Organic LETTERS

Letter

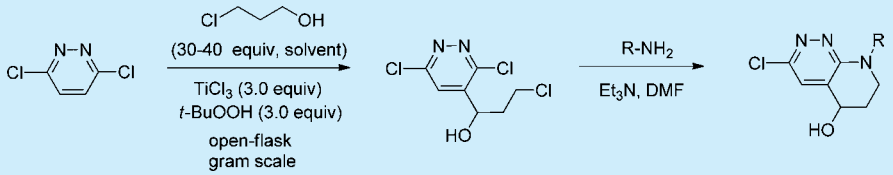
pubs.acs.org/OrgLett

Radical Mediated C−H Functionalization of 3,6-Dichloropyridazine: Efficient Access to Novel Tetrahydropyridopyridazines

Timothy D. Neubert,* Yvonne Schmidt, Erica Conroy, and Dean Stamos

Vertex Pharmaceuticals Incorporated, Department of Chemistry 11010 Torreyana Road, San Diego, California 92121, United States

Supporting Information



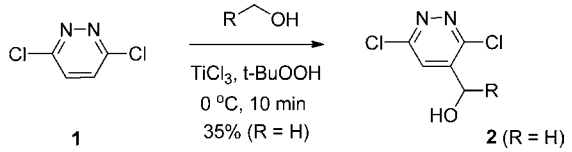
ABSTRACT: A radical mediated C−H functionalization of 3,6-dichloropyridazine using primary alcohols, *t*-BuOOH, and $TiCl_3$ to access alkoxy pyridazines is described. This transformation is conducted open to air and on gram scale. A subsequent cyclization step can then be employed to efficiently access diversely substituted tetrahydropyridopyridazines with multiple functional handles.

C−H functionalization of heterocycles is an effective tool for late-stage structural diversification of bioactive molecules.[1] This method expedites pharmacophore exploration of lead molecules and provides an opportunity (especially for medicinal chemists) to incorporate functional handles at positions that can be difficult to access. Radical based (Minisci-type) approaches have the ability to efficiently incorporate aryl,[2] alkyl,[3] fluoroalkyl,[4] acyl,[5] alcohol,[6] oxetane,[7] azetidines,[7] and silyl[8] functional groups into complex nitrogen containing heterocycles without the need for prefunctionalized starting materials. This method is especially valuable since nitrogen containing heterocycles possess properties (e.g., ease of salt formation and hydrogen bond accepting ability) that make them preferred motifs for drug discovery.[9] However, these innate properties can also make them incompatible partners for other functionalization methods such as those based on transition metals. Thus, the development of new radical based procedures to effectively diversify nitrogen-containing heterocycles remains an attractive goal.

We recognized that the addition of diverse alcohols (via radical intermediates) to pyridazines would be a useful method to access derivatives bearing multiple functional handles. Pyridazines possess varied biological activities including antimicrobial,[10] antihypertensive,[11] anticancer,[12] anti-inflamatory,[13] and antifungal[14] properties, and these intermediates could ultimately lead to novel heterocyclic systems as new scaffolds for drug discovery. Minisci-type additions to pyridazines have been limited to the addition of alkyl groups,[15] aryl groups,[2] fluorinated alkyls,[16] ethers,[7,17] oxetenes,[7] and azetidines.[7] Minisci-type addition of alcohols to complex nitrogen heterocycles has been reported for simple alcohols[6] such as methanol and ethanol as well as more complex alcohols.[18]

In this Letter, we demonstrate the functionalization of pyridazines with functionally diverse alcohols (Scheme 1),

Scheme 1. Hydroxymethyl Radical Addition to 2,5-Dichloropyridazine with Isolated Yield for R = H



1 **2** (R = H)

which represents a significant extension of the scope of these reactions. Our approach rests on the existing precedent that hydroxymethyl radicals, generated using $TiCl_3$ and *t*-BuOOH, readily add into imines.[19] With 2,5-dichloropyridazine as the electrophile under identical conditions, we have been able to successfully access hydroxymethylated pyridazines (Scheme 1).

The transformation in Scheme 1 illustrates the direct access of a hydroxylated building block derived from an inexpensive symmetric pyridazine without the need for protecting groups on the hydroxy group or prefunctionalization. Of note, pyridazine **2** contains three functional handles and should lend itself to efficient diversification.

The functional group tolerability of the alcohol partner was next explored using a range of alcohols (Figure 1). Simple alcohols are readily incorporated in serviceable yields (see **2**−**5**). Secondary alcohols were poor reaction partners. For example, when isopropanol was employed, no detectable yield of pyridazine **14** was obtained. A heteroatom α to the hydroxy-bearing carbon completely shut down radical formation, and none of the corresponding products (e.g., **11** and **12**) were obtained. However, a heteroatom β to the hydroxyl-bearing carbon of the alcohol reacting partner resulted in a productive reaction (for example pyridazines **6** and **7**). Basic

Received: March 24, 2015
Published: April 27, 2015

DOI: 10.1021/acs.orglett.5b00861
Org. Lett. 2015, 17, 2362−2365

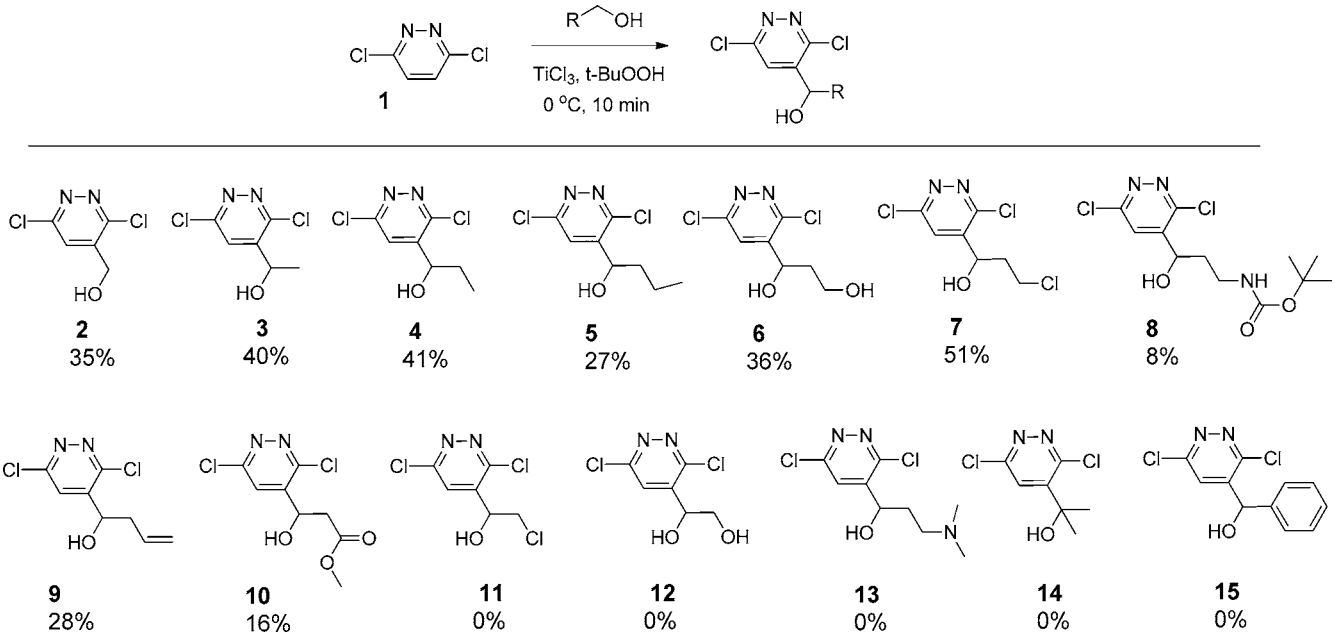


Figure 1. Radical addition of alcohols to 2,5-dichloropyridazine **1** to obtain variously diversified pyridazines **2**–**15** with isolated yield. Conditions: 2,5-dichloropyridazine (1.7 mmol), $TiCl_3$ (5.0 mmol), TBHP (5.0 mmol), alcohol (50 mmol, solvent), 0 °C, 10 min. Reported yields were determined from isolated material. Reactions contained 10–90% unreacted starting material and 30–60% unidentified side products.

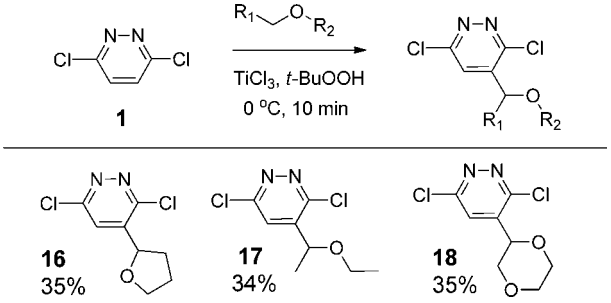
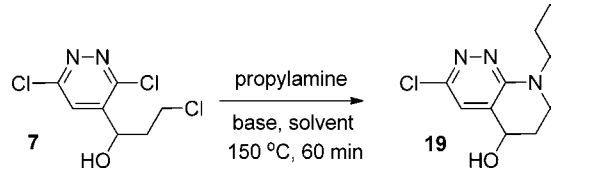


Figure 2. Radical addition of ethers to 2,5-dichloropyridazine **1** to obtain substituted pyridazines **16**–**18** with isolated yields. Conditions: 2,5-dichloropyridazine (1.7 mmol), $TiCl_3$ (5.0 mmol), *t*-BuOOH (5.0 mmol), ether (50 mmol, solvent), 0 °C, 10 min. Reported yields were determined from isolated material. Reactions contained 10–20% unreacted starting material and 40–50% unidentified side products.

amines are incompatible with the desired coupling, and none of the anticipated products (e.g., **13**) were obtained. The incompatibility of tertiary amines is likely due to sequestering of $TiCl_3$, which is required for the radical formation. Functional groups such as the amide of pyridazine **8**, the alkene of compound **9**, and the ester group of pyridazine **10** were all tolerated albeit leading to products in low yield. However, these functional groups illustrate the potential for diverse functional group compatibility.

Multiple attempts were made to improve the low to serviceable yield of this method. Varying reaction temperature, changing equivalents of the $TiCl_3$/*t*-BuOOH radical precursor, or increased reaction time had no dramatic effect on the reported yield. However, the concentration of alcohol did have a substantial effect and running the reaction in neat alcohol using 30–40 equiv proved best. This is indicative of a rapidly produced radical precursor that reacts indiscriminately. Excess alcohol ensures radical formation occurs at the desired site and minimizes undesired radical side reactions. One limitation to excess alcohol is the added expense when using complex or expensive reagents.

Table 1. Optimization of Propylamine Cyclization with Pyridazine 7 To Obtain Tetrahydropyridopyridazine 19[a]



entry	solvent	base	conversion[b]
1	toluene	Et_3N	19%
2	DCE	Et_3N	45%
3	dioxane	Et_3N	67%
4	CH_3CN	Et_3N	72%
5	THF	Et_3N	62%
6	DMF	Et_3N	94%
7	DMF	Hunig's	74%
8	DMF	2,4,6-collidine	8%
9	DMF	DMAP	72%
10	DMF	DBU	0%
11	DMF	K_2CO_3	0%
12	DMF	Cs_2CO_3	0%
13	DMF	DABCO	3%
14	DMF	$NaHCO_3$	80%
15	DMF	no base	67%

[a]Conditions: 3-chloro-1–3,6-dichloropyridazine-4-ylpropan-1-ol (0.1 mmol), propylamine (0.5 mmol), Et_3N (0.3 mmol), solvent (10 vol equiv), 150 °C, 60 min. [b]Reactions were assessed by LC/MS using AUC UV (254 and 220 nM) to determine reported yields.

The addition of ethers to complex nitrogen heterocycles has precedent,[20] and we found that ethers served as effective radical precursors with the $TiCl_3$ method as well (Figure 2). Particularly, symmetrical ethers lead to serviceable yields of the desired functionalized pyridazine adducts (see **16**–**18**).

DOI: 10.1021/acs.orglett.5b00861
Org. Lett. 2015, 17, 2362–2365

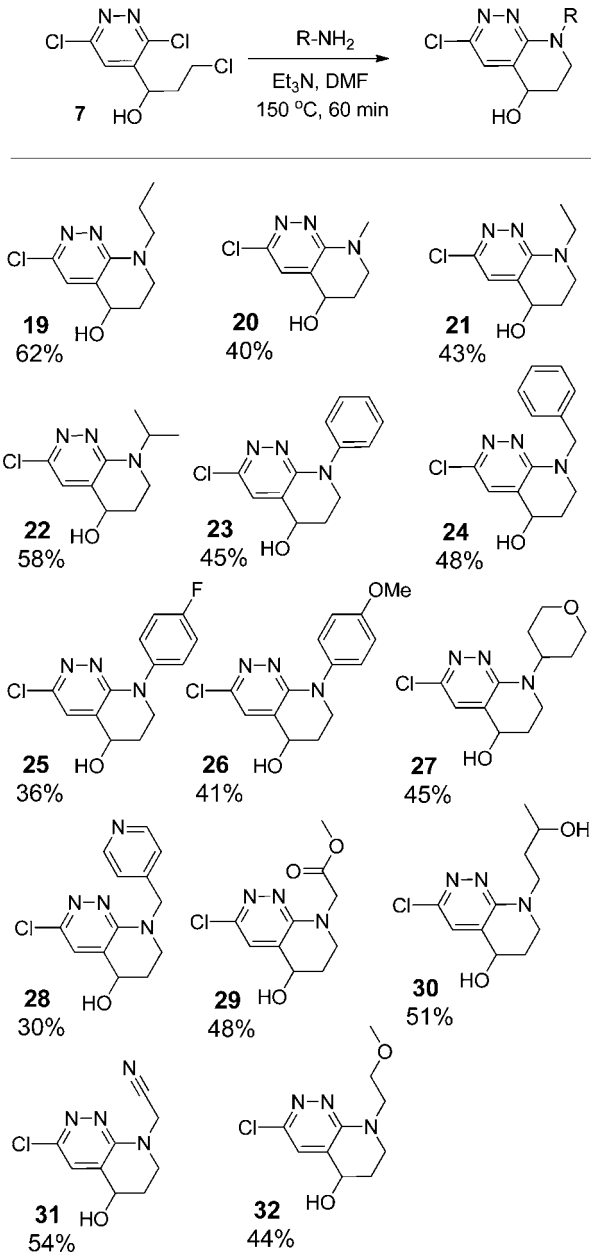


Figure 3. Amines used in the cyclization with pyridazine 7 to access novel tetrahydropyridopyridazines **19**–**32** with isolated yields. Conditions: 3-chloro-1–3,6-dichloropyridazine-4-ylpropan-1-ol (0.61 mmol), amine (3.0 mmol), Et_3N (1.8 mmol), DMF (5 vol equiv), 150 °C, 60 min. Reported yields were determined from isolated material. Reactions contained no unreacted starting material and 38–70% unidentified side products.

These results further illustrate the flexibility of this radical based methodology with respect to the functionalized alkyl coupling partner.

The ability to couple alkyl groups bearing functional handles such as halides (e.g., pyridazine **7**) provided a unique opportunity to access novel pyridazine fused heterocycles. To this end, we explored the coupling/cyclization of pyridazine **7** with propylamine using various bases and solvents (Table 1). With triethylamine as the base (entries 1–6) a survey of solvents revealed that DMF was optimal (entry 6). An investigation of other bases with DMF as the solvent (entries 6–15) led to the conclusion that triethylamine was optimal.

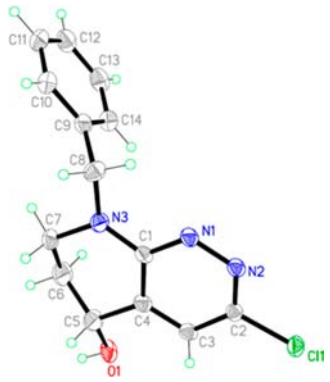


Figure 4. X-ray structural conformation of tetrahydropyridazine **24**.

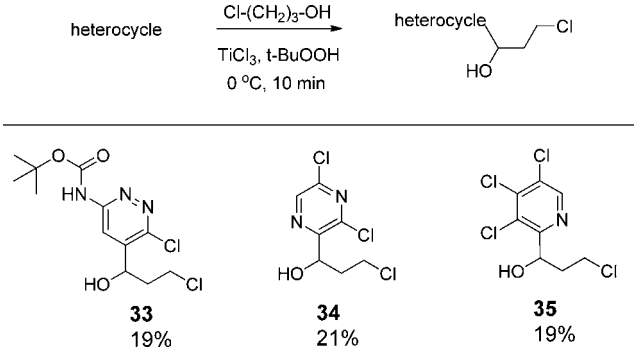


Figure 5. Radical addition of 3-chloropropanol to various heterocycles to obtain compounds **33**–**36** with isolated yields. Conditions: Heterocycle (1.7 mmol), $TiCl_3$ (5.0 mmol), *t*-BuOOH (5.0 mmol), 3-chloropropanol (50 mmol, solvent), 0 °C, 10 min. Reported yields were determined from isolated material. Reactions contained 10–90% unreacted starting material and 30–60% unidentified side products.

We next explored the scope of the amine coupling/annulation of pyridazine **7** using the optimized conditions (Table 1, entry 6). Alkyl and branched amine coupling partners produced serviceable yields of the corresponding products (see **19**–**21**, Figure 3). Variously substituted aryl amines, including those with electron- or electron-withdrawing groups, gave acceptable yields of the bicyclic products (see **23**, **25**, and **26**). The annulation transformations proceed satisfactorily in the presence of basic amines (see **28**) and other functional groups such as esters, alcohols, nitriles, and ethers (see **29**, **30**, **31**, and **32**, respectively). Also, X-ray information structurally confirmed the proposed novel tetrahydropyridazine products (Figure 4), of which only a few examples with different substitution patterns are synthetically known.[21] Overall, the amine coupling/cyclization to form tetrahydropyridopyridazines showed excellent functional group tolerability and illustrates the efficiency with which these novel and complex heterocycles (**19**–**32**) can be assembled in just two steps from pyridazine **1**.

Finally, in order to expand the scope of this radical addition to include other heterocycles and to gain insight into the position selectivity for nonsymmetrical systems, we have explored various pyridazines, pyrazines, and pyridines as coupling partners. Using 3-chloropropanol and *tert*-butyl(6-chloropyridazin-3-yl)carbamate as coupling partners, pyridazine **33** was obtained in 19% yield as the major isomer. The other regioisomer of pyridazine **33** was only detectable in trace amounts and illustrates that regiochemical preferences can exist in nonsymmetrical systems. We next investigated the addition

DOI: 10.1021/acs.orglett.5b00861
Org. Lett. 2015, 17, 2362–2365

of 3-chloropropanol to 2,6-dichloropyrazine and 3,4,5-trichloropyridine in an attempt to obtain compounds **34** and **35** respectively (Figure 5). While these coupling reactions proceeded in low yields, they serve as preliminary results to illustrate that nonpyridazine heterocyclic systems can serve as coupling partners. These latter studies are the subject of future work.

In conclusion, we have demonstrated the direct C−H functionalization of 3,6-dichloropyridazines using diversely substituted alcohols. These reactions, which proceed via radical intermediates, can be conducted open to air, on gram scale with no yield variation. A subsequent coupling and cyclization with amines generates novel fused pyridazines with as many as three functional handles as illustrated by compounds **29** and **30**. This work expands the scope of the Minisci reaction to include products that possess higher polarity and more reactive functionality. The resulting nitrogen containing heterocycles are excellent substrates for further derivatization. Overall, the ability to functionalize nitrogen containing heterocycles by new methods has great utility in drug discovery. Nitrogen containing heterocycles are considered highly privileged and significant structural motifs for pharmaceuticals and represent 59% of all FDA approved small molecule drugs.[9] Future explorations of this direct C−H functionalization should provide access to even more diverse heterocyclic systems.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Timothy_neubert@vrtx.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank Professor Richmond Sarpong, from the Department of Chemistry at the University of California, Berkeley, for useful discussions related to the development of this chemistry.

■ REFERENCES

(1) (a) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122−12134. (b) Duncton, M. A. J. *Med. Chem. Commun.* **2011**, *2*, 1135−1161.

(2) Wang, J.; Wang, S.; Yu, X. Q. *Chem. Commun.* **2012**, *48*, 11769−11771.

(3) (a) Sawada, S.; Okajima, S.; Aiyama, R. *Chem. Pharm. Bull.* **1991**, *39*, 1446−1454. (b) Sawada, S.; Nokata, K.; Furata, T.; Yokokura, T. *Chem. Pharm. Bull.* **1991**, *39*, 2574−2580. (c) Sawada, S.; Matsuoko, S.; Nokata, K.; Nagata, H.; Furuta, T.; Yokokura, T. *Chem. Pharm. Bull.* **1991**, *39*, 3183−3188.

(4) Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949−3952.

(5) Heinisch, G.; Waglechner, R. *J. Heterocycl. Chem.* **1984**, *21*, 1727−1731.

(6) (a) Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* **1985**, *41*, 4157−4170. (b) Katz, R. B.; Mistry, J.; Mitchell, M. B. *Synth. Commun.* **1989**, *19*, 317−326. (c) Correia, C. A.; Yang, L.; Li, C. *Org. Lett.* **2011**, *13*, 4581−4583. (d) Sugimori, A.; Mori, S.; Maeda, K.; Nishijima, M. *Chem. Lett.* **1984**, 769−772.

(7) Duncton, M. A. J.; Estiarte, M. A.; Kelly, J. *J. Org. Chem.* **2009**, *74*, 6354−6357.

(8) Du, W.; Kaskar, B.; Blumbergs, P.; Curran, D. P. *Bioorg. Med. Chem.* **2003**, *11*, 451−458.

(9) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(10) Hassan, M.; Rostom, S. A. F.; Basaif, S. A.; Makki, M. S. T.; Khan, K. A. *Arch. Pharm. Sci. Res.* **2013**, *36*, 1354−1368.

(11) Gil-Longo, J.; Laguna, M.; Verde, I.; Castro, M.; Orallo, F.; Fontenla, J.; Calleja, J.; Ravina, E.; Teran, C. *J. Pharm. Sci.* **1993**, *82*, 286−290.

(12) Bongartz, J.; Stokbroekx, R.; Van der Aa, M.; Luyckx, M.; Willems, M.; Ceusters, M.; Meerpoel, L.; Smets, G.; Jansen, T.; Wouters, W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 589−591.

(13) Mirzoeva, S.; Sawkar, Anu; Zasadzki, M.; Guo, L.; Velentza, A. V.; Dunlap, V.; Bourguignon, J.; Ramstrom, H.; Haiech, J.; Van Eldik, L. J. *J. Med. Chem.* **2002**, *45*, 563−566.

(14) Asif, M. *Curr. Med. Chem.* **2012**, *19*, 2984−2991.

(15) Cowden, C. J. *Org. Lett.* **2003**, *5*, 4497−4499.

(16) Baran, P.; Zhou, Q.; Ruffoni, A.; Gianatassio, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949−3952.

(17) Baran, P.; Fujiwara, Y.; Janice, A.; Dixon, J. A. *Nature* **2012**, *492*, 95−100.

(18) (a) Sugimoto, T.; Murata, S.; Matsuura, S.; Pfleiderer, W. *Tetrahedron Lett.* **1986**, *27*, 4179−4180. (b) Tripathi, A. K.; Mukherjee, D.; Koul, S.; Taneja, S. C. *ARIVOC* **2009**, *xiii*, 241−251.

(19) (a) Rossi, B.; Pastori, N.; Clerici, A.; Punta, C. *Tetrahedron* **2012**, *68*, 10151−10156. (b) Ghilardi, A.; Pastori, N.; Clerici, A.; Punta, C.; Porta, O. *Org. Lett.* **2008**, *10*, 5063−5066.

(20) (a) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G. *J. Org. Chem.* **1986**, *51*, 4411−4416. (b) MacMillan, D. W. C.; Jin, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1−6.

(21) Seitz, G.; L. Görge, L. *Chim. Ztg.* **1984**, *108*, 331−332.

DOI: 10.1021/acs.orglett.5b00861
Org. Lett. 2015, 17, 2362−2365