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Synthesis of Exclusively 4-Substituted β-Lactams through the Kinugasa Reaction Utilizing Calcium Carbide

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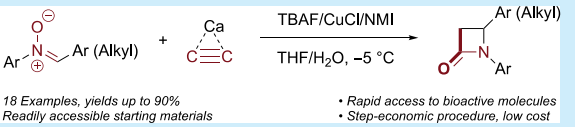
Supporting Information

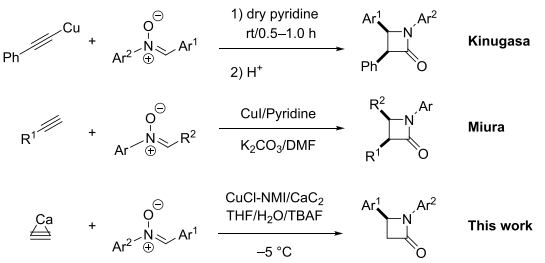
ABSTRACT: A new Kinugasa reaction protocol has been elaborated for the one-pot synthesis of 4-substituted β-lactams utilizing calcium carbide and nitrone derivatives. Calcium carbide is thereby activated by TBAF·3H_2O in the presence of CuCl/NMI. The ease of synthesis and use of inexpensive chemicals provides rapid access of practical quantities of β-lactams exclusively substituted at position 4.



The synthesis of four-membered cyclic amides known as β-lactams has been an active area of research since the discovery of penicillin in 1928.[1] Penicillins are among the most effective antibacterial agents and are considered a great advance in chemotherapy.[2] Since the β-lactam ring is essential for antibiotic activity, a great deal of effort has been devoted to the development of new strategies for the synthesis of novel analogues with improved properties for possible therapeutic use. Novel β-lactam-based antibiotics are also in demand to circumvent bacterial resistance mechanisms.[3] In this context, it was also shown that monocyclic β-lactams possess a wide range of biological properties other than the common antibacterial features of the original penicillins. Therefore, considerable effort has been exerted in the development of efficient synthetic methods for the preparation of functionalized β-lactams. Despite significant advances in the synthesis of fully substituted β-lactams, there have only been a few reports on the synthesis of derivatives exclusively substituted at the 4-position.[4] This subunit is present in numerous synthetic products possessing important biological activities.[5] Furthermore, they serve as precursors for the synthesis of 3-functionalized β-lactams[6] or compounds that could be exploited for the preparation of complex heterocycles.[7] 3-Unsubstituted β-lactams are generally prepared by the Staudinger reaction,[8] Mitsunobu cyclization,[9] Reformatsky reaction,[10] and the decarboxylation of 3-azetidinecarboxylic acids.[11]

Among the different synthetic methods, the Kinugasa reaction is an attractive procedure owing to its simplicity and prospects for large-scale synthesis. In their original brief paper, Kinugasa and Hashimoto reported that the reaction of copper(I) phenylacetylide with nitrone derivatives in dry pyridine readily delivers the corresponding *cis* or *trans* β-lactams in good yields (Scheme 1).[12] Since then, numerous reports have been published on the development and mechanism of the Kinugasa reaction.[13] Early on, Miura and co-workers reported a substantial modification to the original Kinugasa reaction,[14] namely, that the copper acetylide can be generated in situ by deprotonation of a terminal alkyne with stoichiometric or catalytic amounts of copper(I) iodide in the presence of potassium carbonate. Later on, an asymmetric version was

Scheme 1. Progress on the Kinugasa Reaction



developed.[15] A convenient approach using unsubstituted acetylene preferably generated from very cheap CaC_2 remains unexplored in the Kinugasa reaction. CaC_2 offers many advantages over acetylene gas, notably that it is cheap, convenient to handle, and much safer.[16] Over the recent years, CaC_2 has been successfully utilized for a variety of synthetically useful organic transformations, such as Sonogashira cross coupling,[17] ethynylation of aldehydes and ketones,[18] vinylation of alcohols and phenols,[19] and synthesis of enaminones,[20] 2-methylbenzofurans,[21] pyrazoles,[22] and isoxazoles.[23]

Our recent findings on the efficient activation of CaC_2 encouraged us to exploit CaC_2 as the acetylene source to develop a modified Kinugasa reaction for the synthesis of 4-substituted β-lactams via in situ formation of an acetylide "ate" complex.[18b] We began our investigations using diphenylnitrone (**1a**), CaC_2, and copper iodide in DMSO at rt, i.e., conditions derived from our previously established protocol for ethynylation of carbonyl compounds. However, the reaction was not selective, and only low yields of product were obtained (Table 1, entry 1). Lactam (**2a**) was not observed in the absence of the copper catalyst (Table 1, entry 2). Addition of pyridine as a cosolvent improved both the yield and selectivity (Table 1, entries 3 and 4). The yield dropped dramatically when the reaction was performed in the absence of TBAF (Table 1, entry 5). NMI as solvent proved superior to pyridine (Table 1, entry

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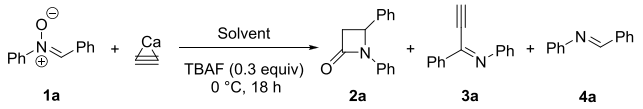
Table 1. Initial Optimization of the Kinugasa Reaction Using Calcium Carbide as the Acetylide Source[a]



1a 2a 3a 4a

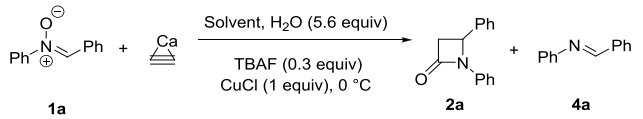
				yield (%)		
no.	solvent	H_2O (equiv)	[Cu] (equiv)	2a	3a	4a
1[b]	DMSO	4.2	CuI (2)	10	8	61
2[b]	DMSO	4.2				16
3[c]	Py/DMSO[d]	4.2	CuI (2)	14		75
4	Py	4.2	CuI (2)	44		39
5[e]	Py	4.2	CuI (2)	11		81
6	Py	5.6	CuI (2)	48		41
7	NMI	5.6	CuI (2)	54		35
8	NMI	5.6	CuCl (2)	61		33
9[f]	NMI	5.6	CuCl (2)	63		31
10	NMI	5.6	CuCl (1)	60		29
11	Et_3N	5.6	CuCl (1)	5[g]	*h*	35
12	TMEDA	5.6	CuCl (1)	10[g]	*h*	85

[a]Reaction conditions: solvent (3 mL), water, TBAF, and copper salt were mixed together, and then calcium carbide (2.5 equiv) and nitrone **1a** (1 equiv) were added under N_2 atmosphere. [b]Reaction at rt. [c]Py = pyridine. [d]1:2 ratio of Py to DMSO. [e]Reaction in the absence of TBAF·$3H_2O$. [f]With 1.3 equiv of CaC_2. [g]Yield determined by NMR. [h]Not determined.

7). Replacement of CuI with CuCl slightly increased the yield; however, further variations did not significantly alter the results (Table 1, entries 8–10). Other chelating solvents such as trimethylamine and TMEDA resulted in only low product yields (Table 1, entries 11 and 12).

In order to reduce the cost and the amounts of waste generated, we aimed at using common organic solvents. DME turned out to be a promising solvent, and NMI was the best ligand among DMAP, 2-methylthiazole, and imidazole under these conditions (Table 2). Increasing the amounts of NMI

Table 2. Effect of Ligand and Solvent on the Kinugasa Reaction Using Calcium Carbide[a]



1a 2a 4a

			yield[b] (%)	
no.	ligand (equiv)	solvent	2a	4a
1	DMAP (2)	DMSO/DMF[c]	9	12
2	DMAP (2)	1,3-dioxalane	20	40
3	DMAP (2)	DME[d]	21	26
4	DMAP (6)	DME	12	31
5	2-methylthiazole (2)	DME	2	17
6	imidazole (2)	DME	26	39
7	NMI (2)	DME	34	43
8[e]	NMI (2)	DME	10	54
9	NMI (6)	DME	41	30

[a]Reaction conditions: Solvent (3 mL), water, TBAF, and copper salt were mixed together, then calcium carbide (1.3 equiv) and nitrone **1a** (1 equiv) were added under N_2 atmosphere. [b]NMR yield. [c]2:1 ratio of DMSO to DMF. [d]1,2-Dimethoxyethane. [e]Reaction in the absence of TBAF.

from 2 to 6 equiv marginally enhanced the yield (Table 2, entries 7 and 9). Similar to the results obtained in pyridine (Table 1, entry 5), the yield of **2a** drastically dropped in the absence of TBAF, emphasizing that TBAF is crucial in this reaction (Table 2, entry 8). It has been reported that copper–imidazole complexes are highly prone to produce peroxo copper complexes upon exposure to air.[24] To probe the effect of air in our reaction, the preparation of **2a** was carried out under argon-degassed conditions. The result was satisfactory and the yield of desired product increased by 11% (Table S1, entry 1); therefore, oxygen-free conditions were employed henceforth. Both purging and freeze–pump–thaw techniques afforded the same results, and no difference was observed between Ar and nitrogen for degasification (Table S1, entries 1 and 2). The yield significantly decreased when TBAF was substituted with TBABr (Table S1, entry 3), supporting our initial hypothesis of F^- activation leading to an "ate complex". The effect of DMAP under oxygen-free conditions was re-examined; however, only low yield was obtained. The use of 6 equiv of NMI was found to be the best (Table S1, entries 5–7). Other solvents such as MeCN, Et_2O, EtOAc, and CH_2Cl_2 were less effective, and only THF gave rather similar results (Table S1, entries 10–13 and 19). We varied the temperature and the amounts of calcium carbide, water, and copper chloride and finally determined that THF is the solvent of choice based on efficiency and cost.

The preoptimized results compelled us to exploit the design of experiments (DoE) for further optimization. DoE is an effective statistical tool for reaction optimization and provides new insight into the interactions of various factors and their significance in a reaction.[25] NMI, H_2O, CaC_2, temperature, CuCl, and TBAF were selected as the main variables, and the ranges were defined on the basis of the results of our initial studies (NMI, 3–9 equiv; H_2O, 4.5–5.6 equiv; CaC_2, 1–2.4 equiv; temperature, −20 to +20 °C; CuCl, 0.26–1 equiv; TBAF, 0.1–0.5 equiv). The designed experiments used a custom approach utilizing JMP software (Table S2). In addition, to gain a better estimate of the model, some validation and follow-up experiments were executed. The predicted plot for the actual vs predicted yield demonstrated a good correlation with $R^2 = 0.98$ (Figure S1). Figure S2 shows the influence of the individual factors NMI, H_2O, CaC_2, temperature, CuCl, and TBAF based on desirability to afford a yield of 87% of lactam product. According to the resulting model, the optimal values for examined parameters are as follows: NMI, 3 equiv; H_2O, 5.6 equiv; CaC_2, 2.4 equiv; temperature, −5 °C; CuCl, 0.76 equiv; TBAF, 0.34 equiv. The optimized values were then applied to the preparation of various functionalized nitrones (Scheme 2). Parent nitrone **2a** afforded the corresponding 2-azetidinone in good yield (Scheme 2, entry 1). The outcome of the reaction was strongly influenced by the nature of substituents on the *N*-phenyl ring. Substrates that possess an electron-withdrawing aromatic ring proceeded more efficiently than those with electron-donating groups. For instance, *N*-(4-carbomethoxyphenyl)-*α*-phenylnitrone afforded the corresponding *β*-lactam in 85% yield, whereas only a moderate yield was obtained when the methoxy substituent was replaced with a methyl ester; the latter preferably gave the imine side product (Scheme 2, entries **2b** and **2d**).

Substituents on the *N*-phenyl ring exert a larger influence on the reaction yield than the 4-substituents (Scheme 2, entries **2e** and **2f**), as evident from *C*-phenyl rings bearing electron-deficient and -donating groups (Scheme 2, entries **2g–2i**). This is in line with the observed selectivities of the addition of

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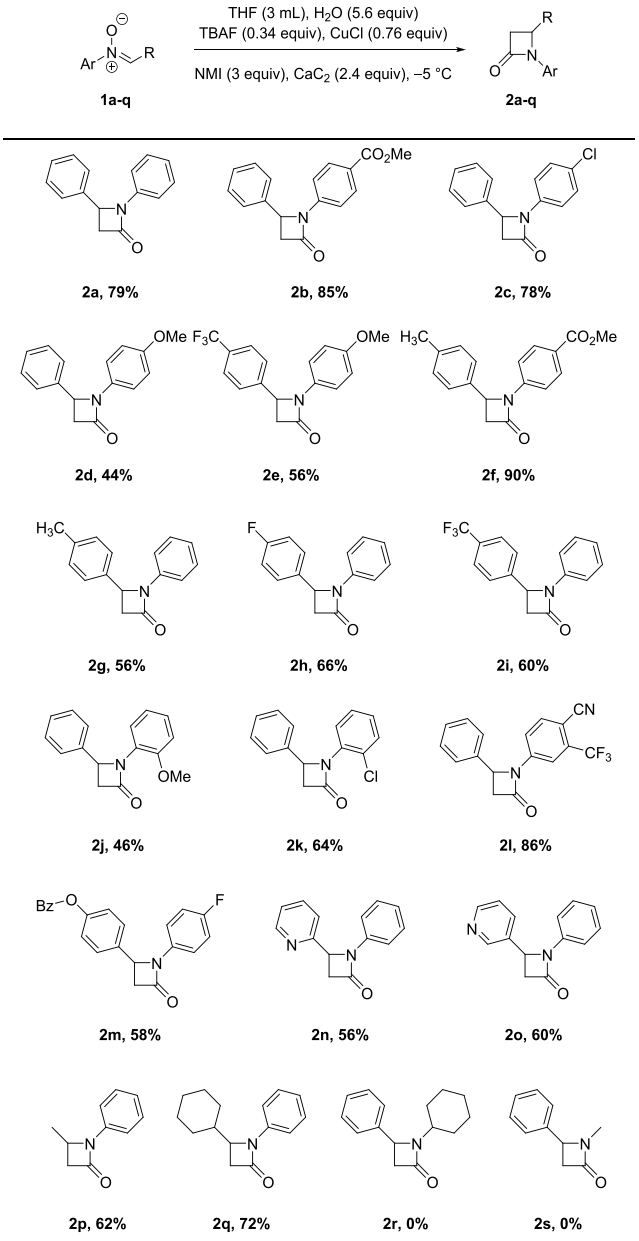
Scheme 2. Kinugasa-Based β-Lactam Synthesis Using Calcium Carbide as Acetylide Source[a]

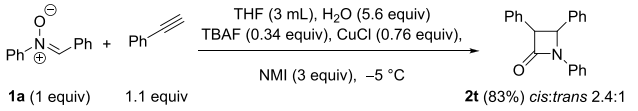


[a]Yields of isolated products.

Reformatsky reagents to aldimines that can be controlled by electron-withdrawing substituents at the imine.[26] To further illustrate the versatility of the method, lactam **2l** was synthesized in 86% yield, proving the efficiency and cost effectiveness of the present protocol as well as its step-economy over previous method (two steps and 74% overall yield).[27] Furthermore, lactam **2m**, an intermediate for the synthesis of *rac*-ezetimibe, was conveniently synthesized in good yield. Similar results were obtained using nitrones bearing a 2- or 3-pyridyl group, where internal chelation is conceivable for the former (Scheme 2, entries **2n** and **2o**).[28] Comparable results were obtained for *C*-alkylated nitrones, whereas *N*-alkylated derivatives gave no product under these reaction conditions (Scheme 2, entries **2p**–**2s**).

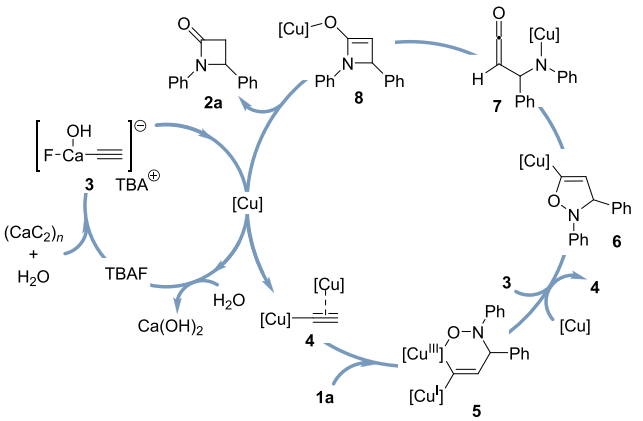
For the sake of completeness, phenylacetylene was used as a substrate under our standard reaction conditions to demonstrate that 3,4-disubstituted products are in principle also accessible when using a substituted acetylene derivative. Pleasingly, we were able to isolate the desired lactam **2t** in 83% yield with 2.4:1 diastereoselectivity with a preference for the *cis* product as is typical for the Kinugasa reaction (Scheme 3).

Scheme 3. Preparation of a Fully Substituted β-Lactam Using Modified Kinugasa Reaction Conditions



The main challenge for the Kinugasa reaction lies in avoiding the formation of the imine. A recently revised mechanism detailed by kinetic analysis for the Cu(I)-catalyzed Kinugasa reaction suggests that the key step involves a retro-cycloaddition, giving rise to the corresponding imine and ketene.[29] This mechanism is consistent for the use of substituted acetylenes, but it is less clear in the case of unsubstituted acetylene where the ketene formed in situ is prone to undergo dimerization.[30] Moreover, substituted ketenes—generated from the corresponding acid chlorides—produce lactams upon treatment with imines (Staudinger reaction), while acetyl chloride affords oxazinones instead. Chuche and Maujean reasoned that the in situ generation of diketene is responsible for the formation of oxazinones.[31] Inspection of Scheme 2 reveals that electron-withdrawing groups on the *N*-phenyl ring favor the formation of β-lactams. This is consistent with the nucleophilic addition of the amine (Umpolung reaction) to the ketene formed in the reaction (nucleophile catalyzed Staudinger reaction);[32] however, this hypothesis was rejected owing to the low efficiency of DMAP vs NMI (for example, the *N* parameter for DMAP in MeCN is much higher than NMI according to Mayr's database of reactivity parameters).[33] The plausible mechanistic proposal in Scheme 4 takes into account our already described activation of calcium carbide with fluoride. The reaction of water with calcium carbide gives ethynylcalcium hydroxide, which is activated with TBAF·3H_2O to deliver a soluble ate complex **3**. Complex **3** then undergoes cation exchange to give copper acetylide **4** that readily performs a [3 + 2] cycloaddition with the nitrone to afford intermediate **5**.

Scheme 4. Suggested Mechanism of the Fluoride/Copper-Catalyzed Kinugasa Reaction



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Subsequent C−O bond-forming reductive elimination of **5** affords the cycloaddition product **6**, which readily decomposes into intermediate ketene **7** where electron-deficient groups on the *N*-phenyl ring stabilize the negatively charged nitrogen atom and prevent decomposition to imine byproduct.[34] An intramolecular cyclization of ketene **7** produces enolate **8**,[35] which is readily protonated to release the desired *β*-lactam.

In conclusion, we developed a modified Kinugasa reaction for the straightforward preparation of exclusively 4-substituted *β*-lactams using calcium carbide as the acetylene source. The process is convenient and operates under mild conditions using commercial starting materials that provide a broad reaction scope. The unsubstituted 3-position opens prospects for lactam bioconjugation and asymmetric functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01192.

Experimental procedures, characterization data, and spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pitts, C. R.; Lectka, T. *Chem. Rev.* **2014**, *114*, 7930.

(2) (a) Kamath, A.; Ojima, I. *Tetrahedron* **2012**, *68*, 10640. (b) Page, M. I. *The chemistry of β-lactams*; Springer Science & Business Media, 2012.

(3) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395.

(4) (a) Palomo, C.; Cossío, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1991**, *32*, 3105. (b) Goyal, S.; Pal, A.; Chouhan, M.; Gangar, M.; Sarak, S.; Nair, V. A. *Tetrahedron Lett.* **2017**, *58*, 346. (c) Banik, B. K.; Ghatak, A.; Becker, F. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2179. (d) Bose, A. K.; Gupta, K.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 86. (e) Deketelaere, S.; Van Nguyen, T.; Stevens, C. V.; D'hooghe, M. *ChemistryOpen* **2017**, *6*, 301.

(5) Carr, M.; Greene, L. M.; Knox, A. J. S.; Lloyd, D. G.; Zisterer, D. M.; Meegan, M. J. *Eur. J. Med. Chem.* **2010**, *45*, 5752.

(6) (a) Kühlein, K.; Jensen, H. *Liebigs Ann.* **1974**, *1974*, 369. (b) Otto, H. H.; Mayrhofer, R.; Bergmann, H. *J. Liebigs Ann.* **1983**, *1983*, 1152. (c) Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 27. (d) Nakayama, K.; Kawato, H. C.; Inagaki, H.; Nakajima, R.; Kitamura, A.; Someya, K.; Ohta, T. *Org. Lett.* **2000**, *2*, 977. (e) Brain, C. T.; Chen, A.; Nelson, A.; Tanikkul, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 1247. (f) Kim, B. J.; Park, Y. S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1705. (g) Fujisawa, T.; Hayakawa, R.; Shimizu, M. *Chem. Lett.* **1995**, *24*, 1013. (h) O'Boyle, N. M.; Pollock, J. K.; Carr, M.; Knox, A. J. S.; Nathwani, S. M.; Wang, S.; Caboni, L.; Zisterer, D. M.; Meegan, M. J. *J. Med. Chem.* **2014**, *57*, 9370.

(7) (a) Shibuya, M.; Jinbo, Y.; Kubota, S. *Chem. Pharm. Bull.* **1984**, *32*, 1303. (b) Bisacchi, G. S.; Slusarchyk, W. A.; Bolton, S. A.; Hartl, K. S.; Jacobs, G.; Mathur, A.; Meng, W.; Ogletree, M. L.; Pi, Z.; Sutton, J. C.; Treuner, U.; Zahler, R.; Zhao, G.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2227.

(8) Kanwar, S.; Sharma, S. D. *J. Heterocycl. Chem.* **2007**, *44*, 1121.

(9) Kern, N.; Hoffmann, M.; Weibel, J.-M.; Pale, P.; Blanc, A. *Tetrahedron* **2014**, *70*, 5519.

(10) Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1989**, *54*, 5736.

(11) Basak, A.; Mahato, T.; Bhattacharya, G.; Mukherjee, B. *Tetrahedron Lett.* **1997**, *38*, 643.

(12) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466.

(13) Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382.

(14) (a) Okuro, K.; Enna, M.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1107. (b) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

(15) Stecko, S.; Furman, B.; Chmielewski, M. *Tetrahedron* **2014**, *70*, 7817.

(16) Rodygin, K. S.; Werner, G.; Kucherov, F. A.; Ananikov, V. P. *Chem. - Asian J.* **2016**, *11*, 965.

(17) (a) Zhang, W.; Wu, H.; Liu, Z.; Zhong, P.; Zhang, L.; Huang, X.; Cheng, J. *Chem. Commun.* **2006**, 4826. (b) Hosseini, A.; Pilevar, A.; Hogan, E.; Mogwitz, B.; Schulze, A. S.; Schreiner, P. R. *Org. Biomol. Chem.* **2017**, *15*, 6800.

(18) (a) Sum, Y. N.; Yu, D.; Zhang, Y. *Green Chem.* **2013**, *15*, 2718. (b) Hosseini, A.; Seidel, D.; Miska, A.; Schreiner, P. R. *Org. Lett.* **2015**, *17*, 2808.

(19) (a) Werner, G.; Rodygin, K. S.; Kostin, A. A.; Gordeev, E. G.; Kashin, A. S.; Ananikov, V. P. *Green Chem.* **2017**, *19*, 3032. (b) Rattanangkool, E.; Vilaivan, T.; Sukwattanasinitt, M.; Wacharasindhu, S. *Eur. J. Org. Chem.* **2016**, *2016*, 4347. (c) Matake, R.; Adachi, Y.; Matsubara, H. *Green Chem.* **2016**, *18*, 2614. (d) Teong, S. P.; Chua, A. Y. H.; Deng, S.; Li, X.; Zhang, Y. *Green Chem.* **2017**, *19*, 1659.

(20) Yu, D.; Sum, Y. N.; Ean, A. C. C.; Chin, M. P.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5125.

(21) Fu, R.; Li, Z. *Org. Lett.* **2018**, *20*, 2342.

(22) (a) Yu, Y.; Huang, W.; Chen, Y.; Gao, B.; Wu, W.; Jiang, H. *Green Chem.* **2016**, *18*, 6445. (b) Yu, Y.; Chen, Y.; Huang, W.; Wu, W.; Jiang, H. *J. Org. Chem.* **2017**, *82*, 9479.

(23) Ledovskaya, M. S.; Rodygin, K. S.; Ananikov, V. P. *Org. Chem. Front.* **2018**, *5*, 226.

(24) (a) Citek, C.; Lyons, C. T.; Wasinger, E. C.; Stack, T. D. P. *Nat. Chem.* **2012**, *4*, 317. (b) Chiang, L.; Keown, W.; Citek, C.; Wasinger, E. C.; Stack, T. D. P. *Angew. Chem.* **2016**, *128*, 10609.

(25) Weissman, S. A.; Anderson, N. G. *Org. Process Res. Dev.* **2015**, *19*, 1605.

(26) Adrian, J. C.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457.

(27) Karageorgis, G.; Warriner, S.; Nelson, A. *Nat. Chem.* **2014**, *6*, 872.

(28) Villamena, F. A.; Dickman, M. H.; Crist, D. R. *Inorg. Chem.* **1998**, *37*, 1446.

(29) Malig, T. C.; Yu, D.; Hein, J. E. *J. Am. Chem. Soc.* **2018**, *140*, 9167.

(30) *Category 3, Compounds with Four and Three Carbon Heteroatom Bonds*; 1st ed.; Danheiser, R. L., Ed.; Georg Thieme Verlag: Stuttgart, 2006; Vol. *23*.

(31) Maujean, A.; Chuche, J. *Tetrahedron Lett.* **1976**, *17*, 2905.

(32) Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586.

(33) *Mayr's Database of Reactivity Parameters*, https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank, accessed February 14, 2019.

(34) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576.

(35) Shintani, R.; Fu, G. C. *Angew. Chem.* **2003**, *115*, 4216.

DOI: 10.1021/acs.orglett.9b01192
Org. Lett. XXXX, XXX, XXX−XXX