Adv. Synth. Catal.* **2013**, *355*, 1098.
(19) Castells, J.; Moreno-Manas, M.; Pujol, F. *Tetrahedron Lett.* **1978**, *19*, 385.
(20) Castells, J.; Llitjos, H.; Moreno-Manas, M. *Tetrahedron Lett.* **1977**, *18*, 205.
(21) De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999.
(22) (a) De Luca, L.; Giacomelli, G. *Synlett* **2004**, 2180. (b) De Luca, L.; Giacomelli, G.; Nieddu, G. *Synlett* **2005**, 223. (c) Jing, Y.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 4932.
(23) Few examples were reported of conversion of aldehydes into the corresponding acyl chloride by the use of disulfur dichloride: (a) Loth, F.; Michaelis, A. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2540. Use of *tert*-pentyl hypochlorite: (b) Musante, C.; Fusco, R. *Gazz. Chim. Ital.* **1936**, *66*, 639. Use of chlorine: Gautier, H. *Ann. Chim. Phys.* **1888**, *14*, 362. Use of TCCA: (c) Komata, T.; Hosoi, K.; Akiba, S. Method for producing 3,3,3-trifluoropropionic acid chloride. EP Patent 2006274A1, Dec 24, 2008. (d) Clamens, S.; Teissier, R. Procédé de préparation d'halogènures d'acide à partir d'aòdéhyde. FR Patent 2633616, Jun 30, 1988.
(24) Few examples were reported of conversion of some aromatic aldehydes into acyl chloride by the use of *tert*-butyl hypochlorite, which was then reacted with large excess of methanol to obtain the corresponding methyl ester. Aromatic aldehydes with electron-withdrawing groups did not react. The reaction of aliphatic aldehydes with *tert*-butyl hypochlorite gave extensive chlorination of the alkyl side chain. The employ of aqueous *tert*-butyl hypochlorite is limited only in cases where the use of an aqueous solution does not interfere with the reaction or the product. The use of aqueous *tert*-butyl hypochlorite has been slowly decreased due to reports of decomposition and instability during transportation and explosion during production: Wilson, S. R.; Tofigh, S.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 1360.
(25) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.
(26) Ginsburg, D. *J. Am. Chem. Soc.* **1951**, *73*, 702.

DOI: 10.1021/acs.orglett.5b01579
Org. Lett. XXXX, XXX, XXX−XXX